Absolute Rheumatology Review

Petros Efthimiou
Editor

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To my wife, Olga, my best friend and gracious critic
To my parents, Vasilios and Angeliki, who convinced me to pursue my dreams and that everything is possible
To my patients who trust me with their health and teach me something new every single day

Foreword

Fellowship training is a wonderful start to mastering the art and science of rheumatology.

Yet, 2 or 3 years of rheumatology fellowship training can be dizzying for the notable volume of work, experiences, knowledge, diagnoses, controversies, and opportunities. The educational sustenance is analogous to drinking from the fire-hose. You'll definitely get wet (experience) but your thirst may go unquenched. Time, perspective, and an ongoing effort to learning are necessary to master the art of rheumatology.

Absolute Rheumatology Review is a new source of perspective and knowledge for the young rheumatologist. It was designed to be the resource for those in training and those preparing for board examinations or recertification examinations.

Textbooks serve the important role of defining the standards of care and where we are in our understanding of rheumatic disorders. This is especially important with complex rheumatologic disorders where innovation, pathogenic advances, and new therapeutics change annually. When such knowledge is applied, patients win with better opportunities for an early diagnosis and optimal outcome.

The chapters included in *Absolute Rheumatology Review* are written by experts who have synthesized historical perspective and recent advances to provide overviews that are accurate, focused, practical, and up-to-date.

In reviewing and reading Dr. Efthimiou's textbook, I can appreciate the selection of authors and the inclusion of many novel chapters germane to rheumatology, including genetics, immunology, epidemiology, regional musculoskeletal disorders, ultrasound, and autoinflammatory disorders. These stand well beside chapters on the most prevalent disorders, such as rheumatoid arthritis, psoriatic arthritis, osteoarthritis, etc.

Chapter design and readability are both easy and incisive. The chapters are led by bulleted key points and finish with test questions to further their educational impact. These are novel, well-done, and highly helpful whether you're a young rheumatologist preparing for board questions or a practicing rheumatologist wishing to stay abreast of the field.

While this compendium will benefit those who are studying rheumatology, it can also exist as a valued source for the rheumatologist engaged in patient care, especially when he or she ponders the last patient, the next drug choice, or the best diagnostic approach.

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Preface

I am pleased to introduce this concise and comprehensive review of rheumatology to physicians preparing for the rheumatology board certification examination. The goal was to provide the most up-to-date information, emphasizing high-yield facts, in an easy-to-read format, accented by tables, figures, and clinical imaging, without burdening the reader with extraneous details. Moreover, each chapter was enhanced by a plethora of board-like, multiple-choice questions for the reader to practice and apply the knowledge gained by reviewing the various topics.

The contributing authors were selected because of their clinical and research expertise as well as their track record on being master educators. The readers will recognize among the authors marquee names in academic rheumatology. Beyond their involvement in every day clinical care, their research has revivified the specialty while themselves have become role models and nurtured the next generation of rheumatology leaders.

The intended audience for the book are in-training rheumatology fellows and practicing rheumatologists preparing for the certification and recertification examinations in rheumatology. I strongly believe that interested physicians will find useful not only the content of this book but also its format; the use of the time-honored Socratic method of learning through questions and answers has served humanity well since its inception in Ancient Greece.

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Chapter 1
Immunological Basis of Inflammatory Arthritides

George D. Kalliolias and Dimitris Skokos

Section 1: Etiology and Pathogenesis of Rheumatoid Arthritis

Key Messages

- 70–80% of patients with rheumatoid arthritis (RA) are seropositive. The typical autoantibodies are rheumatoid factor (RF), antibodies against citrullinated peptides (ACPA), antibodies against carbamylated proteins (anti-CarP), and antibodies against acetylated proteins.
- Seropositive RA displays more aggressive phenotype (more destructive arthritis and more frequent extra-articular comorbidities).
- Seronegative RA is less responsive to treatments targeting adaptive immunity (abatacept and rituximab).
- Emergence of neo-epitopes via post-translational modification of self-proteins (e.g., citrullination, carbamylation, acetylation) is a key event in pathogenesis of seropositive RA.
- The initial immunologic events in pathogenesis of seropositive RA occur in the lung. In genetically predisposed individuals (e.g., carriers of shared epitope or of disease-predisposing *PTPN22* variants), smoking ("first hit")

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triggers citrullination of lung proteins and asymptomatic production of ACPA (preclinical RA).
- Not well-characterized "second hits" trigger a series of immunological events (e.g., changes in the effector functions and antigen specificities of ACPA, cytokine/chemokine production, and activation of resident synovial and endothelial cells) resulting in the onset of early RA.
- Interaction of resident synoviocytes with recruited immune cells, epigenetic imprinting of synovial stromal cells, synovial cytokine networks, local production of antibodies, deposition of immune complexes, and complement activation result in the homing and perpetuation of inflammation in synovial joints (established RA).
- Established RA is characterized by pannus formation, bone and cartilage destruction, systemic osteoporosis, and extra-articular comorbidities (primarily premature atherosclerosis and cardiovascular events).
- Activation of osteoclasts (by RANKL, cytokines, and ACPA) and inhibition of osteoblasts (by inflammation-driven dysregulation of Wnt pathway) result in non-healing bone erosions and systemic osteoporosis.

Historical Perspective

Before the 1800s the term rheumatoid arthritis (RA) was unknown, and the umbrella term "gout" was used to describe inflammatory arthritides, without distinguishing between the different forms. In 1800, Augustin Jacob Landré-Beauvais described "primary asthenic gout" as a distinct clinical entity, which unlike classical gout was chronic and more frequent in women and poor [1]. In 1859, Alfred Garrod concluded that the excess of uric acid in the blood was a distinguishing feature of classic gout from what he called "rheumatic gout" [2]. In 1890, his son Archibald Garrod coined the term "rheumatoid arthritis" to describe "primary asthenic gout" and "rheumatic gout" [2]. Following the clinical description of rheumatoid arthritis as a distinct form of chronic inflammatory arthritis, a series of foundational discoveries resulted in key concepts (summarized in Table 1.1) that have shaped the current model of RA pathogenesis.

Foundational Discoveries Resulting in Key Pathogenetic Concepts

The Discovery of Autoantibodies in RA Patients and the Concept of Autoimmunity

Erik Waaler (1940) and Harry Rose (1948) independently discovered in the serum of RA patients a factor (later named rheumatoid factor; RF) inducing agglutination, and not hemolysis, of antibody-coated red blood cells [3, 4]. In 1957, Henry

Table 1.1 Key pathogenetic concepts in RA

Pathogenetic concept	Consequences
Autoimmunity Mucosal initiation Self-protein modifications Ag presentation by the SE Ab production	Citrullination of self-proteins in the lung generates neoepitopes, which are presented by the shared epitope to cognate T-cells. Then, the activated T-cell provide help to B-cell, which finally differentiate to ACPA-producing plasma cells
Gene-environment interaction	Smoking induces citrullination and inflammation in the lung and triggers ACPA production in carriers of SE or *PTPN22* variants
Epigenetic imprinting	RA FLS possess epigenetic modifications inducing long-lasting changes in the expression of pathogenic genes even in the absence of external stimulation. Imprinted FLS may drive the residual inflammation observed in RA despite aggressive immunosuppression with DMARDs
Cytokine hierarchy	TNF and IL-6 are the dominant upstream inducers of the cascade of mediators that drive synovitis
Inflammatory bone loss Cytokine-driven bone loss ACPA-driven bone loss	Inflammatory cytokines and autoantibodies induce activation of OC and inhibition of OB, promoting systemic and local bone loss. ACPA may drive systemic bone loss in the absence of synovitis

Ag antigen, *SE* shared epitope, *Ab* antibody, *ACPA* anti-citrullinated peptide antibody, *FLS* fibroblast-like synoviocytes, *OC* osteoclasts, *OB* osteoblasts

Kunkel's group characterized rheumatoid factor as an autoantibody against human IgG [5]. Later, new serum factors with autoreactivity against perinuclear antigens, keratin, and filaggrin were identified in RA patients [6–8]. In 1998 was finally discovered that these serum factors were autoantibodies against citrullinated self-peptides (later named Anti-Citrullinated Protein Antibodies; ACPA) [9, 10]. The presence of these two classes of autoantibodies (RF and ACPA) in 70–80% of RA patients suggests that (a) *autoimmunity* is a key pathogenetic concept, at least for seropositive rheumatoid arthritis, and (b) *seropositive* and *seronegative* RA represent two endotypes of RA with serological, clinical, genetic, and pathogenetic differences (summarized in Table 1.2) [11]. More recently, autoantibodies against carbamylated proteins (anti-CarP) and acetylated proteins were identified [12, 13], suggesting that post-translational modifications (e.g., citrullination, carbamylation, and acetylation) of self-proteins result in the emergence of immunogenic neoepitopes that trigger autoimmunity [14]. Anti-CarP were found not only in ACPA-positive but also in 10–20% of ACPA-negative RA patients [14].

The Mucosal Origin of Autoimmunity in RA

The RA-associated autoantibodies can be present in the serum years before the first signs and symptoms of synovitis [15], suggesting that the initial events resulting in the emergence of autoimmunity may occur outside the synovium. The strong association of pulmonary exposures (e.g., cigarette smoking, silica or textile dusts) with the development of ACPA and RA (discussed below) suggests that autoimmunity might be triggered in the lungs [16]. This hypothesis was further supported by

Table 1.2 Key differences between seropositive- and seronegative-RA

	Seropositive RA	Seronegative RA	Comments
Serology	Positive	Negative	In seropositive-RA, positivity for ACPA, RF, and anti-CarP exists in various combinations (e.g., single, double, or triple)
Genetics	Shared epitope *PTPN22*	*PRL* *NFIA*	Distinct and overlapping genetics suggest differences and similarities in pathogenesis. Ag-driven activation of T-cells is more critical in ACPA-positive RA
Environment	Smoking	Unknown	Environmental factors are critical for both serotypes. Lung irritation triggers ACPA production
Joint damage	Destructive arthritis	Less destructive	Bone erosions may occur via cytokine-mediated effects on OC and OB in both serotypes. In ACPA-positive RA, there is an additional ACPA-driven impact
Extra-articular manifestations	Variable	Less frequent	Nodules, vasculitis, and serositis are more frequent in seropositive RA
Treatment	Variable responses	Less responsive to rituximab and abatacept	Cytokine networks involved in both serotypes. B-cells and T-cell co-stimulation less critical in seronegative RA

ACPA anti-citrullinated peptide antibody, *RF* rheumatoid factor, *CarP* carbamylated proteins, *OC* osteoclasts, *OB* osteoblasts

studies in ACPA-positive subjects revealing (a) radiographic signs of parenchymal inflammation in the lung, (b) ectopic lymphoid structures in lung biopsies, and (c) presence of IgA ACPA and citrullinated proteins in bronchoalveolar lavage and sputum [17]. Cigarette smoking creates in the lung a permissive microenvironment for ACPA production: it activates peptidyl-arginine deiminase (PADI) inducing the emergence of citrullinated neoepitopes in a background of local inflammation [18]. Another scenario implicating inflammation in the oral mucosa or intestinal dysbiosis in triggering autoimmunity in RA requires further validation [19].

HLA Association and the Concept of Ag Presentation by the Shared Epitope

In 1969, it was first described that cross-reactivity in mixed lymphocytic reactions was decreased in most RA patients if the stimulating donor was another RA patient [20]. This observation suggested that RA patients share common HLAs. Serotyping experiments in the late 1970s identified that about 70% of RA patients share the same HLA-DR4 alleles [21, 22]. In the late 1980s, the *shared epitope hypothesis* was proposed following the discovery that the majority of RA patients share a

5-amino acid sequence motif in the DRβ chain of HLA-DR4 [23]. A recent study fine-mapped the strongest RA link to amino acids located within the antigen-binding groove of HLA-DRβ chain [24], suggesting that the shared epitope might contribute to disease pathogenesis via *antigen presentation of pathogenic epitopes*. Structural studies indicate that citrullinated peptides "fit better" within the groove of the shared epitope and are presented more efficiently to cognate T-cells [25, 26]. Thus, in shared epitope carriers, citrullination of self-peptides increases their immunogenicity and triggers ACPA production.

Discoveries from Genome-Wide Association Studies (GWAS)

Since the introduction of GWAS in the early 2000s, more than 100 genetic loci have been associated with RA [27]. Prominent among these predisposing loci are genes involved in antigen-mediated activation and co-stimulation of T-cells (e.g., *HLA* class II, *PTPN22*, *CD28*, *CTLA4*), post-translational modification of proteins (e.g., *PADI*), and cytokine signaling (e.g., *TNF*, *IL6R*, *STAT4*, *TYK2*, *TNFAIP3*, *REL*). Each of the non-HLA predisposing loci confers only modest increase in the risk of developing RA (odds ratios ≤ 2) [28]. Notably, the combination of the shared epitope with variants of *PTPN22* and *TRAF1-C5* increases >40-fold the risk of developing RA, suggesting an additive or synergistic effect when several risk-variants are present in the same individual [29, 30]. The long list of RA-associated genetic variations includes genetic loci predisposing also to other autoimmune and inflammatory diseases, suggesting pathogenetic similarities and potential common therapeutic targets among the spectrum of immune-mediated diseases [31]. Another conclusion from GWAS is that between ACPA-positive and ACPA-negative RA there are overlapping and distinct risk variants [32], with shared epitope and *PTPN22* variants contributing primarily to ACPA-positive RA whereas *PRL* and *NFIA* are associated with ACPA-negative RA [17, 33].

Notably, 80% of the RA-associated genetic variations identified by GWAS are localized in non-coding regions [34]; thus it may predispose to RA without altering the amino acid sequence and the function of a gene product. Fine-mapping studies revealed that many of these non-coding variations colocalize with (a) expression quantitative trait loci (eQTL) and (b) DNA-binding sites for STATs [27, 35]. The latter indicates the involvement of Jak-STAT pathway in RA pathogenesis, which is now proven by the success of Jak inhibitors in the clinic [36]. In this context, the non-HLA genetic variations may contribute in RA pathogenesis via two potential mechanisms: (1) by *altering the expression levels of genes* (change the expression or DNA binding of transcription factors) and (2) by *altering the amino acid sequence and the function of proteins* [34].

Link with Cigarette Smoking and the Stochastic Model of Genes-Environment Interaction

The concordance rate of RA between identical twins is only 12–15% [37], suggesting that strong environmental effects (e.g., by cigarette smoking, silica exposure, and microbiome) cooperate with the disease-predisposing genetic background for

the full-blown development of RA [38]. Cigarette smoking is the best characterized environmental risk factor and its link with RA was first described in 1987 [39]. Smoking increases ≥20-fold the risk of developing RA in the presence of the shared epitope or variants of *PTPN22*, revealing the stochastic *synergy between genes and environment* in RA pathogenesis [40, 41]. Smoking induces citrullination of self-proteins in the lung and increases the risk of developing ACPA, especially in shared epitope carriers [42].

Discoveries Leading to the Concepts of Cytokine Network and Cytokine Hierarchy

Seminal observations by the group of Marc Feldnamm and Ravinder Maini established the pathogenetic role of TNF in RA [43]. At first it was shown that in RA, but not osteoarthritic synovial cell cultures, anti-TNF antibodies dramatically reduced the production of a range of proinflammatory cytokines, such as IL-1, GM-CSF, IL-6, and IL-8 [44, 45]. Subsequent proof-of-concept clinical trials demonstrated that ant-TNFs are clinically effective and rapidly reduce serum levels of IL-6 [46, 47]. These observations introduced the concepts of the *cytokine network* and *cytokine hierarchy* in RA pathogenesis: within the RA synovium although many proinflammatory cytokines are highly expressed and share similar signaling pathways there is no biological redundancy; instead there is a cytokine network with hierarchical organization [48]. Hence, there are cytokines (e.g., TNF or IL-6) operating in the context of RA upstream of others (e.g., IL-1) driving the cascade of cytokine production within the inflamed joints. Targeting these upstream cytokines cripples the downstream cascade and has higher therapeutic potential. This concept is further supported by the differential therapeutic effects in RA of the various strategies targeting cytokines expressed in RA synovium: targeting TNF and IL-6 is effective and targeting GM-CSF appears promising [49], whereas targeting IL-1 is moderately effective [50] and trials targeting IL-17 or IL-12/IL-23 have not provided convincing benefit so far [51, 52].

Discoveries Leading to the Concept of Cytokine-Driven Osteoclastogenesis

Three types of bone loss are typically observed in RA: (a) marginal erosions in the interface of synovium with adjacent bone, (b) periarticular demineralization of bones near the inflamed joints, and (c) systemic bone loss [53]. The foundational discoveries of osteoimmunology, the myeloid origin of osteoclasts (OC) and the cytokine-driven osteoclast differentiation/activation, have established the mechanistic link between inflammation and bone destruction [54]. In 1998 it was first described that a cytokine of the TNF-superfamily, now known as RANKL, is the master-regulator of osteoclast generation and function [55]. Subsequent studies in RA revealed abundance of osteoclast precursors and expression of RANKL in the areas of pannus invasion into bone, and have identified activated fibroblast-like

synoviocytes (FLS), T-cells, B-cells, and osteoblasts as the sources of RANKL within RA synovium [56–59]. The effectiveness of denosumab, an antibody against RANKL, in inhibiting the progression of erosions provides in vivo evidence for the contribution of RANK/RANKL-axis in bone destruction during RA [60]. Treatments blocking TNF and IL-6 also prevent bone erosions in RA, indicating that cytokines other than RANKL are also involved in bone destruction. Expansion of OC-precursors' pool, induction of RANKL, and synergy with RANKL pathway are proposed mechanisms for the *cytokine-driven osteoclastogenesis* in RA [53].

Discoveries Leading to the Concept of ACPA-Driven Osteoclastogenesis

The association of ACPAs with higher risk of erosions was known for years in established RA [53]. Recently, it was shown that the presence of ACPAs is also associated with lower bone density in healthy individuals [61]. A mechanistic link between ACPA and osteoclastogenesis has been suggested by the following observations: (1) administration of human ACPA in mice induces systemic bone loss in vivo in the absence of any apparent synovitis [62, 63], (2) ACPA or Fab fragments with ACPA-specificity promote human osteoclastogenesis in vitro, (3) fluorescently labelled ACPA bind to osteoclasts and osteoclast-precursors in murine joints [64], (4) protein citrullination and surface expression of citrullinated proteins is part of the normal process of osteoclast differentiation [62], (5) ACPA with specificity against citrullinated vimentin promote human osteoclastogenesis in vitro [62], and (6) pharmacologic inhibition of citrullination or neutralization of IL-8 diminish ACPA-driven osteoclastogenesis in vitro [63]. These observations suggest Fab-mediated direct binding of ACPA to citrullinated proteins on osteoclasts and osteoclast-precursors and IL-8-mediated pathways as mechanisms for ACPA-driven bone loss.

In addition, a potential role for Fc/Fc Receptor-mediated mechanisms in ACPA-driven bone loss is indicated by the following observations: (1) the sialylation status of Fc fraction of IgGs modulates the binding of IgG-immune complexes to Fc Receptors and alters their osteoclastogenic potential [65], (2) the sialylation status of ACPA modulates in vitro and in vivo their osteoclastogenic potential [66], and (3) RA patients with lower levels of ACPA sialylation displayed lower bone density [66]. All together, these observations suggest that a combination of Fab-mediated and Fc-dependent mechanisms triggers *ACPA-driven osteoclastogenesis* in ACPA-positive individuals, even in the absence of overt synovitis [18].

Discoveries Leading to the Concept of Inflammation-Driven Inhibition of Osteoblasts

In RA patients, repair of existing erosions is infrequent [67], and histopathologic analysis in animal models revealed paucity of mature osteoblasts (OB) in areas of bone erosion [68, 69]. These observations suggest that synovial inflammation not

only induces osteoclastogenesis but also impairs OB differentiation and function. The concept of *inflammation-driven inhibition of OB* is supported mechanistically by studies investigating the in vivo impact of inflammation on the regulation of Wnt pathway, which is the key driver of OB differentiation [70]. In animal models, synovial inflammation upregulates Wnt pathway-antagonists (e.g., DKK1, sclerostin, sFRP1, and sFRP2) with parallel downregulation of Wnt agonists (e.g., Wnt10b) [68, 69, 71]. In RA patients and animal models, the high levels of DKK1 are decreased by treatment with anti-TNF, indicating TNF as a key inducer of DKK1 [71, 72]. Along the same lines, pharmacologic inhibition of DKK1 or sclerostin in animal models prevents bone erosions [71, 73, 74]. These observations suggest that the inflammatory milieu of RA synovitis inhibits OB differentiation/function by deregulating the balance between antagonists and agonists of Wnt pathway.

The Concept of Fibroblast-Like Synoviocytes (FLS) as "Imprinted Aggressors"

The histopathologic hallmark of RA is pannus, which is a hyperplastic synovial lining mass that produces cytokines and proteases, erodes subchondral bone, and degrades the adjacent cartilage. Bone erosion is driven by OC and cartilage degradation is directly mediated by invading FLS [75]. Ex vivo models in immunodeficient mice show that transplanted FLS derived from RA patients retain for months their invasive, migratory, and cartilage-destructive capacity [76, 77]. In vitro studies show that passaged RA FLS retain higher spontaneous and triggered cytokine production, compared to FLS derived from osteoarthritis [78, 79]. These observations reveal that RA FLS possess or acquire an "arthritogenic memory", which is remarkably stable and autonomous from exogenous stimulation. Subsequent studies in RA FLS identified a unique DNA methylation signature, which is dependent on disease duration, persists ex vivo, and impacts the expression of arthritogenic genes [80–82]. Additional epigenetic modifications, such as inflammation-induced changes in histone acetylation and microRNAs' expression, have been associated with the persisting functional abnormalities observed in RA FLS [79, 83–85]. Taken together, these observations suggest that RA FLS are epigenetically imprinted, and the observed epigenetic marks (e.g., DNA-methylation and histone-acetylation) are either inherited or occur de novo as result of inflammation and environmental influences [86].

In this context, RA FLS not only respond passively to the surrounding microenvironment (*passive aggressors*) but also possess an autonomous arthritogenic phenotype due to epigenetic imprinting (*imprinted aggressors*) [86]. The consequence of this model is that RA FLS potentially retain their autonomous pathogenetic functions even under potent immunosuppression, hence the imprinted aggressors may drive disease flares or the residual synovial inflammation observed in inadequate responders to synthetic or biologic DMARDs [87]. In this group of resistant patients, therapeutic targeting of FLS, on top of the standard-of-care immunosuppression, emerges as an attractive option [88]. FLS-targeting approaches, including epigenetic

modifiers and antibodies against FLS-expressing molecules, are currently in early stages of clinical development [89].

The Road Map of RA Pathogenesis: The Stochastic Multistep Model

The Three Phases of RA Pathogenesis

The clinical syndrome of rheumatoid arthritis results from a sequence of events, which unfold in three phases (Fig. 1.1). In the *preclinical phase*, individuals carrying disease-predisposing genetic variants and epigenetic modifications (individuals at risk) develop over time an asymptomatic immune response characterized by autoantibodies (e.g., ACPA, RF, anti-CarP) and systemic production of cytokines/chemokines [90]. This phase is triggered by environmental factors ("first hit") and occurs outside the joints (e.g., in the lungs). The duration of preclinical phase is variable and could be many years before the onset of the first symptoms and signs of arthritis. The transition from preclinical to *early RA* is characterized by serological changes (discussed below), systemic bone loss, arthralgias, and synovitis [30]. Gradually, the disease enters the third phase of *established RA* characterized by destructive synovitis and extra-articular comorbidities [91].

It appears that different pathogenetic pathways drive each phase. Ag stimulation of T-cells, activation of B-cells, and antibody production drive the preclinical phase [90]. Evolution of the adaptive immune response to modified self-proteins (epitope spreading and isotype class switch) together with synovial cell activation drives the phase of early RA [30]. Finally, established RA involves the interaction of resident synoviocytes with recruited immune cells, synovial cytokine networks, and local production of antibodies with deposition of immune complexes that trigger complement activation [30, 91].

Homing to Synovial Joints: The Unique Anatomy of the Joint and the "Second Hit Hypothesis"

The autoantigens in RA (e.g., citrullinated vimentin, enolase, fibronectin, fibrinogen) are not synovial tissue-specific, and autoimmunity emerges outside the joints (e.g., in the lung or oral cavity) [18]. In addition, ACPA alone although directly trigger bone loss are not sufficient to initiate arthritis in humans and mice [18]. In this context, the tropism of RA for synovial joints cannot be fully explained by the development of autoantibodies and by the classical concept of organ/tissue-specific autoimmunity. An alternative hypothesis suggests that the unique anatomy of synovial joints renders them vulnerable to a "second hit" [87].

The synovial lining consists of macrophage-like synoviocytes (MLS) and FLS, which are loosely attached to each other without tight-junctions or basement

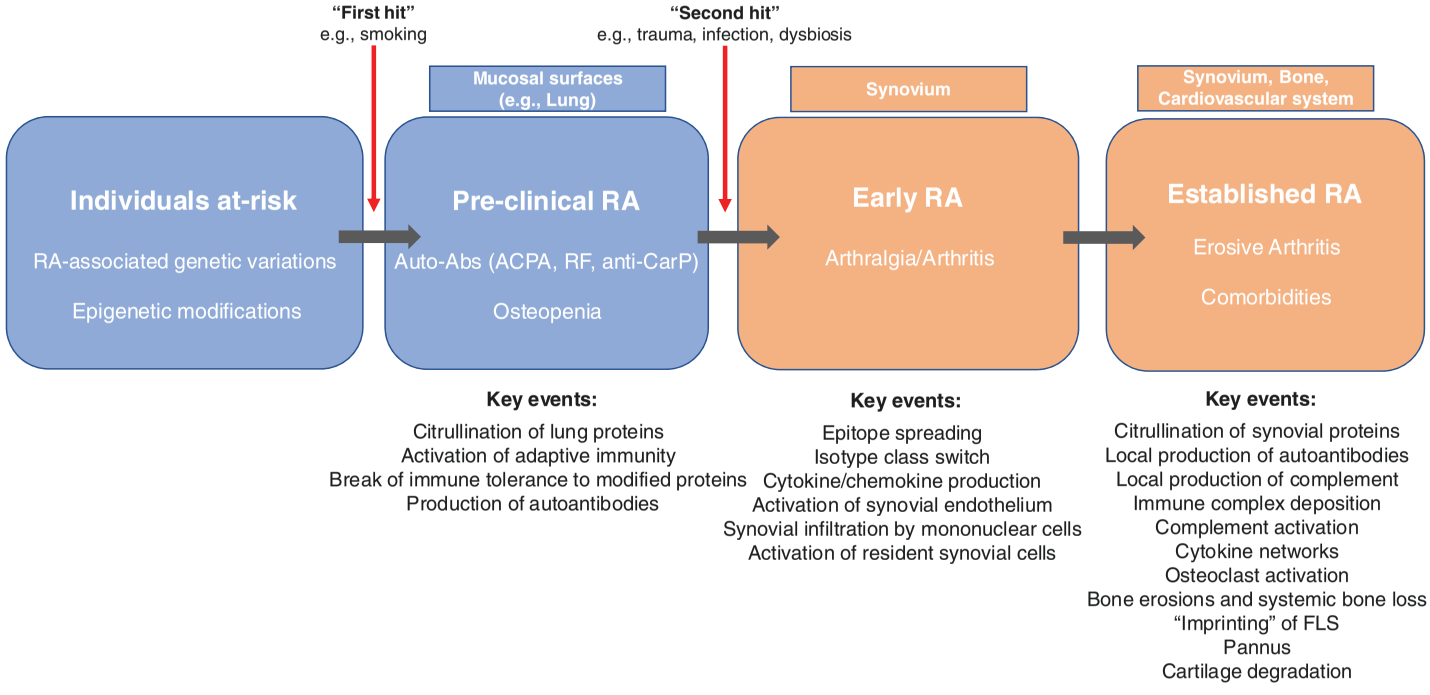

Fig. 1.1 The road map of RA pathogenesis

membrane [92]. The juxtaposition of FLS/MLS favors the development of cytokine networks with feed-forward autocrine and paracrine loops [93]. The lack of physical barriers allows free trafficking of cells and macromolecules (such as antibodies and immune complexes) from the vasculature to the joint. The articular cartilage is a "sticky surface" favoring the non-specific binding of antibodies and immune complexes and, due to lack of complement inhibitors, allows the unopposed activation of complement system [94]. In addition, the extracellular matrix of synovial joints contains long-lived immobile proteins with very low turn-over rate, favoring the accumulation over time of neoepitopes via post-translational modifications [14]. Finally, the presence of cortical bone pores potentially allows the spread of inflammation from the subchondral bone and juxta-articular bone-marrow to the adjacent synovium [95]. All these unique anatomical features render the joint (a) vulnerable to a "second hit" and (b) a "fertile soil" that fuels local inflammation.

The nature of the "second hit" is obscure, but joint inflammation due to local microtrauma or transient infections has been suspected. Then it follows synovial endothelium activation, increased vascular permeability, synovial recruitment of immune cells, and deposition of antibodies and immune complexes [30, 96]. Notably, around the time of transition from preclinical to early RA, there are changes in the status of ACPA (increase in serum titers, isotype-class switch, epitope spreading, modulation of the glycosylation status) [97, 98]. These observations suggest that changes in the effector functions and the antigen specificity of ACPA might contribute to the homing of the disease to synovial joints.

Section 2: Etiology and Pathogenesis of Spondyloarthritides

Key Messages

- Spondyloarthritis (SpA) is a heterogeneous disease and subclassified in many endotypes based on clinical presentation, underlying etiology, and imaging features.
- All SpA endotypes display strong polygenic heritability, with HLA-B27 conferring the higher genetic risk.
- Type 3 inflammation (IL-23/IL-17 pathway) plays a central role in SpA pathogenesis.
- Clinical trials revealed a tissue/organ-specific role for IL-23 and IL-17 in SpA:
  - (a) Inflammation in axial skeleton is IL-17-dependent but IL-23-independent.
  - (b) Inflammation in peripheral skeleton and skin (psoriasis) is IL-17- and IL-23-dependent.
  - (c) Inflammation in the gut (inflammatory bowel disease (IBD)) is IL-23-dependent but IL-17-independent.

- TNF is critically involved in SpA pathogenesis, but the two modalities of blocking TNF (monoclonal antibodies and etanercept) display differences in effectiveness regarding gut and eye inflammation:
  (a) Monoclonal antibodies are superior to etanercept in IBD and uveitis.
  (b) Etanercept and monoclonal antibodies are equally effective in controlling psoriasis and axial/peripheral musculoskeletal manifestations.
- There is a mechanistic link between the development of SpA and events occurring in the gut (gut-joint axis), such as epithelial barrier disruption, dysbiosis, intestinal inflammation, and arthritogenic priming of the immune system.
- Enthesitis and abnormal new bone formation are clinicopathologic hallmarks of SpA triggered by repeated mechanical stress in genetically predisposed individuals.
- Early onset and long-term inhibition of inflammation has the potential to slow new bone formation. It is worth exploring whether a combination of anti-inflammatory drugs with novel inhibitors of bone anabolic pathways will result in more robust prevention of new bone formation and more efficient disease modification.

The Spectrum of Spondyloarthritides

In 1970s, the unifying concept of spondyloarthritis (SpA) was introduced to describe a spectrum of clinical phenotypes [99], which share some key clinicopathological, genetic, and etiopathogenetic features. Based on the clinical presentation and the underlying etiology, SpA is classified into six endotypes: (1) ankylosis spondylitis (AS) [100], (2) psoriatic arthritis (PsA) [101], (3) enteropathic arthritis [102], (4) reactive arthritis (ReA) [103], (5) undifferentiated SpA (USpA) [104], and (6) juvenile SpA (JSpA) [105]. The three hallmarks of all endotypes are (a) strong association with HLA-B27 [106], (b) enthesitis (inflammation of the insertion sites of tendons and ligaments into bone) [107], and (c) abnormal new bone formation (enthesophytes or syndesmophytes) [108].

The endotypes of SpA target in various combinations five anatomical domains: (1) axial skeleton (e.g., sacroiliitis, axial enthesitis, spondylitis), (2) peripheral musculoskeletal structures (e.g., peripheral synovitis, enthesitis, dactylitis), (3) skin (e.g., psoriasis), (4) gut (e.g., inflammatory bowel disease or subclinical intestinal inflammation), and (5) eye (e.g., uveitis) [109]. According to the localization of the dominant musculoskeletal manifestations, SpA is subclassified into axial SpA (axSpA), if the involvement of the axial skeleton predominates [110], and periph-

eral SpA (perSpA) if the main manifestations are peripheral synovitis, enthesitis, or dactylitis [111]. Recently, the concept of non-radiographic SpA (nrSpA) was introduced to allow early diagnosis and treatment based on signs of early inflammation in sacroiliac joints captured by MRI, before the occurrence of radiographically visible structural damage [112]. This chapter focuses on the pathogenetic themes which are common among the SpA endotypes.

The Complex Genetic Landscape of SpA: Strong Polygenic Heritability

The role of heredity in the pathogenesis of SpA was first suspected when Bechterew's disease (now known as AS) was observed to be segregated in families [113]. In the 1970s, three independent studies revealed that 88–96% of AS patients were carriers of HLA-B27 [114–116]. Subsequent studies in identical twins described a concordance rate of 63% for AS and estimated heritability in SpA at 90% [117, 118]. Although HLA-B27 is the strongest genetic risk factor, it explains only 20% of the total genetic predisposition [119]. Using next-generation sequencing technologies, more than 100 polymorphisms in >40 genes were associated with the various SpA endotypes [120–125]. Despite this progress, more than 70% of the genetic contribution remains unknown [119].

Fine mapping of the SpA-associated loci revealed that only a minority are missense variants that change the function of the encoded protein [119]. The best studied example of a missense variant is rs11209026, a single nucleotide polymorphism (SNP) of *IL23R*, which encodes a substitution of arginine with glutamine at position 381 that results in a loss-of-function variation of IL-23 receptor and confers substantial disease protection [120, 126]. Notably, the majority of risk variations are colocalized with epigenetic marks of enhancers and predispose to SpA by regulating the expression of genes [119]. One example is rs6600247, a SNP that reduces the recruitment of IRF4 and decreases the expression of *RUNX3* in CD8 positive T-cells [127].

Further analysis of the genetic landscape of SpA suggests some key pathogenetic themes (presented in Table 1.3). The association of SpA with HLA class I molecules and genes involved in peptide processing implicates *antigen-presentation by HLA class I* in disease pathogenesis [118]. The link with genes regulating IL-23R signaling and IL-17 production indicates the involvement of *type 3 inflammation* (IL-23/IL-17 pathway) [119]. The identification of shared predisposing variants among SpA, inflammatory bowel diseases (IBD) and psoriasis [128], together with the observation that SpA may develops in a background of IBD or psoriasis [101, 102], suggest that *epithelial barrier dysfunction* may contribute to SpA pathogenesis.

Table 1.3 Key pathogenetic themes emerging from SpA genetics

Pathogenetic theme	Supportive genetics
Antigen-presentation via MHC class I	Among the SpA-associated genes are: 1. Genes encoding HLA class I: HLA-B27, other HLA-B genes, HLA-A 2. Genes involved in processing and loading of peptides to MHC class I: *ERAP1*, *ERAP2*, *NPEPPS*
Type 3 inflammation	Among the SpA-associated genes are at least 10 genes regulating IL-17 production: 1. Genes regulating IL-23 signaling: *IL23R*, *IL12B*, *TYK2*, *JAK2*, *STAT3* 2. Genes regulating Th17 polarization/activation: *IL6R*, *IL27*, *CARD9*, *PTGER4* 3. *IL7R*
Epithelial barrier disruption	Shared predisposing variants with epithelial barrier diseases (e.g., inflammatory bowel disease and psoriasis)

Table 1.4 Mechanisms proposed to explain the role of HLA-B27 in SpA pathogenesis

Hypothesis	Putative mechanism
Arthritogenic peptide presentation	Arthritogenic peptides "fit better" within the peptide-binding groove of HLA-B27 and are presented with higher efficiency to cognate CD8+ T-cells
Dimerization	Beta-2-microglobulin free heavy chains of HLA-B27 homodimerize on the cell-surface and are recognized by killer-immunoglobulin-like receptors (KIR) expressed on NK-cells and CD4+ T-cells, inducing their activation and IL-17 production
Misfolding	Intracellular accumulation of misfolded HLA-B27 triggers endoplasmic reticulum stress, autophagy, and IL-23 production
Dysbiosis	HLA-B27 influences the constitution of intestinal microbiome contributing to dysbiosis

Presentation of "Arthritogenic" Antigens by HLA Class I

Despite more than 40 years of investigation, the molecular mechanism by which HLA-B27 contributes to SpA pathogenesis remains elusive (summary of the potential mechanisms in Table 1.4) [106]. According to the classic theory, pathogenic epitopes "fit better" within the groove of HLA-B27, hence they are presented with higher efficiency to CD8+ cells [106]. In support of the antigen-presentation scenario, a recent study has identified polymorphisms at amino acid-position 97, which lies in the floor of the peptide-binding groove of HLA-B molecules, displaying the strongest effect in AS susceptibility [129]. The presence at position 97 of asparagine (found in AS-predisposing variants of HLA-B27) or threonine (found in HLA-B51) increases the risk for AS, whereas the presence of serine (found in HLA-B07 and HLA-B08) or valine (found in HLA-B57) is protective [129]. This study suggests that the amino acid sequence of the peptide-binding groove of HLA-B molecules

determines the risk of developing AS. HLA-B27 is highly polymorphic (about 160 amino acid sequence variations identified so far), and among the different variants there are SpA-predisposing variants (e.g., HLA-B27: 05, HLA-B27:02, HLA-B27:04, HLA-B27:07, HLA-B27:03, and HLA-B27:10) and variants with neutral or even protective impact (e.g., HLA-B27:06, HLA-B27:09) [130]. Notably, between the predisposing and the non-predisposing variants there are differences in the peptide binding repertoire [131], implying distinct antigen-presentation capacities.

In further support of the "antigen presentation theory", among the SpA-predisposing variants there are polymorphisms in genes involved in peptide processing and loading to HLA class I, primarily polymorphisms in the gene encoding endoplasmic reticulum aminopeptidase 1 (ERAP1) (more details on these genes in Table 1.3) [132]. ERAP1 is an enzyme operating as a "peptide ruler", trimming peptides to the optimal size for HLA class I binding [133]. Notably, ERAP1 is in epistasis with HLA-B27 and confers risk for AS only in the presence of HLA-B27 [129], suggesting a pathogenetic partnering of the "peptide ruler" with the "peptide presenter". The locus of *ERAP1* is highly polymorphic and the SpA-predisposing variants increase the enzymatic activity or the expression of ERAP1, modulating the repertoire of peptides that bind to HLA-B27 [132]. In this context, inhibition of ERAP1 emerges as an attractive future therapeutic strategy for SpA.

HLA-B27 Beyond Antigen-Presentation: Misfolding and Homodimerization

Peptides with convincing arthritogenic potential have not been identified yet, and there is very limited evidence so far about the presence of HLA-B27-restricted arthritogenic CD8+ cells in patients with SpA [134]. In addition, HLA-B27 transgenic animal models do not require CD8+ cells or transporters of antigen processing (TAP) for disease development [135–137]. All together, these observations have challenged the concept of presentation of arthritogenic antigens by HLA-B27 to CD8+ T-cells. Two alternative concepts (Table 1.4) have emerged recently suggesting that HLA-B27 contributes to SpA pathogenesis by intracellular misfolding or by cell-surface homodimerization [106]. According to the *misfolding hypothesis*, intracellular accumulation of misfolded HLA-B27 triggers endoplasmic reticulum stress, autophagy, and IL-23 production [138–143]. Notably, a recent study indicates that intracellular accumulation of HLA-B27 and autophagy-triggered IL-23 production occur in the gut of AS patients [144]. According to the *homodimerization hypothesis*, beta-2-microglobulin free heavy chains (FHC) of HLA-B27 homodimerize on the cell-surface and are recognized by killer-immunoglobulin-like receptors (KIR) expressed on NK-cells and CD4+ T-cells, inducing their activation and IL-17 production [145–149]. In support of this scenario, CD4+ T-cells expressing KIR-3DL2 and markers of Th17 lineage commitment were identified in patients with AS [150]. The antigen-presentation

theory and the misfolding and dimerization hypotheses should not be considered mutually exclusive, instead all three mechanisms may contribute in different degrees depending on the context.

Epithelial Barrier Disruption: Dysbiosis or Infection

Clinical observations showing that 10–20% of patients with IBD and 30% of patients with psoriasis develop SpA indicate a potential mechanistic link between epithelial barrier disruption and SpA [100]. In support of this concept, GWAS studies reveal overlapping genetic predisposition among IBD, psoriasis and SpA [128]. The most obvious pathogenetic consequence of a disrupted epithelial barrier (gut or skin) is the entrance into the host of entire microorganisms or their fragments (e.g., antigenic epitopes and molecular patterns) [19]. Along these lines, increased intestinal permeability has been observed in patients with AS [151]. According to this pathogenetic scenario, a "leaky" gut or skin licenses the colonizing microbiome to trigger an arthritogenic immune response or facilitates an arthritogenic infection [19, 152]. The essential role of microbiome in SpA pathogenesis is suggested by observations in animal models of SpA, where the disease does not develop under germ-free conditions [153, 154]. Recent studies reveal changes in the intestinal microbial composition (dysbiosis) in patients with SpA and animal models indicate a potential role of HLA-B27 in this process (Table 1.4) [155–158].

The Gut-Joint Axis: Intestinal Production of IL-23 and Expansion of Arthritogenic Immune Cells

The concept of a *gut-joint axis* was coined to describe the mechanistic link between the development of SpA and events occurring in the gut, such as epithelial barrier disruption, dysbiosis, intestinal inflammation, and arthritogenic priming of the immune system [19]. In support of this concept, subclinical gut inflammation has been identified in all endotypes of SpA and was strongly correlated with the degree of spinal inflammation [159, 160]. The subclinical gut inflammation is characterized by mononuclear cell infiltration, lymphoid follicle formation, IL-23 production, and local expansion of innate immune cells, such as innate lymphoid cells of group 3 (ILC3), γδT-cells, and mucosal-associated invariant T (MAIT) cells [159, 161–163]. Notably, expanded ILC3s expressing the homing integrin α4β7 were identified not only in the gut but also in peripheral blood, synovial fluid and bone marrow of AS patients [164–166]. The expansion and differentiation of these intestinal subpopulations of innate cells depends on local production of IL-7 and IL-23 [167, 168]. Activated paneth cells and intestinal myeloid cells have been identified as the cellular sources of intestinal production of IL-23 in AS patients

[163]. Intestinal activation of autophagy, potentially triggered by intracellular accumulation of misfolded HLA-B27, has been suggested as a molecular pathway inducing the intestinal production of IL-23 in SpA [144].

The above observations suggest that subclinical intestinal inflammation is not an epiphenomenon, but rather an etiologic event that contributes to SpA pathogenesis and indicate the following pathogenetic model: interaction of environmental factors (e.g., microbiome), with genetic factors (e.g., HLA-B27) result in intestinal dysbiosis, disruption of epithelial barrier, activation of autophagy pathway and intestinal production of IL-7 and IL-23 [159]. In genetically predisposed individuals (e.g., carriers of *IL7R* polymorphisms or of variants that increase IL-23R signaling), the cytokines IL-7 and IL-23 trigger intestinal expansion and activation of innate (e.g., ILC3, γδT-cells, and MAIT cells) and adaptive (e.g., Th17) immune cells and induce the expression of homing integrins (e.g, α4β7) and effector cytokines (e.g., IL-17, IL-22, and TNF) [19]. Then, these cells migrate to the axial and peripheral musculoskeletal structures and drive enthesial, synovial, and spinal inflammation [159]. According to this model, the gut (especially the gut-associated lymphoid tissue; GALT) operates as the anatomic location that primes immune cells for a subsequent arthritogenic response [167]. If this pathogenetic scenario is true, inhibition of IL-7 and targeting the effector cells producing IL-17, IL-22, and TNF emerge as promising future therapeutic strategies for SpA.

Type 3 Inflammation: Organ-Specific Role for IL-23 and IL-17

The signature cytokine of type 3 inflammation is IL-17A [166]. The cellular sources of IL-17A are innate (e.g., ILCs, γδT-cells, MAIT cells, and neutrophils) and adaptive (e.g., CD4 + Th17 and CD8 + IL-17+ cells) immune cells, which express the transcription factor RORγt [166, 169]. The IL-23/IL-23R/Jak2-Tyk2/STAT3-axis plays a critical role in the establishment of type 3 inflammation and IL-17 production [166]. In addition, IL-23-independet pathways have been identified to trigger and maintain IL-17 production, especially in ILCs, γδT-cells, and neutrophils [170–173]. Prostaglandin E2 (PGE2) and its receptor EP4 are among the non-IL-23 regulators of IL-17 production [174–176], but whether PGE2/EP4-axis operates independently of IL-23 is not clear.

Human genetics provide the strongest support for the role of type 3 inflammation in SpA pathogenesis [118]. Among the SpA-associated variants, there are polymorphisms in at least 10 genes, which are involved in the regulation of IL-17 production (Table 1.3). Several studies in animal models, reveal the implication of IL-23 and IL-17 in SpA pathogenesis. For example, systemic over-expression of IL-23 in mice was sufficient to induce IL-17-dependent enthesial inflammation and IL-22-dependent enthesial ossification [177]. Cellular and molecular profiling in SpA patients revealed various types of IL-17-producing cells and high levels of IL-23 and/or IL-17A in the gut, PBMC, serum, synovial tissue, synovial fluid, entheses, and facet joints [163, 164, 168, 178–181].

Recent evidence from clinical trials has challenged our initial linear perceptions about the IL-23/IL-17 pathway and its role in the pathogenesis of SpA [182], especially in driving axial skeleton inflammation and IBD [183–186]. Direct targeting of IL-17 pathway (anti-IL17A or anti-IL-17RA) was proven impressively effective in psoriasis and gave favorable responses in peripheral and axial SpA [187–192]. In contrast, trials in IBD either failed or were discontinued due to disease worsening [185, 186]. On the other hand, targeting IL-23 pathway (anti-p19 or anti-p40) was proven very effective in psoriasis and effective in IBD as well as peripheral SpA [193–196], but failed in axial SpA [183, 184]. These observations indicate that skin and peripheral-musculoskeletal manifestations of SpA are IL-17- and IL-23 dependent, axial inflammation is IL-17-dependent and IL-23-indpendent, whereas clinically overt intestinal inflammation is IL-23-dependent and IL-17-independent.

The differential effects of anti-IL-23 and anti-IL-17 in axial skeleton and intestinal inflammation reveal a tissue/organ-specific role for IL-23 and IL-17 [166, 182]. In this context, treatment decisions (targeting IL-17 versus IL-23 pathways) in the spectrum of SpA endotypes should be based on the anatomic domains that are affected in each individual patient [182]. In axial SpA, anti-IL-17 should be considered for treatment, but not anti-IL-23. In peripheral SpA (synovitis, enthesitis, and dactylitis) both anti-IL-17 or anti-IL-23 (anti-p19 and anti-p40) are acceptable therapeutic options, and due to their impact in the skin could be preferable in PsA with extensive skin involvement. Along the same lines, the status of intestinal involvement should be evaluated in SpA patients before considering inhibitors of IL-17. Since there is evidence for homeostatic functions of IL-17 in the gut (e.g., by maintaining the epithelial barrier integrity) [172], blocking IL-17 pathway is not recommended in SpA patients with IBD.

The Pathogenetic Role of TNF

Since anti-TNF therapies have become a standard of care for all endotypes of SpA [197, 198], the essential role of TNF in driving inflammation in the axial and peripheral skeleton, skin, intestine, and eye is well established. The pathogenetic pathways triggered by TNF have been reviewed recently [43]. Notably, the two modalities of blocking TNF (monoclonal antibodies and TNF receptor) display differences in effectiveness, depending on the anatomic location of inflammation [199]. Monoclonal antibodies are more effective from etanercept in intestinal inflammation and uveitis [200, 201], whereas there is equivalent effectiveness in psoriasis and inflammation of axial/peripheral skeleton.

The Enthesial Link Between Mechanical Stress, Inflammation, and Abnormal Bone Formation

One of the clinicopathological hallmarks of all SpA endotypes is the tropism for the axial and peripheral entheses, manifested as inflammation (enthesitis) and ossification (enthesophytes) [107]. One potential explanation for this tropism is tissue-specific

autoimmunity, but so far autoreactive T-cells with specificity against enthesial antigens have not been identified. An alternative pathogenetic scenario has emerged recently with an emphasis on the unique microanatomy of enthesis. According to this hypothesis, mechanical stress, in genetically predisposed individuals, triggers enthesial inflammation and mesenchymal tissue reaction resulting in abnormal bone formation (Fig. 1.2) [107, 202].

Entheses are essential structures, which enable stable anchoring of tendons and ligaments into bones and provide smooth transduction of mechanical forces from muscle to bone (in the case of tendons) and stability (in the case of ligaments) [107]. To fulfill these high mechanical demands, entheses have a unique microanatomy and structure. The bone at enthesial sites is thin and porous, with blood vessels allowing the communication of the entering tendon or ligament with the neighboring bone marrow [107]. In addition, the transition zone (terminal part of tendons and ligaments before entering the bone) of enthesis is comprised of fibrocartilage and resident mesenchymal stem cells (MSC). Repeated mechanical overload may result in enthesitis even in otherwise healthy individuals, but the unique features of SpA-associated enthesitis are remarkable degree of chronicity and ossification [107, 203].

According to the mechanical stress hypothesis (also known as the mechano-inflammation model; Fig. 1.2), repeated microtrauma and additional triggers (such as "leaky" epithelial barriers and immune cells primed in the gut) induce local inflammation in the perienthesial bone marrow (osteitis), which spreads in the neighboring enthesis (enthesitis) [107]. The key molecular mediators for these early local events are PGE2 and cytokines (e.g., IL-23, IL-17, IL-22, and TNF). It is speculated that PGE2 is locally produced by resident mesenchymal cells, which express cyclooxygenase 2 (COX2). PGE2 facilitates the development of osteitis and enthesitis by triggering local vasodilation. The anatomic and cellular sources of IL-23 are not well defined, but distant production in the gut (as described above) or local production by myeloid cells have been suggested. Resident enthesial IL-23R+ cell have been identified in mice and in humans [177, 204], but confirmatory studies are required to validate these observations. The combination of PGE2 and IL-23 fosters the local production of IL-17, IL-22 and TNF by resident and recruited innate (ILC3 and γδT cells) and adaptive immune cells (Th17 cells). IL-17 and TNF act as amplifiers of enthesitis and osteitis by inducing recruitment and activation of neutrophils and macrophages [107].

In SpA patients, the inflammatory phase (osteitis and enthesitis) is followed by a remarkable two-step mesenchymal tissue response. At first, there is a chondroblast-mediated formation of a cartilaginous scaffold, and then osteoblast-mediated ossification occurs [107]. The key effector cells during this tissue response are resident mesenchymal cells, which are differentiated into chondroblasts and osteoblasts [203]. It appears that the initial inflammatory phase fosters the tissue response, since IL-17 and IL-22 activate mesenchymal cells [177, 205–208], and PGE2 is a robust activator of osteoblast differentiation [209–211]. Whether effective targeting of inflammation halts or slows new bone formation is still controversial [212–214]. Studies with non-steroidal anti-inflammatory drugs (NSAIDs), which block PGE2 production, have shown effective control on pain and signs of inflammation, but conflicting results on new bone formation [215–218]. A series of studies with TNF

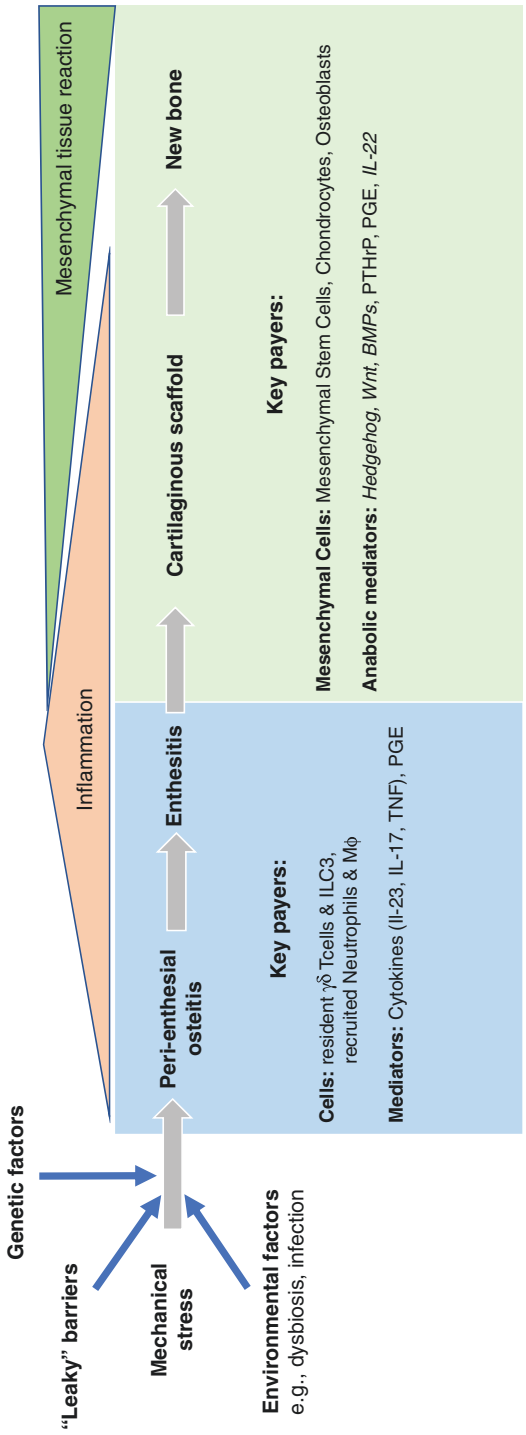

Fig. 1.2 Sequence of events resulting in enthesitis and new bone formation

inhibitors have shown that, despite the effective control in symptoms, signs and biomarkers of inflammation, there is no inhibition on new bone formation over 2 years [219–221]. Since new bone formation is a slow process, more recent studies revealed that an inhibitory impact of anti-TNF becomes apparent radiographically after longer-term follow-up [222–225]. Clinical trials with biologics blocking IL-17 pathway show promising results in arresting new bone formation [226, 227], but additional long-term confirmatory studies are required. The conclusion of all these studies is that early onset and long-term effective inhibition of inflammation has the potential to slow new bone formation.

The key anabolic mediators promoting chondroblast/osteoblast activation in SpA are the Hedgehog proteins, Wnt agonists, bone morphogenetic proteins (BMPs), parathyroid hormone-related peptide (PTHrP), and IL-22 (Fig. 1.2) [107]. In animal models, pharmacologic inhibition of Hedgehog, Wnt, BMP, or IL-22 pathways prevented new bone formation [177, 228–230]. In light of these observations, a combination of anti-inflammatory drugs with inhibitors of the bone anabolic pathways appears a promising strategy for efficient disease modification in SpA with more robust prevention of new bone formation.

Questions

Section 1

1. A 32-year old female presents with symmetric polyarthritis and high titers of rheumatoid factor (RF) and antibodies against citrullinated peptides (ACPA). Which of the following drugs should not be considered as therapeutic options?

   A. Adalimumab
   B. Guselkumab and Secukinumab
   C. Tofacitinib
   D. Tocilizumab

   Correct answer: B
   Explanation: The role of TNF, IL-6, and Jak-STAT pathway in RA pathogenesis is well established and inhibitors of these pathways (such as Adalimumab, Tocilizumab, and Tofacitinib) have been approved for the treatment of RA. Although IL-23 and IL-17 are increased in RA synovium, clinical trials with inhibitors of IL-23 and IL-17 have failed in RA patients, suggesting that these two cytokines are not part of the pathogenetic cytokine network in RA.
2. Which of the following is correct regarding the role of the lung in RA pathogenesis?

   A. Smoking induces citrullination of proteins in the lung.
   B. The initial events in the pathogenesis of seropositive RA occur in the lung.

C. ACPA are produced in the lung during the preclinical phase of RA.
D. All the above.

Correct answer: D
Explanation: Parenchymal lung inflammation with ectopic lymphoid structures, citrullinated proteins and local production of IgA ACPA have been identified in ACPA positive individuals. Pulmonary irritation by cigarette smoking, silica and textile dust has been associated with RA. Smoking induces lung inflammation and activation of peptidyl-arginine deiminase (PADI), creating a permissive microenvironment in genetically predisposed individuals for protein citrullination, emergence of immunogenic neo-epitopes and production of ACPA.

3. Which of the following is correct regarding the molecular mechanisms promoting bone loss in RA?

A. RANKL and cytokines activate osteoclasts.
B. ACPA induce bone loss during the preclinical phase of RA.
C. Cytokines deregulate Wnt pathway and inhibit osteoblasts, preventing healing of bone erosions.
D. All the above.

Correct answer: D
Explanation: RANKL is the master-regulator of osteoclastogenesis and it is expressed in the areas of pannus invasion into bone. Denosumab, a monoclonal antibody against RANKL, has shown effectiveness in halting the progression of erosions in RA patients. Inflammatory cytokines (e.g., TNF and IL-1) promote osteoclastogenesis by expanding the pool of osteoclast precursors, inducing RANKL production and synergizing with RANKL. TNF, in addition to its catabolic function on bone metabolism, displays also anti-anabolic effects by inducing DKK1, which is an antagonist of Wnt pathway. In this context, synovial inflammation not only promotes the activity of osteoclasts and the development of erosions but also inhibits the function of osteoblasts preventing the healing of erosions. Otherwise healthy ACPA positive individuals display lower bone density and administration of ACPA in mice induces in vivo bone loss in the absence of any apparent synovitis. Studies in animal models and in vitro assays suggest that ACPA directly induce osteoclast activation via mechanisms, which are Fc-, Fab-, and IL-8-dependent.

4. Which of the following is correct regarding the phenotype of fibroblast-like synoviocytes in RA?

A. They possess and acquire epigenetic marks that enhance the expression of pathogenetic genes.
B. They are a major source of IL-6.
C. They retain ex vivo increased invasive and migratory capacity.
D. All the above.

Correct answer: D
Explanation: RA FLS display a unique DNA methylation signature, which persists ex vivo and regulates the expression of arthritogenic genes. Inflammatory cytokines, such as TNF and IL-1, induce sustained changes in histone acetylation and microRNA expression, and trigger robust IL-6 production. FLS derived from RA patients, when implanted in immunodeficient animal models retain for months their invasive, migratory and cartilage-destructive capacity.

Section 2

1. A 32-year old HLA-B27 positive male with Ulcerative Colitis develops anterior uveitis and sacroiliac inflammation identified by MRI. Which of the following biologics should not be considered as therapeutic options?

   A. Adalimumab
   B. Etanercept and secukinumab
   C. Infliximab
   D. Golimumab

   Correct answer: B
   Explanation: Etanercept is very effective in axial SpA, but it is less effective, compared to the monoclonal antibodies against TNF (e.g., adalimumab, infliximab, golimumab), in the treatment of inflammatory bowel disease (IBD) and Uveitis. Animal models provide evidence for homeostatic functions of IL-17 in the gut (e.g., by maintaining the epithelial barrier integrity). Clinical trials with inhibitors of IL-17 pathway (such as Secukinumab) whereas display effectiveness in axial SpA, either failed or were discontinued in IBD due to disease worsening.
2. 22-year-old male presents with radiographic sacroiliitis and fulfills the criteria for axial SpA. Which of the following biologics should not be considered as therapeutic options?

   A. Ustekinumab and risankizumab
   B. Sekukinumab
   C. Brodalumab
   D. Etanercept

   Correct answer: A
   Explanation: The IL-23 inhibitors ustekinumab (anti-p40) and risankizumab (anti-p19) have shown efficacy in peripheral SpA but failed in axial SpA. The inhibitors of IL-17 pathway Secukinumab and Brodalumab, as well as the TNF inhibitor Etanercept have shown efficacy in both axial and peripheral SpA. These observations suggest that established axial SpA is responsive to inhibition of TNF or IL-17 pathways but is not responsive to IL-23 inhibition.

3. Which of the following is correct regarding PGE2/EP4 pathway?

   A. Regulates IL-17 production
   B. Promotes osteoblast differentiation
   C. Promotes the development of osteitis and enthesitis
   D. All the above

   Correct answer: D
   Explanation: Evidence from animal models suggest that PGE2 and its receptor EP4 promote the differentiation and expansion of Th17 cells and the production of IL-17. Resident enthesial mesenchymal cells express cyclooxygenase 2 (COX2) and produce PGE2, which triggers local vasodilatation, IL-17 production, peri-entesial bone marrow edema (osteitis) and enthesitis. PGE2 is also a robust activator of osteoblast differentiation promoting new bone formation. NSAIDs are effective in controlling pain and enthesial inflammation, but their effectiveness in halting new bone formation is controversial.
4. Which of the following is correct regarding the role of the gut in the pathogenesis of SpA

   A. It is a source of IL-23 production.
   B. Primes and expands IL-17 producing cells.
   C. Subclinical gut inflammation has been identified in SpA patients and it is correlated with the degree of spinal inflammation.
   D. All the above.

   Correct answer: D
   Explanation: Increased intestinal expression of IL-23 has been observed in SpA patients, and Paneth cells have been identified as one of the main cellular sources of intestinal IL-23 in SpA. Expanded populations of innate IL-17+ cells (ILC3, γδT-cells, and MAIT cells) have been identified in the intestines of SpA patients. Subclinical intestinal inflammation has been identified in 50–60% of patients with ankylosing spondylitis, and it is characterized by mononuclear cell infiltrates and lymphoid follicle formation. Higher degrees of bone marrow edema in sacroiliac joints was observed in Axial SpA patients with subclinical chronic gut inflammation.

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Chapter 2
Clinical Epidemiology in Rheumatology

Bella Mehta

High Yield Review Points

- Continuous variables can exhibit infinite values between minimum and maximum, whereas categorical variables are variables that can be put in particular categories of groups.
- When a categorical nominal or an ordinal variable has just two possibility outcomes, it can be labeled as a binary variable.
- Mean and standard deviation are largely used to describe normally distributed data, whereas modes, medians, and interquartile ranges are used to describe non-normally distributed data.
- In randomized controlled trials, patients are randomly divided into groups, one group receives an intervention, and all patients are followed forward in time.
- In cohort studies, subjects are divided into groups based on the presence or absence of an exposure over a period. Whereas in case-control studies, subjects are divided into groups based on the presence or absence of the outcome of interest.
- Sensitivity is the ability of a test to detect a disease when it is present. [= (all true positive test results)/(true positive and false negative test results)].
- Specificity is the ability of a test to indicate non-disease when disease is not present. [= (all true negative results)/(true negative and false positive results)].

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- Selection bias occurs when the process of sampling introduces an inherent bias into the study.
- Number needed to treat is the average number of patients you need to treat to prevent one additional bad outcome. [1/(Control Event Rate – Experimental Event Rate)].
- Odds ratio is a measure of association between an exposure and an outcome $[(a \times d)/(b \times c)]$.
- A non-inferiority trial is designed to demonstrate that an experimental therapy is not worse than an active control and is commonly analyzed using intention-to-treat methods.

Question

1. Long-term effects of glucosamine sulfate on osteoarthritis progression are studied in a randomized, placebo-controlled clinical trial [1]. The primary outcome of interest is the WOMAC (The Western Ontario and McMaster Universities Osteoarthritis Index). WOMAC is a widely used, proprietary set of standardized questionnaires used by health professionals to evaluate the condition of patients with osteoarthritis of the knee and hip. The visual analog scale version of the WOMAC index is used—i.e., with the patient assessing each question by a 100 mm visual analog scale and the total index score being represented by the sum of the 24 component item scores. A higher WOMAC score represents worse symptom severity, with 2400 mm being the worst possible total score.

   Which of the following types of variables is WOMAC described above?

   A. Categorical variable
   B. Binary variable
   C. Continuous variable
   D. Nominal variable

   Correct answer: C

   Every study or experiment yields a set of data. The things that are changing in a study are called variables. A variable is any factor, or condition that can exist in differing amounts or types. Figure 2.1 demonstrates the types of variables [2].

Continuous variables can exhibit infinite values between the minimum and maximum. For example, WOMAC can take any score from 0 to 2400 mm as in the example above. Another example would be of a visual analog pain score, which could be anywhere between 0 and 10. Age is also a continuous variable.

Categorical variables are also known as discrete or qualitative variables. These variables can be put into categories/groups. Categorical variables can be further characterized as nominal, ordinal, or binary.

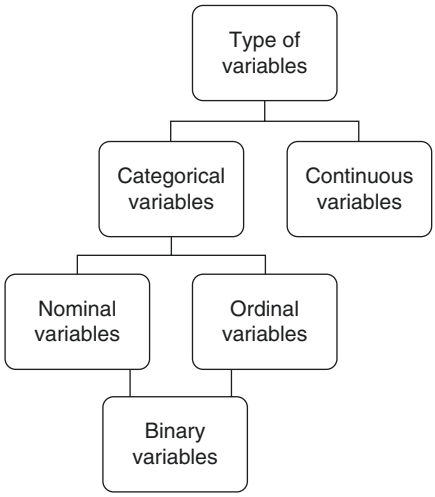

Fig. 2.1 Types of variables

- *Nominal variables* are categorical variables where the groups are related, but there is no natural ordering among them, for example, race, type of insurance, or geographical regions (North, South, East, West).
- *Ordinal variables* are categorical variables where there is a natural order among the groups, such as ranking scales or letter grades. Differences are not precisely meaningful. For example, pain scale whose options are categorized as mild, moderate, and severe—if one patient scores her pain as mild and another as moderate, we cannot say precisely the difference in their scores like in continuous variables; however, it would tell us that moderate is greater than mild.
- *Binary variables* are also called dichotomous variables. A variable is said to be binary when there are only two possible levels. Variables that can be phrased as a yes/no question are in this category. For example, if we were looking at gender, we would most probably categorize somebody as either "male" or "female." This example of a binary variable is also a nominal variable. In another example, if education level of patients were categorized into less than high school and greater than high school, it would be a binary variable. Since there is some order to this classification, it is also an ordinal variable. Thus, when a categorical nominal or an ordinal variable has just two possibility outcomes, it can be labeled as a binary variable.

Continuous variables can be put into categories for analysis. For example, DAS-28 ESR is a continuous variable whose value ranges from 0 to 9.4. It was developed and validated by the EULAR (European League Against Rheumatism) to measure the progress and improvement of Rheumatoid Arthritis. DAS28 is often categorized in clinical trials as clinical remission (0 to < 2.6), low disease activity (2.6 to < 3.2), moderate disease activity (3.2 to 5.1), and high disease activity (> 5.1 to 9.4). This would be a categorical-nominal variable.

2. While studying social determinants of health affecting disease activity in rheumatoid arthritis patients, it was discovered that patient income was not normally distributed in the particular cohort. Around 65% of the cohort had an income level below $30,000 per year.

   While describing the distribution of this data, which of the following measures of central tendency and dispersion would be most appropriate?

   A. Mean and standard deviation
   B. Mean and interquartile range
   C. Median and standard deviation
   D. Median and interquartile range

   Correct answer: D
   Non-normally distributed data is generally presented as median with interquartile range.

   Numerous methods are used to summarize the distribution of data. The distribution of a statistical data set (or a population) is a listing or function showing all the possible values (or intervals) of the data and how often they occur. Two descriptive statistics can provide key information efficiently. The first is the measure of central tendency, which is a way to describe where the center of the distribution of the variable lies. The second is the measure of dispersion, which describes the spread of the variable. Since the measures of central tendency are not adequate to describe data, measures of dispersion add value.

Measures of central tendency include:

- *Mean*—the arithmetic average of the observations in a sample. One needs to add up all the numbers and then divide by the number of numbers. This is usually used to describe normally distributed data.
- *Median*—the middle observation, i.e., half of the observations are smaller and half are larger. To find the median, numbers have to be listed in numerical order from smallest to largest, so you may have to rewrite your list before you can find the median. Like in the question above, this is usually used in non-normally distributed data.
- *Mode*—the observation that occurs most frequently in a sample. If no number in the list is repeated, then there is no mode for the list.

Measures of dispersion include [3]:

- *Range*—the difference between the largest and the smallest observation. This can be used to describe any type of data, and is most useful when one is interested in knowing the most extreme (i.e., highest and lowest or largest and smallest) observations in a sample. The prime advantage of this measure of dispersion is that it is easy to calculate. On the other hand, it has lot of disadvantages. It is very sensitive to outliers and does not use all the observations in a data set.
- *Interquartile Range*—the difference between the 25th and 75th percentiles; in other words the central 50% of all observations. This is most often used in

non-normally distributed data, but can be used to describe the middle 50% of any sample. If the interquartile range is large, it means that the middle 50% of observations are spaced wide apart. The important advantage of interquartile range is that it can be used as a measure of variability if the extreme values are not being recorded exactly. The main disadvantage in using interquartile range as a measure of dispersion is that it is not amenable to mathematical manipulation.

- *Standard Deviation (SD)*—it is the square root of sum of squared deviation from the mean divided by the number of observations. This is used in normally distributed data to describe the spread of the observations about the mean. In other words, it tells you how close the data are to the average value in the sample. The advantage of SD is that along with mean it can be used to detect skewness. The disadvantage of SD is that even though it can detect skewness, it is not an ideal measure of dispersion for skewed data.

The standard deviation can only be calculated accurately in normally distributed data, where the data are distributed symmetrically around the mean. This is crucial, as there are fixed probabilities for intervals around the mean, based on multiples of the standard deviation. For example, 95% of measurements in normally distributed data are within two standard deviations of the mean (Fig. 2.2).

Modes, medians, and interquartile ranges are used to describe non-normally distributed data.

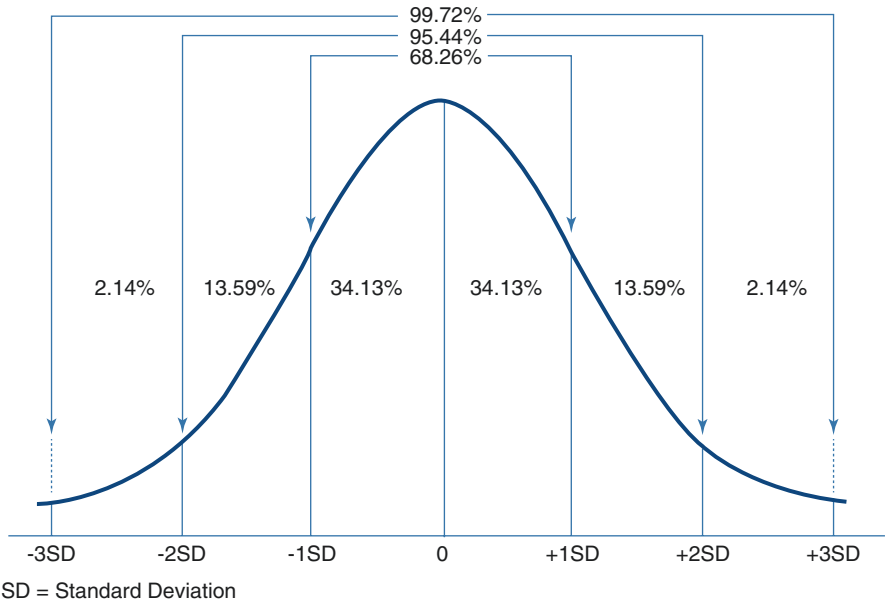

Fig. 2.2 Normal distribution

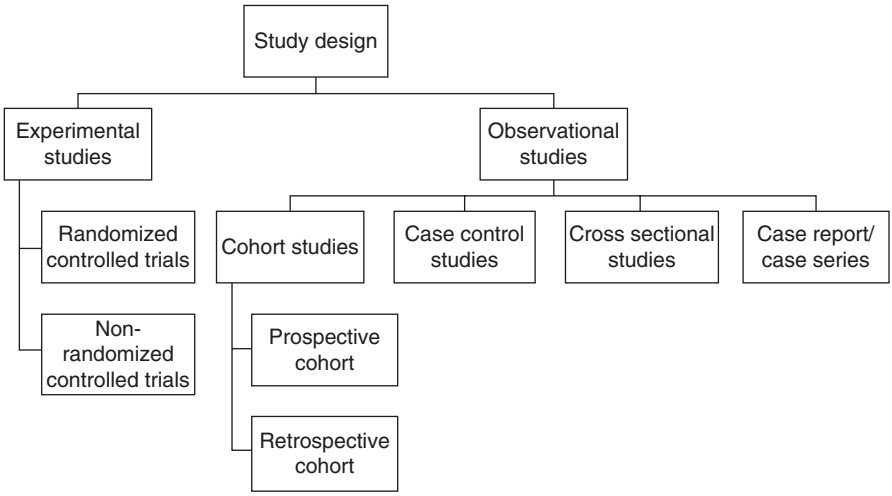

Fig. 2.3 Types of study designs

3. To study the mortality and morbidity in patients with antiphospholipid syndrome, 1000 patients were studied starting in 1999. Assessments of disease activity, complications, hospitalizations as well as deaths were assessed in these patients systematically over time [4].

   What type of study design is described above?

   A. Case control study
   B. Retrospective cohort study
   C. Prospective cohort study
   D. Randomized controlled study

   Correct answer: C
   There are several types of study designs as summarized in Fig. 2.3.

Our first distinction is whether the study is experimental (i.e., there is an active intervention as a part of the study design) or is observational [5].

In *experimental studies*, the researcher manipulates the exposure, that is he or she allocates subjects to the intervention or exposure group.

- *Randomized controlled trials*—subjects are randomly divided into groups. One group receives the intervention (patients and researchers maybe blinded to treatment) and followed forward in time. At the end of the study, the frequency of outcome is compared. This study design reduces the effect of unmeasured (confounding) variables that may influence outcomes of a study.
- *Non-randomized controlled trials*—are similar to randomized controlled trials described above except that it specifically lacks the element of random assignment to treatment or control.

- An *observational study* draws inferences from a sample to a population where the independent variable is not under the control of the researcher because of ethical concerns or logistical constraints.
- *Cohort studies*—subjects are divided into groups based on the presence or absence of an exposure over a period. The frequency of the outcome is compared. When these patients are followed over time, it is known as a prospective cohort study, whereas a retrospective cohort study (also called a historic cohort) is when a group of individuals who have shared a common exposure are compared to individuals who are not and their influence on the incidence of a condition such as disease or death.
- *Case control studies*—subjects are divided into groups based on the presence or absence of the outcome of interest, and then the frequency of risk factors in each group is compared.
- *Cross section studies*—in this type of study, the presence of the presumed risk factor and the presence of the outcome are measured at the same time in a population.
- *Case report/case series*—the studies have a detailed report of signs, symptoms, diagnoses, treatment, and follow-ups; often individual or group of individuals.

4. A rheumatologist designed a screening questionnaire for diagnoses of fibromyalgia. A blind comparison was made with clinician diagnosis of fibromyalgia using chart review for 200 patients. Among the 50 found to be having fibromyalgia according to the standard (clinician diagnosis), 35 were positive according to the screening questionnaire. Among the 150 patients who did not have fibromyalgia as per clinician diagnosis, 30 patients were found to have positive screening questionnaire.

   Which of the following statements is *false*?

   A. Specificity was 80%.
   B. Positive predictive value was 70%.
   C. Negative predicted value was 88%.
   D. The prevalence was 25%.

   Correct answer: C
   Using the information, Table 2.1 is generated, and diagnostic tests are evaluated as described below.

Evaluation of diagnostic tests: This uses a 2 × 2 table comparing the test results with the actual presence of disease (Table 2.2).

Table 2.1 2 × 2 table off the data presented above

Total = 20	Fibromyalgia present	Fibromyalgia absent
Tests positive	35	30
Tests negative	15	120

Table 2.2 Standard 2 × 2 table

	Disease present	Disease absent
Tests positive	True positive (TP)	False positive (FP)
Tests negative	False negative (FN)	True negative (TN)

Sensitivity proportion of all people with disease who test positive, or the ability of a test to detect a disease when it is present [6].

$$\text{Sensitivity} = (\text{all true positive test results}) / (\text{true positive and false negative test results})$$

- Value approaching 1 is desirable for ruling out disease and indicates a low false negative rate. Used for screening in diseases with low prevalence.
- (Remember SNOUT – SeNsitivity rules OUT)

Specificity proportion of all people without disease who test negative, or the ability of a test to indicate non-disease when disease is not present [6].

$$\text{Specificity} = (\text{all true negative results}) / (\text{true negative and false positive results})$$

- Value approaching 1 is desirable for ruling *in* disease and indicates a low false positive rate. Used as a confirmatory test after a positive screening test.
- (Remember SPIN – SPecificity rules IN)

Positive predictive value proportion of positive tests that are true positive [7]

$$\text{Positive predictive value} = (\text{true positive test results}) / (\text{all positive test results})$$

- Probability that person actually has the disease given a positive test result.
- If the prevalence of a disease in a population is low, even tests with high specificity or high sensitivity will have low positive predictive values.

Negative predictive value proportion of negative test results that are true negative [7]

$$\text{Negative predictive value} = (\text{true negative test results}) / (\text{all negative test results})$$

- Probability that person actually is disease-free given a negative test result.

Incidence is the rate of new (or newly diagnosed) cases of the disease. It is generally reported as the number of new cases occurring within a period of time (e.g., per month, per year).

$$\text{Incidence} = \left(\text{new cases in population over a given time period}\right) / \left(\text{total population at risk during that time}\right)$$

Prevalence is the actual number of cases alive with the disease, either during a period of time (period prevalence) or at a particular date in time (point prevalence).

$$\text{Prevalence} = \text{incidence} \times \text{disease duration}$$

- Prevalence is also most meaningfully reported as the number of cases as a fraction of the total population at risk and can be further categorized according to different subsets of the population.

Prevalence is greater than incidence for chronic diseases like diabetes, whereas it is equal to incidence for acute diseases like common cold.

5. A study on mycophenolate mofetil versus cyclophosphamide for induction treatment of lupus nephritis used randomized controlled design to minimize bias. The primary end point was a pre-specified decrease in urine protein/creatinine ratio and stabilization or improvement in serum creatinine. 370 patients were randomly assigned to open label mycophenolate mofetil or intravenous cyclophosphamide [8]. What kind of bias was reduced by randomized controlled trial design?

   A. Recall bias
   B. Lead time bias
   C. Selection bias
   D. Procedure bias

   Correct answer: C
   Bias is defined as a systematic difference in participant enrollment, or in collecting or interpreting data within a study. Bias can lead to inaccurate attribution of a factor as responsible for the observed association, which is one reason bias can be so dangerous. Bias refers to systematic differences, not differences due to random chance. Inconsistency of study results can result from a myriad of reasons, which may or may not involve bias [9]

   Selection/sampling bias—occurs when the process of sampling actually introduces an inherent bias into the study. In the example above, bias occurs when certain groups of patients are assigned a particular medication who may be expected to do well on that.

   Recall bias—a systematic error caused by differences in the accuracy or completeness of the recollections retrieved ("recalled") by study participants regarding events or experiences from the past. Knowledge of presence of disorder alters recall by subjects.

Lead-time bias—early detection confused with increased survival—seen with improved screening (natural history of diseases not changed, but early detection makes it seem as though survival has increased).

Procedure bias—subjects and different groups are not treated the same; for example, a fair amount of pressure is applied to the subjects in a control group forcing them to complete their responses quickly.

6. The mortality rate after disseminated intravascular coagulation in patients with Still's disease with standard of care is 20% in a tertiary care center; however, this rate declines for patients receiving a new drug to 15%. How many patients with this condition must be treated with the new medication to save one life?

A. 20
B. 30
C. 42
D. 5

Correct answer: A
The number needed to treat (NNT) is [1/(0.20–0.15)] = 1/0.05 = 20

The *number needed to treat (NNT)* is an epidemiological measure used in communicating the effectiveness of a health-care intervention, typically a treatment with medication. NNT is the average number of patients you need to treat to prevent one additional bad outcome (death, bleeding, etc.). For example, if a drug has an NNT of 5, it means you have to treat 5 people with the drug to prevent one additional bad outcome [10]

- To calculate the NNT, you need to know the Absolute Risk Reduction (ARR); the NNT is the inverse of the ARR.

$$\mathrm{NNT} = 1 / \mathrm{ARR}$$

- Where ARR = Control Event Rate – Experimental Event Rate
- NNTs are always rounded up to the nearest whole number.
- Whereas, the *number needed to harm (NNH)* is an epidemiological measure that indicates how many persons on average need to be exposed to a risk factor over a specific period to cause harm in one person who would not otherwise have been harmed. When an experimental treatment is detrimental, NNH is often used.
- To calculate the NNH, you need to know the Absolute Risk Increase (ARI); the NNH is the inverse of the ARI.

$$\mathrm{NNH} = 1 / \mathrm{ARI}$$

- Where ARI = Experimental Event Rate – Control Event Rate
- NNHs are always rounded up to the nearest whole number

Table 2.3 2 × 2 table of the data presented above

Total = 150	Sarcoidosis present	Sarcoidosis absent
World Trade Center exposure positive	2	18
World Trade Center exposure negative	10	120

Table 2.4 Standard 2 × 2 table for odds ratio calculation

	Outcome present	Outcome absent
Exposure positive	*a*	*b*
Exposure negative	*c*	*d*

7. 150 fire fighters in the city of New York City are enrolled in a study. An epidemiological survey is performed to see if the firefighters who were World Trade Center first responders during 9/11 developed sarcoidosis due to nanoparticle exposure. All 150 fire fighters were surveyed if they were World Trade Center first responders and if they developed sarcoidosis after 2001. 12 of 150 developed sarcoidosis. Two of the ones who developed sarcoidosis had been World Trade Center first responders. Whereas, 18 of the World Trade Center first responders did not develop sarcoidosis. What is the odds ratio that being a World Trade Center responder was associated with developing sarcoidosis?

   A. 1.33
   B. 0.77
   C. 5
   D. 0.5

   Correct answer: A
   1.33; OR = (2 × 120)/(10 × 18) = 240/180 = 1.33 (Table 2.3)

   - An odds ratio (OR) is a measure of association between an exposure and an outcome. The OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure. Odds ratios are most commonly used in case-control studies; however, they can also be used in cross-sectional and cohort study designs as well [11].
   - OR can be calculated using a 2 × 2 frequency table (Table 2.4).

   a = number of exposed cases
   b = number of exposed non-cases
   c = number of unexposed cases
   d = number of unexposed non-cases

$$\begin{aligned} \text{OR} &= (a/c)/(b/d) \\ &= (a \times d)/(b \times c). \end{aligned}$$

$$\begin{aligned}\text{OR} = &\left((n)\ \text{exposed cases} / (n)\ \text{unexposed cases}\right) / \\ &\left((n)\ \text{exposed non - cases} / (n)\ \text{unexposed non - cases}\right) \\ &\left((n)\ \text{exposed cases} \times (n)\ \text{unexposed non - cases}\right) / \\ &\left((n)\ \text{exposed non - cases} \times (n)\ \text{unexposed - cases}\right)\end{aligned}$$

- OR = 1 Exposure does not affect odds of outcome
- OR > 1 Exposure associated with higher odds of outcome
- OR < 1 Exposure associated with lower odds of outcome

8. In a non-inferiority trial to compare mycophenolate mofetil versus cyclophosphamide for remission induction in ANCA-associated vasculitis, 140 patients were eligibility screened, consented, and randomized. 70 were assigned to the mycophenolate group, and 70 were assigned to the controlled group of pulsed cyclophosphamide. At 18 months, five died and three were lost to follow up/withdrew in the mycophenolate group, whereas in the cyclophosphamide group, four died and two were lost to follow up/withdrew. In an intention-to-treat analysis, mycophenolate was non-inferior to cyclophosphamide for remission induction but resulted in a higher relapse rate [12].

   How many patients were included in an intention-to-treat (ITT) analysis?

   A. 126
   B. 131
   C. 140
   D. 135

   Correct answer: C

   A non-inferiority trial is designed to demonstrate that an experimental therapy is not worse than an active control. This can be important to prove, particularly when there are other potential benefits of the new investigational therapy beyond treatment efficacy. A non-inferiority design tests the null hypothesis that the experimental treatment is inferior to the established treatment by greater than the non-inferiority margin [13]. For example, in the case above, the toxicity potential of mycophenolate may be much lower than cyclophosphamide.

   It is important to note that non-inferiority trials are different than equivalence trials. In an equivalence trial, the effects of the therapies being evaluated cannot deviate from each other by more than a pre-specified equivalence margin in either direction (i.e., one cannot be better or worse than the other by a defined amount). If this is true then the two therapies are deemed equivalent. Equivalence studies are often used to show that biosimilar agents are equivalent to the name brand. This differs from a non-inferiority trial, which only aims to show that the experimental treatment is no worse than the comparator by a specified margin. Therefore, establishing non-inferiority is not the same as establishing equivalence [14].

An intention-to-treat (ITT) analysis evaluates study participants according to the group into which they were randomized, regardless of whether or not they actually

followed the protocol correctly. Thus, the results of an experiment are based on the initial treatment assignment and not on the treatment eventually received. When participants do not follow the study protocol, the two groups become less distinct. This makes it harder to show a statistically significant difference between the groups, since the two groups become more alike. ITT analysis is intended to avoid bias that can arise in trials such as non-random attrition of participants from the study.

So in our example above, in ITT analysis all 140 patients who were randomized would be analyzed. (Please remember that in ITT, "Analyze as you randomize!")

In superiority trail design, the null hypothesis is that the experimental treatment is not different from a control treatment. ITT analyses are the standard analytic approach for superiority trials, since in superiority trials ITT is conservative (i.e., an ITT analysis of a superiority trial makes it less likely you will reject the null hypothesis). However, an ITT analysis is not conservative in non-inferiority trials. ITT still makes it harder to show a difference between the groups, but in non-inferiority trials, the goal is to show the outcome for one group is not much worse than another; therefore, an ITT analysis biases toward finding non-inferiority [15].

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Chapter 3
Osteoarthritis

Matlock A. Jeffries

Take-Home Points

- OA is a systemic (low-level) inflammatory disease characterized by the destruction of articular cartilage, subchondral bone changes, joint pain, and loss of joint function.
- Several factors contribute to the development of OA, including genetic and epigenetic risk, advanced age, obesity, and preceding trauma.
- OA is the leading cause of chronic disability in the USA.
- OA is diagnosed clinically; radiographs and synovial fluid analysis is generally not indicated for the diagnosis.
- The cornerstone of OA treatment involves physical therapy and exercise.
- Pharmacologic therapy for OA should focus on the use of nonsteroidal anti-inflammatory drugs (NSAIDs), either systemic or topical, and intra-articular glucocorticoids in patients with low risk. Alternative treatments, including duloxetine, may be beneficial. There have been no dietary or supplement interventions definitively shown to improve the pain or physical function of OA patients.
- Surgical therapy (arthroplasty) offers substantial relief of pain, above and beyond what is seen with pharmacologic treatment, for OA sufferers, although a portion of patients may experience persistent symptoms.

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Introduction

Osteoarthritis (OA) is a chronic, debilitating musculoskeletal disease characterized by progressive loss of joint function leading to pain, mobility loss, and increased morbidity. It is the leading cause of chronic disability in the USA and affects roughly 23% of all adults, rising to 49.7% of those over 65 years of age [1], and is the most rapidly growing major health condition worldwide [2]. A variety of factors including age, obesity, genetics, mechanical trauma, and inflammation all contribute to the development and progression of OA [3], although patients develop OA at different rates. Especially in early disease, pain and functional limitation are not strongly correlated with severity radiographic joint space loss. Early diagnosis and prediction of those patients who will go on to have rapidly progressive disease remains a challenge and is a topic of intensive biomarker research.

The osteoarthritic joint is characterized by cartilage degradation without an appropriate healing response, sclerosis of underlying subchondral bone, and synovial inflammation [4]. Although many genetic association studies have been performed, a strong genetic component, particularly for knee and hip OA, has yet to be identified. Only a handful of genetic susceptibility loci have been confirmed, all with relatively mild disease contribution (hazard ratios of <2) [5]. Several studies have suggested that age-related changes to epigenetic processes may be a potential cause of late onset human diseases such as osteoarthritis, and recent reports have demonstrated an association between epigenetic changes and the development and progression of knee and hip OA [6].

There have been to date no disease-modifying (cartilage-repairing) drugs approved for the treatment of OA. Management consists of a multimodal therapeutic approach including weight loss, physical therapy, pain-relieving drugs such as nonsteroidal anti-inflammatories (NSAIDs), and intra-articular drugs. The "definitive" treatment for most patients with knee and hip OA remains joint replacement, which offers substantial relief in pain and improvement in physical function in the majority.

In this chapter, we will delve more deeply into this most common of rheumatic diseases, including a discussion of our most up-to-date understanding of the underlying pathophysiology of OA, risk factors for OA development, the clinical presentation and diagnosis of OA, and treatment strategies for OA.

Pathophysiology

The traditional dogma of OA pathogenesis was that it resulted from "wear and tear"; that is, chronic overloading of weight-bearing joints slowly wears away articular cartilage surfaces, leading to eventual failure of the joint. Over the past decades, researchers have come to realize that OA is a much more complex disease than this simplified explanation would suggest. Indeed, a variety of factors, including systemic inflammation (particularly, as we will discuss, the innate immune system), genetic risk, epigenetic responses to local environmental factors and age, and biomechanical changes all contribute to the development of OA, itself a whole-joint (perhaps even whole-body) disease (Fig. 3.1, Table 3.1).

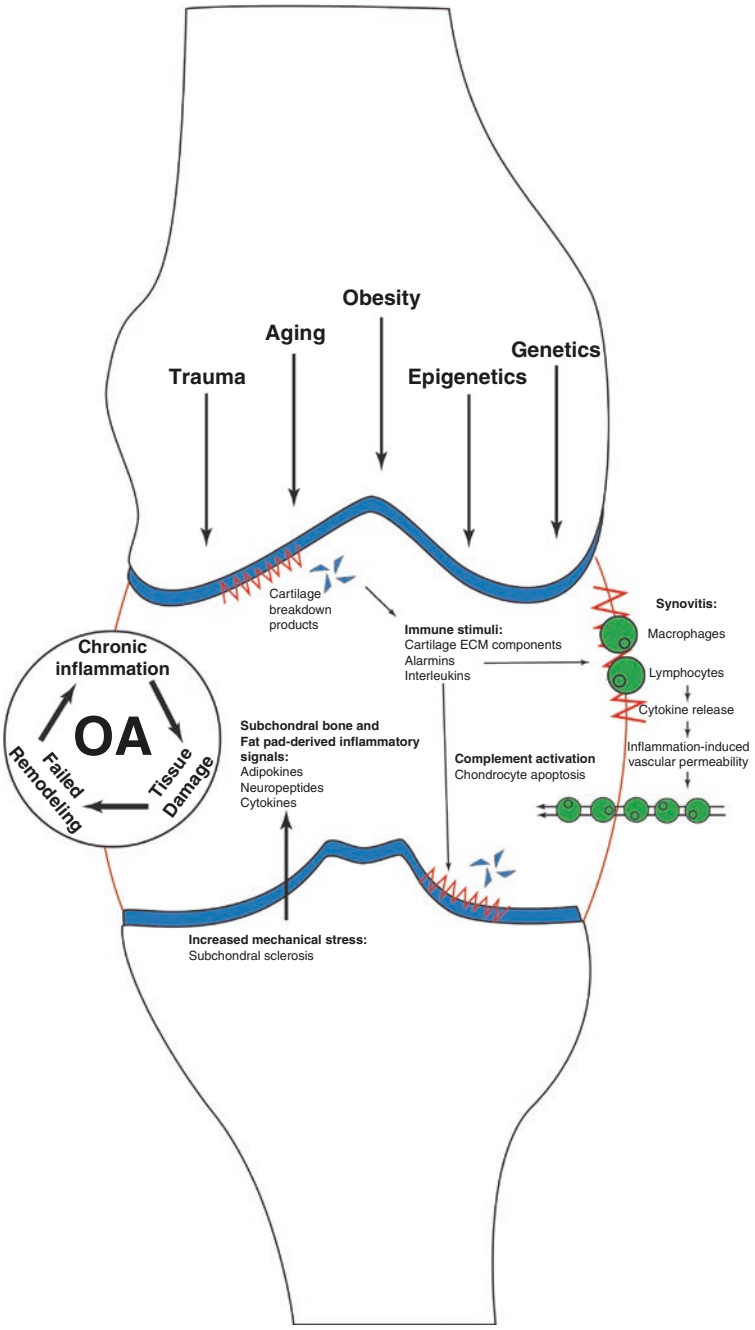

Fig. 3.1 OA pathophysiology. The pathophysiology of OA involves a variety of systemic and local factors, including trauma, aging, obesity, epigenetic, and genetic factors. Chronic inflammation plays a strong role, including inflammatory signals from local (cartilage breakdown products stimulating the innate immune system) and distant (adipose tissue-derived adipokines) sources. The end result is chronic tissue damage which does not undergo appropriate wound healing

Table 3.1 Pathophysiology

Mechanism	Consequence
Aging	Increased cellular senescence Increased systemic inflammation Reduced ability of periarticular structures to absorb stress
Genetic risk	Unclear. Potential defects in growth and remodeling, potential defects in vitamin A metabolism, cartilage calcification
Epigenetic risk	Create a gene regulatory environment permissible for overexpression of cartilage-destroying enzymes, inflammatory cytokines. Downregulation of collagen. May mediate, in part, aging risk
Trauma	Produces localized cartilage defects, increased extracellular matrix breakdown products, increased stress on subchondral bone, musculature, ligaments
Inflammation	Chronic systemic inflammation stimulated by cartilage breakdown products. Synovitis further stimulates immune responses, increases vascular permeability, and allows additional inflammatory cells to migrate to joint tissues. ECM breakdown also assembles complement and increases destruction of cartilage cells
Obesity	Increases systemic inflammation, leading to paracrine effects, further worsening chronic joint inflammation. Increases joint load

Among the first changes in OA joints are inflammation within the synovial lining (synovitis), focal changes within bone marrow underlying the joint (bone marrow lesions, characterized by fibrosis, necrosis, and trabecular abnormalities), and matrix changes within the cartilage itself [7, 8]. The end-stage pathology of OA consists of erosion of articular cartilage, subchondral bone change, and loss of function of the joint "unit" in diarthrodial joints. Grossly, OA joints exhibit joint space narrowing, subchondral sclerosis of underlying bone, hypertrophic osteophyte formation of neighboring bone, and subchondral cyst formation. Moderate-to-severe cases of OA may demonstrate fibrillated cartilage, especially in areas of maximal loading, an irregular and disordered attempt at cartilage regrowth [9]. We will briefly discuss each of these joint components individually.

Articular cartilage undergoes substantial changes during the development of OA. Although the majority of the physical load of a joint is borne by extra-articular structures (musculature, menisci, subchondral bone), normal cartilage provides a remarkably low-friction surface for smooth movement of a joint throughout its range of motion. Cartilage itself is made up of relatively scant, long-lived, metabolically inactive chondrocytes embedded within a tightly woven extracellular matrix (ECM) consisting of collagen fibers and proteoglycans coated by lubricin, a protein which reduces friction [10]. As OA develops, chondrocytes begin to proliferate and aggregate into nests, and switch from an anabolic gene transcription program to a catabolic one. Counterintuitively, this switch results in the production of matrix metalloproteinases and other enzymes which begin actively breaking down neighboring ECM, led principally by the actions of ADAMTS5 and the matrix metalloproteinases MMP-9 and MMP-13 [11]. Large shifts in epigenetic regulation occur within OA chondrocytes, providing a gene transcription regulatory pattern permissive for these changes [6, 12]. Remarkably, this transcriptomic shift closely

resembles cellular changes seen in the senescence-associated secretory phenotype (SASP) of senescent cells seen in other body tissues, leading some to speculate that the predilection for OA development later in life is due, at least in part, to age-related senescence [13].

Although the inciting event(s) remain unclear and are most likely multifactorial, a proinflammatory environment is created once cartilage breakdown begins which propagates and further accelerates OA joint damage. A variety of ECM components stimulate the innate immune receptors of macrophages and other antigen-presenting cells via toll-like receptors (TLRs) recognizing danger-associated molecular patterns (DAMPs) [14, 15]. This immune stimulation, and the cytokine production that results from it, further stimulates the production of catabolic enzymes. The complement cascade is important as well, as cartilage ECM components also catalyze the assembly of various complement proteins, further disrupting cartilage homeostasis. Elevations of inflammatory markers, including tumor necrosis factor-alpha (TNF alpha) and interleukin-6 are seen in synovial fluid of patients with progressive OA [16]. Furthermore, low-level systemic inflammation is also seen in patients with OA. For example, baseline prostaglandin E2 synthase levels in peripheral blood leukocytes can easily distinguish OA patients from controls, and a variety of cytokines, including interleukin-1 beta, TNF alpha, and cyclooxygenase 2 are increased in OA peripheral blood leukocytes and predict future rapid radiographic progression [17].

Cartilage is not the only tissue which undergoes extensive alteration during the development of OA. The *subchondral bone* plate is a thin cortical lamella directly underlying calcified cartilage. Although it is not a trabecular structure, it nonetheless has quite high porosity and contains channels for arteries, veins, and nerves, which can reach up to the cartilage surface [18]. During OA development, stress on the subchondral bone plate underlying damaged cartilage regions increases substantially, resulting in reactive thickening [19] and leading to the radiographic appearance of subchondral sclerosis. Inflammatory markers released during this bone remodeling process can reach the overlying articular cartilage [20]. Osteophytes, another hallmark feature of OA, originate in the periosteum [21] next to the bone/cartilage interface. They are a reactionary feature thought to develop in response to joint instability; one key player in the development of osteophytes is bone morphogenic protein-2 (BMP2) [22]. Interestingly enough, the inflammatory cytokine (and target of rheumatoid arthritis drugs) TNF alpha also plays a role in osteophyte formation [23]. Bone marrow lesions are present in symptomatic OA joints as well. Sometimes erroneously referred to simply as bone marrow "edema," these are defined as discrete regions of hyperintense marrow signal in fat-suppressed magnetic resonance imaging sequences. Gene transcription analysis of these lesions demonstrates substantial upregulation of genes involved in pain sensitization, extracellular matrix, and proinflammatory gene signaling [24]. The baseline volume of these lesions in OA patients is highly correlated with both joint pain and future radiographic narrowing of OA-affected joints [25].

Unlike cartilage, *synovium* is richly innervated and highly vascularized. Early OA is characterized almost universally by a degree of synovial inflammation, or synovitis. This is characterized by distinct histological findings, including syno-

vial hypertrophy and hyperplasia, infiltration by mononuclear cells (T and B lymphocytes, tissue macrophages, monocytes), and increased angiogenesis. Inflamed synovial tissue itself releases a variety of proinflammatory cytokines and catabolic factors in OA, including interleukins, TNF alpha, matrix metalloproteinases, bone morphogenic proteins, and pain-producing neurotransmitters (i.e., nerve growth factor, substance P) [26, 27]. Although it may not be as clinically apparent as the florid synovitis seen in autoimmune forms of arthritis, MRI-detectable synovitis is strongly correlated with knee radiographic OA severity [28]. This is not limited only to large-joint OA; the interphalangeal joints of hand OA patients also demonstrate increases in synovitis compared to non-OA controls, which correlates with both pain and radiographic severity [29]. As one might expect, patients with the erosive hand OA subtype exhibit additional increases in joint synovitis scores [30].

Risk Factors for OA Development

Genetics certainly play a role in the development of OA. The overall genetic contribution to OA can be estimated through the use of twin studies, where a comparison is made between the "shared" genetic risk of identical, monozygotic twins and compared to the "half-shared" genetic risk of fraternal, dizygotic twins. Older twin studies of hip OA studies, including the UK Adult Twin Registry, have estimated genetic contributions to hand OA at around 50% and hip OA at around 60% [31]. A newer study published in 2018 used more advanced data modeling techniques to adjust for modifiable risk factors and included a large number (n = 18,058) of twins from Norway [32]. Their model suggested that 73% of hip and 45% of knee variance was genetically determined.

Investigations into individual genetic risk alleles (*single nucleotide polymorphisms*, SNPs) in OA have been somewhat less fruitful, and are quite specific to joint site (hand vs. hip vs. knee). The largest genome-wide association studies (GWAS) have been performed in knee and hip OA. The only risk alleles that have been independently confirmed for knee OA include mutations in the collagen gene *COL11A1* and vascular endothelial growth factor *VEGF* [33]. Another gene, growth differentiation factor 5 (*GDF5*), deserves special mention. This gene and the rs143383 SNP located within it have been strongly associated with both hip and knee OA in both humans and mice; furthermore, the risk allele causes reduced gene expression in joint tissues [34–37]. *GDF5* is also under epigenetic control via changes in DNA methylation, and this conspires with underlying genetic changes to modulate gene expression further [38]. Relatively fewer genetic studies have been performed in hand OA; in fact, only two large GWAS studies have been completed to date. The first study, in 2014, found an association with the retinaldehyde dehydrogenase gene *ALDH1A2*, involved in vitamin A metabolism [39]. The second study, published in 2018, identified changes within the matrix GLA protein (*MGP*) gene, involved in cartilage calcification [40].

Epigenetics also play a role in OA development, as mentioned previously. A number of epigenome-wide association studies have been performed in both hip

and knee OA, and have both identified and confirmed a number of genes and genetic pathways as strongly dysregulated in OA cartilage and subchondral bone [6, 12, 41–44], including a number of inflammatory pathways and inflammation-related transcription factors. As in genetics, epigenetic patterns are distinctly geographic (different in knee OA samples compared to hips).

The strongest *environmental risk factor* for OA is advanced age, although how exactly age contributes to OA is still somewhat unclear. Aging increases levels of c-reactive protein (C-RP), interleukin 6 (IL6), and tumor necrosis factor alpha (TNFα), a phenomenon known as "inflammaging" [34]. Levels of systemic inflammatory mediators correlate with knee pain and decreased functional capacity in older adults with knee OA [35, 36]; furthermore, elevated levels of C-RP and IL6 are found in patients with knee OA and the level of these markers are related to the risk of OA progression [37, 38]. A dysregulated epigenome appears at least partly responsible for this phenomenon [39]. For example, using a DNA methylation-based age estimator, OA cartilage has been shown to be epigenetically "older" than control cartilage [45]. Autophagy, the process by which normal cells "clean up" old proteins, is defective in both aging and in OA articular cartilage and has been proposed as another possible explanation for the increased risk of OA associated with aging [46]. Supporting this theory, aged mice also demonstrate a reduced autophagy phenotype in cartilage, and this defect precedes the development of OA-like cartilage damage [47].

Another quite important risk factor for OA development is *obesity*. Notably, like epigenetic and genetic risk, the risk conferred by obesity varies by joint. In knees, those with the highest body mass index (BMI) have an approximate 8.5-fold increased risk for OA compared to individuals with a "normal" BMI [48]. Even more striking, each 2-unit increase in BMI equates to an increase in OA risk by 1.36-fold. A recent meta-analysis of 14 studies confirmed this finding that being overweight increased the risk of knee OA by 2.45-fold and obesity carried an increased risk of 4.55-fold [49]. In hips, the risk is somewhat lower, with increased risk of around 1.1-fold [50]. Hand OA is also associated with obesity, with increased risk in the 1.1-fold range [51]. How obesity contributes to OA pathogenesis is complex and is not simply related to increased stress on the joint itself; rather, it likely also involves the increased basal systemic inflammation related to obesity, as well as an increased production of "adipokines," inflammatory signaling molecules originating in adipose tissue [52, 53].

Trauma and "traumatic" occupations also increase the risk of OA. Dock workers, agricultural workers, carpenters, and cleaners have an increased risk of OA [54, 55]. Perhaps counterintuitively, running does not carry an increased risk for OA [56], nor does running worsen OA when it already is present [57]. However, "elite" athletes, mainly those with a history of high impact activities, do have a higher chance of developing OA as they age [58]. A history of previous injury is strongly associated with OA; this is perhaps best seen in the military population, where soldiers are more than five times more likely to develop PTOA compared to the general population. Soldiers with a history of knee joint trauma during active duty have a 5.7-fold increased risk of knee OA compared to those without a history of trauma [59].

Clinical Presentation

The clinical presentation of OA can vary dramatically between individuals, although the unifying feature in nearly all patients is *pain* (Table 3.2). The pain associated with osteoarthritis is distinct from autoimmune-related arthritis in that it is associated with minimal (generally <30 minutes) of morning stiffness and is characterized by worsening with activity. Researchers have been quite interested over the past several years in identifying the earliest pain patterns seen in OA to improve early diagnosis. The most detailed analysis of these patterns was published in 2014, based on the large, longitudinal Osteoarthritis Initiative (OAI) study [60]. They analyzed nearly 5000 individuals who developed knee OA during the study, retroactively examining their data for the first signs and symptoms, and identified pain on using stairs was the first positive symptom, followed by pain on walking, later pain on standing without walking, pain on lying or sitting, and finally, pain in bed. Others have previously identified similar "stages" of pain in OA, including Stage 1, being defined as predictable sharp pain on high-impact activity, Stage 2, constant pain

Table 3.2 Clinical presentation

OA-involved joint	Clinical presentation	Radiographic appearance
Knee	*Early*: pain on strenuous activity, walking up or down stairs *Intermediate*: pain in everyday activity *Late*: constant rest pain	*Early*: tibial spine sharpening, subchondral sclerosis, subchondral cyst formation *Intermediate*: joint space loss (usually medial>lateral), marginal osteophyte formation *Late*: complete cartilage loss, bone-on-bone appearance, joint deformity
Hip	*Early*: occasional pain on activity, referred to groin or to knee; pain on internal rotation or full flexion *Intermediate*: pain with activity, walking *Late*: constant rest pain	*Early*: asymmetrical joint space narrowing *Intermediate*: diffuse joint space loss, subchondral sclerosis *Late*: marginal osteophyte formation, bone-on-bone appearance
Hand	*Early*: occasional stiffness and pain on repetitive motion *Intermediate*: predictable pain with certain movements, stiffness daily, Heberden's and Bouchard's nodes may develop *Late*: pain with minimal movement, perceived loss of hand "strength"	*Early*: DIP and thumb 1st CMC joint space narrowing *Intermediate*: Substantial joint space narrowing, marginal osteophyte formation *Late*: Fixed flexion deformities develop, marginal osteophyte formation may cause lateral or medial distal phalanx deviation
Hand: erosive OA subtype	Rapidly progressive PIP, DIP joint pain and stiffness with significant synovitis	Characteristic "gull-wing" and "sawtooth" appearance of DIP, PIP, respectively. Substantial soft tissue swelling. Spontaneous joint fusion may occur. Significant marginal osteophyte formation and bony proliferation

that starts to affect daily activities, and Stage 3, consistent, dull or aching pain that is punctuated by periods of intense pain which severely limits range of motion and joint function [61]. The specific location of knee OA-related pain is related to the compartment affected, with localized anteromedial pain (medial compartment) or anterior pain (patellofemoral compartment) being common [62]. Hip OA generally presents as groin pain, although it can radiate down the leg and be misinterpreted as knee pain. Both active and passive movements, especially internal rotation of the hip while flexed, is a characteristic finding [63].

Other frequently-occurring signs and symptoms include bony hypertrophy, reflecting osteophyte formation (see section "Pathophysiology"), which tends to occur on marginal surfaces of OA-affected joints. Osteophyte formation and/or cartilage degradation can lead to frank joint deformities, which subsequently lead to joint instability. In fact, joint "buckling" or "giving out" is a very common symptom, particularly of knee OA. Over a quarter of patients with physician-diagnosed knee osteoarthritis will report knee instability symptoms, and a substantial number of these also report falls. Frequent falls in elderly OA patients can lead not only to fractures and other sequelae, but perhaps even more damaging, to fear of falling and poor balance confidence which can reduce physical activity further and worsen pre-existing deconditioning [64].

Hand OA generally affects the distal interphalangeal joints (DIP), first carpometacarpal joint (CMC, base of the thumb), proximal interphalangeal (PIP) joints, and occasionally the index and long finger metacarpophalangeal (MCP) joint, especially in cases associated with calcium pyrophosphate deposition disease. Like large-joint OA, hand OA is generally characterized by pain with activity. Some patients may complain mainly of stiffness, although this is generally less prolonged than autoimmune causes of hand arthritis. A frequent finding in hand OA are Heberden's (DIP) and Bouchard's (PIP) nodes. The appearance of these nodules is the result of early inflammation at the insertion of ligaments on the phalanges [65], further reinforcing the role of inflammation in OA. A less common but more aggressive variant of hand OA, known as *erosive OA*, is characterized by synovitis of the DIP joints with more extensive pain, erythema, and tenderness than one would expect of typical hand OA [66]. Erosive OA tends to progress more rapidly than traditional hand OA. Cartilage and joint capsule erosion lead to lateral DIP instability and sclerosis, causing characteristic "twisting" and lateral deviation of the distal phalanges, with eventual and spontaneous DIP fusion a common finding. As one might expect, this erosive form of OA carries with it worse functional outcomes [67].

Diagnosis

We lack well-defined criteria for the diagnosis of OA; most practitioners use a combination of symptoms and x-ray findings, although such definitions can be overly restrictive and lead to prevent early diagnosis. There are no formalized diagnostic criteria put forth by any of the major research societies, although classification

criteria do exist from the American College of Rheumatology, for hip, knee, and hand OA (Table 3.3). They suggest a diagnosis of knee OA with greater than 3 of the following: age greater than 50, less than 30 minutes of morning stiffness, with crepitus, bony tenderness, bony enlargement, and no palpable synovitis [68]. Hip guidelines are similar, with the addition of range of motion restriction and an allowed increase in morning stiffness threshold to 60 minutes [63]. The ACR hand OA criteria rely on bony enlargement of hand joints in addition to pain, aching, or stiffness [69]. It should be stated that these classification criteria have a variety of faults, perhaps most notably their lack of ability to capture early OA patients, where pain on activity is the predominant symptom and in which the development of osteophytes has not yet occurred.

When the suspicion for OA is high based on clinical symptoms, there is not generally an indication for additional testing, and empiric treatment can commence. The presence of atypical symptoms may, however, indicate the need for additional workup; these include rapid progression of pain (imaging may be necessary here), a clear-cut periodicity of symptoms (periodic symptoms self-resolving after just a few days to weeks is suggestive of a crystal arthritis), or other constitutional symptoms such as weight loss, fevers, recent or current infections, etc. Testing for autoantibodies associated with rheumatoid arthritis (rheumatoid

Table 3.3 ACR classification criteria [63, 68, 69]

Joint involved	Classification criteria (using history and physical examination)
Knee	Pain in the knee and at least 3 of: >50 years of age Less than 30 minutes of am stiffness Crepitus on active range of motion Bony tenderness Bony enlargement No palpable warmth of synovium
Hip	Pain in the hip and: >50 years of age Internal hip rotation ≥15 degrees Pain associated with internal hip Morning stiffness of the hip less than 60 minutes Or Internal hip rotation <15 degrees Hip flexion ≤115 degrees
Hand	Pain, aching, or stiffness in the hand and at least 3 of: Bony enlargement of 2 or more of: 2nd and 3rd distal interphalangeal (DIP) 2nd and 3rd proximal interphalangeal (PIP) 1st carpometacarpal joint of the thumb (CMC) Bony enlargement of 2 or more distal interphalangeal (DIP) Less than 3 swollen MCP joints Deformity of at least one of: 2nd and 3rd distal interphalangeal (DIP) 2nd and 3rd proximal interphalangeal (PIP) 1st carpometacarpal joint of the thumb (CMC)

factor and anti-cyclic citrullinated peptide), along with systemic inflammatory markers (erythrocyte sedimentation rate or c-reactive peptide) can be useful in ruling out an autoimmune cause of arthritis symptoms in patients with a more inflammatory presentation.

Radiography is not generally indicated for the diagnosis of OA but can be useful in ruling out alternative causes for arthritis, making a diagnosis of erosive OA, and in monitoring the degree of cartilage loss if one is considering joint replacement. Moderately to severely affected OA joints are characterized radiographically by joint space narrowing (generally asymmetrical), subchondral sclerosis, marginal osteophyte formation, and the presence of subchondral cysts. Hand and knee radiographs are frequently obtained in patients with OA-like symptoms to rule out cartilage calcification, which is suggestive of concomitant calcium pyrophosphate deposition disease. Erosive OA of the hands is associated with a particular appearance of DIP joints, including cartilage erosion leading to a "gullwing" pattern in DIP joints and/or "sawtooth"-type pattern in PIP joints [70]. Magnetic resonance imaging (MRI) can allow for direct quantitation both of synovitis, cartilage thickness, and screen for the presence of chondral lesions. Although MRI screening and monitoring of OA is not routinely done, it can predict patients who will have subsequent clinical OA progression [71]. Finally, synovial fluid analysis is not generally indicated to diagnose OA; however, it can be quite useful in ruling out alternative diagnoses, particularly the crystalline arthropathies.

Treatment

Although there are several in development, there are as yet no disease-modifying anti-osteoarthritic drugs (DMOADs) available for the treatment of OA. Therapeutic efforts, therefore, focus on improvements in physical function and pain relief. A well-conceived OA treatment plan should include efforts in three domains: attention to modifiable risk factors, including weight loss if at all possible, physical therapy regimens including an exercise and strengthening program, and pharmacologic and/or surgical treatment tailored to the individual needs and additional medical comorbidities of the patient (Table 3.4). We will consider each of these individually.

First, *modifiable risk factors* should always be addressed. Weight loss should be discussed with every OA patient, and dietary changes made (including referral to a dietician if necessary) to achieve sustained weight loss. Several studies have indicated that even as little as 10% weight loss has substantial benefits in reducing OA-related pain and decreasing functional disability in OA patients. For example, a recent large study combined dietary and exercise interventions in knee OA patients and resulted in a mean weight loss of 11%. In the intervention group, significant reductions in pain and improvements in function were noted, along with better physical health-related quality of life scores and even reductions in serum levels of

Table 3.4 Treatment

Treatment intervention or drug	OA subtype where specific treatment is appropriate (knee-only vs. multi-joint, with vs. without comorbidities)
Land-based exercise	*All*
Water-based exercise	*All*
Weight management	*All*
Strength training	*All*
Intra-articular steroid injection	*All*
Oral nonselective NSAIDs	Knee-only and multijoint OA without comorbidities
Oral COX2-selective NSAIDs	Knee-only and multijoint OA without comorbidities, or with up to moderate comorbidity risk
Topical NSAIDs	Knee-only OA both with and without comorbidities
Duloxetine	*All*
Acetaminophen	Appropriate for knee-only and multijoint OA without comorbidities. (∗Note: more recent data suggest benefit no greater than placebo)
Hyaluronic acid	Uncertain for knee-only OA, not appropriate for multijoint OA
Opioids	Uncertain for all forms of OA
Glucosamine/ chondroitin	Not recommended for any form of OA

Adapted from 2014 OARSI guidelines for treatment of knee OA [77]

the inflammatory cytokine interleukin 6 (IL6) [72]. Bariatric surgery, both for the treatment of OA and as an adjunct to total joint replacement, has been the focus of recent interest. Although studies have shown that massive weight loss induced by bariatric surgery does improve both pain and serum inflammatory markers in knee OA [73], several studies have also shown that bariatric surgery before joint replacement does not improve postarthroplasty functional or pain outcomes [74]. There have not been definitive studies to indicate that one particular diet is any better than another for the treatment of OA symptoms, and no dietary supplements have been shown effective for OA.

Physical therapy should be a part of every OA prescription. *Exercise* in essentially any form is beneficial in OA and should be part of every OA treatment plan. There do not appear to be differences between land-based and water-based exercise from an efficacy standpoint, and the beneficial effects of exercise last for up to 6 months after cessation (although patients should be encouraged to continue an exercise regimen indefinitely) [75]. Tai Chi, a Chinese martial art practiced with slow, methodical movements and an emphasis on balance, has a similar benefit in improving OA pain, physical function, and quality of life when compared to physical therapy regimens, with the added benefit of improving depression in OA patients [76].

Pharmacologic treatment in OA consists of a stepwise approach to analgesia. The best practice guidelines for the treatment of knee and hip OA come from several national and international societies, including the Osteoarthritis Research

Society International (OARSI), the American College of Rheumatology (ACR), and the American Academy of Orthopedic Research (AAOS). The most recently updated of these are the OARSI guidelines for the management of knee osteoarthritis [77], and will be the basis for the following recommendations. Contrary to popular practice, acetaminophen has little place in the modern treatment of OA, as it has been demonstrated in multiple meta-analyses to be no better than placebo at pain relief in OA [78]. The first question when treating a patient with OA regards their comorbidities. These include comorbidities which place the patient at moderate risk, including diabetes, advanced age, hypertension, cardiovascular disease (CVD), acute renal failure, history of gastrointestinal (GI) complications, depression, or physical impairment resulting in severe limitation of activity or exercise, including obesity. High-risk comorbidities include a history of a GI bleed, history of myocardial infarction, and chronic renal failure. Patients are then subdivided into knee-only OA or multijoint OA.

For knee-only OA without comorbidities, pharmacologic treatment may include nonsteroidal anti-inflammatory medications (NSAIDs), either "traditional" nonselective NSAIDs (i.e., naproxen), or COX-2-selective NSAIDs (i.e., celecoxib), or via topical application (i.e., diclofenac gel), or intra-articular (IA) therapies. Knee-only OA with comorbidities should avoid systemic nonselective NSAIDs and use instead IA treatments and topical NSAIDs. Multijoint OA benefits from systemic NSAIDs and IA treatments; generally, topical NSAIDs are not recommended, as the maximum dose may be inadequate to treat all involved joints. Multijoint OA in patients with comorbidities represents a challenge, with IA therapy and COX-2-selective NSAIDs being the preferred pharmacologic agents.

There have been surprisingly few head-to-head studies comparing the efficacy of various individual NSAIDs. One recent large meta-analysis including 76 individual trials suggested that the most effective oral NSAID for pain relief in OA was diclofenac at a dose of 150 mg total daily dose, followed by ibuprofen at 2400 mg total daily dose and naproxen at 1000 mg total daily dose [79]. This should be interpreted with caution, however, given the lack of direct comparison in published data. There was some concern recently over the cardiovascular safety of COX-2-selective NSAIDs (the one in the US market being celecoxib) when compared to nonselective NSAIDs; however, the Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen (PRECISION) trial, published in 2016, did not find evidence for an increased risk of celecoxib compared to either ibuprofen or naproxen [80]. One area where there is a clear difference based on COX selectivity is in the risk of GI bleed, where COX-2-selective NSAIDs are strongly superior to nonselective NSAIDs; in patients with a past history of GI bleed, topical NSAIDs should be used if at all possible, with COX-2-selective oral NSAIDs used cautiously, and consideration given to concomitant proton pump inhibitor therapy. Nonselective NSAID use should be avoided in these patients. Duloxetine, an oral serotonin-norepinephrine reuptake inhibitor (SNRI), is a nonopiate, non-NSAID alternative appropriate for OA treatment and has good evidence for its efficacy; it may be an appropriate choice in patients

with contraindications for NSAID or IA therapy or to be used in combination with NSAIDs [81]. Other oral pharmacologic therapies with dubious evidence for efficacy (and not recommended) include glucosamine/chondroitin, diacerein, both oral and transdermal opiates, and risedronate.

IA corticosteroid injections should also be considered. IA steroids have strong evidence for pain improvement in the short term, although longer-term data are lacking. A trial published in 2017 also demonstrated a statistically significant increase in the rate of cartilage loss after 2 years of every-three-month short-acting steroid injection, although the incremental cartilage loss was not likely to be clinically significant [82]. An extended-release steroid preparation of triamcinolone for IA injection has been recently approved which may offer both extended symptom improvement and a reduction in systemic side effects owing to a reduction in acute diffusion of steroid out of the joint [83]. The other intra-articular therapy frequently used for knee OA, hyaluronic acid, does not have robust support in the literature and has received either an "inappropriate" or "not certain" recommendation from OARSI [77, 84].

Surgical treatment is the only definitive therapy available to physicians for knee and hip OA at the present time and demonstrates substantial pain relief and improvement of physical function that are better than the best pharmacologic management. The benefits of joint replacement for OA should not be overstated, however, as a measurable percentage (up to one-third in some studies) of patients have persistent symptoms following arthroplasty [85]. The morbidity and mortality associated with joint replacement is low but should always be carefully considered before a decision is made to go to the operating room, with patient age and the presence of medical comorbidities (diabetes, obesity, and cardiovascular risks) being the strongest predictors of poor outcomes [86].

Questions

Scenario 1

A 65 year-old Caucasian woman (BMI 35, sedentary, history of GERD with a treated gastric ulcer 2 months ago) presents to your clinic complaining of a 1-year history of steadily worsening bilateral medial knee pain and hip pain, worse with exercise, better with rest. When asked, she has morning stiffness lasting less than 30 minutes in both of her knees. She does not complain of any periodicity (i.e., no "flares" lasting for days to weeks) in any of her joints. She has tried over-the-counter acetaminophen, up to 1000 mg three times daily, without any benefit.

Physical examination reveals an obese woman not in obvious distress. Her bilateral hips have range of motion limited to internal rotation of 12 degrees and flexion of 90 degrees. She has bony enlargement of both knees and a mild cool effusion. She has bony enlargement of her bilateral 1st carpometacarpal joints and two bilateral distal interphalangeal joints without an effusion.

1. For her potential knee OA, what additional testing (if any) is indicated at this time?

   A. Standing anterior/posterior radiographs
   B. MRI
   C. Joint aspiration with gram stain, culture, cell count with differential, and crystal analysis
   D. No additional testing indicated at this time

   Correct answer: D
   Critique: This patient meets ACR criteria for hip, knee, and hand OA. Her history and physical examination are not suggestive of an autoimmune arthritis (no substantial morning stiffness, no synovitis on examination), nor is it suggestive of a crystal arthropathy (no substantial periodicity, no history of podagra-like symptoms). Imaging is *not* indicated to make a diagnosis of OA; in fact, an MRI would almost certainly show cartilage defects given her bony hypertrophy. Joint aspiration is indicated only in the setting of symptoms suggestive of a septic joint, or a crystal arthropathy.
2. She asks about the risk of passing her arthritis on to her children. Which of her arthritic complaints are most likely genetic or hereditary?

   A. Hip OA
   B. Knee OA
   C. Neither is genetic
   D. Both have equal hereditary components

   Correct answer: A
   Critique: Both historical and modern twin studies suggest that hip, knee, and hand OA have a genetic component; however, the most recent data support the notion that hip OA has a substantially larger genetic component than does knee OA.
3. She prefers a nonoperative approach to the treatment of her multijoint OA. She has heard that physical activity can make her joints worse by "wearing them down." What is your response to this?

   A. This is true, OA patients should avoid physical activity, as it will only make their joints worse.
   B. We do not have clear data on this topic.
   C. Physical exercise is a cornerstone of OA therapy and will reduce OA-related pain even without additional interventions.
   D. Physical exercise may improve OA but should be utilized only after maximizing pharmacological therapy.

   Correct answer: C
   Critique: Multiple studies have indicated that physical therapy can have dramatic effects in improving OA patients' quality of life, pain, and physical function scores. The data are so strong, in fact, that they are the cornerstone of therapy for OA in the guidelines of all major OA-related societies, including the most recent OARSI recommendations. Physical exercise should be prescribed for all OA patients regardless of pharmacologic treatment.

4. Now having convinced her that she should pursue a physical exercise regimen, she wants to know which type of exercise will work the best for her. What is your response to this?

   A. Land-based exercise (running, walking).
   B. Water-based exercise (swimming, water aerobics).
   C. Yoga.
   D. A and B are equally effective.

   Correct answer: D
   Critique: Multiple studies have proven the benefits in both OA-related pain and disability for physical exercise, but no particular regimen is superior to the others. Therefore, OARSI recommends either a land-based or water-based regimen. Yoga has been studied but has not been shown to be superior to other exercise regimens. Tai Chi, a Chinese martial art with an emphasis on balance, has been extensively studied and may offer additional benefits beyond other forms of exercise, but does not yet carry a separate OARSI recommendation.
5. She would like to start a medication to help improve her multijoint OA, since acetaminophen has not helped her. She has considered taking over the counter nonsteroidal anti-inflammatory drugs (NSAIDs), like naproxen. What is your recommendation regarding this?

   A. Naproxen is recommended for multijoint OA; she should begin this treatment.
   B. Acetaminophen has been shown superior to oral NSAIDs and should be tried again in her case.
   C. There are no recommended oral medications for multijoint OA in her case.
   D. An oral nonselective NSAID is not the appropriate choice in this situation given her recent gastric ulceration; a medication like duloxetine may be more appropriate.

   Correct answer: D
   Critique: It is accurate that nonselective oral NSAIDs are recommended for multijoint OA, but she is a high-risk patient given her recent gastric ulceration. Preference would be to start with medications which do not carry a substantial GI risk; duloxetine is a recommended medication in the OARSI guidelines for a situation like this. If she fails duloxetine, consideration could be given to a combination of a COX2-selective NSAID (celecoxib) plus an oral proton pump inhibitor (omeprazole), although caution should be exercised.

Scenario 2

A 60 year-old African-American man (no significant past medical history, BMI 25) presents to your clinic complaining of steadily-worsening right knee pain over the past 2 years. He recalls injuring this joint when he was a teenager. He does not have periodic “flares” of pain, although he notes that his first pain in this joint started

when walking upstairs and it now bothers him walking on level ground. He has previously been told that he did not have joint space narrowing on plain radiographs done about 2 years ago. He has tried physical therapy, exercise, and topical and oral nonselective NSAIDs without any relief.

Physical examination reveals a mild cool effusion in the right knee with no active synovitis, and mild bony hypertrophy is present. He has no other joint abnormalities. You diagnose him with unilateral primary knee osteoarthritis.

6. He first asks whether he should take high-dose acetaminophen or glucosamine sulfate for his knee OA. What is your response?

   A. Either of these medications can be used; studies have indicated they are as effective as NSAIDs for relieving pain in knee OA.
   B. Neither of these medications has strong evidence of efficacy, and they are less likely to work than the NSAIDs he has previously tried.
   C. Glucosamine, but not acetaminophen, has strong evidence for its effectiveness and should be tried.
   D. Acetaminophen, but not glucosamine, has strong evidence for its effectiveness and should be tried.

   Correct answer: B
   Critique: A multitude of studies indicate that the effect on OA-related pain of acetaminophen is small and generally equivalent with oral placebo; NSAIDs have a much higher effect. Glucosamine has been shown in several meta-analyses to be no better than placebo for OA-related pain.
7. He asks if his previous injury decades ago has something to do with his OA. What is your response?

   A. Preceding joint injury is a strong risk factor for subsequent OA development.
   B. Joint injury decades ago is unlikely to have long-lasting consequences.
   C. Preceding joint injury has not been studied in the context of OA.
   D. Too much exercise following his joint injury, and not the injury itself, is likely the cause of his OA.

   Correct answer: A
   Critique: Preceding joint injury is one of the strongest risk factors for OA; this is perhaps best seen in the military population, where so-called post-traumatic OA (PTOA) is a major concern. Soldiers with a previous history of joint trauma have a roughly sixfold higher risk of subsequent knee OA than soldiers without a history of trauma. There is no evidence that postinjury exercise exacerbates OA.
8. He is tired of trying oral and topical medications that do not work and asks about potential intra-articular (IA) injections; specifically, he has friends who have told him steroids work. What is your response?

   A. There is no evidence for the efficacy of steroids in knee OA.
   B. There is evidence for IA steroids, but IA hyaluronic acid derivatives work better.

C. IA NSAIDs should be tried next.
D. IA steroids are an appropriate choice in his situation, and he should receive this treatment immediately.

Correct answer: D
Critique: The OARSI guidelines recommend a physical therapy and exercise regimen for all patients with knee OA and suggest first-line treatment with oral or topical NSAID agents. IA corticosteroids have strong evidence for efficacy, particularly in knee OA, and can be used as second-line agents. IA hyaluronic acid derivatives have less robust support in the literature, and only receive a conditional recommendation by OARSI. IA NSAIDs (ketorolac specifically) has been examined in a few small (positive) studies, but no large analyses have yet been done.

9. He asks if there are any supplements or dietary changes he should make at this time which would help his knee OA. What is your response?

A. No dietary changes or supplements have been definitively shown to improve OA pain or function.
B. He should follow a gluten-free diet.
C. He should take supplemental vitamin C.
D. He should follow a low-fat diet.

Correct answer: A
Critique: Although much has been made in the lay media regarding the effects of particular diets on joint pain, no large, well-conducted studies have ever demonstrated a benefit of a particular diet in OA patients.

10. He has heard "horror stories" about individuals having substantial pain following knee replacements, and wants to know if arthroplasty, on average, offers "better" pain relief for knee OA than injections or other medications. What is your response?

A. Joint arthroplasty is often the only treatment available for end-stage OA, although the data suggest that it is not as effective as oral medications at treating OA pain.
B. Joint arthroplasty is not only effective but has a very low (<5%) incidence of postoperative pain persistence.
C. Joint arthroplasty and oral NSAIDs are roughly equivalent at relieving pain.
D. Joint arthroplasty has the strongest pain-relieving effect of any intervention for knee OA at the present time, although it does carry a risk (up to one-third of patients) of persistent postop pain.

Correct answer: D
Critique: Although no panacea, joint arthroplasty generally offers an effect size on OA-related pain (difference in pain improvement with intervention subtract pain improvement with placebo) roughly double that of any intra-articular, oral, or topical OA drug. The decision to pursue joint arthroplasty should not be taken lightly, but nevertheless strongly considered once more conservative treatments have failed.

Scenario 3

A third-year medical student on a rheumatology rotation is researching OA and has a few questions.

11. "I have heard that OA is a wear-and-tear phenomenon, caused by repetitive joint damage wearing away cartilage, is that true?"

    A. Although microtrauma may play a role, OA is not a wear-and-tear phenomenon, and instead is a systemic, chronic, low-level inflammatory disease.
    B. OA is indeed a wear-and-tear disease limited to specific joints.
    C. OA is a fully genetic disease, we just have not isolated the causative gene yet.
    D. OA is a systemic autoimmune disease.

    Correct answer: A
    Critique: Multiple lines of evidence support the fact that OA is a systemic, chronic, low-level inflammatory disease. It is not a result of wear-and-tear; in fact, physical activity improves OA symptoms. Several well-controlled, large genetic association studies have been performed on OA and have revealed single nucleotide polymorphisms (SNPs) with relatively low contribution to the disease; it is certainly not a fully genetic disease. Finally, OA as we currently understand is not a systemic autoimmune disease and does not generally respond to autoimmune disease-targeted therapy.
12. "I have heard a lot about epigenetics lately in several chronic diseases, does OA pathogenesis have anything to do with this?"

    A. No, OA is a purely physical phenomenon.
    B. Yes, research has indicated substantial OA-related epigenetic changes within joint tissues, which point toward a potential role in pathogenesis.
    C. No, OA is a purely genetic disease.
    D. Not sure, no studies have been performed in this regard.

    Correct answer: B
    Critique: Neither a purely physical nor genetic disease, multiple lines of evidence have recently shown that substantial epigenetic changes exist within OA tissues, particularly within cartilage and subchondral bone, and are related to chronic inflammatory pathways. This may be a way in which environmental perturbations (trauma, aging, inflammation) interact with underlying genetic risk to lead to the development of OA.

Scenario 4

A 75 year-old Latina woman presents to your office complaining of a 6-month history of steadily worsening distal interphalangeal (DIP) pain in the index fingers of both hands. She has noticed some swelling, heat, and warmth, and they seem

to be worsening steadily. She has about 45 minutes of stiffness of these joints every morning, and then they hurt when she is using (flexing) them. She has no personal or family history of psoriasis, ankylosing spondylitis, or inflammatory bowel disease.

Physical exam shows an otherwise healthy woman with swelling, warmth, and mild heat of her index finger DIPs bilaterally. She has joint space loss, restriction in range of motion, and a mild lateral deviation of her distal phalanx bilaterally.

13. What radiographic findings would be most consistent with this patient's most-likely diagnosis?

    A. Subchondral cysts at the distal portion of the middle phalanx bilaterally
    B. Chondrocalcinosis of the affected DIP joints bilaterally
    C. Central cartilage erosions with gullwing formation
    D. Marginal erosions

    Correct answer: C
    Critique: This patient is presenting with likely erosive OA, an aggressive subtype of OA which presents generally with mild synovitis and is rapidly progressive. A characteristic radiographic finding is central cartilage erosions forming a "gullwing" or "sawtooth" sign. Subchondral cysts would be expected with traditional OA, whereas chondrocalcinosis would be more typical for CPPD (and is unlikely to affect the DIP joints). Marginal erosions would be classic for an autoimmune type of arthritis; given the joints involved, consideration for a seronegative spondyloarthropathy.

14. She is concerned about the risks of starting an oral COX2-selective NSAID, as she has heard that heart disease risk is worsened in patients taking COX2-selective NSAIDs compared to nonselective NSAIDs. What is your response?

    A. This is accurate, COX2-selective NSAIDs have an increased relative risk of heart disease; in fact, this is why previous COX2-selective NSAIDs were removed from the US market.
    B. Nonselective NSAIDs have a higher cardiac risk.
    C. NSAIDs carry no additional risk of heart disease.
    D. COX2-selective and nonselective NSAIDs appear to have the same cardiac risk profile.

    Correct answer: D
    Critique: Although previous data had suggested a potential increase in cardiac risk among patients taking the COX2-selective drug celecoxib (approved in the USA), the large PRECISION trial, recently completed, found no additional risk when comparing celecoxib to naproxen and ibuprofen. Certainly, nonselective NSAIDs do not place an individual at a higher risk than a COX2-selective agent. Several meta-analyses do indicate that taking any oral NSAID does produce a somewhat increased risk of heart disease.

15. She has seen commercials for etanercept for the treatment of "hand arthritis" and asks if this would be appropriate for her. What is your response?

    A. OA is a noninflammatory disease, so a TNF inhibitor such as etanercept has no place in its management.
    B. Etanercept might be useful for the treatment of hand OA, it should be tried.
    C. Although OA is an inflammatory disease, etanercept has been tried and failed for hand OA and should not be used.
    D. Etanercept should be used only after failing an oral NSAID.

    Correct answer: C
    Critique: Several studies have examined the potential benefits of using rheumatoid arthritis-approved biologics (and oral DMARDs) in the treatment of hand OA, including erosive OA. None of these drugs have been confirmed as effective in the treatment of hand OA and place the patient at significant increased risk of adverse effects (i.e., infection). At this time, it is not recommended that hand OA patients be administered biologic drugs given their lack of efficacy.

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Chapter 4
Regional Musculoskeletal Syndromes and the Use of Musculoskeletal Ultrasound

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Introduction

Regional musculoskeletal pain is a common complaint. Knowledge of clinical anatomy and careful clinical evaluation is key to delineating the cause of pain. Pain with active and passive range of motion suggests pain of articular origin. In contrast, if the origin of pain is extra-articular, then passive range of motion may elicit minimal or no pain. Despite careful clinical examination, it may be difficult to pinpoint the pathoanatomical basis of pain. The advent of musculoskeletal ultrasound (US) has provided a means of visualizing soft tissues and using dynamic movements to correlate the source of pain. In the following chapter, regional pain syndromes have been divided into joint areas and then further into anatomical areas. Clinical description of the syndromes will be followed by sonographic correlations in majority of these areas.

Upper Limb

Shoulder

Shoulder pain is one of the most common musculoskeletal conditions encountered in primary and specialty care. Most of the diagnosis can be made from relevant history and targeted examination. A summary of the most commonly used tests is given in Table 4.1, although there are more than 120 special tests for the shoulder [1]. Ultrasonography has become an important complementary imaging tool [2], and if

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Table 4.1 Index tests for impingements [76]

Test	Exam maneuver	Positive test
Neer test	Tester forcibly flexes the sitting patient's internally rotated arm, while inhibiting scapular movement by pressing down on the clavicle and acromion with the other hand	Pain indicates subacromial impingement
Hawkins-Kennedy test	The upright patient's arm is passively positioned in 90° of flexion at the shoulder and elbow. The tester then forcibly medially rotates the patient's shoulder	Pain indicates subacromial impingement
Empty Can test (Jobe's test)	The shoulder is fully internally rotated, abducted to 90° and placed in 30° forward flexion as if emptying a beverage can. The tester applies a downward pressure as the patient attempts to maintain this position	Pain indicates impingement whereas weakness indicates a supraspinatus tear
Internal rotation lag sign	With patient sitting, the examiner stands to the back of the patient, brings the patient's hand behind the back and flexes the elbow to 90°, so that the back of the hand rests on the spine at waist level. Gripping the patient's wrist, the examiner then lifts the back of the hand clear of the spine until the shoulder is in almost full medial rotation. The examiner continues to support the elbow but releases the wrist and asks patient to actively maintain this position	If the patient is unable to maintain arm position off back this is a positive test and indicates a subscapularis tear

done by an experienced operator, it can be as reliable as MRI or surgery in diagnosing most causes of shoulder pain [3].

Biceps Tendon Pathology

The long head of the biceps (LHB) tendon arises from the posterosuperior labrum and supraglenoid tubercle and lies within the bicipital groove [4]. The sheath of the LHB is continuous with the glenohumeral joints synovial lining, thus tendinopathy and bicipital tendon sheath effusions can be seen with rotator cuff pathology as well as joint synovitis [5, 6]. Patients often report anterior shoulder pain on resisted supination of the forearm and focal tenderness over the bicipital groove. Sonography of the biceps tendon can identify tendinitis, tendon tears, rupture, and subluxation. LHB tendinitis presents with diffuse hypoechogenicity and thickening [7]. In chronic tendinitis, the tendon may appear frayed and fibrous tissue may replace the fibers [8]. Partial-thickness tears appear as hypoechoic areas within the tendon echotexture. Complete tendon ruptures are visualized as two tendon ends floating within a hematoma. The "empty groove" sign is an indirect sign of complete tendon rupture [9]. Subluxation of the LHB tendon usually occurs medially, under the subscapularis tendon.

Rotator Cuff Tears and Impingement Syndrome

Impingement syndrome is the pinching of soft tissue structures between the humerus and the coracoacromial arch with movement. Rotator cuff dysfunction results in incomplete depression of the humerus in abduction. As a result, the humeral head gets closer to the coracoacromial arch causing impingement of the cuff tendons. Table 4.1 shows tests for the assessment of impingement.

On US, rotator cuff tears may appear as focal to complete hypoechoic defects within the tendon [9]. Irregularities of the greater tuberosity of the humerus, focal tendon discontinuity, and the cartilage interface sign are highly suggestive of rotator cuff tears. Complete supraspinatus tears are notable for complete absence of fibrillar echotexture and replacement by the deltoid in its space (Fig. 4.1). Table 4.2 describes the findings in different types of rotator cuff tendon tears [3]. Rotator

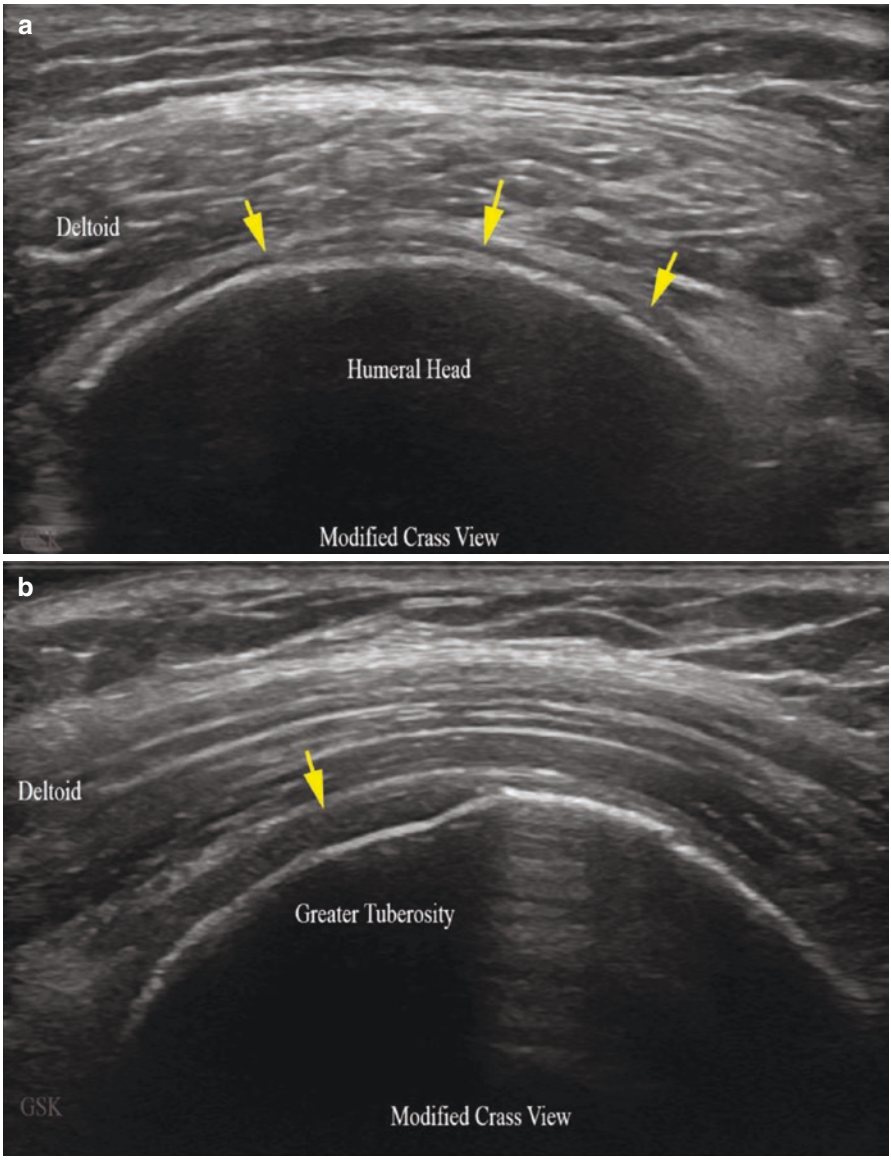


Fig. 4.1 (**a**) Full-thickness supraspinatus tendon tear with absence of tendon fibers indicated by arrows. (**b**) The same patient with long-axis views showing hypoechoic material and lack of a fibrillar structure about the greater tuberosity (arrow)

Table 4.2 Sonographic definitions of rotator cuff tears [3]

Type of tear	Findings
Complete tear	Absence of tendon fibers
Full-thickness tear	Tear extending from bursal surface to articular surface
Partial-thickness tear	Bursal thinning on the bursal aspect of the tendon Articular thinning at the articular portion of the tendon
Rim rent tear	Tear at the footprint of the tendon insertion

cuff calcification appears as hyperechoic areas with a posterior acoustic shadow and is reliably identified by US and may be detected earlier than conventional radiography [9, 10].

Adhesive Capsulitis (Frozen Shoulder)

In this condition, there is limited range of movement of the shoulder with both active and passive range of motion with a normal radiograph. It occurs several months to years after any cause of shoulder pain, or it can occur with systemic conditions such as diabetes.

Acromioclavicular Joint

The acromioclavicular (AC) joint is found between the lateral end of the clavicle and a small facet on the acromion of the scapula [11]. Pain from an abnormal AC joint is reliably induced by cross abducting the shoulder. Degenerative changes usually affect this joint and can be seen on US as irregularity of the bony surfaces, joint effusions, as well as osteophytes demonstrated by hyperechoic projections.

Glenohumeral Joint

The glenohumeral (GH) joint is formed by the head of the humerus with the glenoid cavity of the scapula [11]. Clinically pain from the joint is elicited with both passive and active range of motion. Pain may be due to osteoarthritis or inflammatory arthritis affecting the joint. GH joint erosions can be seen by sonography as cortical defects or irregular contours of the humeral head. Osteophytes are noted as hyperechoic projections from the humeral head. Erosions >1 mm are found in up to 23% of asymptomatic individuals 20–60 years of age [12]. Posterior transverse scan in external rotation is the most sensitive position for the detection of GH effusion and a bone to capsule distance >0.31 cm is suggestive of a pathologic effusion [13].

Subacromial-Subdeltoid Bursa

The subacromial-subdeltoid (SA-SD) bursa is located between the rotator cuff (RC) and the coracoacromial arch (subacromial bursa) and between the RC and deltoid muscle (subdeltoid bursa) [2]. The SA-SD bursa overlies the bicipital groove anteriorly and extends to the coracoid process medially and to variable distances laterally below the greater tuberosity. The bursa facilitates the motion of the rotator cuff [2]. SA-SD bursitis is commonly associated with shoulder pain independently or with underlying pathology such as RC tears, impingement syndrome, or AC joint arthritis. In primary SA-SD bursitis, there will be focal tenderness at the area of the bursa [14]. On US the SA-SD bursa appears as a 2-mm-thick complex with an inner layer of hypoechoic fluid inferior to the hyperechoic peribursal fat layer [15] (Fig. 4.2). Fluid collections accumulate along the lateral edge of the greater tuberosity, producing a "teardrop" appearance [15]. With supraspinatus dysfunction, the bursa is caught between the greater tuberosity and the acromion resulting in an effusion [3].

Elbow

The location and quality of elbow pain can generally be localized to four anatomic regions: anterior, medial, lateral, or posterior. Table 4.3 shows the differential diagnosis of elbow pain based on anatomical location.

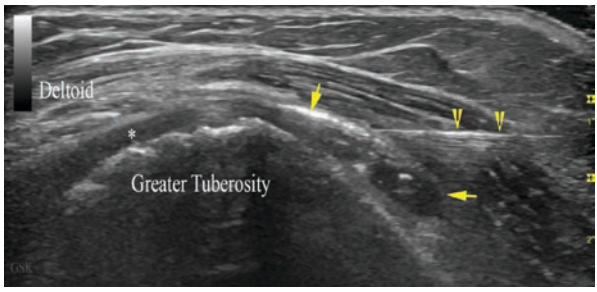


Fig. 4.2 Subacromial-subdeltoid bursa (full arrows) actively being injected (arrow heads pointing to a needle). Full-thickness tear of the supraspinatus (labeled with an asterisk) with underlying cortical irregularity can also be seen

Table 4.3 Differential diagnosis of elbow pain based on anatomical location [18]

Anterior	Anterior capsule strain Biceps tendinopathy Pronator syndrome
Lateral	Lateral epicondylitis Radial tunnel syndrome
Medial	Medial epicondylitis Ulnar collateral ligament injury
Posterior	Olecranon bursitis Olecranon stress fracture Triceps tendinopathy

Lateral Epicondylitis (Tennis Elbow) and Medial Epicondylitis (Golfer's Elbow)

The most common disorder of the elbow is lateral epicondylitis [16]. In lateral epicondylitis, maximal tenderness can be elicited 1 cm distal to the epicondyle at the origin of the inflamed extensors and with maneuvers such as resisted wrist extension [17]. Medial epicondylitis is caused by tendinitis of wrist flexors and forearm pronators. Patients typically report insidious onset of medial elbow pain, which can be elicited by palpation of the wrist flexors and pronators or with resisted wrist flexion [18]. Some of the US findings in patients with epicondylitis include intratendinous calcification, tendon thickening, adjacent bone irregularity, focal hypoechoic regions, diffuse heterogeneity, and increased vascularity with power-Doppler examination [19, 20] (Fig. 4.3).

Ulnar Nerve Entrapment (Cubital Tunnel Syndrome)

The ulnar nerve originates from C8 and T1 and it lies in the cubital tunnel formed by the medial epicondyle and olecranon process side by side, medial collateral ligament (MCL) along with elbow capsule as the floor and the Osborne's ligament

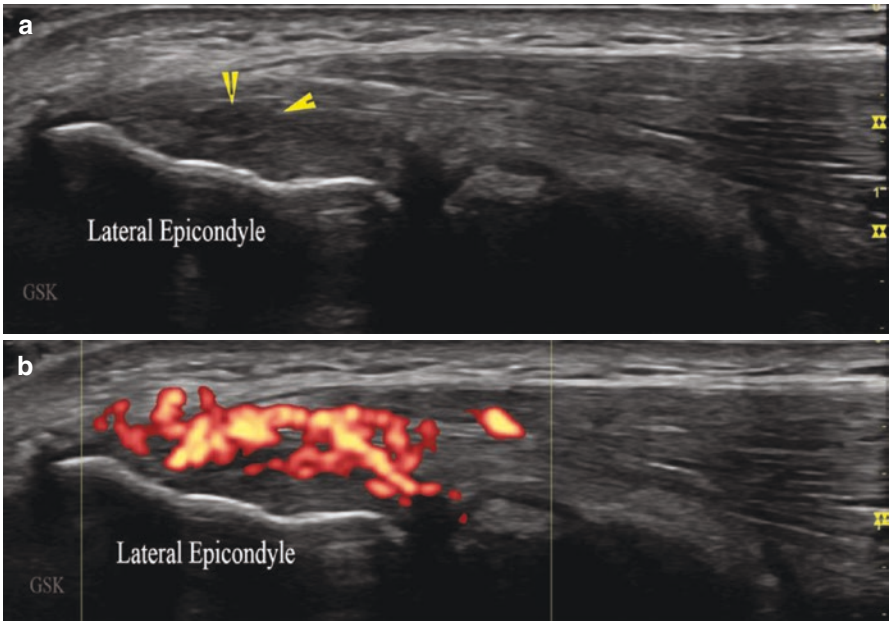


Fig. 4.3 (**a**) Lateral epicondylitis-tendinosis of the common extensor origin. The lateral epicondyle is shown where the extensor tendons attach. There are tendon thickening, focal hypoechoic regions, and diffuse heterogeneity as shown by the arrow heads. (**b**) Positive power Doppler of the extensor tendons as they insert onto the lateral epicondyle indicating neovascularization

(cubital tunnel retinaculum) as the roof [21]. Patients may present with acute numbness of the area of the hand supplied by the ulnar nerve (fourth and fifth digits) as well as pain in the elbow and forearm. With chronic compression, loss of motor function of the lumbricals as well as deformities can occur [21]. On US, prestenotic dilatation indicated by a cross-sectional area of greater than 9 mm^2 is suggestive of entrapment. Dynamic testing is also useful for evaluation of ulnar nerve subluxation [19, 22].

Hand and Wrist

Carpal Tunnel Syndrome (CTS)

CTS is a condition caused by compression of the median nerve at the wrist. Patients may present with pain and weakness of the hand, numbness, and tingling of the thenar eminence, thumb, index, and middle fingers. Tinel's and Phalen's maneuvers can be performed to reproduce symptoms. On US, the median nerve is identified in the short axis where the hypoechoic nerve fascicles and surrounding hyperechoic connective tissue create a characteristic honeycomb appearance [23, 24]. Nerve enlargement is assessed in the transverse plane proximal to the carpal tunnel (Fig. 4.4). The median nerve is considered enlarged if the cross-sectional area is ≥14 mm^2 (continuous boundary trace) [25]. Cross-sectional median nerve area <8 mm^2 rules out CTS [24]. For high suspicion and if the cross-sectional area is 12–14 mm^2, the proximal median nerve can be compared. The median nerve can be measured at the wrist and then 12 cm proximally in the forearm and a wrist-to-forearm ratio (WFR) calculated. A WFR of ≥1.4 has nearly 100% sensitivity for detecting patients with CTS [26]. A difference in median nerve cross-sectional area between the region of the proximal carpal tunnel and the region of the proximal third of the pronator quadratus muscle of greater than 2 mm^2 of the median nerve [27] and greater than 4 mm^2 in a bifid nerve provides [28] the best sensitivity and specificity for diagnosis of carpal tunnel syndrome.

De Quervain's Tenosynovitis

The most common etiology of this condition is thickening of the retinaculum as well as tendinopathy of the abductor pollicis longus and extensor pollicis brevis tendons. Patients report pain at the base of the thumb as well as lateral aspect of the wrist. A positive Finklestein's maneuver supports the diagnosis. US findings include thickened tendons, retinacular thickening, distension of the tendon sheath with fluid and hypervascularity on color Doppler [29] (Fig. 4.5).

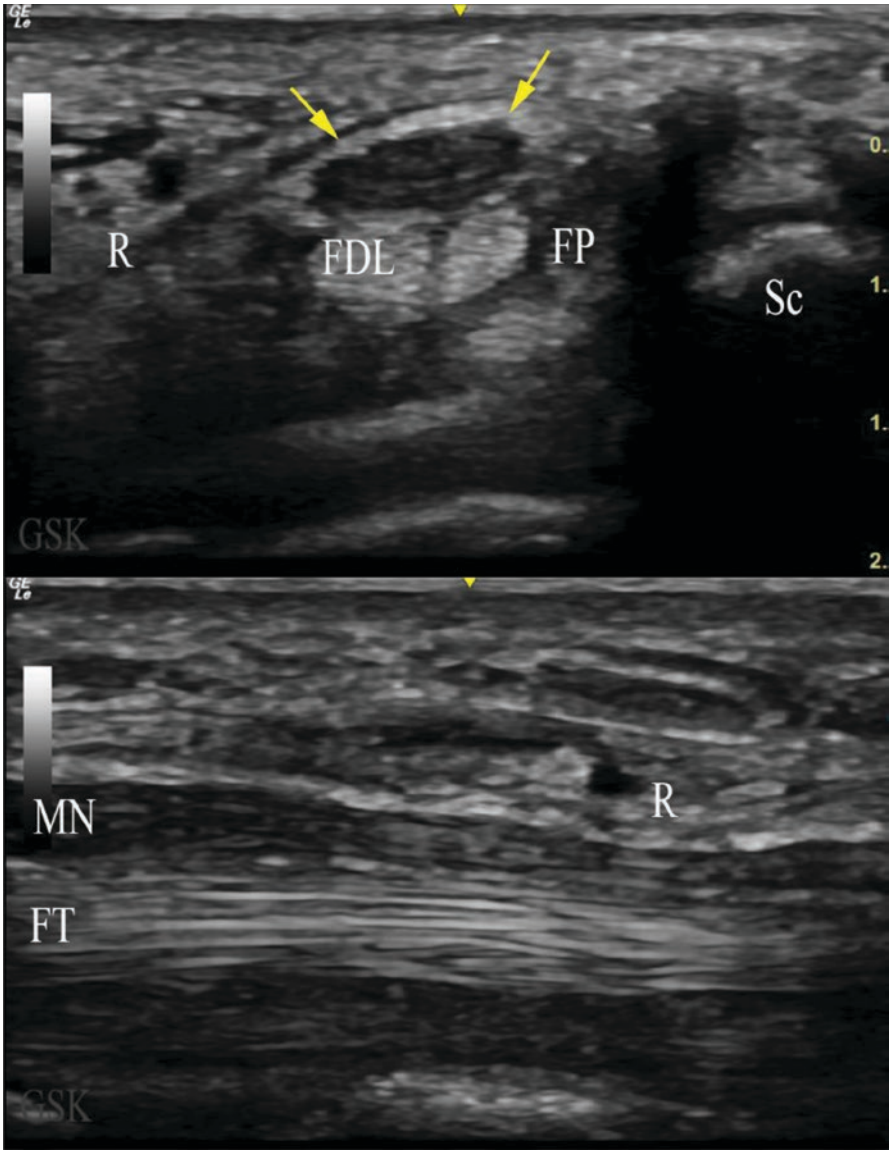


Fig. 4.4 Carpal Tunnel syndrome. *Top*: Enlargement and edema of the median nerve are shown in cross section (arrows). R: Retinaculum; FDL: Flexor Digitorium Longus; FP: Flexor Pollicis Longus; FT: Flexor Tendons. *Bottom*: Enlarged median nerve (MN) in longitudinal section with focal narrowing under retinaculum (R)

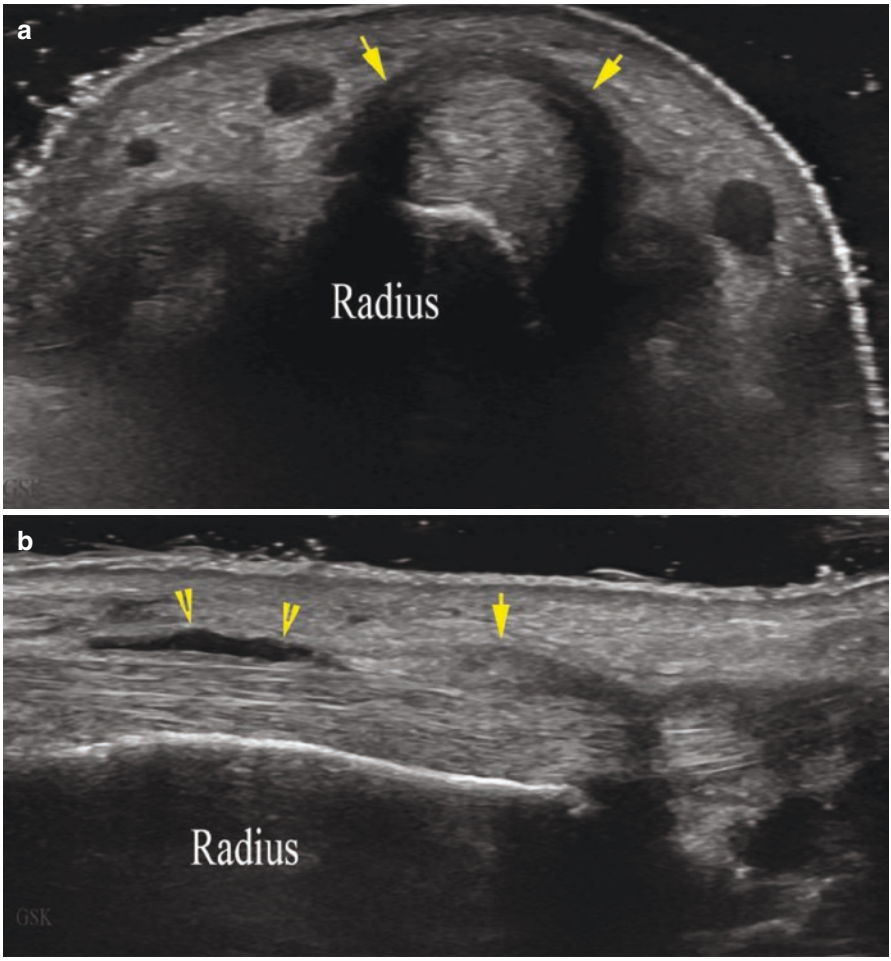


Fig. 4.5 (**a**) De Quervain's tendinopathy. Thickening and distension of the tendon sheaths of the abductor pollicis longus and extensor pollicis brevis tendons as indicated by arrows. (**b**) Fluid around the abductor pollicis longus and extensor pollicis brevis tendons (arrow head) in longitudinal section. Thickening of the retinaculum is noted distally (arrow)

Trigger Finger

The pulley system around the flexor pollicis longus (FPL) tendon is important for digit functioning. There are six pulleys, with the A1 pulley being the most common site for trigger finger [30]. Patients complain of painless clicking or painful locking or catching during active flexion or extension. A painful nodule as a result of

intratendinous swelling may be palpated in the line of the flexor digitorum superficialis (FDS), just distal to the metacarpophalangeal (MCP) joint in the palm. On US, trigger fingers can be visualized with thickening and hypervascularization of the A1 pulley, distal flexor tendinosis, and impingement of the flexor tendon with dynamic imaging [31].

Palmar Fibromatosis (Dupuytren's Contracture, Dupuytren's Disease)

Dupuytren's is a fibroproliferative disorder causing permanent flexion contractures, commonly involving the fourth and fifth digits [32]. It is associated with diabetes, alcohol abuse, smoking, HIV, epilepsy, and manual labor with vibratory exposure. On examination, thickening or a nodule in the palm can be found. It can progress and cause loss of motion of the affected fingers. Palmar fibromatosis appears hypoechoic on US and is located directly superficial to the flexor tendons with hyperemia and calcification [33].

Lower Limb

Hip

Hip pain can originate within the joint itself (intra-articular) or outside the joint (extra-articular). True hip pain refers to the groin area.

Anterior Hip Pain

Anterior groin pain is the most common presenting symptom of intra-articular hip pathology. Physical examination is generally sensitive but not specific for intra-articular hip problems [34]. There are a number of special provocation tests used to evaluate for hip pathology (Table 4.4). Sonography can readily depict the bony contours of the anterior hip as well as distension of the capsule indicating effusion or fluid; however, the joint is deep, and thus it may be difficult to differentiate fluid from synovial hypertrophy [35]. US can also identify incidental iliopsoas bursitis, acetabular osteophytes, or paralabral cysts and tears.

Coxa Saltans (Snapping Hip Syndrome)

Snapping hip syndrome manifests with a palpable or an audible snap or click that occurs with movement of the hip joint. This can be divided into two types: extra-articular and intra-articular; and then further into external and internal causes. Intra-articular snapping can be caused by acetabular labral tears, cartilage defects,

Table 4.4 Provocation tests used to evaluate for hip pathology [77]

Test	Exam maneuver	Positive test
FABER (flexion, abduction, external rotation) test, Patrick's test	Lying supine the patient is instructed to place one leg in the "Fig. 4.4" position: FABER. The examiner applies a downward pressure on the leg (above the knee) of the leg that is crossed over	Pain in ipsilateral groin indicates intraarticular hip pathology; pain in sacroiliac (SI) joint is suggestive of SI joint pathology
Straight leg raise (test of Lasègue)	Patient lying supine with knee in extension, examiner raises the leg by flexing the hip and maintaining knee in extension until discomfort is experienced at the full range of motion	Pain radiating distally along the leg usually in the posterior thigh, radiating into the calf and perhaps the foot prior to the end of normal ROM (70°) indicates sciatic nerve irritation/ compression
Obers test	Patient lies on contralateral side of the painful side, the bottom hip and knee are flexed. The examiner passively flexes the knee to 90°, then passively extends the top hip and abducts the hip. The muscles should be relaxed and allowed to drop to the table	If the leg stays above the table, or feels tight when overpressure is applied, indicates tightness of the Iliotibial band
Trendelenburg test	The examiner stands behind the patient, patient stands with the weight evenly distributed between both feet. The patient's shorts are lowered to the point at which the iliac crest or posterior superior iliac spines are visible. The patient lifts the leg opposite the side being tested	Pelvis dropping toward the unsupported limb indicates weakness of the gluteus medius muscle
Ludloff test	With patient sitting on a chair, the patient's hip is flexed to about 90° and the femur is internally rotated against resistance or the leg is lifted with the knee extended	Production of deep groin pain indicates pathology of the Iliopsoas muscle's tendinous insertion onto the lesser trochanter
FAIR (flexion, adduction, and internal rotation) test	Patient lying on side with the tested hip on top, the lower extremity is passively moved into flexion, 90° adduction, and internal rotation. The examiner stabilizes the hip and applies downward pressure to the knee to internally rotate and adduct the hip	Pain produced in the sciatic/ gluteal area indicates piriformis syndrome
Stinchfield test	With the patient lying supine, the hip is flexed to about 30° with knees straight first against gravity and then with the examiner applying resistance	Pain produced in the groin or thigh indicates intraarticular hip pathology
Thomas test	With the patient lying supine with knees bent at the end of the table, one leg is passively flexed to the patient's chest, allowing the knee to flex during the movement. The opposite leg (the leg being tested) rests flat on the table	The involved leg rises off the table. This indicates tightness of the iliopsoas muscles

fracture fragments, and loose bodies [36, 37]. These patients present with mechanical symptoms such as locking or giving way [38]. Lateral external snapping hip syndrome is caused by movement of the iliotibial band (ITB) over the greater trochanter. These patients may have tenderness over the proximal ITB, lateral margin of the gluteus maximus, or trochanteric bursa. These symptoms can be reproduced with the Ober and FABER (flexion, abduction, external rotation) tests (Table 4.4). In most cases, the diagnosis can be made clinically. If the physical exam is equivocal, then US can be used to depict snapping of the ITB or anterior gluteus maximus muscle over the greater trochanter [38]. Anterior hip snapping is caused by abnormal movement of the iliopsoas tendon when it gets caught within the iliacus in hip flexion and snaps back in place on extension [38]. Anterior hip snapping syndrome usually causes snapping with active movement of the hip from flexion, abduction, and external rotation to extension, adduction, and internal rotation between 30° and 45° of hip flexion. The Thomas test and Stinchfield test may also confirm pain symptoms (Table 4.4).

Rectus Femoris Tendinopathy

Rectus femoris tendinopathy can affect both the direct and indirect head and is common among athletes [39]. Patients experience pain in the groin with jumping and running. Clinical signs include focal tenderness over the anterior-inferior iliac spine and limited hip flexion [40]. US can demonstrate the direct head of the rectus femoris with insertion site calcification and may be amenable to ultrasound guided injection [41].

Femoroacetabular Hip Impingement (FAI)

FAI occurs secondary to developmental hip abnormalities and environmental factors [42]. There are two main subtypes, Cam and Pincer type, with Cam-type impingement seen in young athletic males while Pincer-type impingement more commonly seen in athletic middle-aged women [42, 43]. Patients typically experience groin pain that is worse with prolonged sitting, prolonged walking, or hip flexion-type movements. On examination, there is decreased range of movement with passive flexion, internal rotation, and adduction of the hip. With the pincher type of FAI, hip extension and external rotation may also elicit pain.

Posterior Hip Pain

Piriformis Syndrome

Piriformis syndrome is caused by compression of sciatic nerve in the infrapiriformis canal. This results in numbness or tingling in the buttocks along the sciatic nerve down to the posterior thigh and knee. Palpation, prolonged sitting, or muscular

contraction may increase the pain. The FAIR (flexion, adduction, and internal rotation) test can reproduce symptoms (Table 4.4).

Proximal Hamstring Tendinopathy (Hamstring Syndrome)

Proximal hamstring tendinopathy produces pain in the lower gluteal region, which radiates along the hamstrings to the posterior thigh [44]. Examination may reveal a muscular defect or tenderness over the ischial tuberosity against resisted knee flexion or hip extension and pain with passive stretching of the muscle [45, 46]. Tendinosis and calcification of the proximal hamstrings may be seen on US [35].

Lateral Hip Pain Syndromes

Meralgia Paresthetica

This condition is caused by entrapment of the lateral femoral cutaneous nerve, which innervates the anterolateral thigh [47]. It is associated with wearing tight pants, belts, or girdles; and in diabetics, obese patients and occasionally with surgery. Symptoms include numbness, paresthesias, and pain over the distribution of the nerve [48]. Conservative therapy is the usual plan of care. Sonography may be able to identify the site of nerve impingement for a targeted injection [49].

Lateral Hip Pain Syndrome: Gluteal Tendinopathy and Trochanteric Bursitis

Traditionally, lateral hip pain was diagnosed as trochanteric bursitis, but this diagnosis has been challenged as gluteal medius and minimus tendinopathy is felt to be the basis of lateral hip pain. Gluteal tendinopathy commonly manifests as pain and tenderness laterally over the greater trochanter and radiates down the lateral thigh. It may be aggravated by lying on the affected side or by activities that involve extending the hip such as rising to stand or walking after sitting. The resisted external derotation test from a hip that is in a flexed and externally rotated position may be positive.

Knee

Anterior Knee Pain

Patellar Tendinopathy

Patellar tendinopathy presents with anterior knee pain with stair climbing, jumping, squats, sit to stand, and prolonged sitting [50]. Clinical features include worsening pain as load increases, presence of a warm up phenomenon and

increased pain the day after activity [51–53]. Examination findings include point tenderness at the inferior patellar pole, superior patellar pole, tibial tuberosity, and hamstring and quadriceps tightness. On US, this can be depicted with ligament thickening, loss of fibrillar echotexture, neovascularity, and calcification [54] (Fig. 4.6).

Patellofemoral Pain Syndrome (PFPS)

PFPS is associated with overactivity, malalignment of the lower extremity, muscular imbalance of the lower extremity, and lateral patellar maltracking [55]. Symptoms include anterior knee pain that worsens with prolonged rest and with activities that cause an increased load on the *patellofemoral joint*, such

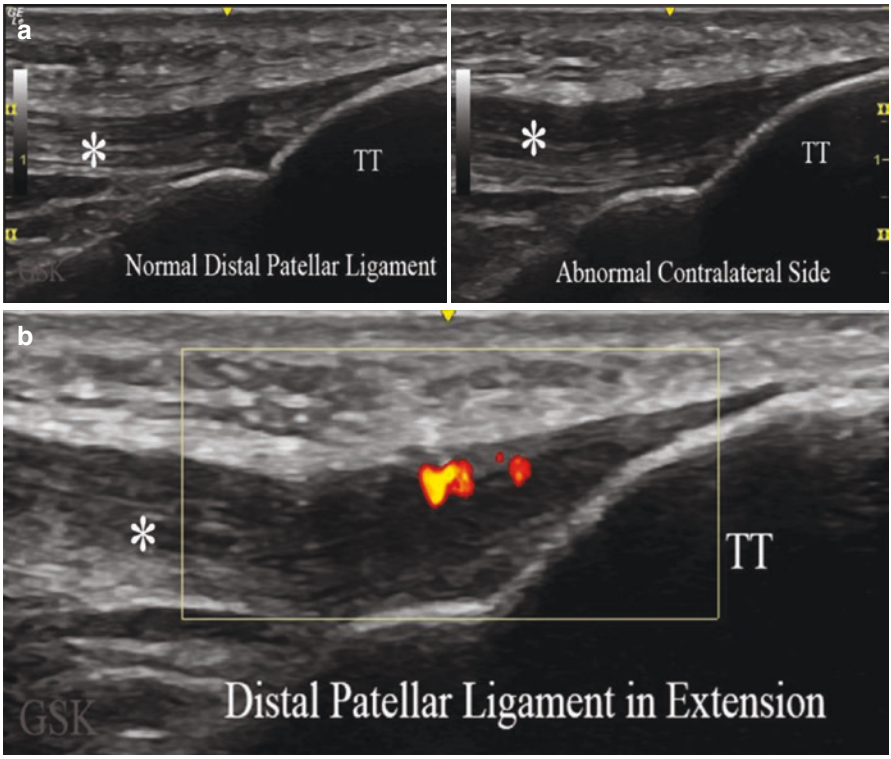


Fig. 4.6 (**a**) Normal distal patellar ligament (asterisk) as it attaches to the tibial tuberosity (TT). Adjacent image shows patellar tendinopathy—abnormal distal patella ligament (asterisk). There are ligament thickening and loss of fibrillar echotexture. (**b**) Increased vascularity (neovascularity) as indicated by positive power Doppler is seen in patellar tendinopathy. Of note the knee is in extension to maximize Doppler sensitivity

as squatting, jumping, and running. The best available test for PFPS is anterior knee pain elicited during a squatting maneuver [56]. Other findings may include vastus medialis atrophy, angular and rotational deformities of the lower extremity, patella facet or retinaculum tenderness, discomfort with displacement of the patella medially or laterally (apprehension maneuver), or crepitus with flexion. Recent literature has suggested a key role of hip abductor weakness in predisposing to PFPS [57, 58].

Prepatellar Bursitis

The prepatellar bursa is located between the subcutaneous tissue and the patella. Activity that requires prolonged or repetitive kneeling can predispose to prepatellar bursitis [59, 60]. In acute bursitis, the area may be swollen, tender, and warm to the touch. In cases of chronic bursitis, the patient may have a history of swelling and pain that waxes and wanes. The presence of significant erythema, warmth, or systemic features, such as a fever and malaise should increase suspicion for a septic bursitis. Sonography may help to differentiate swelling of the knee arising from the prepatellar bursa rather than the joint, as well as allowing needle guidance for aspiration if needed [54].

Ligamentous and Meniscal Injuries

Most acute anterior cruciate ligament (ACL) injuries typically involve a sudden change of direction such as pivoting or landing from a jump. The patient may hear a "pop" at the time of injury and often feels the knee is unstable or "slipping out of place". ACL integrity can be evaluated with the Lachman and anterior drawer tests (Table 4.5).

Posterior cruciate ligament (PCL) or posterolateral corner injuries may present with vague, subacute, or chronic symptoms. The mechanism of injury involves a direct force to the proximal tibia such as falling against a step, motor vehicle collision, or a football helmet striking the knee. PCL can be evaluated by the posterior drawer test (Table 4.5).

Collateral ligament injuries occur with twisting of the leg or a direct blow leading to varus or valgus displacement. Valgus displacement (knee forced inwards) injures the medial ligament while varus displacement (knee forced outwards) injures the lateral ligament. The lateral collateral ligament can be assessed by the varus stress test while the medial collateral ligament can be assessed by the valgus stress test (Table 4.5).

Acute meniscal tears often develop following twisting injuries while chronic degenerative tears occur with minimal twisting or stress. Pain is intermittent and usually localized to the joint line with the exception of meniscal root tears, which

Table 4.5 Provocation tests for knee ligamentous and menisci injuries [78]

Test	Exam maneuver	Positive test
Anterior drawer test	With patient lying supine with hip flexed to 45° and knee to 90°, the examiner grasps the tibia just below the joint line of the knee. Thumbs are placed along the joint line on either side of the patellar tendon. The index fingers are used to palpate the hamstring tendons to ensure that they are relaxed. The tibia is drawn anteriorly	An increased amount of anterior tibial translation compared with the opposite (uninvolved) limb or the lack of a firm end point implies a strain of the anteromedial bundle of the anterior cruciate ligament (ACL) or a complete tear of the ACL
Posterior drawer test	Lying supine with hip flexed to 45° and knee to 90°, the patient's tibia is stabilized in neutral position and then drawn posteriorly	An increased amount of posterior tibial translation compared with the opposite (uninvolved) limb or the lack of a firm end point implies a strain of the posterior cruciate ligament
Lachman test	While the examiner supports the weight of the leg, one hand grasps the tibia around the level of the tibial tuberosity and the other hand grasps the femur just above the level of the condyles. The knee is flexed to 20°–25°, the tibia is drawn anteriorly while a posterior pressure is applied to stabilize the femur	An increased amount of anterior tibial translation compared with the opposite (uninvolved) limb or the lack of a firm end point implies a strain of the posterolateral bundle of the Anterior cruciate ligament (ACL) or a complete tear of the ACL
McMurray test	With the patient lying supine and the tibia maintained in neutral position, a valgus stress is applied while the knee is flexed through its available ROM. A varus stress is applied as the knee is returned to full extension. The examiner internally rotates the tibia and applies a valgus stress while the knee is flexed through its available ROM. A varus stress is applied as the knee is returned to full extension With the tibia externally rotated, the examiner applies a valgus stress while the knee is flexed through its available ROM. A varus stress is applied as the knee is returned to full extension	A popping, clicking or locking of the knee; pain emanating from the menisci; or a sensation similar to that experienced during ambulation implies a meniscal tear
Varus stress test	With the patient lying supine with the involved leg close to the edge of the table, the examiner supports the lateral portion of the tibia, while the other hand grasps the knee along the medial joint line. A lateral (varus force) is applied to the knee while the distal tibia is moved inward. To isolate the Lateral collateral ligament (LCL), the knee is flexed to 25°	Increased laxity, decreased quality of the end point, or pain compared to the uninvolved limb implies a strain of the LCL

Table 4.5 (continued)

Test	Exam maneuver	Positive test
Valgus stress test	A medial (valgus force) is applied to the knee, while the distal tibia is moved laterally	Increased laxity, decreased quality of the end point, or pain compared to the uninvolved limb implies a strain of the medial collateral ligament (MCL)
Apprehension test	Patient lying supine with the knees extended. The examiner gently displaces patella medially and ask patient to contract the knee. Repeat the process with lateral displacement of the patella	Pain indicates patellar maltracking, which may give rise to chondromalacia patella

causes posterior knee pain. Patients typically report clicking, catching, locking, pinching, or a sensation of the knee giving way. Meniscal injury can be evaluated by the McMurray test (Table 4.5).

Posterior Knee Pain

Baker's cyst, also known as popliteal synovial cysts, occurs due to herniation of the synovial membrane through the posterior capsule or escape of synovial fluid through an anatomic bursa next to semimembranosus or gastrocnemius. Symptoms include posterior or posteromedial fullness with aching or it can be asymptomatic [61]. If palpable, the cyst is often firm when the knee is extended and soft when flexed. This finding is known as "Foucher sign" [62]. If the cyst ruptures, joint fluid can dissect inferiorly resulting in pain and swelling of the leg. The patient may have a positive Homan's sign which might lead to a misdiagnosis of deep vein thrombosis [63]. On sonography, the popliteal cyst can be demonstrated as a comma shaped cyst in short axis at the medial gastrocnemius and semimembranosus junction (Fig. 4.7). If it has already ruptured, the cyst has a pointed appearance inferiorly in long axis. Popliteal cysts may be aspirated and injected under ultrasound guidance [64]. Care needs to be exercised not to mistake a popliteal cyst for a popliteal aneurysm, which can be identified on power Doppler by its pulsatility.

Calf Pain

"Tennis Leg": Gastrocnemius Injury

Tennis leg is a caused by injury to the medial head of the gastrocnemius, gastrocnemius-soleus aponeurosis, or plantaris rupture. It is provoked by extension of the knee and forced dorsiflexion of the ankle [65]. The classic presentation is acute mid-calf pain with snapping sensation felt or heard by the patient [65].

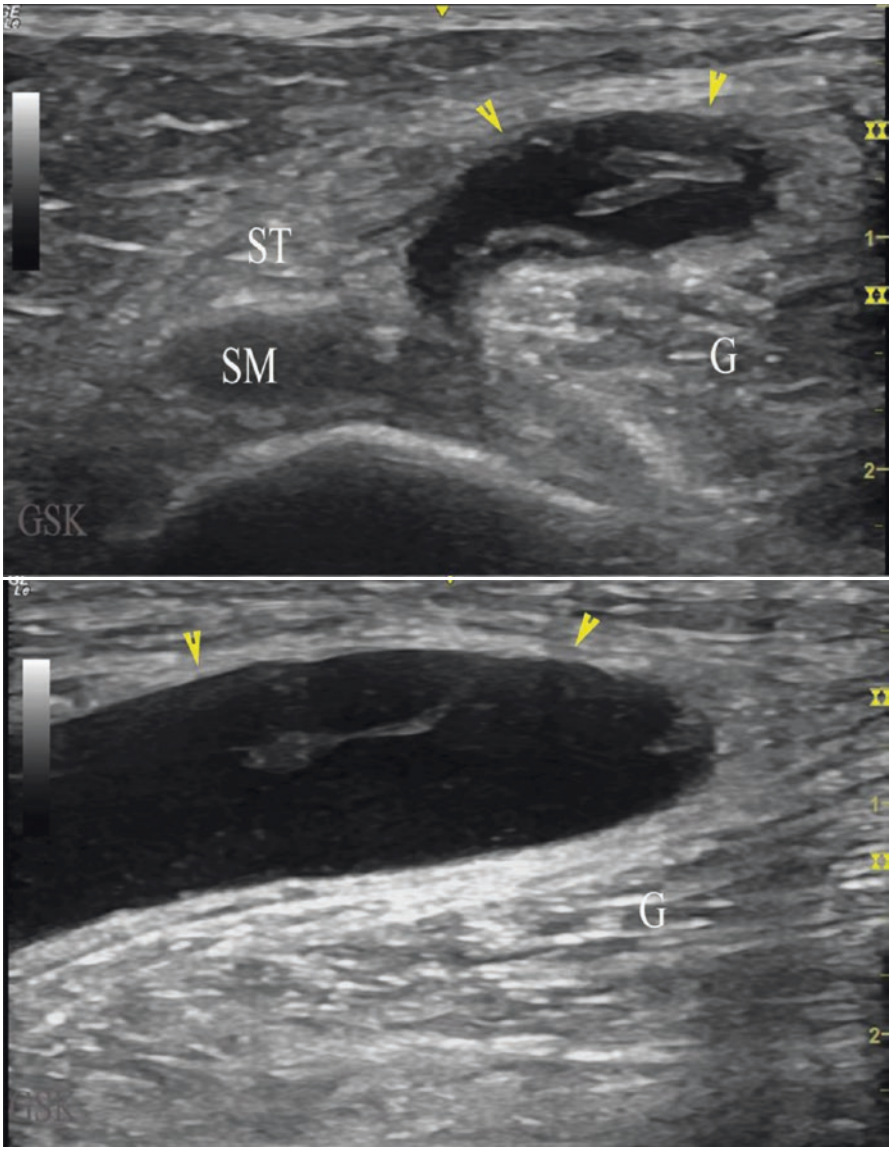


Fig. 4.7 Arrow heads showing popliteal synovial cysts (Baker's cyst) as it pouches out between the heads of the semimembranosus tendon (SM) and the medial gastrocnemius (G). ST: Semitendinosus tendon

Ankle

The assessment of foot and ankle pathology can be challenging, hence the importance of following a systematic method for its clinical assessment. The first component is inspection including dynamic inspection. The shape of the foot, the presence

of deformities, scars, erythema, varicosities, bunions, or swelling should be noted. Palpation should be performed next, to evaluate for warmth, swelling, or areas of tenderness. It is recommended to start proximally and move distally, palpating every aspect of the foot and ankle including the hindfoot, midfoot, ankle, forefoot, and calcaneus.

Anterior Ankle Pain

Pathological conditions affecting the anterior ankle include joint effusions, intra-articular bodies, extensor tendon disease, and ligamentous. The term anterior ankle impingement syndrome encompasses a broad spectrum of joint pathology involving both osseous and soft tissue abnormalities. It is characterized by anterior ankle pain with limited and painful dorsiflexion and swelling. US may reveal three major anterior tendons, tenosynovitis as hypoanechoic distension of the synovial sheath, or effusions in the tibiotalar or talonavicular joint. Anterior ankle pain can also present as sequelae to ligament sprains. The most common anterior ligaments involved in sprains are the anterior tibiofibular and anterior talofibular ligaments which can be examined by static and dynamic sonography [66].

Posterior Ankle Pain

Achilles Tendinopathy

Achilles tendinopathy commonly affects the midsubstance of the tendon or less commonly at its insertion in the calcaneus. Patients complain of pain or stiffness in the Achilles 2–6 cm above the calcaneal insertion [67]. There may be gait abnormalities, increased thickness of the tendon, or a bony prominence at the posterosuperior aspect of calcaneum known as Haglund deformity. Passive dorsiflexion of the foot may elicit pain. Sonographic features of Achilles tendinopathy include thickening, loss of fibrillar echotexture, increased vascularity, tendon calcification, or calcaneal irregularities (Fig. 4.8).

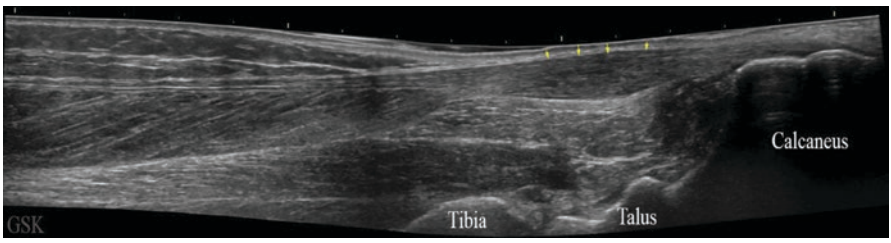


Fig. 4.8 Fusiform Achilles tendon showing thickening and loss of fibrillar echotexture (arrows) of the Achilles tendon as it attaches onto the calcaneus

Achilles Tendon Rupture

Achilles tendon rupture is due to disruption in the conjoined tendon of the gastrocnemius and soleus muscles, and occurs approximately 6 cm proximal to the insertion of the tendon on the calcaneus. Symptoms include sudden, sharp pain in the heel or a snapping sound as the tendon breaks with difficultly walking. With a complete rupture, a palpable gap in the tendon and the Thompson test may be positive (Table 4.6). Tendon tears appear as a focal discontinuity on ultrasound.

Table 4.6 Provocation tests used to evaluate for ankle pathology [79]

Test	Exam maneuver	Positive test result
Thompson test	The examiner squeezes the calf musculature while observing for plantar flexion of the foot with patient lying prone and foot off the edge of the table	When the calf is squeezed, the foot does not plantar flex. This implies the Achilles tendon has been ruptured
Anterior drawer test	With patient sitting over the edge of the table with the knee flexed, to prevent gastrocnemius tightness from influencing the outcome of the test, the calcaneus and talus are drawn forward while providing a stabilizing force for the tibia	The talus slides anteriorly from under the ankle mortise compared with the opposite side (assuming it is normal). There may be an appreciative clunk as the talus subluxates and relocates or the patient may describe pain. This implies a sprain of the anterior talofibular ligament and the associated capsule
Inversion (talar tilt) stress test	The examiner grasps the calcaneus and talus as a single unit and maintains the foot and ankle in 10° of dorsiflexion to isolate the calcaneofibular ligament. The opposite hand stabilizes the leg, the thumb and forefinger is placed along the calcaneofibular ligament so that any gapping in the talus away from the mortise can be felt. The hand holding the calcaneus provides an inversion stress by rolling the calcaneus medially, causing the talus to tilt	The talus tilt or gaps excessively (i.e., >than in 10°) compared with the uninjured side or pain is produced gives an indication of the integrity of the calcaneofibular ligament
Eversion (talar tilt) stress test	The hand holding the calcaneus rolls it laterally, causing the talus to tilt and causing a gap on the medial side of the ankle mortise	The talus tilt or gaps excessively compared with the uninjured side or pain is produced. This gives an indication of the integrity of the deltoid ligament
External rotation test (Kleiger's test)	The foot and talus are externally rotated, while maintaining a stable leg. To stress the syndesmosis, place the ankle in dorsiflexion. To stress the deltoid ligament, place the ankle in the neutral position or slightly plantar flex	Deltoid ligament involvement: Medial joint pain: The examiner may feel displacement of the talus away from the medial malleolus Syndesmosis involvement: Pain is described in the anterolateral ankle at the site of the distal tibiofibular syndesmosis

Retrocalcaneal Bursitis

The retrocalcaneal bursa is located between the calcaneus and the anterior surface of the Achilles tendon. When inflamed it causes posterior heel pain. Examination may reveal point tenderness and swelling lateral to the Achilles at the level of the posterosuperior calcaneus [68, 69] and painful ankle dorsiflexion. Retrocalcaneal bursitis is seen as a hypoanechoic distension posterior to the Achilles tendon. For small amounts of fluid, dynamic flexion and extension of the ankle may reveal fluid at the border of Kargers fat pad and calcaneus [66].

Medial Ankle Pain

Medial foot pain can be caused by posterior tibial tendon dysfunction, tenosynovitis of the medial group of tendons, as well as tarsal tunnel syndrome.

Posterior Tibial Tendon Dysfunction

Posterior tibial tendon dysfunction causes pain in the medial hindfoot, exacerbated by standing on the toes, walking up or down stairs or uneven surfaces. Examination may reveal flatfoot deformity, inability to perform single heel raise and "too many toes" sign. This sign allows visualization of more than one to two toes along the lateral aspect of the affected foot [70, 71] as seen from behind the patient, when the hindfoot is in valgus and the forefoot is abducted. The posterior tibial tendon is the most anterior of the three tendons and can be followed along its length to its insertion about the navicular bone via US. Tendinosis often occurs where the tibial tendon has a zone of relative hypovascularity distal to the medial malleolus. Sonographic findings range from tendon thickening, tenosynovitis, loss of echotexture, hypervascularity, and navicular bone irregularities.

Lateral Ankle Pain

Peroneal Tendinopathy and Tenosynovitis

Pain from the lateral peroneal tendons may manifest from tendinosis, tenosynovitis, or subluxation. It is most commonly seen in those who engage in running, competitive walking, and ballet dancing. It also occurs in elderly, diabetics, patients with inflammatory arthritis, and individuals with displaced fractures of the lateral malleolus and calcaneus. Patients may present with pain and swelling distal to the

lateral malleolus, aggravated by activity. Examination may reveal pain during active eversion and dorsiflexion against resistance. On sonography, tendinosis, tenosynovitis, tendon tears and subluxation may be demonstrated.

Midfoot Pain

The midfoot connects the hindfoot and forefoot. Midfoot osteoarthritis occurs in 12% of patients over the age of 50 [72].

Forefoot Pain

Metatarsalgia

Metatarsalgia refers to pain localized in the forefoot and under the second through fourth metatarsal heads. The pain is aggravated during walking or running. Metatarsalgia is frequently associated with deformity of first and fifth rays, as well as the toes. Examination includes palpable point tenderness at the distal end of the plantar metatarsal fat pad and on the plantar surface of the metatarsal head with callus formation.

Morton's Neuroma

Morton's neuroma is one of the most common causes of metatarsalgia. Neuroma formation occurs due to interdigital nerve compression. It most commonly affects the third interdigital nerve in the third webspace [73]. Symptoms include numbness, tingling, and burning in the third and fourth digits, as well as the plantar aspect of the foot, located between the metatarsal heads. Patients may report the feeling of "walking on a lump" in the ball of the foot. The pain is aggravated with tight shoes or heels. On examination, there may be tenderness on compression of the metatarsals and enlargement of the interdigital space. On US, Morton's neuromas appears as a hypoechoic area in the plantar intermetatarsal space which may be displaced by Mulders maneuver or by pushing on the dorsum of the respective webspace [74].

Tarsal Tunnel Syndrome

Tarsal tunnel syndrome is a compressive neuropathy of the posterior tibial nerve and lies in a fibro-osseous tunnel beneath the flexor retinaculum on the medial side of the ankle. Patients complain of burning, tingling, and pain along the plantar

Table 4.7 Tests used to evaluate for foot pathology [79]

Test	Exam maneuver	Positive test
Mulder sign	The forefoot is compressed	A click, pain, or reproduction of symptoms indicates the presence of an intermetatarsal neuroma
Dorsiflexion-eversion test	The examiner passively everts the heel (calcaneus and talus) while passively dorsiflexing the foot and toes. This position is held for 5–10 seconds	Provocation of pain and/or paresthesia radiating into the foot implies posterior tibial nerve dysfunction

region aggravated with walking, prolonged standing, or use of high-heeled shoes. Examination may reveal trophic changes of the foot and nails in chronic cases. Pes planus is often associated with this syndrome. Percussion of the tibial nerve results in pain and paresthesias along its course (Tinel sign). The dorsiflexion-eversion test may also reproduce the symptoms of pain or paresthesia radiating into the foot (Table 4.7). In tarsal tunnel syndrome, US is used to exclude space-occupying lesions such as ganglia.

Subtalar Joint (Talocalcaneal Joint and Talocalcaneonavicular Joint)

The subtalar joint is one of the three hindfoot joints. It participates in eversion and inversion of the foot. To examine the subtalar joint, one should orient oneself by finding the sinus tarsi, which is an anatomical space bound by the talus and calcaneus. It is a soft tissue depression anterior to the lateral malleolus. Once this area is correctly located, then the anterior and posterior processes of the subtalar joint can be easily identified. Tenderness to palpation of this region may indicate subtalar injury or arthritis. Other findings may include an antalgic gait, hindfoot swelling, pain with inversion/eversion of the hindfoot and limited range of motion of the subtalar joint. Subtalar joint motion may be measured by maximally inverting and everting the heel. The normal range of movement is 5°–10° in eversion, and 25°–30° in inversion [75].

Questions

1. A 45-year-old woman has right hip pain that is elicited by external rotation and abduction of the right leg. Palpation of the right greater trochanter reproduces the symptoms. Injection of which of the following anatomical sites is the most appropriate for interventional therapy for this patient?

   A. Ischial bursa
   B. Hip joint
   C. Right sacroiliac joint

D. Trochanteric bursa
E. Piriformis muscle

Correct answer: D
Trochanteric bursitis typically presents with pain and tenderness primarily at the greater trochanter, which radiates around the trochanter and often down the lateral thigh. It may be aggravated by lying on the affected side or by activities that involve extending the hip such as rising to stand or walking after sitting.

2. A patient 3 weeks after laparoscopic hernia surgery complains of numbness, pain, and decreased sensation of the lateral left thigh. What is the most likely cause?

   A. Lateral femoral cutaneous nerve entrapment
   B. Femoral nerve entrapment
   C. Peroneal nerve entrapment
   D. Iliotibial band syndrome

   Correct answer: A
   Meralgia paresthetica is a condition caused by entrapment of the lateral femoral cutaneous nerve of the thigh. It is associated with numbness and pain of the upper lateral thigh area. This condition is associated with wearing tight pants, belts, or girdles; diabetes and obesity.

3. A 42-year-old female started running 4 months ago. She complains of right knee pain for the past 3 months, which has worsened over the last month. She localizes the pain to the anterior knee but denies swelling. She reports noise in her knee and increased pain when climbing stairs. Which of the following is the most likely diagnosis?

   A. Osgood-Schlatter disease
   B. Patellofemoral pain syndrome
   C. Baker's cyst
   D. Hamstring tendonitis

   Correct answer: B
   This patient has patellofemoral pain syndrome. This usually presents with anterior knee pain. Activities such as squatting, jumping, and running that cause an increased load on the patellofemoral joint may aggravate symptoms. Examination findings may include tenderness of the articular surface of the patella, discomfort with displacement of the patella medially or laterally (apprehension maneuver) and crepitus with flexion and extension.

4. A 36-year-old woman who likes wearing high-heeled shoes complains of increasing pain and numbness in her foot around the base of the third and fourth toes. What is the most likely diagnosis?

   A. Morton's neuroma
   B. Tarsal tunnel syndrome

C. Retrocalcaneal bursitis
D. Midfoot osteoarthritis

Correct answer: A
Morton's neuroma presents with forefoot pain and commonly affects the third intermetatarsal space, but it can also affect the second intermetatarsal space. It is caused by entrapment of the interdigital nerve about the intermetatarsal ligament, resulting in neuroma formation.

5. During an examination by his rheumatologist, a 24-year-old soccer player is asked to lie prone on the table with the knees passively flexed. The calf is then squeezed and there is an absence of plantar flexion. What disorder does the patient have?

A. Achilles tendon rupture
B. Baker cyst
C. Retrocalcaneal bursitis
D. Peroneal tendinopathy

Correct answer: A
In the Thompson test, the patient is asked to lie prone with the knees passively flexed. The calf is squeezed and normally there is plantar flexion of the foot. The absence of plantar flexion is considered a positive test for Achilles tendon rupture.

6. A 23-year-old male presented with left shoulder pain for 2 weeks duration. He doesn't recall any injury but he had to stop his swimming practice because of pain. On examination, there is no swelling or redness of the shoulder. Pain is aggravated with resisted supination of the forearm. He also has tenderness over the anterior shoulder. What is the likely etiology of his shoulder pain?

A. Adhesive capsulitis of the shoulder
B. Acromioclavicular joint arthritis
C. Bicipital tendinopathy/ tendinitis
D. Chronic dislocation of the glenohumeral joint

Correct answer: C
In bicipital tendinopathy, which is inflammation of the long head of the biceps, there will be tenderness over the bicipital grove at the anterior shoulder. Pain is elicited with resisted supination of the forearm, as well as direct palpation of the tendon anteriorly.

7. A patient with long-standing history of seropositive rheumatoid arthritis came for a follow-up to discuss changing medications because of a possible new deformity. She described that her third and fourth fingers lock up and she is unable to fully extend her fingers. On examination there is a nodule palpated along the tendon about the MCP. In this condition, the nodule correlates with:

A. Extensor digitorum tenosynovitis
B. Flexor pollicis longus tenosynovitis

C. Flexor digitorum superficialis tenosynovitis
D. A1 pulley thickening

Correct answer: D
Patient has trigger finger due to impingement of the flexor digitorum tendons within the A1 pulley. The most common cause of trigger finger is thickening of the A1 pulley, which results in narrowing of the tunnel through which the tendons pass.

8. Which ultrasound scan position is the most sensitive position for the detection of glenohumeral joint effusions?

A. Anterior longitudinal
B. Posterior longitudinal
C. Posterior transverse
D. Axillary view

Correct answer: C
The posterior transverse ultrasound scan position with the shoulder in external rotation is the most sensitive position for the detection of glenohumeral joint effusions. A bone to capsule distance of more than 0.31 cm is suggestive of pathologic effusion.

9. Carpal tunnel syndrome (CTS) can be assessed in the transverse plane just proximal to the carpal tunnel, where the median nerve is considered enlarged if the cross-sectional area is greater than 14 mm^2. When the cross-sectional area is less than 14 mm^2, what other sonographic technique can infer carpal tunnel syndrome?

A. Measurement of median nerve cross-sectional area at the level of the pronator teres muscle
B. Measuring the cross-sectional area in the wrist and proximally in forearm and calculation of wrist-to-forearm ratio (WFR)
C. Measuring the diameter of the median nerve at the level of the pronator quadratus muscle as it dives under the muscle
D. Measuring the cross-sectional area of the median nerve distal to the carpal tunnel with an area less than 8 mm^2.

Correct answer: B
The median nerve can be measured at the wrist and then 12 cm more proximally in the forearm and a wrist-to-forearm ratio (WFR) calculated. A WFR of $\geq$1.4 gives 100% sensitivity for detecting patients with CTS, while using only median nerve area at the wrist resulted in a sensitivity of 45–93%, depending on the cut-off value used.

10. De Quervain's tenosynovitis is caused by thickening and entrapment of the synovial sheaths of which of the following tendons?

A. Abductor pollicis longus and extensor carpi radialis longus tendons
B. Extensor carpi radialis brevis and extensor pollicis brevis tendons

C. Abductor pollicis longus and extensor pollicis brevis tendons
D. Abductor pollicis longus and Extensor carpi radialis brevis tendons

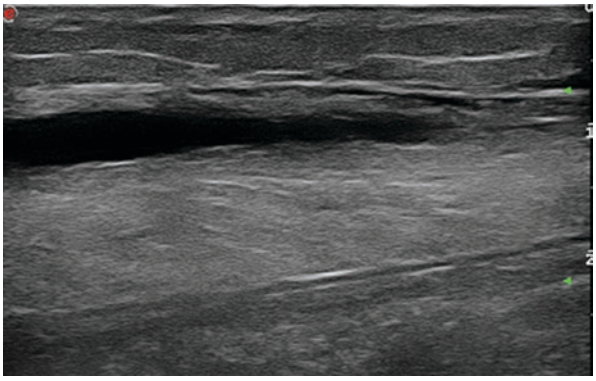
Correct answer: C
De Quervain's tenosynovitis is thickening and entrapment of the synovial sheaths of the abductor pollicis longus and extensor pollicis brevis tendons. US findings are thickening of the dorsal retinaculum in majority of the cases and distension of the tendon sheath with fluid and hypervascularity on color Doppler US.

11. What is the most commonplace for subluxation of the long head of the biceps tendon?

A. Medially, under the subscapularis tendon.
B. Inferior to the supraspinatus tendon
C. Under the coracoacromial arch of the scapula
D. Inferior to the subscapularis tendon

Correct answer: A
Subluxation of the long head of the biceps tendon usually occurs medially, under the subscapularis tendon.

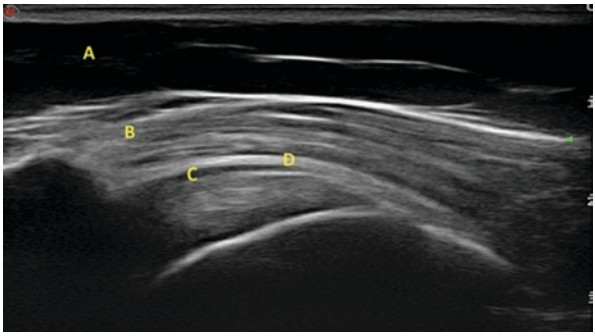
12. The following longitudinal scan of the posteromedial aspect of the knee indicates:



A. An intact popliteal cyst
B. An intact pes anserine bursa
C. Ruptured popliteal cyst
D. Interstitial edema

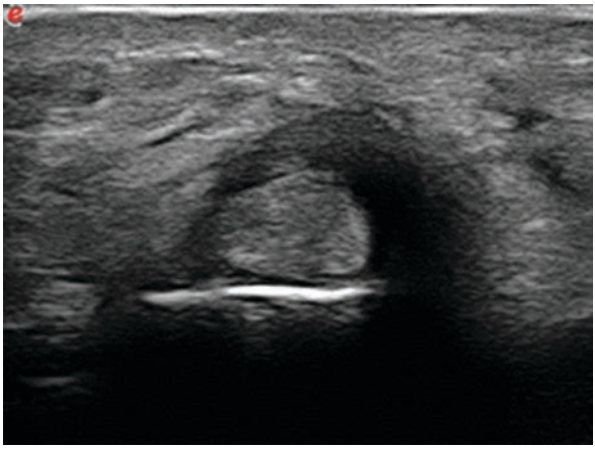
Correct answer: C
A popliteal cyst is seen above the medial head of the gastrocnemius. The pointed inferior border indicates that it has already ruptured.

13. The following image is acquired at the lateral shoulder in neutral position. Which of the following would be a target for subacromial subdeltoid bursa injection?



Correct answer: C
The anechoic area is the subacromial-subdeltoid bursa, which lies under the peribursal fat stripe (D). The deltoid muscle is represented by B and the subcutaneous tissue by A.

14. The following image is acquired in short axis at the distal lateral radius in a patient with lateral wrist pain.



The findings are most compatible with:

A. Tenosynovitis of the extensor carpi ulnaris tendon
B. Tenosynovitis of the extensor digitorum tendon
C. Tenosynovitis of the abductor pollicis longus and extensor pollicis brevis tendons
D. Thickening of the dorsal compartment one retinaculum

Correct answer: D
The abductor pollicis longus and extensor pollicis brevis tendons form the dorsal compartment 1. The ultrasound demonstrates marked thickening of the dorsal retinaculum corresponding to a clinical diagnosis of De Quervains tendinopathy.

15. A 24-year-old male presents to the ER after sustaining a blow to the knee during soccer practice. On knee examination, there is significant forward translation of the tibia when the knee is in 20° of flexion and the tibia is forced forward while the femur is stabilized. Which of the following knee maneuvers does this represent?

    A. Anterior drawer sign
    B. Ober test
    C. Lachman test
    D. McMurray test

    Correct answer: C
    The Lachman test is performed to evaluate the anterior cruciate ligament. While the examiner supports the weight of the leg and the knee is flexed to 20°–25°, the tibia is drawn anteriorly while a posterior pressure is applied to stabilize the femur. An increased amount of anterior tibial translation compared with the opposite (uninvolved) limb or the lack of a firm end point implies a strain of the posterolateral bundle of the ACL or a complete tear of the ACL.

16. During a soccer game, a 19-year-old male student is tackled and another player collides with the outside of his knee. He immediately experiences pain over the inner aspect of his knee. On examination he has a positive valgus stress test but with a firm end point. What is the most likely knee injury that he sustained?

    A. Lateral collateral ligament injury
    B. Medial collateral ligament injury
    C. Anterior cruciate ligament injury
    D. Posterior cruciate ligament injury

    Correct answer: B
    Medial collateral injury typically follows a valgus force. On examination there is tenderness over the origin of the medial collateral ligament and the valgus stress test is positive. With this test, a medial (or valgus) force is applied to the knee while the distal tibia is moved laterally. This results in increased laxity, decreased quality of the end point, or pain compared with the uninvolved limb.

17. Which of the following is true about medial epicondylitis?

    A. Resisted wrist extension typically causes tenderness over the medial epicondyle
    B. Increased pain is noted with resisted supination

C. Power Doppler ultrasound examination is not useful to aid diagnosis
D. Resisted wrist flexion typically causes tenderness over the medial epicondyle

Correct answer: D
Medial epicondylitis is caused by tendinitis of wrist flexors and forearm pronators. Patients typically report insidious onset of medial elbow pain, which can be elicited by palpation of the wrist flexors and pronators or with resisted wrist flexion.

18. A 45-year-old woman is evaluated for a 6-day history of right shoulder pain. The pain is worse with overhead activities. On examination she experiences pain when the upright right arm is passively positioned in 90° flexion at the shoulder and elbow, while the examiner attempts to medially rotate the patient's shoulder.

Which of the following is the most likely diagnosis?

A. Acromioclavicular joint degeneration
B. Adhesive capsulitis
C. Rotator cuff impingement syndrome
D. Rotator cuff tear

Correct answer: C
The patient most likely has rotator cuff impingement syndrome. This syndrome may be identified by the Hawkins test. In this test the upright patient's arm is passively positioned in 90° flexion at the shoulder and elbow, and the examiner then forcibly medially rotates the patient's shoulder. The presence of pain suggests rotator cuff Impingement.

19. A 68-year-old man with a past medical history of diabetes presents complaining of gradually worsening left shoulder pain. He admits difficulty lifting his left arm. Examination reveals that his left shoulder has globally reduced range of movement. X-ray of the left shoulder is normal. What is the most likely diagnosis?

A. Osteoarthritis of the glenohumeral joint
B. Adhesive capsulitis
C. Bicipital tendinopathy/ tendinitis
D. Rotator cuff tear

Correct answer: B
This patient has adhesive capsulitis, also known as frozen shoulder. It results in limited active and passive range of motion of the shoulder but has a normal radiograph. It can occur with systemic conditions such as diabetes.

20. A 74-year-old woman with a past medical history of varicose veins and a non-displaced right talus fracture 2 years ago complains of burning, tingling, and pain along the plantar region of the right foot and toes. Compression of which of the following nerves is the most likely cause of her symptoms?

A. Common peroneal nerve
B. Superficial peroneal nerve
C. Anterior tibial nerve
D. Posterior tibial nerve

Correct answer: D
This patient has tarsal tunnel syndrome, which is caused by a compressive neuropathy of the posterior tibial nerve.

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Chapter 5
Infectious Arthritis

Nicola Berman and Brian D. Golden

Introduction

Septic arthritis is a true rheumatologic emergency that may lead to disability or death, needing prompt surgical evaluation [1]. Septic arthritis refers to an infection involving a joint. Most commonly this is due to a bacterial infection; however, viruses, fungi, and parasites can also invade articular surfaces and lead to infection. Septic arthritis affects two cases per 100,000 people per year [2]. Currently, the most commonly described organisms are *Staphylococcus aureus* – with MRSA increasing in incidence commensurate with the global increase, followed by gram-negative enteric organisms [3, 4]. Knowledge of the host, risk factors, and clinical presentation is crucial to allow for appropriate investigations, empiric antibiotic therapy, and management, particularly as this is a rheumatologic emergency.

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Pathogenesis

A pathogen can gain access to a joint by a number of methods. An occult bacteremia is the most common cause of septic arthritis. Penetrating trauma, arthrocentesis, or joint injections can introduce infection, as well as smaller breaks in skin or mucous membranes may allow staph/strep to gain access to bloodstream. Septic arthritis from gram-negative enteric organisms is usually due to loss of integrity from the gastrointestinal or genitourinary tract [4, 5].

Clinical Manifestations

In general, septic arthritis presents with a swollen, painful joint. Patients will typically display restricted movements on both active and passive movements, compared to a periarticular condition which should only elicit pain on active movements. The joint will typically be held in position of maximal intra-articular space [6]. In addition, septic arthritis will usually manifest with micro-motion tenderness, where even slight movements will exacerbate the pain. Most commonly patients will also have the classic signs of infection, including fevers; however, the elderly or immunosuppressed populations may not mount an infectious response.

The knee is involved in over 50% of cases; in addition the hip (15%), ankle (9%), elbow (8%), wrist (6%), and shoulder (5%) are commonly infected [7, 8]. Oligoarticular and polyarticular infection occurs in approximately 20% of septic joint infections and usually involves two or three joints – this has been reported more in the population of patients with inflammatory arthritis, namely, those with rheumatoid arthritis. This is of course exacerbated by immunosuppression with both DMARDs and biologics [9]. In addition, infections with pneumococcus, group B streptococcus, and gram-negative enteric organisms are more likely to present with polyarticular disease [7]. Importantly, particularly in cases of oligoarticular or polyarticular involvement, there should be a high index of clinical suspicion for hematogenous seeding, and a thorough evaluation for other sources of infection, including blood cultures, should be sought.

The cartilaginous joints including the pubic symphysis and sternoclavicular and sacroiliac joints are more likely to be affected in patients who use intravenous drugs. In these cases, it is recommended to evaluate for endocarditis [10].

Diagnosis

The initial and imperative step to evaluating patients when there is any suspicion for septic arthritis is a joint aspiration. Ideally this is performed prior to administration of antibiotics. All synovial fluid specimens should be sent for gram stain, culture,

and cell count with differential. Additional tests for *Mycobacterium*, *Neisseria*, and *Borrelia burgdorferi* should be done in the appropriate clinical setting. When infected, the synovial fluid will typically be purulent and the leukocyte count is over 50,000, and these patients should be treated empirically for septic arthritis. Of note, if patients are either debilitated or immunosuppressed, they may have lower synovial fluid counts [11]. The gram stains are helpful when positive but not sensitive for the diagnosis of septic arthritis, and approximately 20% of suspected septic arthritis will have negative cultures on synovial fluid on solid media [12]. Serum procalcitonin level may be helpful in diagnosing septic arthritis [13]. It is also important to obtain blood cultures, as at least 1/3 of all patients with septic arthritis have associated bacteremia [2].

Microbiology

Septic arthritis is monomicrobial in most cases, but polymicrobial infections may occur. This is usually in the setting of either hematogenous seeding from a polymicrobial bacteremia, direct extension from the bowel, or in the setting of penetrating trauma involving the joint space [14].

See Table 5.1 for a list of the most common pathogens.

Staphylococcus

Staphylococcus is the most common cause of septic arthritis, seen in about 50% of cases. Septic arthritis caused by *Staphylococcus* is due to a transient bacteremia from a skin or mucous membrane source [16]. About half of these are MRSA joint

Table 5.1 Common pathogens in septic arthritis [15]

	Joint involvement	Pathogen
Soft tissue skin infection	Monoarticular, polyarticular	*S. aureus* *Streptococcus*
Sexually active	Polyarticular	*Neisseria gonorrhoeae*
Elderly, UTI, skin breakdown	Monoarticular	Gram-negative rods including enteric organisms
IVDU	Sternoclavicular, sacroiliac, pubic symphysis	*Pseudomonas*, *S. aureus*
Rheumatoid arthritis	Monoarticular	*S. aureus*
Anti-TNF therapy	Monoarticular	*Salmonella*, *Listeria*
Animal bites	Small joints	Oral flora including anaerobes, *Pasteurella multocida*
Southwestern USA, Central and South America	Knee	*Coccidioides immitis*

infections, which are associated with worse outcomes. This is also due to the fact that MRSA tends to affect older persons. It also reportedly commonly affects the shoulder – which is a difficult site to access [17].

Streptococcus

Though the majority of streptococcal infections are monoarticular, polyarticular involvement has been reported in up to 36%. The incidence of *S. pneumoniae* has declined due to pneumococcal vaccinations. Beta-hemolytic strep seems most common in the elderly, those with diabetes, cirrhosis, and neurologic disease. Group B streptococcus has a high frequency of bacteremia with polyarticular involvement as a result. The mortality from septic arthritis caused by pneumococcus is high [18].

Gram-Negative Enteric Organisms

Gram-negative enteric organisms are seen most often in intravenous injection drug users, neonates, older adults, and the immunosuppressed population. They account for up to 10% of cases of septic arthritis [19, 20]. Outcomes are found to be favorable for these patients [21].

Gonococcus

Usually present in sexually active individuals. Seventy-five percent of cases occur in women; menses and pregnancy increase the risk of disseminated infection. There are two classic presentations of a disseminated gonococcal infection, the arthritis-dermatitis syndrome and a purulent arthritis. Patients with a disseminated gonococcal infection usually present with fevers, skin lesions, polyarthralgias, and tenosynovitis. Within a few weeks, these can evolve into a persistent monoarticular or oligoarticular arthritis. This purulent arthritis is characterized by abrupt onset, usually involving distal joints with knees, wrists, and ankles, with the knee being the most common. Axial involvement is rare. Routine cultures wont usually establish the diagnosis [22]. In order to isolate the organism, synovial fluid nucleic acid amplification testing or a culture on a chocolate agar or Thayer-Martin medium is usually required [22, 23]. That said, gonococci are recovered from joint fluid in fewer than 50% of cases. Current rising rates of gonorrhea resistant to fluoroquinolones and azithromycin suggest that epidemic gonorrhea may be recurring [7].

Mycobacterium

Mycobacterium tuberculosis should be suspected in cases of an indolent presentation of persistent culture-negative monoarticular or oligoarticular arthritis in the setting of relevant epidemiologic exposure. The most common sites are the hip or knee and this is most often monoarticular – multifocal lesions are seen in 10–15% of cases [24]. Symptoms can be present for an average of a year before diagnosis. If patients present late in the course of they disease they may have evidence of joint destruction with deformity or reduced range of motion or chronic draining sinuses. The affected joint is generally cold, and obvious cardinal signs of infection, such as erythema and warmth, are usually absent. Constitutional symptoms such as fever and weight loss are seen in about 30% [7]. In order to isolate mycobacteria, a Ziehl-Neelsen stain is used, but it is important to note that this has low sensitivity for detecting acid-fast bacilli. The diagnosis is most accurately established via synovial membrane biopsy with histopathology and culture [25].

Fungal Infections

Septic arthritis caused by fungal species usually has an indolent presentation. Similar to TB, this will be noted to have a persistent culture-negative oligo- or monoarthritis in the setting of relevant epidemiologic exposure. It is most commonly seen in those who are immunosuppressed. Fungal causes include sporotrichosis, coccidioidomycosis, and candidiasis. Diagnosis is established by a fungal stain and culture of synovial fluid or via synovial membrane histopathology and culture [26].

Viral Arthritis

Usually present with polyarthritis and joints are sterile. Patients usually present with systemic symptoms including fevers, myalgia, and rashes. Examples include dengue, chikungunya, Zika, parvovirus, and rubella.

Parvovirus

The spectrum of clinical disorders associated with B19 ranges from benign to life-threatening depending on age, hematologic status, and immunologic status of the host. Erythema infectiosum "fifth disease" is most common in children with fever, malaise, slapped cheek rash, and a maculopapular rash involving the trunk and limbs. Arthralgias may be seen in erythema infectiosum, but arthropathy usually

only presents in adults and is more prevalent in women. The arthritis can mimic rheumatoid arthritis and is typically a sudden onset symmetric polyarthritis primarily affecting the wrists, knees, ankles, and MCPs. The articular symptoms are usually brief in duration, but some do have prolonged symptoms that last weeks to years. The pathogenesis of arthritis in parvovirus is thought to be due to deposition of immune complexes in the synovial tissue because the onset coincides with appearance of B19-specific antibodies in the serum. Diagnosis is made by the presence of parvovirus IgM in serum. Treatment is supportive, and arthritis responds well to NSAID therapy [27].

Chikungunya

Chikungunya virus is a single-stranded RNA virus and is transmitted by the Aedes vector. Generally there are two phases of the virus; the initial acute phase of the disease is called chikungunya fever and presents with high fever, rash, headache, severe polyarthralgia, and myalgias. This is usually followed by episodic and debilitating joint pain with joint swelling, and these patients may also have associated fatigue, myalgia, depression, and cognitive disorders. The inflammatory arthritis will often present in the acute phase and is unremitting; however, there can also be a phase of temporary remission prior to the development of a persistent arthritis. The arthritis is usually a symmetric polyarthritis involving the PIPs, MCPs, wrists, ankles, and knees, but there have been additional reports of hip, shoulder, and temporomandibular joint involvement. The arthritis can mimic other forms of inflammatory arthritis, such as rheumatoid arthritis, and it has been suggested by the ACR that patients with rheumatic symptoms persistent for more than 3 months should be referred for evaluation and classification as rheumatoid arthritis, spondyloarthritis, or undifferentiated polyarthritis. These patients can be treated with DMARDS also [28].

Acute Lyme Arthritis

Caused by *Borrelia burgdorferi*. Acute monoarticular arthritis occurs in the setting of epidemiologic exposure in an endemic area. Erythema migrans, rash, fever, and migratory arthralgia may occur weeks or months prior. Diagnosis is usually established by serologic testing. The infection initially causes viral-like migratory arthralgia, followed by an intermittent oligoarticular arthritis that most commonly involves the knee but is also seen in other large joints. The diagnosis of Lyme arthritis can be made with a two-step serologic testing process involving enzyme-linked immunosorbent assay, followed by confirmation with a western blot or immunoblot test. *B. burgdorferi cannot* be cultured from synovial fluid, but PCR testing is positive in 85% of patients with Lyme arthritis, so this can also be used as a confirmatory test [29].

Less Common Pathogens

Meningococcal Arthritis

This usually develops several days into antibiotic therapy and the joint fluid is sterile. Patients present with an isolated septic joint or an arthritis dermatitis syndrome similar to that of gonococcal arthritis.

Mycoplasma/Ureaplasma

These infections usually occur in the setting of hypogammaglobulinemia or organ transplantation [30, 31].

Whipples (*Tropheryma whippelii*)

In the majority of cases, this causes a nondestructive peripheral arthritis preceding the onset of abdominal pain, diarrhea, malabsorption, and weight loss by a mean of 8 years. These patients are often HLAB27 positive. Accompanying symptoms also include fever, lymphadenopathy, cutaneous hyperpigmentation, and cardiac and neurologic involvement. In order to make a definitive diagnosis, a small bowel biopsy is needed to isolate the organism, but PCR of synovial fluid may also be used [32].

Brucella

This involves the sacroiliac joint in 54% and about 7% develop spondylitis. It occurs in countries where livestock are not vaccinated and unpasteurized dairy products are consumed [33, 34].

Prosthetic Joint Infections

Prosthetic joint infections occur in about 1% of knee and hip arthroplasties. These infections may lead to failure of the joint replacement [35]. Prosthetic joint infections are usually caused by gram-positive cocci, including coagulase-negative staphylococci and *S. aureus*. Risk factors for the development of prosthetic joint infections include previous fracture, seropositive rheumatoid arthritis, obesity, revision arthroplasty, and surgical site infections [36]. It is important to note that the intra-articular WBC cutoff values for a prosthetic joint infection may be as low as 1100. Another additional caveat making the diagnosis more difficult is the indolent

Table 5.2 Empiric antibiotic therapy for suspected bacterial arthritis [6]

Gram stain	Antibiotic
Gram-positive cocci	Vancomycin
Gram-negative cocci	Ceftriaxone
Gram-negative rods	Ceftazidime, cefepime, piperacillin/tazobactam, carbapenems. If penicillin allergic: aztreonam, fluoroquinolones
Negative gram stain	Vancomycin plus either ceftazidime or an aminoglycoside

clinical presentation. Antimicrobial treatment, debridement, exchange, or permanent removal of the prosthesis may be required. In some patients, long-term suppressive antimicrobial therapy may be warranted [37].

Treatment

Empiric therapy depends on the gram stain (see Table 5.2 for an approach to treatment therapy). Failure to initiate antibiotics within 24–48 hours of onset can cause subchondral bone loss and permanent joint dysfunction. Given the increasing importance of MRSA as a cause of septic arthritis, the initial regimen should generally include an antibiotic active against MRSA such as vancomycin, along with a drug active against gram-negative bacilli with anti-pseudomonal coverage if critically ill or have a higher risk of gram-negative infection such as the elderly, immunocompromised, or IVDU [7]. The duration of therapy in patients with non-gonococcal arthritis is typically 3 or 4 weeks, usually 2 weeks parenteral therapy followed by 2 weeks of oral therapy, tailored to the microbial organism [38].

Drainage should be performed in setting of septic arthritis. This can be in the form of a needle aspiration, arthroscopic drainage, or open surgical drainage. Surgical drainage is indicated for septic arthritis of the hip, failure to respond to antibiotics after 5–7 days of antibiotic therapy and arthrocentesis, and soft tissue extension of infection. Of note, there is no data to support the efficacy of surgical drainage over arthrocentesis [6, 39].

Prognosis and Complications

Predictors of mortality include age over 65, confusion at presentation, and polyarticular disease along with coexistent renal or cardiac disease and immunosuppression. Predictors of joint damage include age over 65, diabetes, and infection with beta-hemolytic strep [7]. If untreated, septic arthritis of the sternoclavicular or sacroiliac joint can lead to osteomyelitis as these are cartilaginous joints [10].

Questions

1. A 37-year-old male presents with 2 days of pain and swelling in his L knee. He recently returned from a trip to Seattle with his friends, where he had two sexual partners and denies using any form of contraception. He denies any history of gout, or episodes of podagral. His vital signs are T 37.9, BP 122/78, HR 66, RR 18, POx 100% on room air. His CBC, CMP, and uric acid are unremarkable and his ESR is 42. On physical examination, you note no other systemic manifestations including absence of rashes and tenosynovitis. His knee is warm, with limited range of motion, and a palpable effusion. You decide to perform an arthrocentesis. In addition to routine cell count, gram stain, culture, and sensitivity, what else would you do at this time?

   A. Empiric treatment with vancomycin for septic arthritis
   B. Send additional synovial fluid to be cultured on Thayer-Martin media
   C. Send fluid for crystal analysis
   D. Start oral prednisone for a presumed gout flare

   Correct answer: B
   A disseminated gonococcal infection (DGI) can comprise of two major clinical syndromes: the arthritis-dermatitis syndrome and a localized purulent arthritis without associated skin lesions. There are also patients who present with symptoms that overlap these two presentations. This patient has presented with the localized purulent arthritis. Gonococcus will not culture on basic culture media and therefore requires Thayer-Martin media or chocolate agar to culture, and the diagnosis can be missed in cases where this is not properly assessed. At this time, if clinical suspicion was high, it would also be appropriate to start systemic treatment with IV ceftriaxone [40].

   Vancomycin does not cover gram-negative enteric organisms or gonococcus, and monotherapy with vancomycin alone would not be appropriate treatment at this time.

   Though a diagnosis of gout should be considered in young males presenting with acute monoarticular joint pain, septic arthritis should always be ruled out first as treating with steroids could exacerbate the septic arthritis. In addition, the presence of crystals alone does not rule out a concomitant infection.
2. A 75-year-old male presents to your office with 3 days of left shoulder pain. He was recently discharged from the hospital after a 2-week stay for cellulitis, complicated by a CHF exacerbation. He was discharged to an inpatient rehab facility 8 days ago. On physical exam his shoulder appears erythematous and swollen, and it is warm to palpation, and he has severe pain and limitation on both active and passive range of motion. His vital signs are T 100.9, BP 110/80, HR 101, RR 20, POx 95% on room air. You perform an arthrocentesis in your office and send off preliminary lab testing, which returns as follows:

- WBC: 14.7
- Hgb: 10.8
- Plt: 200
- BUN: 32
- Cr: 1.50
- ESR: 90
- CRP: 7.9

Synovial fluid analysis:

- Cell count 52,000 w/ 68% neutrophils
- Gram stain: numerous gram-positive cocci in clusters
- Crystals: none
- Culture: pending

What is your next step in management?

A. Oral Bactrim with close follow-up.
B. Await final culture data until deciding which organism to treat for.
C. Admit to hospital for IV vancomycin and contact orthopedic surgery for potential washout.
D. Admit to hospital for IV cefazolin and contact orthopedic surgery for potential washout.

Correct answer: C
This man has multiple risk factors for methicillin-resistant *S. aureus* (MRSA) including age and recent hospitalization, and he is currently also residing in a nursing home. For this reason, he should be empirically treated for MRSA until the culture data and sensitivities return [7]. Cefazolin does not cover for methicillin-resistant *S. AUREUS*.

Oral Bactrim would be inappropriate, as septic arthritis should always initially be treated with parenteral antibiotics as well as drainage.

Septic arthritis represents a medical emergency and should be treated with empiric antibiotics if there is any clinical suspicion, until an alternative diagnosis is made or infection is ruled out; therefore, it would not be correct to wait to treat until the culture data returns.

3. A 46-year-old male with a history of NIDDM presents with lower back pain for 2 months. He is a farmer and occasionally helps out his younger brothers on a farm in Mexico. He has not visited this farm in 2 years, but states that when he last returned 2 years ago, he had a 2-week flu-like illness. He states the pain is localized to the right buttocks and is most severe when he wakes up in the morning, usually feeling stiff for about 2 hours. He denies any other joint pain. You obtain radiographs of his lumbosacral spine and sacroiliac joints which reveal sclerosis and pseudo-widening at the right sacroiliac joint but are otherwise unremarkable.

What is the most likely pathogen?

A. *Brucella*
B. *E. coli*
C. *S. aureus*
D. *Pasteurella multocida*

Correct answer: A
Patient presents with sacroiliitis and a history of travelling to a farm in Mexico followed by a flu-like illness. This organism is most commonly found in those exposed to unpasteurized milk products. *Brucella* will usually present with a classic flu-like illness with fevers, myalgias, and arthralgias, and, if untreated, long-term complications can result in endocarditis, orchitis, and sacroiliitis [33, 34].

The other organisms mentioned are not typical pathogens that cause sacroiliitis.

4. A 27-year-old female who works as a nanny presents with diffuse joint pain in her MCPs, PIPs, and wrists as well as the MTPs. This started 4 days ago. She states that her joints feel stiff. She states she has also been feeling unwell and reports she measured her temperature yesterday and it was 100.4. She has no visible rashes, and her preliminary lab workup is essentially unremarkable with the exception of a low WCC 3.0 and an ESR of 50. Two days later, her parvovirus IgM returns highly elevated. You call her to discuss the results, and she is concerned about developing deformities in her joints.

   What do you tell her with regard to the long-term outcome?

   A. She is at increased risk of developing rheumatoid arthritis.
   B. She will likely develop some deformities in her MCPs.
   C. There is no risk of the development of deformities after a parvovirus infection.
   D. She is at increased risk for developing lupus.

   Correct answer: C
   Patient presents with an acute parvovirus B19 infection, which can present with a polyarticular arthritis or arthralgias, mainly affecting the small joints of the hands and feet, as well as knees and wrists. This can mimic many other forms of arthritis such as rheumatoid arthritis and Jaccoud's arthritis in SLE; however, these patients will not develop deformities or erosions, and the articular symptoms should resolve in less than 6 weeks [41].

5. The following is a predictor of joint damage in patients with septic arthritis:

   A. Diabetes
   B. Infection with MRSA
   C. Confusion at presentation
   D. Polyarticular disease

Correct answer: A
Diabetes is a predictor of joint damage in patients with septic arthritis. Confusion at presentation and polyarticular disease are predictors of mortality [7].

6. Which of the following organisms would be expected to present with a lower cell count in synovial fluid?

   A. *Neisseria gonorrhoeae*
   B. *S. aureus*
   C. *S. pneumoniae*
   D. *Borrelia burgdorferi*

   Correct answer: A
   Patients with *Neisseria gonorrhoeae* can present with lower synovial fluid counts, sometimes in the inflammatory range. For this reason, in the appropriate clinically setting, a high index of suspicion should remain for a septic arthritis due to gonococcus and appropriate, and evaluation and treatment should be performed.

7. A 26-year-old female returns to your office for follow-up. One month ago you diagnosed her with Lyme arthritis after she presented with monoarticular swelling in her knee in the setting of a recent tick bite and positive western blot. You treated her with a 28-day course of doxycycline 100 mg BID, and she returns today reporting suboptimal improvement.

   What is your next step in management?

   A. Admit for IV ceftriaxone.
   B. Reassurance and supportive care with NSAIDs.
   C. Repeat with another course of doxycycline 100 mg BID for 28 days.
   D. Amoxicillin 500 mg BID for 30 days.

   Correct answer: C
   According to the Infectious Disease Society of America, patients with Lyme disease should be treated with a 30-day course of oral doxycycline 100 mg twice daily or amoxicillin 500 mg three times daily. If there is residual joint swelling after a 30-day course of oral antibiotics, then it is advised to repeat the oral regimen for another 30 days. If this second antibiotic course does resolve the arthritis, patient should be admitted for IV ceftriaxone. Of note, there is no added efficacy of treating with amoxicillin over doxycycline [42].

8. A 37-year-old male who recently moved to the United States from Bangladesh presents to your office with 3 weeks of pain and swelling in his MCPs and wrists bilaterally. Two months ago he developed a dry cough and notes intermittent fevers, but he has not been to see a doctor since this began.

   He is currently afebrile, BP 101/78, HR 88, RR 18, pOx 95% on room air. On physical exam there is a notable symmetric polyarthritis involving the MCPs, PIPs, and wrists without visible deformities. There are reduced breath sounds in the right upper lobe.

What is the next step in evaluating this patient?

A. Check RF and CCP.
B. Check hepatitis serologies.
C. Check quantiferon and chest XR.
D. XR of bilateral hands.

Correct answer: C
Poncet's disease is a form of reactive arthritis that develops in patients with active tuberculosis (TB). It is a nondestructive para-infective symmetric polyarthritis that can present in a similar nature to RA, predominantly involving the MCPs, PIPs, and wrists. PD is essentially a diagnosis of exclusion and requires a high degree of clinical suspicion. The dramatic response of arthritis in PD on starting anti-tubercular treatment substantiates the diagnosis [43].

9. A 44-year-old women who works at a daycare presents low-grade fevers to your office. She has rheumatoid arthritis and is currently taking methotrexate 25 mg weekly and adalimumab 40 mg SQ every 2 weeks and has recently tapered off a 3-month course of prednisone. Given her immunosuppression, you send her to the hospital for further evaluation. She gets admitted and found to be parvovirus B19 positive. Given her level of immunosuppression, which treatment could exacerbate her joint and cutaneous symptoms?

A. Tacrolimus
B. Prednisone
C. Indomethacin
D. IVIG

Correct answer: C
In patients who are immunosuppressed, including those treated with chronic corticosteroids and biologic therapy, parvovirus may not present with the classic symptoms and signs and may only manifest with fever. In these cases, treatment with IVIG could exacerbate the musculoskeletal and cutaneous manifestations of parvovirus [27].

10. A 26-year-old female presents to your office after a trip to the Caribbean. She presents with fever to 101, a diffuse maculopapular rash, arthralgias, and periorbital pain. After discussion with your colleague who is an infectious disease specialist, you send off viral serologies which return positive for both dengue fever and chikungunya. Her most debilitating symptom is her arthralgia and she asks you what she can take for pain. What would you recommend for her to take at this time?

A. Indomethacin
B. Acetaminophen
C. High-dose aspirin
D. Ibuprofen

Correct answer: B
In cases of a co-infection of parvovirus with dengue fever, aspirin or NSAIDs can exacerbate the hepatitis and bleeding complications associated with dengue fever and should be avoided [28].

Key Points

- Septic arthritis is a true rheumatologic emergency requiring prompt surgical evaluation.
- Bacterial infections are usually monoarticular and the knee is the most common joint involved.
- Bacterial infections are the most prevalent, of which *S. aureus* being the most common organism, with the incidence of MRSA on the rise.
- Multiple viral infections can mimic inflammatory arthritis as the arthritis is present mostly in the smaller joints in the hands and feet; these joints are often sterile.
- Gonococcal arthritis should be considered in young patients presenting with monoarticular knee arthritis, particularly if there is coexisting tenosynovitis or skin lesions.
- Fungal infections usually have an indolent presentation, considered in immunosuppressed.
- Prosthetic joint infections are usually caused by GPCs and may present with lower cell counts and a more indolent presentation.
- In the immunosuppressed population, the presentation may be atypical, with absence of fever or classic erythema, warmth, and limited range of motion.
- The most important step in both evaluation and for guiding treatment is arthrocentesis in order to identify the organism and rule out differential diagnoses such as crystalline arthritis.
- Empiric antibiotic therapy should be started immediately following aspiration to avoid subchondral bone loss and permanent joint dysfunction.
- Involvement of orthopedic surgery early on is necessary for drainage of the involved joint.

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Chapter 6
Rheumatoid Arthritis

Saleha Riaz and Apostolos Kontzias

Epidemiology

Rheumatoid arthritis is a systemic, chronic, autoimmune inflammatory arthritis that primarily involves diarthrodial joints affecting twice as many women as men with a mean age of 40–60 years. It afflicts all races worldwide with a higher prevalence observed in Native Americans.

Pathophysiology

Our knowledge with regard to the etiopathogenesis of rheumatoid arthritis has expanded over the past two decades. The phenotype of rheumatoid arthritis is exerted by the interplay of perturbed innate and adaptive immunity pathways triggered by environmental stimuli in a genetically susceptible host [1].

Genetics

A direct role of genetic inheritance is suggested by twin studies in which the concordance rate is approximately 15% when one twin is affected, compared with 1% for the general population [2].

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Additional early evidence of genetic susceptibility in RA belies in the presence of HLA-DR4 (an MHC II molecule) in 70% of patients with RA, compared to about 30% of control subjects rendering a fourfold to fivefold relative risk of RA in people who possess it. More recent studies have accurately specified that the epitope is in the third hypervariable region of DRβ chains, from amino acids 70 through 74 in up to 96% of patients. The sequence called *shared epitope* found in DRB∗0401, DRB∗0404, DRB∗0101, and DRB∗1402 loci is glutamine–leucine–arginine–alanine–alanine (QKRAA), and it is a predictor of extra-articular erosive disease. The cognate antigen recognized by the epitope is yet to be elucidated [3].

There are two prevailing hypotheses on the role of the epitope in RA pathogenesis. The first suggests that the epitope serves as an autoantigen and by way of molecular mimicry generates an autoreactive T- cell response. This is corroborated by the presence of the same sequence on viral proteins such as the gp110 of the Epstein–Barr virus (EBV). Alternatively, the shared epitope modulates the T-cell repertoire by binding more avidly citrullinated peptides such as vimentin, fibronectin, and α-enolase that are known to possess properties contributing to RA pathogenesis. Specifically, citrullinated peptides (as opposed to non-citrullinated peptides) bound to the HLADR are more efficiently presented in T cells, and this leads to an enhanced proinflammatory response with higher IL-17 and interferon-gamma (IFNγ) production [3].

More recently, genome-wide association studies (GWAS) have implicated non-MHC alleles contributing to genetic susceptibility such as single nucleotide polymorphisms (SNP) in the promoter of tumor necrosis factor (TNF), the TNF gene itself, Fc receptor, and interleukin 6 (IL-6) [1]. The relative risk that these confer is not as strong compared to HLADR4 but interestingly these are located in regions resulting in products well embedded in the pathophysiology of RA. Another reported association exists in SNPs of genes that are involved in the post-translational modification of arginine to citrulline (Peptidyl arginine deiminase, type I or *PADI* genes). SNPs in PADI genes confer a twofold risk in RA susceptibility especially in Asian populations and provide a link between the enhanced T cell recognition of citrullinated peptides in RA patients who possess the shared epitope. Interestingly, the presence of antibodies to citrullinated protein antigens (ACPAs) and HLADR4 is associated with more aggressive disease, yet in early undifferentiated arthritis cohorts, presence of ACPAs was associated with disease progression irrespective of HLADR4 presence suggesting that the role of susceptibility loci is more complex [4].

Environmental Triggers

There is robust evidence that cigarette smoking, obesity, and microbiome perturbations are directly and indirectly involved in RA pathogenesis. In the preclinical phase of RA, smoking induces the expression of *PADI* genes in the mucosal airways and enhances peptide citrullination generating ACPAs. There is a known synergistic effect of smoking and HLADR4 in increasing the risk of RA by 40-fold [5].

Mucosal surfaces in airways, gut, and oral mucosa are considered to be the primary sites where break of tolerance occurs. *Porphyromonas gingivalis* causing periodontitis facilitates local peptide (fibronectin) citrullination and preliminary studies have shown that periodontal treatment decreases levels of antibodies to *Porphyromonas gingivalis* and citrulline in patients with rheumatoid arthritis and periodontitis [6]. Endogenous protein alteration by microbiome renders these proteins immunogenic instructing adaptive immune responses.

There is an increasingly recognized role of innate immunity on initiating inflammatory cascades in RA based on the clinical observation that infectious agents can trigger an RA phenotype. This is accomplished by direct impact on synovium and recognition from pathogen-associated pattern recognition receptors (PARPs) or via molecular mimicry [7]. Well-known infectious agents causing a clinical picture resembling RA include parvovirus B19, EBV, and Mycoplasma. Toll-like receptors expressed on the surface of innate immune cells within the synovium once engaged by structural components of infectious agents trigger or exacerbate arthritis as evidenced in preclinical models. Additionally, TLR engagement provides the first signal for the activation of inflammasome. One of the best characterized inflammasomes is the NLRP3. NLRP3 is an intracellular multiprotein complex which is highly expressed in fibroblast-like synoviocytes and peripheral blood cells of RA patients. It possesses caspase-1 which converts inactive pro-IL1β to IL1β. This line of evidence justifies the use of anakinra an interleukin 1 receptor antagonist in the treatment of RA.

The role of estrogens based on the 2:1 to 3:1 prevalence ratio of female-to-male patients has been long postulated. Additionally, the majority of pregnant patients with RA remit even though most of them flare upon delivery. The exact mechanisms of hormonal fluctuations and networks contributing to RA remain to be determined.

Serologic Evidence of Autoimmunity

The predominant school of thought is that RA represents a continuum of a process which starts at the humoral level before it becomes clinically apparent affecting articular and extra-articular structures. Rheumatoid factor (RF) which is an autoantibody (predominantly IgG or IgM) that binds to the Fc portion of IgG provided initial direct evidence of autoimmunity playing a role in RA. Seventy-five percent of patients have a positive RF and are more likely to have severe disease.

Subsequently, identification of ACPAs in RA patients was a seminal discovery with prognostic implications. They are present in 80–90% of patients with established RA and they are 95% specific as opposed to RF which carries a specificity of about 85%. In the setting of undifferentiated early arthritis, ACPAs predict progression toward RA. More recently antibodies against carbamylated proteins are discovered which are highly specific and notably present in up to 10% of ACPA-negative RA patients. In prospective cohorts, these autoantibodies are shown to be present in up to 40% of clinically asymptomatic patients who eventually evolve into RA adding to the notion that the disease is a clinical continuum.

Synovial Histopathology

Histopathologic hallmarks of RA are synovial intimal lining hyperplasia and presence of mononuclear cells, especially T cells and macrophages within the synovium. Normally, synovial lining is a thin layer comprised of two cell types: a macrophage-like synoviocyte (type A synoviocyte) and an FLS (type B synoviocyte). In response to inflammatory molecules such as Platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β, TNF, and IL-1 both cell types proliferate. The proliferative synovium is called *pannus*. FLS express surface molecules such as VCAM-1 which act as chemoattractants for macrophages retained in the intimal lining. The histopathologic architecture of synovial lining in RA is maintained by the adhesion molecule cadherin -11 expressed by FLS [8]. Within RA synovium, FLS acquire properties akin to locally invading tumors such as defective contact inhibition and expression of proto-oncogenes typically observed in tumor cells. Their ability to circulate via lymphatics and blood stream is similar to the metastatic capacity of malignant cells and provide a potential mechanism explaining the polyarticular nature of RA [9]. Thirty to fifty percent of synovial cells are composed of T cells the majority being CD4. B cells and plasma cells constitute 5% of cellular composition and often lymphocytes are structured within lymphoid aggregates in up to 20% of RA patients. Macrophages and dendritic cells may be present peripherally as seen in true germinal centers.

Cytokine Perturbations

RA pathogenesis is driven by cytokines generated by both innate immune cells such as macrophages and adaptive cellular players such as different T cell subsets. Synovial fibroblasts and macrophages are major sources of the pro-inflammatory cytokines IL-1, IL-6, TNF, IL-18, IL-33, and granulocyte–monocyte colony stimulating factor (GM-CSF). Many of these have been the target of a number of successful therapeutic agents. Counter-inflammatory cytokine networks within the synovium such as IL-1 receptor antagonist, IFNβ, and IL-10 fail to provide a checkpoint in the inflammatory cascade. Additionally, T cell-driven cytokines such as IFN-γ and IL-17 produced by Th1 and Th17 cells, respectively, are considered to play a central role in initiating and perpetuating synovitis as well as contributing to osteoclast activation leading to erosive disease. Suppression of Th2 pathway further contributes to cytokine milieu imbalance. Increasing knowledge of the intricate cytokine signaling via intracellular pathways such as Janus kinase and the signal transducers and activators of transcription (JAK/STAT), mitogen-activated protein kinases (MAPK), and nuclear factor-κB (NF-kB) have led insofar to the successful use of JAK inhibitors tofacitinib and baricitinib in RA [10].

Diagnosis Versus Classification Criteria

Diagnosis of RA is made on clinical grounds based on history and clinical examination in conjunction with laboratory parameters and at times synovial fluid analysis. Tenderness, swelling, and warmth of small joints and medium-size joints in hands, feet, wrists, and ankles along with prolonged morning stiffness usually more than 60 minutes are a typical presentation. Constitutional symptoms such as fatigue or low-grade fever may be reported but high fever should prompt alternative diagnoses. Examination is consistent with synovitis and impaired active and passive range of motion (ROM). Periarthritis referring to inflammation of periarticular structures such as tendons, bursas may yield symptoms and signs upon active ROM as opposed to passive ROM. A number of inflammatory conditions need to be entertained in the differential diagnosis as discussed below. Classification criteria serve as a way to generate homogeneous patient populations for clinical trial purposes, yet low specificity suggests that they should not be interchangeably used for diagnosis. According to the American College of Rheumatology and European League against Rheumatism, RA classification requires patients to have ≥6 out of 10 points (Table 6.1). The criteria demonstrate a sensitivity of 96% and specificity of 55% [11]. This set of criteria replaced the 1987 criteria so as to capture earlier disease in addition to incorporating serologic profile and markers of inflammation. Both criteria require at least 6 weeks of symptomatology to eliminate the possibility of alternative self-limited processes such as viral syndromes. Some patients will not meet the criteria for RA and have undifferentiated arthritis. Over time, 33% will progress to RA, 33% will have remission, and 33% will meet the criteria for other inflammatory arthropathy.

Table 6.1 2010 RA classification criteria

2010 ACR/EULAR classification criteria for RA	
Joint involvement	*0–5 points*
1 medium/large joint	0
2–10 medium joints	1
1–3 small joints	2
4–10 small joints	3
>10 joints	5
Serology	*0–3 points*
Negative RF and negative ACPA	0
Low positive RF or low positive ACPA	2
High positive RF or high positive ACPA	3
Acute phase reactants	*0–1 points*
Normal ESR and normal CRP	0
Abnormal ESR or abnormal CRP	1
Duration of symptoms	*0–1 point*
<6 weeks	0
≥6 weeks	1

Differential Diagnosis

Rheumatoid arthritis must be differentiated from a number of other disorders. Many connective tissue diseases, seronegative spondyloarthropathies, infection-related reactive arthropathies, and endocrine related disorders may have symptoms in common with rheumatoid arthritis and thus should be part of the differential diagnosis when considering rheumatoid arthritis. Ten percent of RA patients may present in an asymmetric oligoarticular fashion. Inflammatory back pain affecting lumbarsacral spine and sacroiliac joints is not part of the clinical picture but cervical spine involvement is seen in up to 50% patients especially with advanced disease [12]. Thirty percent of patients may present with palindromic symptoms defined as fleeting up to 72 hours of inflammatory arthropathy. Up to 50% of them are seropositive (either RF and/or CCP positive) and may progress to develop typical RA symptoms and signs [13]. Palindromic rheumatism needs to be differentiated from crystal arthritis and viral syndromes. PMR usually affects proximal joints but it can affect peripheral joints in up to 50% of patients. Systemic symptoms to include fever, rash, lymphadenopathy should dictate work up for viral infections or Still's disease. Fibromyalgia may present with diffuse pain affecting muscles and joints along with fatigue and sleep disturbances and may superimpose inflammatory symptoms in RA patients. Reaching an accurate diagnosis requires a careful examination focusing on identifying synovitis and enthesitis, along with directed imaging to unravel other common causes of regional pain syndromes or post-inflammatory osteoarthritis paired with labs such as ESR and CRP.

Clinical Presentation

Patients with rheumatoid arthritis can present in several ways. The typical presentation, in about 50% of the patients, is the insidious onset of arthritis symptoms with number of joints increasing. However, patients can present in subacute, acute, and variant patterns. Palindromic symptoms affect joints in a migratory fashion with resolution of 72 hours, only for these to recur in random intervals either in the same or different joint. Arthritis robustus reflects an often relatively asymptomatic presentation usually in men causing bulky, erosive arthritis with deformities.

The joints most commonly affected in rheumatoid arthritis in decreasing frequency include metacarpophalangeals, proximal interphalangeal, wrists, knees, shoulders, metatarsophalangeals, ankles, cervical spine, elbows, hip, and temporomandibular joints. Smaller joints are usually symptomatic first. Involvement of the sacroiliac, thoracic, and lumbar spine is rare in rheumatoid arthritis.

Hand deformities are common in patients with rheumatoid arthritis (Fig. 6.1). The most common ones are ulnar deviation with radial deviation of the wrist causing ulnar deviation of fingers; swan neck deformity with flexion of the MCP joint, hyperextension of PIP, flexion of DIP joint; boutonniere deformity with flexion of

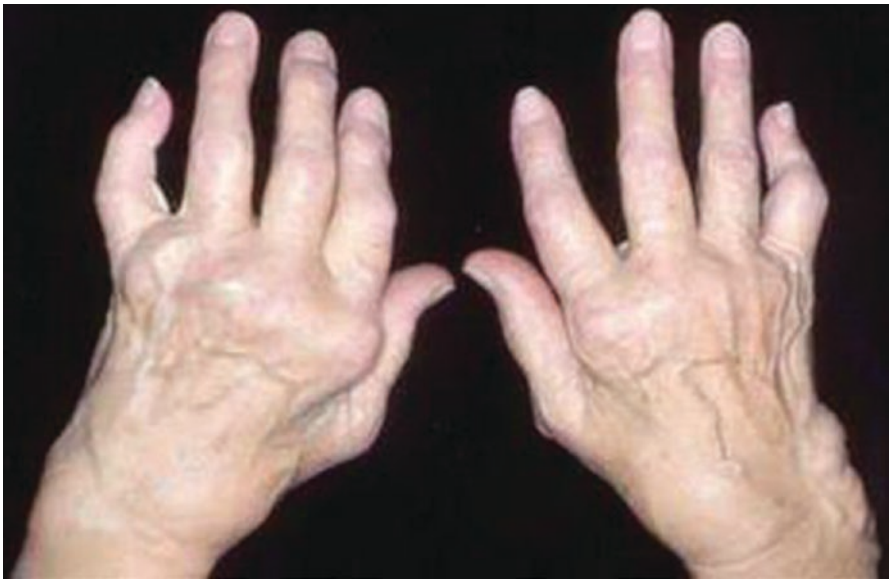

Fig. 6.1 Cardinal clinical features of RA include bilateral radial deviation of the wrists, symmetric MCP synovial thickening with ulnar deviation of fingers, interosseous muscle atrophy, early boutnniere deformity of right second digit and hitchhiker thumb on the right

the PIP, hyperextension of the DIP joint; hitchhiker thumb with hyperextension of the IP joint, flexion of MCP, and adduction of first metacarpal.

Cervical spine involvement is seen in 30–50% of patients with C1–C2 the most commonly affected level. It can lead to instability and potential impingement of the spinal cord as a result of subluxation, compression, and subaxial involvement. C1–C2 anterior subluxation >3 mm can lead to spinal cord impingement or compression. In C1–C2 compression there is cephalad movement of odontoid into the foramen magnum potentially leading to impingement of brain stem. Subaxial involvement usually at C2–C4 levels occurs later than other forms of cervical involvement. Neurologic symptoms such as paresthesias, loss of bowel or bladder control, loss of fine motor skills and new onset neck stiffness and pain should prompt urgent work up.

Rheumatoid nodules are present in 30% of patients with RF-positive RA and occur over pressure points typically extensor surface of the forearms, olecranon bursa, sacrum, occiput, heels, and fingers. Other common conditions to consider in a patient with arthritis and subcutaneous nodules include granuloma annulare, tophaceous gout, SLE, multicentric reticulohistiocytosis, calcinosis (as part of limited systemic sclerosis), and rheumatic fever. Rheumatoid nodules are composed of a central area of fibrinoid necrosis surrounded by histiocytes and connective tissue (Fig. 6.2). Small vessel vasculitis is to be the underlying culprit. Ten percent of patients treated with methotrexate can rapidly develop nodules often referred to as accelerated nodulosis. Discontinuing methotrexate often leads to nodule resolution.

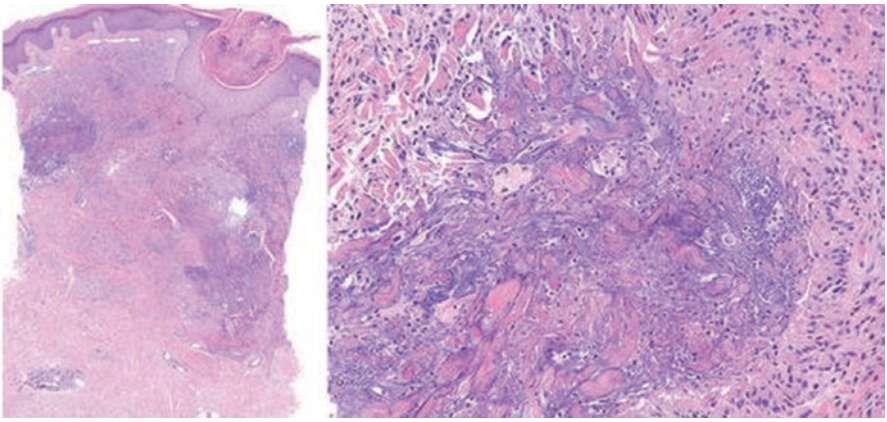

Fig. 6.2 Histopathology of a rheumatoid nodule depicts central fibrinoid necrosis with peripheral histiocytes and lymphocytes

Table 6.2 Extra-articular manifestations of rheumatoid arthritis

General	Low grade fever, fatigue, weight loss
Cardiac	Pericarditis −50%, myocarditis, coronary vasculitis, atherosclerotic disease
Pulmonary	Pleuritis (20%), nodules, pulmonary fibrosis, bronchiolitis obliterans (uncommon but poor prognosis), cryptogenic organizing pneumonia (COP formerly known as bronchiolitis obliterans with organizing pneumonia-BOOP), cricoarytenoid arthritis, ILD-UIP (Usual Interstitial Pneumonia most commonly, and NSIP (nonspecific interstitial pneumonitis less common)
Hematologic	Anemia, thrombocytosis, Lymphomas, Felty syndrome, large granular lymphocyte syndrome (LGL syndrome)
Renal	Reactive amyloid, membranous glomerular nephropathy
Neurological	Entrapment neuropathy, peripheral neuropathy, mononeuritis multiplex, cervical myelopathy
Dermatologic	Subcutaneous nodules
Ocular	Keratoconjunctivitis sicca, episcleritis, scleritis, uveitis, vasculitis
Vascular	Leukocytoclastic vasculitis, small arteriolar vasculitis, medium vessel vasculitis, pyoderma gangrenosum

Extra-articular manifestations (Table 6.2) occur in up to 50% of RA patients more commonly the seropositive ones and confer poor prognosis. Most common ones include pulmonary such as pleuritis, interstitial lung disease (more commonly UIP pattern), cardiac such as pericarditis, dermatologic such as subcutaneous nodules and vasculitis. Renal, neurologic, and ocular manifestations are relatively less common. Hematologic stigmata include anemia and thrombocytosis and rarely Felty's syndrome constituting a triad of RA, splenomegaly, and neu-

tropenia. It is seen in 1% of RA patients with longstanding severe, seropositive disease and may be accompanied by hepatomegaly, thrombocytopenia, lymphadenopathy, and fevers. Complications include bacterial infections and non-healing ulcers along with a 13-fold increased risk of development of non-Hodgkin's lymphoma. A clinically similar syndrome named large granular lymphocyte syndrome (LGL syndrome) is associated with leukopenia and presence of large granular lymphocytes in the peripheral blood and bone marrow. These cells are predominantly activated cytotoxic T cells and natural killer (NK) cells. LGL is not specific for RA and is observed in SLE, myelodysplastic syndromes requiring low threshold for extensive work up to discern the diagnosis. Treatment for both syndromes in the context of RA should be directed toward the underlying autoimmune process [14].

Laboratory Tests

The typical laboratory findings present in RA include anemia and thrombocytosis, elevated ESR and CRP. However, these represent nonspecific markers of inflammation and can be elevated in the setting of infection, tissue injury, and malignancy. Rheumatoid factor (RF) is positive in 70–80% of patients. RF positivity is associated with severe disease, extra-articular manifestations, and increased mortality. RF titer does not correlate with disease activity. Elevated anti-CCP antibodies are present in 80–90% of patients highly specific for RA (95%) and are associated with severe, erosive disease. Nonspecific elevation of antinuclear antibodies (ANA) is observed in 30% of patients.

Synovial Fluid Analysis

Synovial fluid (SF) is inflammatory (WBC count >5000) predominantly composed of polymorphonuclear cells as opposed to synovial tissue where neutrophils are rare. SF is also comprised of T cells with CD8/CD4 at an inverse ratio compared to the pannus and peripheral blood.

Radiographic Features

The radiographic hallmarks of rheumatoid arthritis are soft tissue swelling, periarticular osteoporosis, joint space narrowing, marginal erosions with potentially subluxation of joints (Fig. 6.3). Soft tissue swelling can result from tenosynovitis

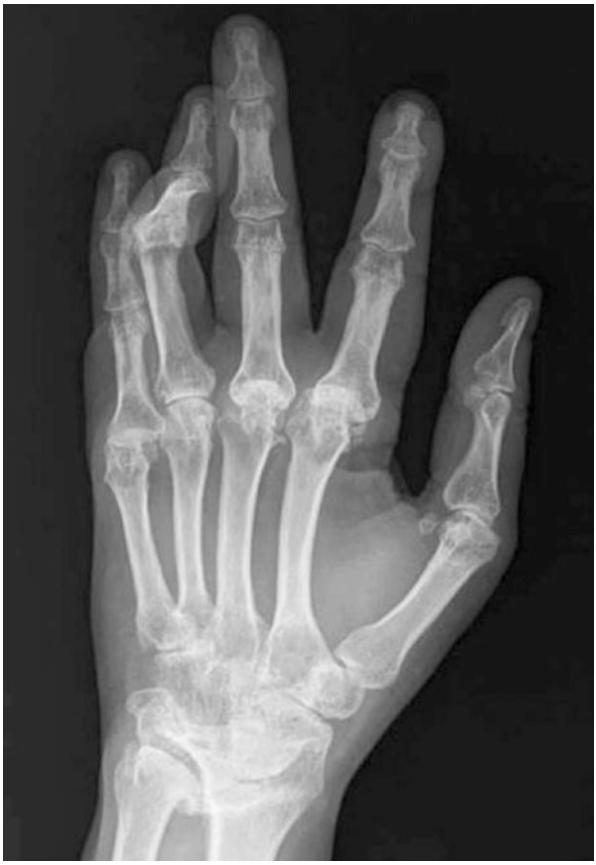

Fig. 6.3 Classic findings on hand XRs in RA include periarticular osteoporosis, joint space narrowing in 2nd and 3rd MCPs and carpal joints which has resulted in carpal fusion. Marginal erosions can be seen such as in the 4th and 5th MCPs. Boutonniere deformity can be seen in the 4th digit

and joint effusions. Common joints for early erosions include 2nd and 3rd MCPs and 1st and 5th MTP. Ultrasound and MRI may detect erosions not radiographically apparent in early RA. Four patients need to be screened with US in order to detect an additional patient with an erosion in comparison with conventional radiographs [15].

Therapeutic goals

The treatment of rheumatoid arthritis has evolved and changed dramatically during the past 20 years. Therapeutic goals include early diagnosis and treatment focusing on low disease activity or remission according to validated disease activity scores. Targeting low disease activity is accomplished by using disease modifying

anti-rheumatic drugs (DMARDs)- both conventional and biologic. By definition, a DMARD has the ability to change the course of RA and retard radiographic progression.

Strategies to achieve remission vary from patient to patient depending on severity and presence of extra-articular manifestations, comorbidities, patient preferences, and cost. Clinically available validated instruments to monitor RA activity incorporate tender and swollen joint count, labs, and patient and physician assessment of disease activity. Examples include Disease Activity Score in 28 joints (DAS28), Clinical Disease Activity Index (CDAI), and Routine Assessment Patient Index Data (RAPID) scores. No tool has advantage over the other and selection is influenced by resource setting and ease of application within the clinic.

Treatment

There is an urgent need to identify predictors of response to treatment on individual patients as the known adverse prognostic factors for aggressive disease do not always inform about viable treatment options.

Treatment of DMARD-Naive Patients: Monotherapy Versus Combination Therapy

The decision of which DMARD to initiate at the individual patient level is complex depends on the clinical situation. Starting with DMARD monotherapy is well substantiated by the TICORA, BeST, and TEAR trials [16, 17]; MTX is the initial DMARD prescribed for the majority of patients. It is inexpensive, well tolerated, and improves survival rates. MTX is usually administered orally at first or subcutaneously to improve bioavailability in sub-optimally treated patients at doses 20–25 mg weekly. Combination therapies at the onset result in earlier remission (e.g., within 6 months in TEAR trial) but at 2 years clinical and radiographic parameters are similar to the monotherapy. Long-term radiographic data beyond 2 years are needed to assess outcomes on combination regimens. It is key to note that patients who fail to achieve remission within 6 months of initial treatment (either combination or monotherapy) they require escalation. Based on the BeST trial switching between DMARDs is not effective compared to transitioning to combination regimens. Switching to biologics in patients with active disease who are receiving triple therapy provides additional benefit, as does switching to triple therapy in patients with active disease despite taking MTX and biologics. A cost-effective combo therapy ("triple therapy") is methotrexate, hydroxychloroquine, and sulfasalazine at maximum tolerated doses (see Table 6.3).

Table 6.3 Therapeutic agents for treatment of rheumatoid arthritis

DMARD	Mechanism of action	Dose	Side effects	
Conventional agents				
Hydroxychloroquine	Increases lysosomal pH in antigen presenting cells and blocks TLR signaling	200–400 mg/day <5 mg/kg	Nausea, rash, retinopathy	
Sulfasalazine	Converted into sulfapyridine and 5-ASA. Sulfapyridine has antinflammatory and immunomodulatory properties	1–3 grams/day	Nausea, rash, cytopenia	
Methotrexate	Folic acid antagonist, decreases pyrimidine synthesis, increases release of adenosine, disrupts cellular functions by inhibiting transmethylating enzymes	7.5–25 mg/week PO, SQ, IM	Nausea, diarrhea, alopecia, elevated liver enzymes, myelosuppression, pneumonitis	Teratogenic
Leflunomide	Converted into teriflunomide, inhibits synthesis of pyrimidine-ribonucleotide uridine monophosphate pyrimidine (rUMP).	10–20 mg/day	Nausea, diarrhea, alopecia, elevated liver enzymes	Teratogenic
Biologic agents				
TNF antagonist			Injection site/ infusion reaction, latent TB reactivation, opportunistic infections	Increased risk malignancy, demyelinating disease, autoimmune phenomena, CHF
Etanercept	Dimeric, soluble, TNF receptor that binds TNF-a, TNF-b	50 mg/weekly SQ		
Adalimumab	Fully human IgG monoclonal AB that binds soluble and transmembrane TNF-a.	40 mg SQ every other week		
Infliximab	Chimeric mouse-human monoclonal AB that binds TNF-a	Loading dose 3 mg/kg IV at week 0,2,6 and then every 8 weeks Dose can be increased to 5–10 mg/kg every 4 weeks		
Certolizumab	Recombinant, humanized anti-TNF monoclonal AB	400 mg SQ at week 0,2,4 then 200 mg every 2 weeks		
Golimumab	Fully human IgG monoclonal AB that binds soluble and transmembrane TNF-a.	50 mg SQ every 4 weeks 2 mg/kg IV 0,4 weeks and then every 8 weeks		

Table 6.3 (continued)

DMARD	Mechanism of action	Dose	Side effects	
Costimulatory modulator				
Abatacept	CTLA4 agonist	125 mg SQ weekly <60 kg: 500 mg IV 60–100 kg: 750 mg IV >100 kg: 1000 mg IV Every 4 weeks	Infusion reaction, infection	Caution in COPD
IL-6 receptor antagonist				
Tocilizumab	Monoclonal antibody against IL-6R	<100 kg: 162 mg SQ every other week >100 kg: 162 mg SQ weekly IV: 4 mg/kg every 4 weeks Can be increased to 8 mg/kg every 4 weeks	Infusion reaction, elevated liver enzymes, cytopenia, Lipid abnormalities	Increased risk for GI perforation
Small molecules				
Tofacitinib	JAK 3/JAK1 inhibitor	5 mg bid PO	Nasopharyngitis, diarrhea, Headache, elevated liver enzymes, cytopenias	Increased risk for Herpes Zoster
Baricitinib	JAK 1/JAK2 inhibitor	2 mg daily PO	GI perforations, hematologic and hepatic toxicity, lipid abnormalities, thrombosis, latent TB reactivation	
Anti CD-20				
Rituximab	Monoclonal antibody against CD20 antigen	1000 mg IV repeated once 2 weeks later then every 6 months	Infusion reaction	Increased risk for viral infections, hypogammaglobulinemia, cytopenia
IL-1 inhibitors				
Anakinra	IL-1 receptor antagonist	100 mg SQ daily	Injection site reaction, cytopenia	

Abbreviations: *TLR* toll-like receptor, *5-ASA* 5-aminosalicylic acid, *PO* per os, *SQ* subcutaneously, *IM* intramuscular, *TNF* tumor necrosis factor, *AB* antibody, *CTLA4* Cytotoxic T-Lymphocyte Associated Protein 4, *JAK* Janus activation kinase

Introduction of Biologics

MTX remains the anchor drug on any RA regimen. Evidence on the decision to add conventional DMARDs as opposed to biologics stems from the RACAT trial which suggests that adding conventional therapies to MTX is not inferior to first adding biologic agents to MTX [18]. In SWEFOT trial, an open label trial on MTX treated active RA patients comparing adding sulfasalazine and hydroxychloroquine with infliximab, there was no difference in clinical responses and work disability at 2 years [19]. Being one of the first classes of biologics used to treat RA, TNF inhibitors are usually prescribed as first-line biologics, yet other biologics can also be used and agent selection is dependent on comorbidities, patient preferences, and cost. For example, the ORBIT trial showed that initial treatment with rituximab is non-inferior to initial TNF inhibitor treatment in patients seropositive for rheumatoid arthritis and naive to treatment with biologicals and is cost saving over 12 months [20].

Treatment of Refractory Patients Despite TNF Inhibition

Any patient who is deemed resistant to first line DMARDs and first choice of biologic requires careful review of previous treatments to ensure patients were appropriately managed. Specifically, maximum tolerated doses of the triple therapy and/or biologics should have been achieved and administered for an appropriate time up to 6 months. It is important to discern if agents were discontinued because of toxicity, intolerance, or primary inefficacy. For example, switching to a second TNF inhibitor is not advocated in patients with primary inefficacy. For patients who are truly refractory, options include the following: rituximab, abatacept, tocilizumab, tofacitinib, and baricitinib. Rituximab tends to be more effective on seropositive patients. Currently, data directing therapeutic choices are limited. In a monotherapy trial (ADACTA), tocilizumab was superior to adalimumab and in another trial abatacept was similar to infliximab, with lower rates of serious infections in the background of MTX [21]. In a Bayesian network meta-analysis of randomized controlled trials (RCTs) examining the efficacy and safety of tocilizumab, rituximab, abatacept, and tofacitinib in patients with RA inadequately responding to TNF inhibitors, tocilizumab 8 mg was the second-line non-TNF biologic with the highest performance regarding an early good response based on ACR20 response rate and acceptable safety profile, followed by rituximab, abatacept, and tofacitinib [20].

JAK inhibitors tofacitinib (a JAK3/1) and more recently baricitinib (JAK1/2) have the capacity to block multiple cytokine signaling pathways. Tofacitinib is effective both as monotherapy and in the background of MTX and is shown to be non-inferior to adalimumab. During a 24-week period, tofacitinib had efficacy and rates of adverse effects comparable with currently available biologic DMARDs in the treatment of patients with RA who had a prior inadequate response to TNF inhibitors [22].

Combination of Biological Agents

Efforts to combine biologic agents have not met with success due to increased risk of serious infections.

Comorbidities and Prognosis

Patients with rheumatoid arthritis carry a 50% increased risk of CVD morbidity and mortality compared to general population. Ischemic heart disease, cerebrovascular accidents, and congestive heart failure are leading causes. Pro-inflammatory cytokines such as IL-1, TNFα, IL-6, and IL-17 have been implicated in endothelial cell activation observed in atherosclerosis [23]. Aggressive modification of traditional cardiovascular risk factors along with early and appropriate RA treatment is warranted. Infections are the second most common cause of morbidity and mortality in RA certainly driven by immunosuppressive treatments. There is only a modest (5–10%) increase in overall malignancy in RA compared to general population. However, the risk of developing lymphoproliferative malignancies, including Hodgkin and non-Hodgkin lymphoma is two- to threefold higher than general population and this risk increases with high RA disease activity. The incidence of lung cancer in patients with RA is reported to be increased compared to that in the general population, especially in men over 55 years of age and in those with Felty syndrome. Immunosuppressive medications may influence risk of certain malignancies [24]. Other conditions that occur with increased frequency include secondary Sjogren syndrome and osteoporosis attributed to both disease activity and medications. Work disability is reported at 25% within the first 6 years of disease onset but aggressive treatment with DMARDs (conventional and biologics) has decreased incidence of joint replacement surgery and mortality due to RA [25].

Questions

1. A 46-year-old female with rheumatoid arthritis presents to your office for an f/u visit. She has moderately active rheumatoid arthritis despite maximum methotrexate therapy. You plan to initiate a TNF inhibitor. She tells you that she immigrated from Pakistan 30 years ago and remembers receiving the BCG vaccination as child. She denies any recent travel or exposure to anyone with active TB.

   How would you screen this patient for latent TB infection?

   A. Tuberculin skin test
   B. IFN gamma release assay
   C. Chest X-ray

D. Tuberculin skin test followed by chest X-ray if skin induration is greater than 10 mm
E. Tuberculin skin test followed IFN gamma release assay if skin induration is greater than 10 mm

Correct answer: B
All patients should be screened for latent TB prior to starting TNF inhibitor therapy. The specificity of tuberculin skin test is reduced in patients vaccinated with BCG, or has exposure to non-TB mycobacteria. IFN gamma release assay has increased specificity for detecting latent TB and is the screening test of choice for latent TB in patients with prior BCG vaccination. Chest X-ray can help assess active TB. In latent TB, chest X-ray abnormalities are present in only 10–20%, making it less effective as a screening tool.

2. A 55-year-old female with rheumatoid arthritis presents to your office with polyarthritis involving her hands, wrists, and feet. She is currently on methotrexate 20 mg sc once weekly and 10 mg of prednisone daily. On physical examination she has eight tender and swollen joints. You plan to initiate a TNF inhibitor. She tells you that she is interested in receiving the 23 valent pneumococcal vaccine. Which of the following can interfere and impair the patient's response to the vaccine?

A. Methotrexate 20 mg sc once weekly
B. Prednisone 10 mg orally daily
C. Adalimumab 40 mg sc every other week
D. Etanercept 50 mg sc weekly

Correct answer: A
The CDC recommends that all immunosuppressed patients receive the 23-valent pneumococcal vaccine. Studies have shown impaired antibody response to patients taking MTX. Patients taking TNF inhibitors— adalimumab and etanercept—did not show impaired antibody response. Furthermore, patients on combination therapy with TNF inhibitor and MTX showed poor antibody response compared to patients treated with TNF inhibitors alone. Patients on prednisone had no difference in antibody response. Thus patients should receive the 23-valent pneumococcal vaccine prior to starting MTX if possible.

3. A 33-year-old male with a PMH of DM and HTN presents to the ER with a 2-month history of pain and swelling to right wrist and left second to third MCPs. He has tried OTC Tylenol and Motrin with no significant relief of symptoms. He is a carpenter. Denies trauma. Denies family history of autoimmune disease.

What of the following is the best predictor that the patient will progress to develop RA?

A. Low number of joints involved
B. Positive CCP antibodies
C. Male sex
D. No response to OTC Tylenol and Motrin
E. Occupation

Correct answer: B
The best predictors that a patient will progress to RA include: Higher number of joint involved, positive CCP antibody and or positive RF, female sex, older age, prolonged morning stiffness, and elevated inflammatory markers.

4. A 55-year-old female presents for an initial evaluation for RA. She complains of a one-year history of intermittent pain and swelling to bilateral wrists, MCPs, PIPs, and elbows. She has morning stiffness of 90 minutes daily. She denies fever. She is currently taking Tylenol 650 mg BID with mild improvement in symptoms. You suspect RA and would like to start her on DMARDs after reviewing her blood work.

   Which of the following clinical problems is the patient at risk for?

   A. Infertility
   B. Atherosclerosis
   C. Malignancy
   D. Depression
   E. Kidney failure

   Correct answer: B
   RA patients develop atherosclerosis 10 years earlier compared to patients who do not have RA. They are not at increased risk for infertility, malignancy, depression, or kidney failure. Caution should be used when treating patients with underlying malignancy, depression, or kidney failure, as certain medications may be contraindicated.

5. A 63-year-old female with a 40-year history of seropositive rheumatoid arthritis is scheduled to undergo left hip arthroplasty. Her current rheumatoid arthritis treatment consists of methotrexate 20 mg orally weekly and adalimumab 40 mg sc every other week. She has no other medical problems.

   Which of the following is the most important next step in the preoperative assessment?

   A. MRI of the cervical spine
   B. Echocardiography
   C. XR of the cervical spine in lateral flexion/extension views
   D. Pulmonary function tests
   E. Repeating serologies

   Correct answer: C
   The risk for cervical cord atlantoaxial subluxation is significant in patients with long standing rheumatoid arthritis. Asymptomatic and symptomatic patients must be radiographically evaluated if the surgery requires intubation. The best initial imaging test is XR of the cervical spine in lateral flexion/extension views.

6. A 60-year-old female presents to your office for an initial evaluation. She has a 1 year history of symmetrical polyarthritis of her hands, elbows, and feet. She reports a history of alcohol abuse, but currently sober and denies any alcohol use for the last 5 months. On physical examination, she has active synovitis in her MCPs, wrists, elbows, ankles, and MTPs.

Initial laboratory work up reveals Hepatitis C infection with high titer viremia. Which of the following medications is a potential treatment option for the patient?

A. Abatacept
B. Tocilizumab
C. Etanercept
D. Rituximab

Correct answer: C. Etanercept
Etanercept is the most commonly used medication in patients with RA and HCV infections and the 2012 ACR recommendations for RA treatment recommend Etanercept for the treatment of concurrent RA and hepatitis C. Patients with RA treated with etanercept have shown stable levels of viral load when used in combination with IFN-ribavirin. However, close monitoring is required.

7. A 65-year-old female with rheumatoid arthritis presents to your office with polyarthritis involving her hands, wrists, and feet. He is currently on triple therapy with methotrexate 20 mg sc once weekly, hydroxychloroquine 400 mg daily and sulfasalazine 1 g bid, and 20 mg of prednisone daily. She has a history of moderate to severe COPD, bowel perforation in the background of diverticulitis, and two episodes of shingles one involving the eye. On physical examination she has eight tender and swollen joints. What is the next best treatment option?

A. Rituxan
B. Addition of a TNF inhibitor
C. Abatacept
D. Tocilizumab
E. Tofacitinib

Correct answer: A
Baseline use of corticosteroids of 10 mg/d or greater among all disease indications is associated with elevated risk of herpes zoster compared with no baseline use. For patients with RA, adjusted incidence rates are similar between anti-TNF and nonbiologic DMARD initiators. Abatacept is not a preferred agent in moderate to severe COPD. Rituxan, tocilizumab, and tofacitinib have a risk of bowel perforation. Tofacitinib is associated with increased risk of herpes zoster compared to nonbiologic and other biologic DMARDs especially in the background of prednisone. For patients with RA, adjusted incidence rates of herpes zoster are similar between anti-TNF and nonbiologic DMARD initiators.

8. A 30-year-old female with rheumatoid arthritis presents to your office for a follow up visit. She is currently on leflunomide 20 mg orally daily. She discloses that she wishes to become pregnant in the next year and asks about the risks of fetal toxicity of leflunomide.

In addition to stopping leflunomide, what is the best recommendation?

A. Check a leflunomide level before setting up a detoxification protocol
B. Start deferoxamine
C. Start cholestyramine for 11 days
D. Wait 1 year before conceiving
E. Wait 6 months before conceiving

Correct answer: C
Leflunomide is a teratogen and classified as category X. It is potentially harmful to the fetus and patients should be instructed not to conceive while on these medications. If the patient wishes to conceive or becomes pregnant while on Leflunomide, drug elimination is warranted. Cholestyramine should be administered for 11 days and then a leflunomide level should be checked. If the leflunomide level is elevated a repeat course of cholestyramine should be administered.

9. A 46-year-old female with RA presents to your office for an f/u visit. She has been treated with hydroxychloroquine 400 mg daily for the past 10 years. She feels well overall and denies any joint pain and swelling. However, over the last 1 month she is noticing halos around light in her eyes.

   What is the most likely hydroxychloroquine related ophthalmic toxicity?

A. Corneal deposits
B. Retinopathy
C. Optic neuritis
D. Ocular myopathy

Correct answer: A
Corneal deposits are related to high daily doses of antimalarial medications or its metabolites and are more common with chloroquine. Deposits are rare with hydroxychloroquine. The deposits usually do not affect vision but can create halos that are heightened by light. Retinopathy is the most fearsome complication of antimalarial therapy caused by retinal pigment epithelial cell depigmentation in the central macula. The early abnormalities are asymptomatic and can only be detected by ophthalmologic examination. Within 10 years of use, the prevalence of retinal toxicity is low (<2%) but rises to nearly 20% after 20 years of use.

10. A 37-year-old male with a PMH of DM, HTN, and RA presents to the ER with a 2-month history of pain, swelling, and nodular growth to the right elbow. He denies any fever, chills, or drainage of fluid. He has tried over the counter acetaminophen and ibuprofen with no significant relief of symptoms.

    What is the most likely etiology of the swelling/nodular growth on the right elbow?

A. Rheumatoid nodule
B. Osteoarthritis
C. Lyme disease
D. Cellulitis

Correct answer: A
Rheumatoid nodules are composed of a central area of fibrinoid necrosis surrounded by histiocytes and connective tissue. They are present in 30% of patients with RF positive RA and typically occur over pressure points. Typical locations: extensor surface of forearms, olecranon bursa, sacrum, occiput, and heels.

11. A 70-year-old female with a past medical history of melanoma, diagnosed 10 years ago, presents to your office for a follow-up for seropositive rheumatoid arthritis. The patient is currently on methotrexate 20 mg orally weekly and hydroxychloroquine 200 mg BID. She is complaining of worsening pain and swelling in her hands, knees, and feet. You plan to escalate therapy and add another biological DMARD.

    Which of the following medications should be avoided in this patient?

    A. Anakinra
    B. Infliximab
    C. Rituximab
    D. Abatacept

    Correct answer: B. Infliximab
    The relative risk for nonmelanoma skin cancer among users of all anti-TNF biologics is increased twofold. There is a 1.5-fold increased risk of melanoma in TNFa-treated patients compared to the general population and no increased risk in RA patients not on TNFa inhibitors. The overall relative risk for all forms of cancer, excluding nonmelanoma skin cancer, in patients on anti-TNF biologics is 0.99.

12. A 60-year-old male presents to your office for a follow up for seropositive rheumatoid arthritis. The patient is currently on hydroxychloroquine 200 mg BID. He is complaining of worsening pain and swelling in his wrists, hands, and feet. On physical examination, he has tenderness and synovitis to his MCPs and MTPs. You plan to escalate therapy and add methotrexate.

    Which of the following vaccines would you recommend before starting treatment with methotrexate?

    A. Influenza
    B. Hepatitis B
    C. Tetanus
    D. Pneumococcal polysaccharide
    E. Meningitis

    Correct answer: D
    The pneumococcal polysaccharide vaccine should be given to patients prior to initiating treatment with methotrexate because methotrexate reduces the response to the pneumococcal polysaccharide vaccine. The response to influenza vaccine is not reduced. The effect on the Hepatitis B, tetanus, and meningitis vaccination is unknown.

13. A 70-year-old male with a history of rheumatoid arthritis is being evaluated for a left total knee arthroplasty. His rheumatoid arthritis is well controlled on methotrexate 15 mg orally weekly. On physical examination, he has left knee pain and limited range of motion. There is no tenderness or swelling to any joint. His labs are normal.

    How should methotrexate be managed perioperatively?

    A. Stop methotrexate 2 weeks before surgery and resume after surgery
    B. Continue methotrexate up to the time of surgery and resume after surgery
    C. Stop methotrexate 2 weeks before surgery and resume 2 weeks after surgery
    D. Continue methotrexate up to the time of surgery and resume 4 weeks after surgery

    Correct answer: B
    Studies have shown no difference in surgical complications and infections in patients who continued therapy with methotrexate up to the time of surgery and resumed after surgery to patients who stopped methotrexate 2 weeks before surgery and resumed 2 weeks after surgery. Additionally, rheumatoid arthritis flares occurred less in patients who continued methotrexate than patients who stopped methotrexate.

14. A 24-year-old female presents to your office for an initial evaluation. She reports to have a 6-week history of bilateral symmetrical pain and swelling to her hands, knees, ankles, and feet. She states that her symptoms started when she went to visit her mother in southern Florida. Initially she developed fever, chills, myalgias, and rash, which have since resolved.

    Which of the following is the most likely cause of the patient's symptoms?

    A. Rheumatoid arthritis
    B. Psoriatic arthritis
    C. Chikungunya infection
    D. Fibromyalgia

    Correct answer: C
    Chikungunya viral infection is transmitted to humans by a mosquito bite. The patient seems to have locally acquired the infection in Florida. The common manifestations include fever, chills, polyarthralgias, myalgias, and maculopapular rash. Although rheumatoid arthritis could explain the symmetrical polyarthritis, it generally would not cause fever and chills.

15. A 35-year-old female with a past medical history of hypertension, hyperlipidemia, and rheumatoid arthritis presents to your office for a follow-up visit. On physical examination she has no tenderness or active synovitis and has a low disease activity score. Her laboratory tests are normal. She is currently eating a healthy diet and wants to know what she should include in her diet to improve her disease?

    A. Increasing alcohol consumption
    B. Increasing gluten consumption

C. Increasing omega- 3 fatty acid consumption
D. Increasing folic acid consumption

Correct answer: C
Studies have shown that omega- 3 fatty acid consumption of more than 3 grams daily can decrease tender and swollen joint count and decrease inflammatory markers by altering the fatty acid composition of cell membranes and thus inflammatory mediators. There is no evidence that increasing folic acid and gluten improves tender and swollen joint count and decreases inflammatory markers.

16. A 75-year-old male with seropositive, erosive rheumatoid arthritis presents to your office for a follow-up visit. He is taking adalimumab every two weeks and methotrexate weekly with good response. On physical examination he has mild tenderness in the occipital region. No tenderness or active synovitis to his other joint and has a low disease activity score. His laboratory tests are normal. Although you do not suspect atlantoaxial subluxation, which of the following factors can increase this patient's risk for atlantoaxial subluxation?

A. Male gender
B. Erosive disease
C. Concurrent methotrexate and adalimumab use
D. Methotrexate use alone

Correct answer: B
Erosive disease can increase your risk for developing atlantoaxial subluxation. Patients with more than 10% peripheral damage are more likely to develop atlantoaxial subluxation compared to patients with less than 10% peripheral damage. Age, gender, or medications used for treatment of rheumatoid arthritis does not increase the risk for developing atlantoaxial subluxation.

17. A 60-year-old male presents to your office for a follow-up for seropositive rheumatoid arthritis. The patient is currently on methotrexate 20 mg orally weekly. He is complaining of worsening pain and swelling in his wrists, hands, and feet. On physical examination he has tenderness and synovitis to his MCPs and MTPs and a painful rash with blisters located on his abdomen concerning for herpes zoster. You plan to escalate therapy and add a disease modifying agent.

Which of the following medications confers the highest risk for shingles?

A. Leflunomide
B. Sulfasalazine
C. Anakinra
D. Tofacitinib
E. Etanercept

Correct answer: D
Tofacitinib can cause nasopharyngitis, diarrhea, headache, elevated liver enzymes, and cytopenias. It also increases the risk for herpes zoster infection

by a factor of 2 compared to TNF inhibitors. Leflunomide can cause nausea, diarrhea, alopecia, and elevated liver enzymes. Etenarcept is also associated with increased risk of shingles but less so compared to tofacitinib. Anakinra can cause injection site reaction and cytopenias, and sulfasalazine can cause nausea, rash, and cytopenias.

18. A 35-year-old female with a past medical history of hypertension, hyperlipidemia, asthma, and rheumatoid arthritis presents to your office for a follow-up visit. She is currently on Tofacitinib. On physical examination she has no tenderness or active synovitis and has a low disease activity score. Her laboratory tests are normal. The patient is interested in receiving the influenza vaccination.

    What would you tell the patient prior to giving her the vaccination?

    A. Patients with rheumatoid arthritis should not receive the influenza vaccination
    B. Patients that are treated with tofacitinib should not receive the influenza vaccination
    C. She can only receive the intranasal influenza vaccination
    D. She can receive the vaccination
    E. She can receive the vaccination, but she will first need to switch to another DMARD

    Correct answer: D

    Patients with rheumatoid arthritis should be vaccinated against influenza. Medications that can impair the response to the influenza vaccination include methotrexate, rituximab, and abatacept. Tofacitnib does not impair the response to the influenza vaccination and she can receive the injectable version.

19. A 45-year-old female with a history of diabetes, seropositive erosive rheumatoid arthritis on methotrexate 15 mg PO weekly, hydroxychloroquine 200 mg bid and sulfasalazine 1 g bid, and prednisone 5 mg daily comes for evaluation of subacute onset of left elbow pain and swelling over the past 10 days. She denies any trauma. She reports being more fatigued and endorses night sweats but no fevers. Examination shows erythema and swelling of her elbow with painful passive and active range of motion upon extension and flexion. There are no nodules and no olecranon erythema or pain. Her labs show mild leukocytosis 13000 with neutrophilia, mild anemia Hb 11.5 mg/dL, platelet count 430000, and CRP of 30 mg/dL. What is the next best step?

    A. Administer prednisone over 12 days and reassess for response.
    B. Optimize treatment by increasing methotrexate to 20 mg weekly and reassess in 4 weeks.
    C. Aspirate elbow and send for crystals, GRAM stain, cell count, and cultures.
    D. Administer corticosteroid injection with a presumptive diagnosis of adhesive capsulitis.
    E. Obtain XRs of the elbow.

Correct answer: C

This patient presents with an "out of phase" joint previously fairly controlled. It would be unusual for a rheumatoid arthritis flare to present in a monoarticular fashion. Insidious onset does not suggest crystal arthritis. Presence of constitutional symptoms and very high CRP in the background of risk factors for infection (DM, prednisone use) warrant aspiration to rule out infection. The elbow is not a typical joint for adhesive capsulitis and corticosteroid injection without a definitive diagnosis is not recommended. Although XRs may be informative for the underlying elbow osseous pathology, there is no history of trauma and it would not be of high diagnostic yield compared to aspiration and synovial fluid analysis.

20. Which one of the following statements is true?

A. Rituximab is not recommended for seronegative rheumatoid arthritis
B. Abatacept blocks CD28 on T cells and therefore inhibits T cell activation
C. Tocilizumab is a humanized monoclonal antibody against interleukin-6
D. Tofacitinib inhibits TNFa and interleukin 1 signaling by blocking JAK3 and JAK1
E. Hydroxychloroquine interferes with TLR7 and TLR9 signaling to exert its function

Correct answer: E

The presence of RF, low baseline functional disability, and no more than one previous anti-TNF are predictors of good response to RTX, yet seronegative patients also respond better than placebo. Abatacept inhibits T-cell (T lymphocyte) activation by binding to CD80 and CD86, thereby blocking interaction with CD28. Tocilizumab is a humanized monoclonal antibody against interleukin-6 receptor. Tofacitinib inhibits JAK/STAT pathway utilized by cytokines such as IL7, IL15, IL21, IL6, IFNα, and IFNβ. Interleukin 1 and TNFα signaling does not involve the JAK/STST pathway.

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Chapter 7
Psoriatic Arthritis

Fardina Malik, Rebecca Haberman, and Jose U. Scher

Key Points

- Psoriatic arthritis should be considered in patients with asymmetric inflammatory arthritis and clinical features such as enthesitis, dactylitis, and sacroiliitis. In these patients, a thorough skin exam must be performed, including the scalp, groin, and intergluteal folds.
- Patients with PsA have elevated risk of cardiovascular disease, metabolic syndrome, inflammatory bowel disease, uveitis, and psychiatric disease such as depression and anxiety.
- New evidence points to the entheses as the initial site of inflammation.
- Delay in treatment of as little as 6 months can lead to worse disease outcomes, and treatment should be initiated with a treat-to-target approach.
- TNF inhibitors are effective in both peripheral and axial disease.

Introduction

Psoriatic arthritis is one of the subtypes of seronegative spondyloarthritis, affecting up to 30% of patients with psoriasis [1]. It is characterized by widespread musculoskeletal inflammation manifesting with peripheral arthritis (synovitis and enthesitis) and axial/spinal inflammation. Pierre Bazin first coined the term *psoriasis arthritique* in 1860, and later Boudillion described the details of its presentation in his doctoral thesis "Psoriasis et Arthropathies," but the disease was not acknowledged

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as a unique entity until Moll and Wright published the clinical features of psoriatic arthritis in great detail in 1973 [2].

PsA is a complex, multiorgan system disease. In addition to skin, joints, and entheseal inflammation, PsA is associated with multiple comorbidities in the gastrointestinal, cardiovascular, and even psychiatric domains. Its heterogeneous presentation can make it particularly difficult for practitioners to diagnose, which can lead to delayed treatment and poorer outcomes [3]. Hence, early recognition, diagnosis, and treatment are of utmost importance since a treat-to-target approach can lead to improved clinical responses [4].

Epidemiology and Disease Burden

The prevalence of PsA is now estimated at 6–25/10,000 people and is on the rise [5–7]. Furthermore, these numbers likely underestimate the true prevalence as PsA is typically underdiagnosed; as much as 15% of patients with psoriasis have undiagnosed psoriatic arthritis [8]. Psoriatic arthritis occurs in up to 30% of patients with skin psoriasis, with an annual incidence rate of 2–4% per year [6, 8], affecting equally males and females. The arthritic component develops on average 5–7 years after the first skin manifestations. However, in up to 15% of cases, joint symptoms present either simultaneously or prior to skin psoriasis [9]. Plaque psoriasis and psoriasis vulgaris is thought to be most common skin subtype associated with psoriatic arthritis while there is an inverse relationship with palmoplantar pustular psoriasis with arthritis. Nail disease can be present in up to 80% of patients with PsA [5].

Given the multiorgan effects of psoriatic arthritis, the disease has a large individual and societal burden. Individuals with psoriatic arthritis have a decreased quality of life, worse than that of psoriasis alone [10, 11]. Furthermore, patients have higher rates of unemployment, absenteeism, and productivity [12]. Direct healthcare costs alone are estimated at about $1.9 billion in the United States [13].

Clinical Features

Moll and Wright originally described five different clinical subtypes of PsA in their 1973 seminal paper (Table 7.1). Prevalence of individual subtypes varies for different epidemiological studies. However, more recently, psoriatic arthritis is being thought about in five different domains: peripheral arthritis, enthesis, axial disease, skin, and nails [14]. Enthesitis, inflammation at tendon or ligament insertion into the bone, was not described among the five original subtypes. It is a clinical feature unique to all subtypes of seronegative spondyloarthritis and occurs in up to 50% of patients with PsA. For this reason, it is hypothesized by some to be the primary site of initial inflammation, and linking nail disease and synovitis [15] in this disease.

Table 7.1 Major clinical subtypes of psoriatic arthritis with clinical features and prevalence rates

Clinical patterns	Important clinical features	Prevalence
Asymmetric oligoarthritis	≤4 joints involved Asymmetric in distribution Most common	~20–55% [5]
Symmetric polyarthritis	≥5 joints involved Symmetric in distribution Similar to rheumatoid arthritis	~20–62% [5]
Predominant DIP involvement disease	Typically DIPs are involved May or may not have concurrent nail involvement [16] Distribution similar to DIP OA	~<5–20% [2, 5]
Axial spondyloarthritis	Sacroiliitis as well as other areas of spinal involvement Similar to other seronegative SpA May or may not be associated with peripheral PsA Can be asymptomatic	Up to 40% [1, 5]
Arthritis mutilans (destructive)	Rare Asymmetric Severe osteolysis of involved joints resulting telescoping of digits Severe disease	~5% [2]
Dactylitis	Inflammation of IP joints and surrounding tendon sheath resulting in classic sausage-shaped swelling Characteristic feature Most common in 3rd and 4th toes Can be acute or chronic Often associated with severe disease with bone erosion	40–50% [1]
Enthesitis	Most commonly Achilles tendinitis and plantar fasciitis Other less common areas: iliac crest, around the patella, epicondyles, etc.	30–50%

DIP = distal interphalangeal joints

There are no formal validated diagnostic criteria for psoriatic arthritis, but diagnosis should be suspected when a patient presents with any of the above manifestations in the setting of current or previous history of psoriasis. Plaque psoriasis (Fig. 7.1a, b), guttate psoriasis (Fig. 7.2a), inverse psoriasis (Fig. 7.2b), pustular (Fig. 7.3a), and erythrodermic psoriasis are five major types of skin psoriasis. Dactylitis (Fig. 7.4) and enthesitis are thought to be typical features of PsA and are helpful in establishing diagnosis. But these features may be absent and it can be particularly difficult to identify PsA, as patients may not be aware of their skin psoriasis (or skin disease may not be obvious on initial evaluation). Hence, a thorough skin examination must also include the umbilicus, scalp, anus, and postauricular areas. Isolated nail involvement (Fig. 7.3b) is also seen with presence of pitting, oil spots, and onycholysis, which can confirm diagnosis. Family history of psoriasis and psoriatic arthritis are often present. Presence of other extra-articular diseases, such as IBD and uveitis, also heightens suspicion.

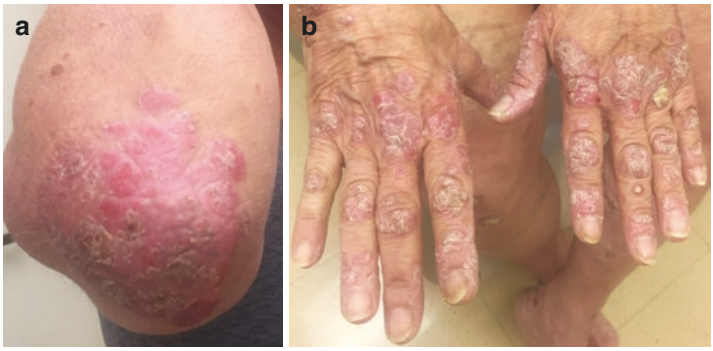

Fig. 7.1 (**a**) Plaque psoriasis along the extensor surface of elbow with erythematous base with silvery scales. (**b**) Plaque psoriasis involving dorsal aspects of the joints. (Photo Credit: Andrea L. Neimann, MD)

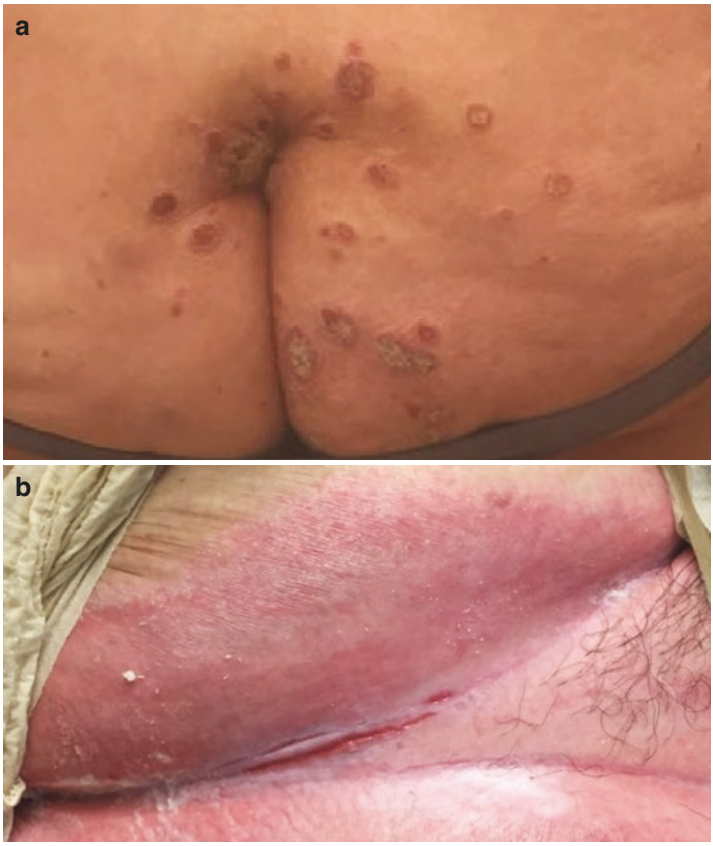

Fig. 7.2 (**a**) Guttate psoriasis presents with numerous small drop-like papule with a silvery scales. (**b**) Inverse psoriasis presenting along the inguinal folds. Scales typical of psoriasis tends to get macerated in these moist areas of body leaving a shiny erythematous surface. (Photo Credit: Andrea L. Neimann, MD)

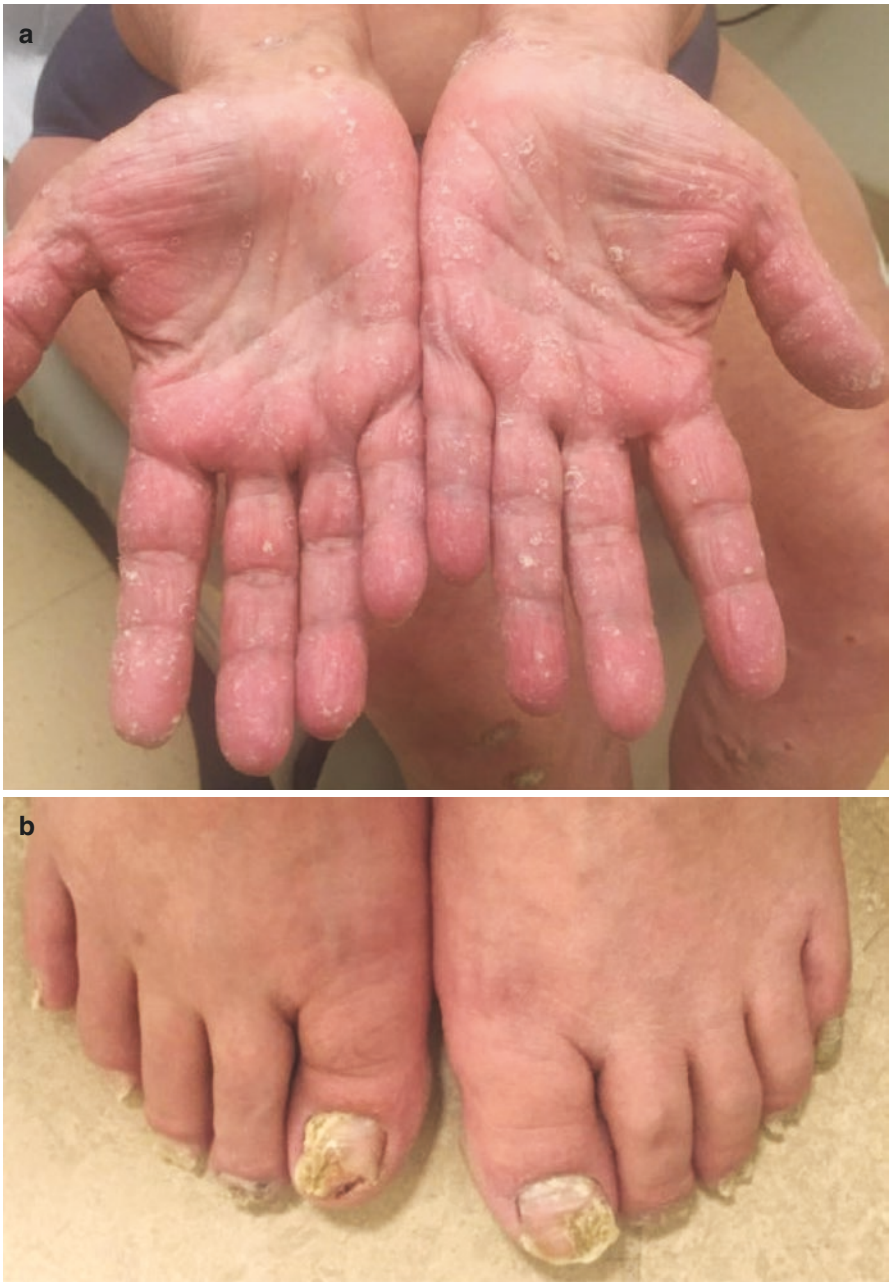

Fig. 7.3 (**a**) Palmar pustular psoriasis presents with tiny yellowish pustules, which are sterile. (**b**) Nail psoriasis with numerous vertical ridges and dystrophic nails. Pitting, oil spots, onycholysis are other nail changes seen in psoriatic nail diseases. (Photo Credit: Andrea L. Neimann, MD, and Fardina Malik, MD)

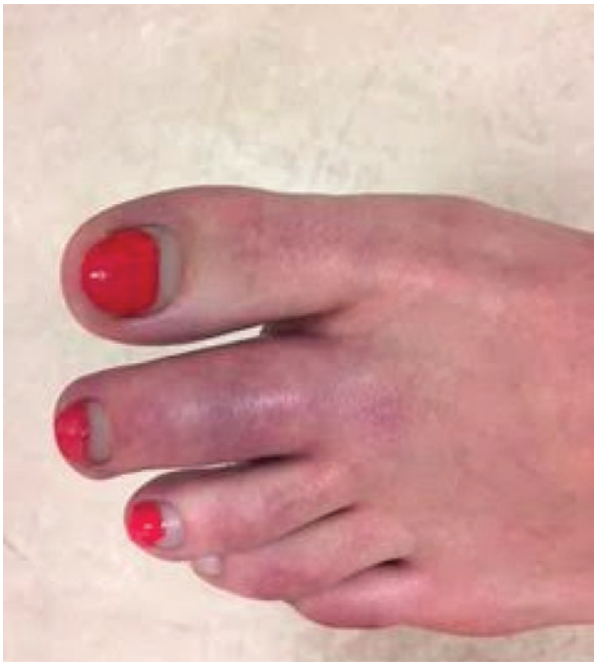

Fig. 7.4 A 33-year-old female with no evidence of skin psoriasis presented with acute painful swelling of left 2nd toe. Laboratory test showed elevation of c-reactive protein. She was also noted to be HLA B-27 positive. (Photo credit: Fardina Malik, MD)

Table 7.2 Classification criteria of peripheral psoriatic arthritis (CASPAR = classification for psoriatic arthritis)

Patient with inflammatory articular diseases (joints, spine, or enthesitis) with ≥3 points from the following five categories:	
Criterion	Points
1. Evidence of psoriasis	
Current psoriasis (examined by dermatologist or rheumatologist)	2
Personal history of psoriasis (provided by patients or physician)	1
Family history of psoriasis (1st or 2nd degree relative)	1
2. Psoriatic nail dystrophy (onycholysis, pitting, or hyperkeratosis) present currently	1
3. Negative test for RF by any test except latex (ELISA and nephelometry preferred)	1
4. Dactylitis	
Current dactylitis	1
History of dactylitis (according to a rheumatologist)	1
5. Radiographic features of juxtaarticular new bone formation (ill-defined ossification near joint margin, excluding osteophytes)	1

RF = Rheumatoid Factor

Classification criteria for psoriatic arthritis (CASPAR) (Table 7.2) can often guide clinicians, but it is primarily intended to enroll patients in clinical studies or trials given much higher specificity (~99%) (Table 7.2).

Laboratory Features

There are no definitive laboratory tests for psoriatic arthritis. Inflammatory markers (i.e., erythrocyte sedimentation rate and C-reactive proteins) can be elevated on polyarticular diseases but remains normal in ~60% of patients. Absence of rheumatoid factor (RF) and cyclic citrullinated peptide (CCP) antibodies is seen in 95% of cases and is helpful to distinguish from RA, especially when PsA presents in a similar fashion. HLA-B27 is present in ~25% of patients.

Radiological Features

Plain X-Ray

Plain X-ray is considered "gold standard" to assess characteristic bony changes in PsA since two-third of these patients can have radiological changes [17]. Similar to rheumatoid arthritis (RA), X-ray shows erosions of bones and joint space narrowing but distribution tends to be more asymmetrical and erosions are marginal (Fig. 7.5a, b). Unlike RA, involvement of DIP joints in PsA with bony erosion and resorption can lead to classic "pencil-in-cup" deformity (Fig. 7.6a) in contrast with DIP joint involvement seen in osteoarthritis leads to "gull wing" changes. Another distinctive

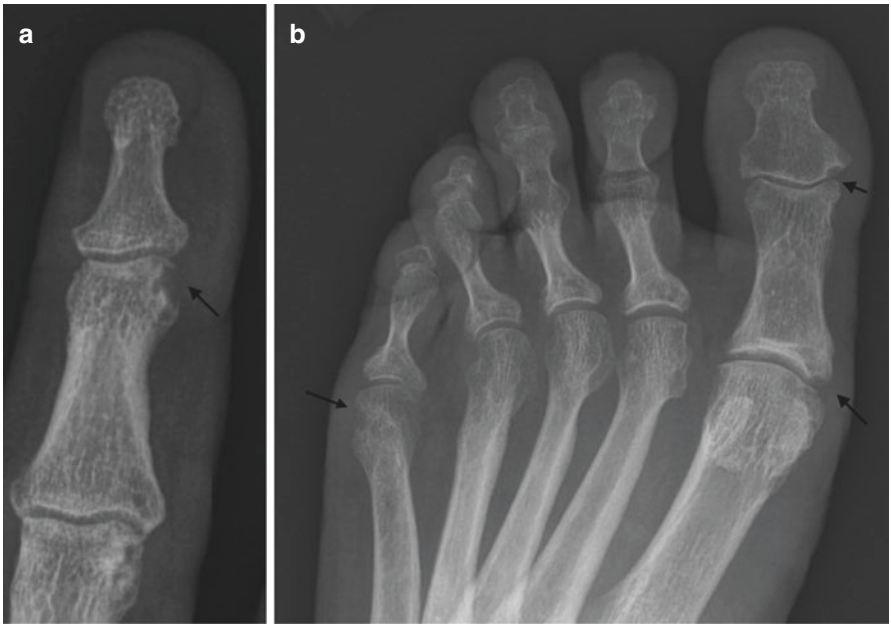

Fig. 7.5 Focal marginal erosions seen in peripheral psoriatic arthritis (black arrows) involving. (**a**) DIP of hands and (**b**) MCPs and PIPs of left foot. (Image credit: Soumya Reddy, MD)

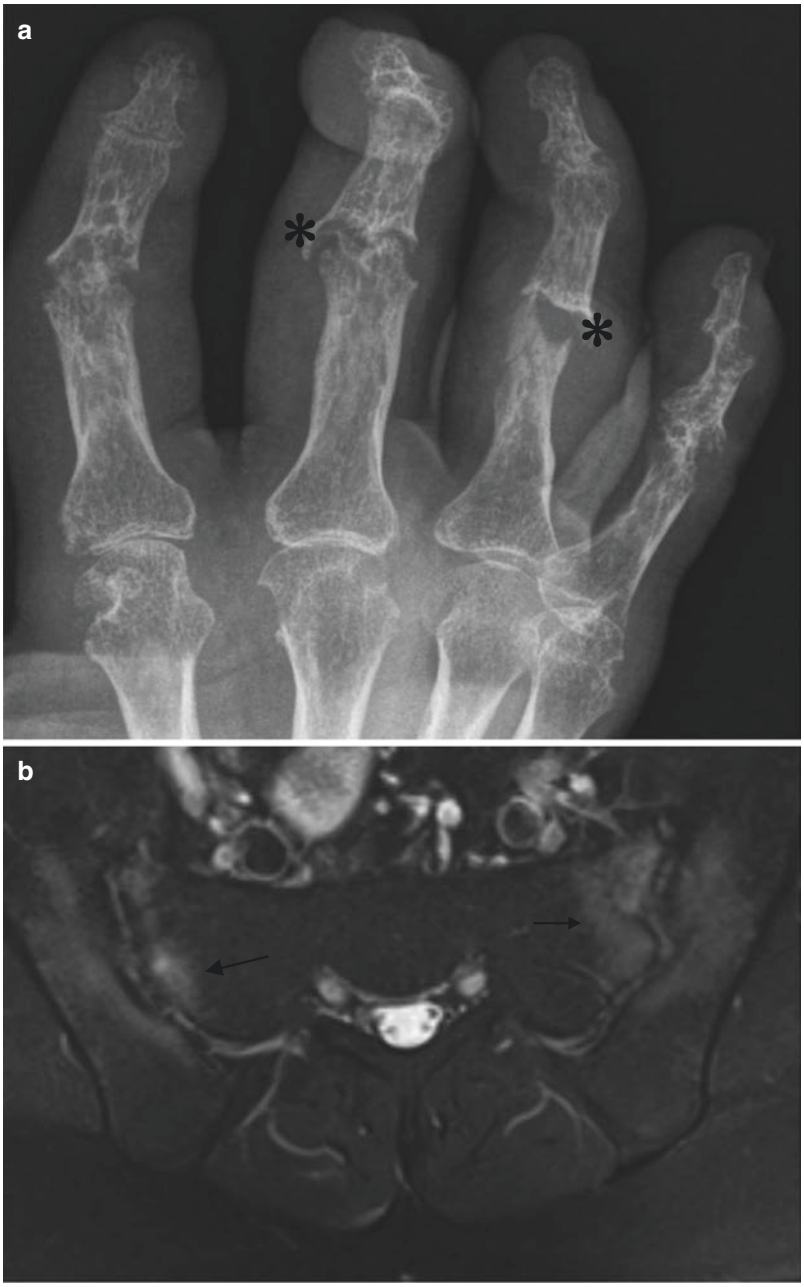

Fig. 7.6 (**a**) Arthritis mutilans in PsA presenting with severe destruction of joints and resorption of adjacent bones (osteolysis) of the PIPs. Classic X-ray finding of "pencil-in-cup" deformity shown with asterisk. (**b**) T2 short-tau inversion recovery (STIR) sequence of magnetic resonance imaging (MRI) of bilateral sacroiliac joints shows acute bone marrow edema (black arrows) adjacent to the joints. (Image credit: Fardina Malik, MD)

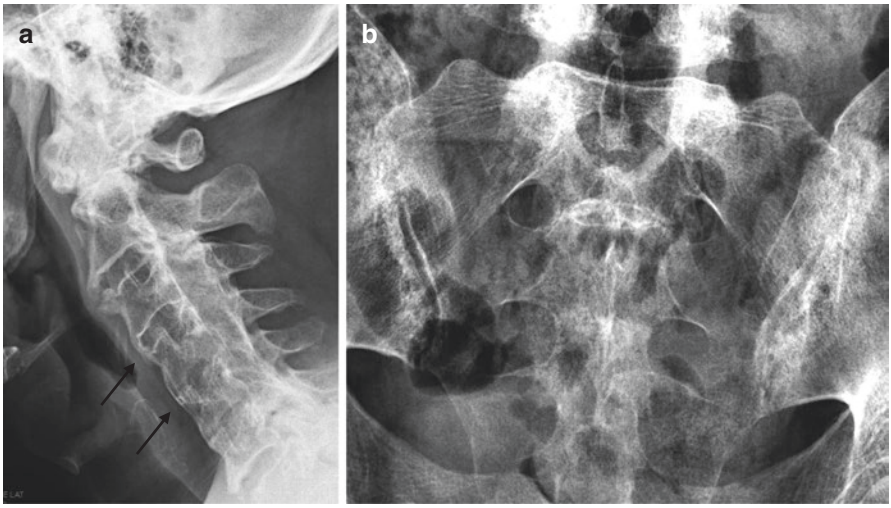

Fig. 7.7 Axial involvement in psoriatic spondyloarthritis. (**a**) Bridging syndesmophytes involving the lower cervical vertebrae leading to complete fusion. (**b**) Bilateral sacroiliitis with evidence of complete ankylosis of left SIJ and partial ankylosis on right. Right SIJ also shows subchondral sclerosis. (Image credit: Soumya Reddy, MD)

feature of PsA is pathologic new bone formation characterized by periostitis, bony ankylosis, and enthesophytes (abnormal bony projection at the entheseal sites). Axial involvement in PsA manifests on X-ray as unilateral sacroiliitis and paramarginal and vertical syndesmophytes (whereas spinal involvement in ankylosing spondylitis tends to be bilateral) [1] (Fig. 7.7a, b).

Musculoskeletal Ultrasound (MSKUS)

MSKUS is particularly helpful in detecting enthesitis in PsA as it shows entheseal thickening, changes in echogenicity of tendons (hypoechoic), and increased power Doppler signals indicating increased vascularity. In addition, it shows erosions and enthesophytes around the entheses. It can also show combination of synovitis and tenosynovitis that leads to dactylitic changes of a digit. Studies further suggest MSKUS is more sensitive than in clinical examination to detect synovitis [18, 19]. This could be helpful to detect subclinical or preclinical synovitis in patients with skin psoriasis.

Magnetic Resonance Imaging (MRI)

Resolution of MRI is excellent to detect bone marrow edema seen at the site of entheseal inflammation, especially in acute sacroiliitis or other areas of spinal

involvement (Fig. 7.6b). MRI is also employed to detect focal bony erosions, synovitis of peripheral joints, as well as entheseal involvement (such as Achilles tendinitis and others).

Differential Diagnosis

It is important to distinguish PsA clinically as several clinical, laboratory, and radiological features can overlap with forms of arthritis (Table 7.3).

Comorbidities

In addition to the skin and joint manifestations, psoriatic arthritis is associated with a variety of comorbidities that are associated with increased morbidity and excess mortality. Patients have higher prevalence of traditional cardiovascular risk factors (i.e., hypertension, hyperlipidemia, diabetes mellitus, and obesity) as well as increased prevalence of myocardial infarction and stroke that is independent of these risk factors [20–23]. There is also an increased prevalence of inflammatory bowel disease (particularly Crohn's disease) as well as ophthalmologic manifestations, uveitis being the most common [24–26]. Furthermore, these patients also suffer from higher rates of depression and anxiety, which may impact psoriatic clinical outcomes [27, 28].

Pathogenesis

PsA results from a complex interplay of genetic and environmental factors. Twin studies in psoriasis showed a threefold higher concordance rate in monozygotic twins than dizygotic twins [29]. Furthermore, prevalence of psoriasis and psoriatic arthritis in first-degree relatives of patients with PsA is much higher than general population [30]. Unlike RA, psoriasis and PsA are associated with major histocompatibility complex (MHC) class I alleles. HLA-C∗w6 has been found in 60% patients with psoriasis, but the association is not strong in arthritis. Association of PsA with HLA-B∗08, B∗27, B∗38, and B∗39 have been observed. Additionally, genome-wide association studies have observed association of PsA with single nucleotide polymorphisms (SNP) of IL23 receptor (IL23R), IL12A, IL12B, nuclear factor κB (NF-κB), and protein tyrosine phosphatase (PTPN22) [31–33]. These findings highlight the importance of heritability but risk is substantially lower than monogenic diseases and thereby indicates environmental role in PsA pathogenesis.

Similar to Koebner's phenomenon observed in skin psoriasis [34], a deep Koebner's phenomenon (trauma to deep tissues or entheses) is thought to play a role

Table 7.3 Differential diagnosis of PsA and distinguishing features

Clinical features					
Features	PsA	RA[a]	ReA[b]	OA[c]	Gout
Pattern of joint involvement	Asymmetric (more common) and symmetric	Symmetric	Asymmetric	Asymmetric or rarely symmetric	Asymmetric or rarely symmetric (esp. polyarticular disease)
Number of joints involved	Oligoarticular most common. Polyarticular less common	Polyarticular	Oligoarticular	Monoarticluar or oligoarticular	Monoarticluar or oligoarticular
Unique joint involved	DIP	Proximal (never DIP)		DIP (associated with Heberden's nodes)	
Dactylitis	Unique feature (common)	Not seen	Present but uncommon	Not seen	Confused with an acute gout flare
Skin involvement	Psoriasis	Rheumatoid nodules	Keratoderma blennorrhagicum	No associated skin disease	Tophi
Axial (spinal and SIJ)	Present in ~50% cases (inflammatory)	Uncommon and never involves SIJ	Present in 100% cases (inflammatory)	Common (degenerative etiology)	Absent
Lab features					
RF and CCP	Only <5% cases	Present	Absent	Absent	Absent
Hyperuricemia	Can be present as an associated comorbidity	Less common association	Less common	Comorbidity	Unique feature
Radiological features	Erosion and pathological new bone formation (enthesophytes)	Erosion but no pathological new bone information	Enthesophytes are seen	Osteophytes	Erosions (juxtaarticular)

[a]RA = Rheumatoid arthritis
[b]ReA = Reactive arthritis
[c]OA = Osteoarthritis

in PsA [35, 36]. Severe skin disease, nail psoriasis, genital psoriasis, and obesity are among other environmental triggers that play a role in initiation of PsA [37].

T cells, especially CD8+ and CD4+ Type 17 (Th17) play a pivotal role in PsA pathogenesis. Macrophage-/monocyte-derived tumor necrosis factor-α (TNF-α) in synovial fluid plays a critical role, as evident by therapeutic efficacy of TNF-α inhibitors in psoriasis and PsA. More recent work suggests entheseal sites being the initial sites of initial inflammation leading to synovitis of psoriatic arthritis. A novel population of T cells (CD3+CD4−CD8−) resident to entheses responds to circulatory IL23 [38] and elaborates IL17 and IL22. Synovia of PsA patients are particularly enriched with Th17 cells, and downstream complex effect of IL23/Th17 axis leads to joint inflammation and erosion [39]. A recent novel murine model (STAT3 overexpression) of PsA further highlights the role of Th17 cell types on PsA pathogenesis [40].

Similar to other subtypes of seronegative SpA, gut-joint axis plays an important role. Up to 70% patients with PsA were shown to have subclinical or microscopic gut inflammation. Moreover, intestinal microbiome is presumed to regulate immune system via Th17 pathway—a key cell population in PsA pathogenesis. Perturbation of intestinal microbiota (specifically lower relative abundance of *Akkermansia* and *Ruminococcus*) was shown to be associated with PsA [41].

Treatment

Treatment for psoriatic arthritis is based on the extent of disease and the domains that are affected in an individual patient (Table 7.4). However, the guiding principle is that early treatment leads to improved outcomes. Delays in treatment for as little as 6 months can lead to increased clinical and radiologic damage [42, 43]. Applying a treat to target approach in newly diagnosed disease also leads to improved clinical outcomes [4].

NSAIDs can be an effective treatment for mild peripheral and axial disease. Intra-articular steroid injections can also be used for peripheral disease that is monoarticular or oligoarticular. However, many patients will eventually require disease modifying antirheumatic drugs (DMARDs). Although these are little randomized control trial data about traditional DMARDs, methotrexate, sulfasalazine, and leflunomide are commonly used and likely all have a small effect on joints, dactylitis, skin, and nails. MTX, in a randomized control trial, was found to have limited effect compared to placebo; however, the study may not have been powered appropriately, and the mean dose of MTX used was lower than is often prescribed in clinic [44]. Nonrandomized control studies have found some effect with MTX [45], and it continues to be the most prescribed medication for psoriatic arthritis worldwide. Synthetic DMARDs, however, have not been shown to have an effect on axial disease. Apremilast, a PDE4 inhibitor, is a small molecule oral medication that also has modest effect in the joints and skin. While not as effective as biologics discussed below, it has a favorable side effect profile compared to many of the other possible treatments [46, 47].

TNF inhibitors have become a large aspect of psoriatic arthritis treatment and have been shown to be effective in all domains. They all have similar efficacy in

Table 7.4 Medications used in the treatment of psoriatic arthritis

Medication	Joints	Skin	Radiography	Side effects
Methotrexate [44, 45]	++	+	NA	GI upset, hepatic effects
Leflunomide [60, 61]	+	–	NA	GI upset, renal effects
Sulfasalazine [62, 63]	+	–	NA	GI upset, neutropenia
PDE4 inhibitor: Apremilast [46, 47]	++	+	NA	GI upset, weight loss
TNFi				
Adalimumab [50]	+++	++	++	Infections, demyelination, lymphoma, nonmelanoma cancer
Certolizumab [51]	+++	++	++	Infections, demyelination, lymphoma, nonmelanoma cancer
Etanercept [52]	+++	+	++	Infections, demyelination, lymphoma, nonmelanoma cancer
Golimumab [49]	+++	++	++	Infections, demyelination, lymphoma, nonmelanoma cancer
Infliximab [48, 64]	+++	+++	++	Infections, demyelination, lymphoma, nonmelanoma cancer
IL17 inhibitors				
Ixekizumab [54]	+++	++++	+	Candida infections, injection site reactions
Secukinumab [55]	+++	++++	+	Candida infections
IL12/23 inhibitor: Ustekinumab [53]	+++	++++	+	Infections
JAK inhibitor: Tofacitinib [57]	+++	+	NA	Infections, zoster, increased LDL
Abatacept [58]	++	+	+	Infections, headache

joint response, although etanercept has been shown to be less effective in the treatment of skin. In addition to clinical improvement, all have been shown to slow radiographic progression of disease [48–52].

Additional biologics have also been approved for the treatment of psoriatic arthritis. IL17A inhibitors, secukinumab and ixekizumab, have similar effects in the joints to TNF inhibitors but are more effective in the clearance of skin psoriasis. They also slow radiographic progression of disease [53–55]. Ustekinumab is an IL12/IL23 inhibitor that works through blocking their shared p40 subunit. Like the IL17 inhibitors, it has similar levels of joint improvement and slows radiographic progression like TNF inhibitors, while having greater impact on skin disease. However, ustekinumab did not meet its primary end points for axial disease, it should not be used as first-line for this domain [53]. Tofacitinib is a JAK inhibitor that works by downregulating a number of cytokines implicated in the pathogenesis of psoriatic arthritis such as IFN-γ, IL12, and those involved in the IL23 and IL23 pathways [56]. It has been found to be effective for the arthritic component, although less effective on skin than the IL17 and IL12/23 inhibitors. There is not yet enough evidence to discuss its effect on radiographic progression [57]. Abatacept, a soluble, fully human fusion protection consisting of the extracellular domain of CTLA-4 linked to a modified Fc portion of human IgG1. Abatacept selectively inhibits T cell activation via competitive binding to CD80

or CD86 and decreases serum levels of cytokines and inflammatory proteins. While very effective in rheumatoid arthritis, it has a slightly lower effect on joints and very little effect of the skin component of psoriatic disease [58, 59].

Outcomes

PsA is an inflammatory arthritis that can lead to erosive and deforming damage in 40–60% of patients [13]. Damage can occur quickly in the course of disease, within as little as 6 months [42, 43]. In fact, despite treatment with DMARDs with clinical improvement, up to 47% of patients have radiographic damage at 2 years [65]. Extensive inflammation and an elevated CRP at baseline are the most predictive factors of the development of radiologic damage [66]. Biologics such as the TNF inhibitors have been shown to slow this damage and have good rates of remission. However, the relapse rates are high when these agents are discontinued [67].

Questions

1. A 60-year-old woman with history of hypertension, hyperlipidemia, and skin psoriasis since age 42 presents with 6 months of pain in her hands, mostly localized to the distal interphalangeal joints. Her family history is notable for a sister with psoriatic arthritis. She reports 15 min of morning stiffness. Pain is also worsened with washing dishes. She was seen by a rheumatologist and was started on methotrexate without improvement. CRP and ESR were both normal. X-ray of her hand was performed and shown below:

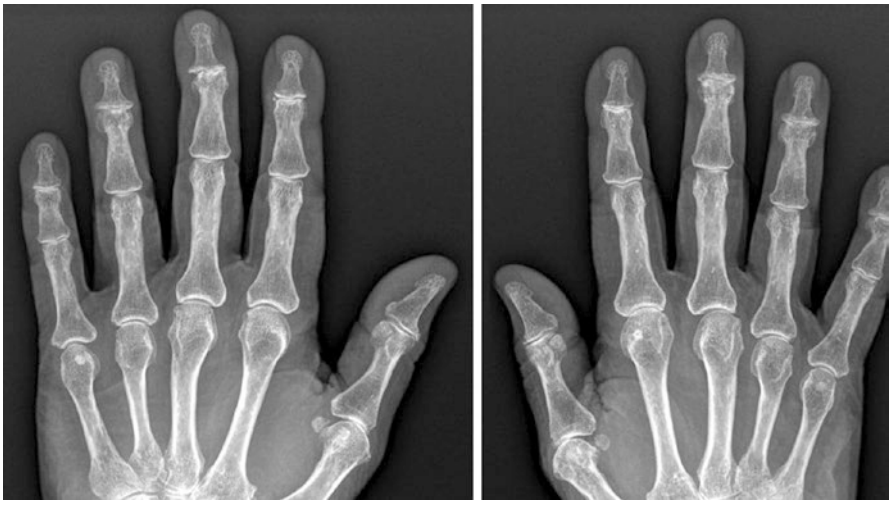

Image credit: Fardina Malik, MD

What are the next steps in treatment?

A. Add TNF inhibitor to MTX.
B. Stop MTX and start TNF inhibitor.
C. Stop MTX and start Tylenol.
D. Obtain MRI of bilateral hands.

Correct answer: C. Despite a history of skin psoriasis and history of first degree relative with psoriatic arthritis, patient's hand X-ray features are characteristics of hand OA showing "gull-wing" changes in DIPs, and she does not have clinical or laboratory symptoms of inflammatory arthritis. Therefore, stopping MTX and starting Tylenol is the most appropriate treatment option.

2. What is the mechanism of action of ustekinumab?

A. Blocks the shared p40 subunit of IL12/IL23
B. Blocks p19 subunit of IL23
C. Blocks TNF
D. Blocks IL17

Correct answer: A. Ustekinumab is an IL12/23 inhibitor that works by inhibiting the shared p40 subunits. Guselkumab blocks the p19 subunit of IL23 and secukinumab blocks IL17.

3. A 29-year-old man with history of skin psoriasis since age 12 presents severe low back pain with stiffness that lasts for more than 1 hour in the morning. Pain improves with activity and stretching. MRI shows acute, bilateral sacroiliitis. He is currently on topical medications for skin psoriasis, but still has a psoriasis body surface area of 2%. He is currently on NSAIDs, which have only partially improved his back pain. He was referred to rheumatology for further evaluation. What is the next step in management?

A. Start MTX.
B. Start anti-TNF.
C. Start Ustekinumab.
D. Continue NSAIDs and physical therapy.

Correct answer: B. In patients with axial spondyloarthritis who fail NSAIDs, the next step is management with TNF inhibitors (or secukinumab). MTX and ustekinumab did not show efficacy for axial SpA. Continuing NSAIDs and starting physical therapy could be an option; however, this patient remains symptomatic with presence of severe disease on MRI which carries risk of radiographic progression of SpA.

4. A 30-year-old female with psoriatic arthritis, severe depression, and anxiety presents with left knee and right ankle swelling. Knee joint was aspirated and shows inflammatory fluid. Thus far she has been treated solely with NSAIDs. Her skin disease is mild. What is the next best step in management?

A. Start MTX.
B. Start apremilast.

C. Continue with NSAIDs.
D. Continue NSAIDs and start prednisone.

Correct answer: A. This patient with mild skin disease and peripheral arthritis would likely benefit from starting MTX as she has continued to flare through NSAIDs alone. According to 2018 ACR guidelines, TNFis may be used for treatment of naïve patients for severe, active disease over starting with an oral small molecule (i.e., methotrexate, sulfasalazine); however, this answer choice is not given. Apremilast should not be used in patients with severe depression as there is a risk of suicidality.

5. A 38-year-old female with no past medical history presents with 5 months of low back pain. The pain is associated with morning stiffness that lasts for more than 2 hours and improved with exercise. About 2 weeks ago, she developed acute left 2nd digit toe pain after hitting it against a table. The pain has not improved despite ice and elevation. On physical exam, her toes look as below. She has limited forward bend and left SI joint tenderness. The rest of her joints are unremarkable, and she has no rashes on exam. Her father has gout and her sister has skin psoriasis. What is the most likely diagnosis?

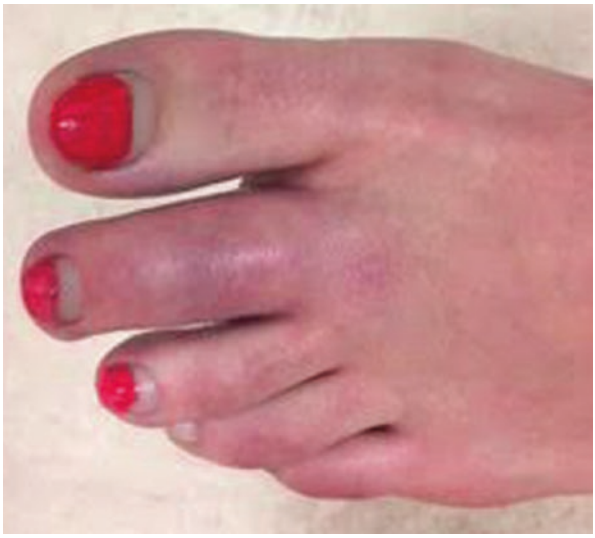

Image credit: Fardina Malik, MD

A. Gout
B. PsA
C. Trauma and mechanical strain
D. Erosive OA

Correct answer: B. This patient has classic features for PsA including inflammatory back pain and dactylitis. While she does not have psoriasis, up to 15%

of patients will not present with skin psoriasis first, and she does have a first degree relative with skin psoriasis (which is included in CASPAR criteria). Her toe swelled after a trauma and remained swollen, likely representing a flare after trauma to the region (Koenber's phenomenon). Her back pain is more indicative of inflammatory rather than trauma. Gout and OA are also less likely.

6. What gene has the strongest association with skin psoriasis?

   A. HLA DRB1
   B. HLA B27
   C. HLA Cw6
   D. HLA B08

   Answer C. Skin psoriasis is most strongly associated with HLA Cw6. Only 25% of patients with PsA are HLAB27+. HLAB08 is associated with PsA while HLA DRB1 is associated with rheumatoid arthritis.

7. Patients with PsA are at higher risk of all of the following except:

   A. Depression
   B. Diabetes mellitus
   C. Uveitis
   D. Interstitial lung disease

   Correct answer: D. Patients with PsA are at higher risk for diabetes mellitus (and metabolic syndrome), depression and anxiety, uveitis, inflammatory bowel disease, and cardiovascular disease. However, there is no increased risk of ILD in these patients.

8. A 22-year-old man with skin psoriasis presents complaining of 4 months of left hip pain. Pain is associated with significant morning stiffness that lasts for more than 1 hour and prevents from sleeping at night. On exam, he has tenderness at the L sacroiliac joint and decreased lateral bend. Exam of the bilateral hips joints is unremarkable. ESR and CRP are normal. X-rays of the bilateral hips and bilateral sacroiliac joints are normal. What is the next step in work up of this patient?

   A. Obtain CT pelvis.
   B. Obtain MRI of the SI joints with contrast.
   C. Obtain MRI of the SI joints without contrast.
   D. No further work up necessary.

   Answer. C. Despite a normal SIJ X-ray, this patient has symptoms that are very concerning for axial psoriatic spondyloarthritis. The patient should undergo an MRI to assess for any sacroiliitis and joint damage. This is best evaluated on an MRI without contrast on the STIR (short-tau inversion recovery) images, which are fluid sensitive showing bone marrow edema around the SIJ. ASAS (Assessment of Spondyloarthritis International Society) criteria for axial SpA require presence of bone marrow edema on MRI of SIJ to fulfill imaging arm.

9. Which of the following is a classic X-ray finding of peripheral PsA?

   A. "Gull wing" changes
   B. "Pencil in cup" deformity
   C. Osteophytes
   D. Large erosion with overhanging edge

   Correct answer: B. A pencil-in-cup deformity is classically seen in PsA. Gull wing changes are associated with erosive OA, osteophytes are seen in OA, and large erosions with overhanging edges are seen with gout.

10. Which of the following is not a component of CASPAR criteria?

    A. Positive RF
    B. Family history of psoriasis
    C. Psoriatic nail disease
    D. New bone formation on X-ray

    Correct answer: A. CASPAR criteria include a *negative* RF. The other options are parts of CASPAR criteria.

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Chapter 8
Axial Spondyloarthritis

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Introduction

Spondyloarthritis (previously referred to as seronegative spondyloarthropathies, herein abbreviated as SpA) is an overlapping family of disorders that share clinical features involving oligoarthritis, enthesitis, and dactylitis. The different types of spondyloarthritis are divided into two categories based upon axial versus peripheral joint involvement. Axial SpA includes predominantly ankylosing spondylitis (AS), non-radiographic axial SpA (nr-SpA), and undifferentiated SpA. AS is a type of inflammatory spine disease affecting primarily the sacroiliac (SI) joints causing back pain, stiffness, and ultimately spinal fusion. nr-SPA is defined as clinical AS without radiographic (X-ray) features but MRI features are evident. Undifferentiated SpA is defined as clinical symptoms or findings of a spondyloarthritis, but no classifiable diagnosis; generally, only SI involvement is present. The classical peripheral SpA, psoriatic (PsA), reactive, and inflammatory bowel disease (IBD)-associated SpA can involve the spine as well. Psoriatic arthritis is defined as an inflammatory arthritis in patients with skin psoriasis. Reactive arthritis is an inflammatory arthritis that develops in the setting of inciting event, such as infection, usually in the genitourinary or gastrointestinal tract. IBD-associated arthritis is an inflammatory arthritis in the setting of Ulcerative Colitis or Crohn's Disease. Sometimes, these disease processes act in a distinct manner, but there is oftentimes overlap with features of multiple processes. One of the hallmarks of this family of diseases is seronegativity for rheumatoid factor.

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Pathophysiology/Etiology

The main pathophysiologic features that differentiate SpA from other classes of inflammatory arthritides include enthesitis and bone formation. Enthesitis, which is defined as inflammation of the insertion site of tendons or ligaments to bones is a specific finding for SpA [1]. Enthesitis is now believed to be a more diffuse process that involves adjacent bone and soft tissue. Repeated biomechanical stress at this site is thought to cause microdamage that then triggers synovial inflammation leading to synovitis [2]. The most common sites of enthesitis are the Achilles' tendon, tibial tuberosity, and iliac crest. In the axial diseases, bone formation occurs not in the vertebral body, but more at the periosteum-cartilage junction. Acute and chronic spondylitis with destruction and rebuilding of the cortex and spongiosa occurs. Square vertebral body development occurs due to a combination of destructive osteitis and repair [3].

While the precise trigger(s) for SpA remain unknown, several mechanisms are supported in the literature. First, there is a strong genetic component. Within AS, the MHC class I allele HLA-B27 is strongly associated with disease. The prevalence of the HLA-B27 gene is 80–95% in individuals with AS, but only 5% of individuals in the general population with a positive HLA-B27 will go on to develop AS. Thus, the presence of HLA-B27 positivity portends 20–25% risk for AS, which increases to 40% if the individual also has a first-degree relative with AS [4].

Additional genetic risk loci in large population studies have further pointed toward altered immune function in the etiology of disease [5]. There is an emerging component of SpA pathogenesis involving HLA-B27 misfolding related to accumulation within cells leading to SpA. Improperly folded HLA-B27 proteins can accumulate in the endoplasmic reticulum, and cause activation of the IL-23/IL-17 pathway. While HLA-B27 appears to have the largest contribution in pathogenesis, there are also non-MHC genes that have been noted in the pathogenesis of SpA. Other important genes include IL-17, IL-23, ERAP1/2, TNF family, and the IBD associated genes. Some of these pathways including IL-17, IL-23, and the TNF family are therapeutic targets in SpA.

Cyclooxygenases (COX) and other proinflammatory compounds such as prostaglandins have been found to have an important role, and also constitute a therapeutic target. COX-2 is an inducible enzyme involved in the conversion of arachidonic acid to prostaglandin E2, which is involved in bone metabolism, and explains how continuous NSAID usage can prevent radiographic progression of spondylosis by inhibiting bone formation [3].

There is also a large overlap with inflammatory bowel disease, and there are at least 65 known genes overlapping between AS and Crohn's disease and ulcerative colitis. Some of these gene overlaps cause either clinical or subclinical gastrointestinal symptoms. The hypothesis regarding the GI/SpA overlap is based upon the thought of defects in the GI mucosal barriers allowing a systemic immune response with the activation of IL-23. Th17 cells then secrete IL-17 and stimulate TNF-alpha producing monocytes that initiates the development of SpA [6].

Epidemiology

In the United States, the overall prevalence of all forms of SpA is 0.9% (CI 0.7–1.1), and is higher in women (1.3 vs 0.4%) [7]. AS has a prevalence in the United States of 0.13% [8]. The prevalence of AS is less in other continents, in Europe being 0.12–1.0%, Asia 0.17%, Latin America 0.1%, and Africa 0.07% [9]. PsA in the United States has a prevalence between 0.10% and 0.16%. There is limited data with regard to the prevalence of IBD-SpA, but Italian studies have shown 0.09% and Swedish studies 0.02%. Reactive arthritis has a prevalence between 0.09% and 1.0% [10].

Diagnosis

The diagnosis of SpA is based largely upon the history, physical exam, and imaging. The Assessment of Spondyloarthritis International Society (ASAS) classification criteria were developed to categorize research subjects with either axial or peripheral disease but have not been validated for clinical use (Table 8.1) [11]. Nevertheless, these criteria establish a guide for a clinician's assessment of a patient with suspected SpA.

Table 8.1 ASAS criteria for the diagnosis of spondyloarthropathy [11]

Axial SpA		Peripheral SpA	
Back pain ≥3 months Age of onset <45 years		Peripheral arthritis and/or enthesitis and/or dactylitis and either column below	
Sacroiliitis on imaging (Acute inflammation on MRI OR definite radiographic sacroiliitis) AND ≥1 SpA feature (next column)	HLA-B27 positive AND ≥2 other SpA features: Inflammatory back pain Arthritis Enthesitis Uveitis Dactylitis Psoriasis IBD NSAID response Family history of SpA HLA-B27 Elevated CRP	≥1 SpA feature: Uveitis Psoriasis IBD Preceding infection HLA-B27 Sacroiliitis on imaging	≥2 other SpA features: Arthritis Enthesitis Dactylitis Inflammatory back pain Family history of SpA

Patient History

The patient history is an important feature in the diagnosis of SpA. Classic historical features involve inflammatory back pain, enthesitis, peripheral arthritis, and dactylitis. The cornerstone for diagnosis of axial SpA is dependent on the patient reporting the presence of inflammatory back pain lasting longer than 3 months, which began in an individual before the age of 45 years old. Inflammatory back pain is defined as having an insidious onset, improving with exercise and not with rest, and oftentimes pain at night that improves upon getting up and moving. Peripheral SpA is based upon a history of oligoarticular arthritis, enthesitis, or dactylitis. There are other historical non-musculoskeletal features that are important to elucidate and include inflammatory eye symptoms (photophobia, blurred vision), inflammatory bowel symptoms (diarrhea, hematochezia), recent GI or GU infection, and psoriasis. As one hallmark of SpA is a favorable response to NSAIDs, it is useful to assess if the patient has tried these drugs and their effect on the presenting symptoms. Finally, family history of SpA, psoriasis, uveitis/iritis, or IBD should be assessed.

Physical Exam

On physical exam, it is important to evaluate for axial, peripheral, and non-musculoskeletal findings. Axial symptoms can be investigated by looking for low back pain associated with sacroiliac joint tenderness and decreased range of motion. There are multiple objective measurements that can be performed to monitor disease progression over time. These include the Schober's test (measuring lumbar flexion distance at the level of L5), occiput-to-wall (measuring cervical neck extension), lateral spine side flexion, thoracic chest expansion, and hip internal rotation. Enthesitis is a hallmark of SpA, and there are multiple sites of ligament and tendon insertions that can be evaluated, but most commonly the Achilles tendon insertion of at the heel is assessed. There are multiple validated enthesitis indices from the Berlin Enthesitis Index (BEI), Masstricht AS Enthesitis Score (MASES), and Spondyloarthritis Research Consortium of Canada (SPARCC) that can be performed [12]. A full peripheral joint exam should be performed to assess for tenderness, effusions, warmth, and limitation of range of motion as well as evidence of dactylitis in the fingers or toes.

A full physical exam should additionally be conducted to evaluate for extra-articular manifestations. This should include a thorough skin evaluation to look for signs of psoriasis along extensor surfaces, behind ears, in the umbilicus, and within the crease of the buttocks; evaluation for signs of gastrointestinal or sexually transmitted diseases; and evaluation for SpA comorbidities such as cardiovascular and respiratory disease.

Lab Testing

There are no diagnostic labs for SpA. Common lab tests include HLA-B27 and acute phase reactants such as ESR or CRP, which may serve to support clinical suspicion. It is important to note that the absence of these does not rule out SpA. Additional tests may be ordered related to details of the history and physical exam, such as fecal calprotectin or sexually transmitted infection testing if considering IBD-associated SpA or reactive arthritis, respectively. All patients need to be assessed for blood cell counts, liver and kidney function, hepatitis and HIV screening, and TB screening depending upon their treatment plan.

Imaging

X-rays are the first-line imaging modality, which can demonstrate SI joint abnormalities ranging from blurring of the joint margins to evidence of sclerosis and erosions and ultimately with complete joint fusion. These images can also be obtained using the Ferguson view, entailing a 20-degree caudocephalic AP X-ray. The findings are usually bilateral in SpA, and unilateral findings should prompt one to consider alternative diagnoses. Spinal X-rays in AS can demonstrate vertebral body squaring, shiny corner sign (small erosions at the corners of the vertebral bodies), ossification of spinal ligaments/discs, enthesophytes, and progressive bamboo spine. Peripheral joint X-rays are more variable and may not always demonstrate abnormality. However, in PsA, X-rays in established disease often demonstrate erosive disease, particularly in the hands and feet in which the classic pencil-in-cup appearance of IP joints can be observed.

MRI can also be performed in the appropriate clinical setting, such as a high suspicion for axial SpA in the setting of normal X-rays but a suspicious clinical history. The most appropriate MRI sequences to identify SI joint inflammation are T1 and STIR. MRI findings will demonstrate synovial enhancement and increased STIR signal representing edema during acute inflammation and increased T1 signal representing bone marrow metaplasia suggesting past inflammation.

Imaging can also be useful for monitoring progression over time or to determine changes in therapy. For example, a patient with AS may complain of continued back pain while on therapy, and X-rays have not changed in the past several years. In this case an MRI can help determine if features of joint inflammation are present to warrant therapy changes.

Differential Diagnosis

Based upon the appropriate workup, an appropriate differential diagnosis must be considered that includes both inflammatory and noninflammatory disorders. Other disease processes to consider include the following: mechanical back pain, osteoarthritis, fibromyalgia, diffuse idiopathic skeletal hyperostosis (DISH), iliac condensans ilii, Paget's disease, Brucellosis, Whipple's disease, SI joint infection, gout, and osteochondrosis.

Treatment

The 2016 SPARTAN/GRAPPA recommendations for the management of axial SpA support use of physical therapy for all patients. NSAIDs are recommended as first-line therapy, followed by TNF-inhibitors and then alternate biologic agents [13]. Specific agents and uses are discussed below.

NSAIDs

The first line of therapy for all SpAs is scheduled high-dose NSAIDs. After the initial diagnosis of axial SpA, the treatment requires a minimum of two separate NSAIDs at maximum dosage for a total of 2–4 weeks each before escalation of therapy. Consideration must be taken with other comorbidities such as coronary artery disease and chronic kidney disease and the risk of long-term NSAID usage. NSAIDs have demonstrated an ASAS20 (20% partial response) rate of >70% and ASAS40 (40% partial response) rate of >50% in patients that start with an NSAID [14].

Conventional Synthetic DMARDs

Conventional synthetic DMARDs are generally ineffective in the setting of axial disease, but can be beneficial in peripheral joint symptoms. Sulfasalazine has demonstrated some efficacy in the setting of peripheral arthritis and decreased inflammatory markers, with no evidence for benefit in spinal mobility, patient/physician assessment, or enthesitis [15]. Methotrexate has been found to have similar lack of efficacy with regard to axial symptoms but also found to have lack of efficacy for peripheral joint symptoms in AS [16]. For PsA, though, the csDMARDs methotrexate, sulfasalazine, leflunomide, and cyclosporin all have demonstrated efficacy for arthritis and varying results for skin [17].

Biologic DMARDs

There are a number of biologic medications that have been FDA approved for SpA or are under investigation. Table 8.2 summarizes currently approved medications, targets, and indications. TNF-alpha inhibitors such as infliximab, etanercept, adalimumab, golimumab, and certolizumab are first-line biologic therapies and highly effective. The number needed to treat to achieve partial remission is between 2.3 and 6.5 [18]. Whether TNF-inhibitors halt radiographic progression remains a question; overall, they may not have a significant impact, but early (within 5 years of disease onset) and sustained use may reduce progression [19]. Etanercept has less clinical efficacy in the setting of GI symptoms and uveitis [20]. The most significant contraindications to TNF-inhibitor therapy include active infection (including latent or active tuberculosis), advanced heart failure, systemic lupus erythematosus, and multiple sclerosis.

Newer FDA-approved biologics target the Th17 pathway. The side effect profile of these agents is similar to TNF-inhibitors. There is some caution advised for use of IL-17 inhibitors in individuals with IBD as there is rare occurrence of developing IBD while on the drug and the phase II trial of secukinumab in Crohn's disease demonstrated worsening of bowel inflammation [21].

Abatacept acts on T-cell costimulation and is currently approved for PsA. Abatacept prevents CD28 from binding to CD80/CD86. The side effect profile of abatacept is similar to TNF-alpha inhibitors.

Target-Specific DMARDs

Apremilast is a newly approved medication that is indicated for PsA. The mechanism of action involves inhibition of phosphodiesterase-4. Clinical efficacy has been shown in multiple clinical trials, and it is recommended not to be used in combination with other biologic medications.

Table 8.2 Currently approved biologic medications with target and indication

Drug	Target	Indication
Infliximab	TNF-alpha	PsA, AS, IBD associated SpA
Etanercept	TNF-alpha	PsA, AS
Adalimumab	TNF-alpha	PsA, AS, IBD-associated SpA, uveitis
Golimumab	TNF-alpha	PsA, AS
Certolizumab	TNF-alpha	PsA, AS, nr-SpA
Secukinumab	IL-17A	PsA, AS
Ixekizumab	IL-17A	PsA
Ustekinumab	IL-12 and IL-23 common subunit (p40)	PsA
Abatacept	T-cell co-stimulation	PsA
Apremilast	Phosphodiesterase-4	PsA
Tofacitinib	JAK kinase	PsA

Janus kinase (JAK) inhibitors are currently also being investigated for use in the treatment of SpA. Thus far tofacitinib has been approved for PsA with numerous others currently in the clinical trial phase. Clinical trials have shown tofacitinib to be comparable in efficacy to TNF-alpha inhibitors.

Other Treatments

Other important treatment modalities for patients with SpA include physical therapy (PT), intra-articular steroid injections, and possible surgical interventions to help with pain and quality of life. Physical therapy has a large role in the management of pain and physical function. Cochrane review data shows that an individual home based or supervised exercise program is better than no intervention, supervised PT is better than home exercise, and spa-exercise therapy with PT is better than PT alone [22]. Intra-articular injections can be beneficial in the management of isolated inflamed joints, including SI joints, and systemic steroids can have a role in peripheral disease (ineffective in axial disease). It is generally advised to avoid any type of surgery in axial SpA except for emergent situations due to risk of severe fracture.

Disease Monitoring

Regular follow-up is recommended to assess disease activity and determine whether a change in therapy is indicated. Clinically, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) can be utilized (Table 8.3) [23]. A thorough history and exam should be performed at each visit and imaging considered. The clinical measurements that are listed above in the examination section such as Schober's test and occiput-to-wall measurements can be performed and help guide therapy. The combination of patient reported symptoms, physical exam findings (including measurements), lab data, and imaging can all help to guide therapy and decide whether or not an escalation or change in therapy is warranted.

Comorbidities

There are a number of relevant comorbidities in patients that have SpA, including cardiovascular disease (CVD), obesity, diabetes, inflammatory bowel disease, ophthalmic disease, malignancy (lymphoma), restrictive lung disease, liver/kidney disease, and depression/anxiety. Cardiovascular disease has an incidence between 3.3% and 9.6% in patients with PsA [24], and a hazard ratio of 1.41 relative to

Table 8.3 BASDAI score for AS disease severity [23]

Answer the following questions on a scale from 1 (minimal) to 10 (severe) for activities during the past week
1. How would you describe the overall level of fatigue/tiredness you have experienced?
2. How would you describe the overall level of ankylosing spondylitis neck, back, or hip pain you have had?
3. How would you describe the overall level of pain/swelling in joints other than neck, back, or hips you have had?
4. How would you describe the overall level of discomfort you have had from any areas tender to touch or pressure?
5. How would you describe the overall level of discomfort you have had from the time you wake up?
6. How long does your morning stiffness last from the time you wake up? Scale from 0 to 2 hours
Scoring:
1. Add up the scores from questions 1 to 4
2. Add up the scores from questions 5 and 6, then divide by 2
3. Add the results of parts 1 and 2 for a total BASDAI score
Interpretation:
Scores ≥4 indicate high disease activity and need for aggressive treatment

matched controls in AS [25]. The rheumatologist should help manage cardiovascular risk in conjunction with the Primary Care Physician. EULAR recommendations for CVD management include optimally controlling rheumatologic risk and using NSAIDs with caution. Basic screening should be performed with regard to monitoring blood pressure, monitoring lipids, and counseling on smoking cessation. Other relevant screening should be performed such as monitoring for obesity with appropriate counseling, monitoring fasting blood glucose or hemoglobin A1C, monitoring liver and kidney labs, and monitoring for symptoms regarding eye or GI involvement of disease.

Prognosis

Overall outcomes are generally good for SpA if diagnosed and treated in an appropriate amount of time; however, up to 30% of patients with SpA will be on disability 20 years after diagnosis [26]. Earlier diagnoses usually manifest as undifferentiated SpA, which carries a 40% progression rate to diagnosed AS [27]. Patients with SpA are at high risk of bone fracture, and require close monitoring for bone health, as well as an ongoing need for physical and occupational therapy. Trauma is also a concern in these patients, as the higher rate of spinal fracture can lead to neurologic emergencies such as spinal cord impingement or cauda equina syndrome.

Questions

1. A 45-year-old man with known psoriasis and psoriatic arthritis presents to clinic with worsening skin plaques. Symptoms were previously well controlled on Etanercept. The patient reports abrupt worsening of plaques diffusely across his trunk, elbows, and knees.

   On examination, the patient has a temperature of 100.8 degrees Fahrenheit and is hemodynamically stable. Synovitis is noted diffusely throughout the bilateral PIPs, DIPs, wrists, knees, and ankles. Skin plaques are noted diffusely throughout the aforementioned areas.

   What is the next appropriate step in the management of this patient?

   A. HIV testing
   B. HLA-B27 testing
   C. Blood cultures and empiric antibiotics
   D. Switch etanercept to adalimumab

   Correct answer: A
   Explanation: This question addresses the concerning situation of rapidly progressive, widespread psoriasis in the setting of HIV infection. A patient who is well controlled on current therapy with a rapid progression of psoriasis (and psoriatic arthritis) warrants evaluation for HIV. There is no indication to check HLA-B27 (choice B) as this patient has known Pso/PsA and a positive HLA-B27 would not change management. There does not appear to be a systemic bacterial infection despite the mild fevers, and this patient is otherwise stable. Diffuse joint pain with synovitis is unlikely to be infectious. Thus, there is no indication for blood cultures and empiric antibiotics (choice C). A change in therapy could be considered if there were an insidious worsening of symptoms, but this question stems around a more rapid, abrupt progression in symptoms. There is no indication to change medication management at this point (choice D).
2. A 22-year-old woman presents to clinic with worsening low back pain. Her symptoms are worse in the morning, and she describes approximately 1 hour of low back stiffness that resolves with ambulation. She also describes symmetric buttock pain without radiation to her legs. There is no history of trauma. Over-the-counter ibuprofen has helped somewhat with pain control.

   On examination, vital signs are normal. There is tenderness to palpation in both sacroiliac joints. Range of motion testing is normal. There is no evidence of peripheral arthritis or skin rash. X-rays of the lumbar spine and sacroiliac joints are unremarkable. ESR is elevated to 60 mm/hour, and HLA-B27 is positive.

   What is the next step in obtaining a diagnosis?

   A. No further testing is required.
   B. MRI of lumbar spine and SI joints.
   C. RF and CCP.
   D. CRP.

Correct answer: B

Explanation: This question is describing a patient with inflammatory low back pain: morning stiffness that improves with ambulation and buttock pain without radiation into the legs are significant clues. Exam findings of bilateral SI joint tenderness, elevated inflammatory markers and positive HLA-B27 are consistent with the clinical suspicion for SpA. X-rays do not demonstrate any abnormalities in the lumbar spine or SI joint. The next best step would be MRI of the lumbar spine and SI joints (choice B) to confirm axial inflammation. MRI is a better imaging modality and can detect early SI joint inflammation before X-ray findings are apparent. There is no indication to check RF and CCP (choice C), as the patient's symptoms are more concerning for SpA than rheumatoid arthritis. CRP (choice D) would not change management. MRI would be the next appropriate step for diagnosis verification rather than presumption (choice A).

3. A 22-year-old man presents to clinic with 2 weeks of worsening bilateral ankle pain. He reports that his pain is worse in the morning when he wakes up, and generally lasts for approximately 45 minutes. He reports no other joint symptoms or rashes. He has a history of *Clostridium difficile* infection approximately 5 weeks ago that was successfully treated with oral vancomycin. There has been no further diarrhea or gastrointestinal symptoms. No recent sexual contacts.

   On examination, vital signs are normal. There is redness, warmth, and swelling of the bilateral ankles. The remainder of the physical exam is normal. Labs reveal an elevated ESR to 46 mm/hour. X-rays of both ankles are normal.

   What is the next step in the management of this patient?

   A. Joint aspiration
   B. Gonorrhea and chlamydia testing
   C. RF and CCP
   D. No further workup

   Correct answer: D

   Explanation: A young healthy male with lower extremity inflammatory oligoarthritis is concerning for reactive arthritis in the setting of recent GI infection. This patient describes inflammatory arthritis symptoms 5 weeks after *C. difficile* infection. While his GI symptoms are improving, arthritis has now developed. Both ankles have effusions and inflammatory markers are elevated. Reactive arthritis is a clinical diagnosis in the appropriate setting, such as this patient with recent GI infection. It is unlikely to have bilateral septic or crystalline arthritis so there is no indication for aspiration (choice A). He has no recent sexual contacts and no GU symptoms, so there is no indication for STI testing (choice B), although gonococcal arthritis can present similarly. While acute lower extremity inflammatory arthritis could possibly be rheumatoid arthritis (choice C), this is less likely in the clinical context and would not be a classic presentation. There is no indication for further workup, and conservative management (NSAIDs) is appropriate.

4. A 31-year-old woman is diagnosed with non-radiographic SpA. She is initially started on high-dose NSAID treatment for 1 month and changed to a different NSAID 1 month later due to lack of efficacy and continued low back pain. At a follow-up visit 1 month following initiation of the second NSAID, she continues to report approximately 1 hour of morning stiffness with significant bilateral SI joint tenderness on examination. She reports no peripheral joint symptoms, and no eye or gastrointestinal symptoms.

   What is the next therapeutic step in the management of this patient?

   A. Start methotrexate.
   B. Start certolizumab.
   C. Continue NSAIDs.
   D. Start ustekinumab.

   Correct answer: B
   Explanation: Non-radiographic SpA is a clinical diagnosis in which classical X-ray findings are absent but the MRI demonstrates inflammation. She has failed an appropriate trial of two separate NSAIDs, and it is time to start a biologic medication (choice B) according to SPARTAN-SAA-GRAPPA guidelines. Methotrexate is helpful with peripheral joint symptoms, but does not help axial symptoms (choice A). It would not be appropriate to continue NSAIDs at this point as this patient has already failed two separate therapeutic trials (choice C). She has no contraindications to biologic therapy that are mentioned, and certolizumab would be appropriate as an approved TNF-inhibitor for nr-SpA. Ustekinumab is currently FDA approved for psoriatic arthritis, and not for nr-SpA (choice D).
5. A 62-year-old man with ankylosing spondylitis is involved in a motor vehicle accident. On evaluation by EMS the patient is having mild symmetric weakness in his bilateral legs. There is no loss of urine or stool. Vital signs are stable.

   The patient has an extensive history of ankylosing spondylitis with near complete fusion of his lumbar spine. He has remained on adalimumab for many years without complications. He has required a walker for ambulation due to significant back disease.

   The patient is stabilized in the field and transported to the nearest trauma center. What is the next step in evaluation of this patient?

   A. EMG
   B. Spine MRI
   C. Physical therapy
   D. Emergent neurosurgery evaluation

   Correct answer: D
   Explanation: This patient has advanced AS with spinal fusion. He was involved with a motor vehicle accident, and his complaints of mild symmetric leg weakness are very concerning for spinal fracture. Patients with SpA are higher risk for fracture, and this patient has symptoms associated with spinal cord damage. This requires emergent neurosurgical evaluation for repair (choice D). Spine MRI (choice B) or CT will need to be considered at some point on arrival to a

trauma center, but the lower extremity weakness needs to be evaluated for emergent surgery. After further workup, it could be reasonable to consider EMG (choice A) or physical therapy (choice C) if this was found to not be a surgical process.

6. A 66-year-old woman presents with worsening lower back pain over the past 5 years. She reports having approximately 1 hour of morning stiffness daily. High-dose ibuprofen was tried by her primary care provider with some improvement in symptoms. Laboratory data demonstrate a positive HLA-B27.

   X-rays are notable for SI joint sclerosis along the ileal margin and small osteophytes at the inferior aspects bilaterally. There are no erosions, joint space narrowing, or subchondral sclerosis.

   Which of the following is the most likely diagnosis?

   A. Ankylosing spondylitis
   B. Osteitis condensans ilii
   C. Osteoarthritis
   D. Psoriatic arthritis

   Correct answer: B
   Explanation: Osteitis condensans ilii is a mimic of SpA caused by sclerosis of the ileal bone next to the SI joints, usually in a triangular pattern on X-rays. This causes SI joint pain that can present similar to SpA. This 66 year old female with 5 years of low back pain is unlikely to be classified with axial SpA at the age of 61 (choice A) per ASAS criteria. While this could be osteoarthritis (choice C), the presence of ileal sclerosis on X-rays indicates osteitis condensans ilii (choice B) as the more likely cause. This is unlikely to be psoriatic arthritis given only axial involvement with no evidence of skin psoriasis (choice D).

7. A 78-year-old man presents to his PCP with worsening back pain. The patient reports the symptoms have been worsening over the past year. Pain is diffuse throughout the spine, causing significantly decreased range of motion and mobility. The symptoms have no temporal relation, and acetaminophen causes some relief.

   On examination, vital signs are normal. There is bilateral bony hypertrophy of both knees with crepitus. There is minimal tenderness to palpation along the spine. Decreased range of motion is present throughout the thoracic and lumbar spine, with pain on extension and flexion.

   X-rays demonstrate contiguous osteophytes from T12-L4. Sacroiliac joints are patent with no evidence of sclerosis. There is no spinal canal narrowing or notable degenerative disease.

   What is the most likely diagnosis?

   A. Osteoarthritis
   B. Diffuse idiopathic skeletal hyperostosis
   C. Ankylosing spondylitis
   D. Rheumatoid arthritis

   Correct answer: B

Explanation: This patient presents with diffuse back pain that is noninflammatory in nature. There is decreased range of motion throughout the spine. X-rays show contiguous osteophytes from T12-L4, which is a finding associated with diffuse idiopathic skeletal hyperostosis (DISH, choice B). DISH is a disorder identified by abnormal calcification and bone formation throughout the anterior longitudinal ligament in a continuous pattern of multiple vertebrae and occurs more often on the right side. These presenting symptoms could be due to osteoarthritis, but with diffuse pain and X-rays lacking evidence of degenerative disease, it would be unlikely to have such significant symptoms (choice A). Ankylosing spondylitis is unlikely given the patient's age, lack of predominant low back symptoms, and noninflammatory presentation (choice C). Rheumatoid arthritis is unlikely to present with isolated back pain with no peripheral involvement, as well as a lack of inflammatory symptoms (choice D).

8. What is the mechanism of action of secukinumab?

   A. IL-12/23 inhibition
   B. TNF-alpha inhibition
   C. T-cell costimulation inhibition
   D. IL-17A inhibition

   Correct answer: D
   Explanation: Secukinumab is an IL-17A inhibitor (choice D). It is currently FDA approved for psoriatic arthritis and ankylosing spondylitis. Ustekinumab is another interleukin inhibitor that acts on IL-12/23 (choice A), and is currently approved for psoriatic arthritis. Numerous TNF-inhibitors (choice B) are approved for multiple indications related to SpA. Abatacept acts on T-cell costimulation by preventing CD28 from binding to CD80/CD86 (choice C).

9. A 54-year-old man with known PsA and psoriasis presents for follow-up. He has previously been on adalimumab, etanercept, infliximab, secukinumab, and methotrexate, which were stopped due to adverse reactions or loss of efficacy. The patient is currently experiencing worsening joint pain throughout, as well as worsening plaque psoriasis compared to last visit. A decision is made to start tofacitinib.

   In addition to a blood cell counts and liver and kidney function, which of the following must be monitored while on tofacitinib?

   A. Hemoglobin A1C
   B. Lipid panel
   C. Pulmonary function tests
   D. Creatinine

   Correct answer: B
   Explanation: This patient has psoriatic arthritis with significant disease that has been difficult to manage. He has failed csDMARD therapy, as well as three TNF-inhibitors and one IL-17A inhibitor. Thus, the plan is to start JAK kinase inhibitor, tofacitinib. One potential side effect of tofacitinib is elevated cholesterol, which must be monitored at baseline, 4–8 weeks after initiation of tofaci-

tinib, and then every 3 months (choice B). If cholesterol levels rise, a statin should be initiated based upon ASCVD risk guidelines. Tofacitinib has no known effect on hemoglobin A1C (choice A), and monitoring should be based on patient risk factors for diabetes. There is no noted chronic pulmonary side effects related to tofacitinib (besides increased infection risk), and there is no indication for monitoring pulmonary function tests (choice C). There is no significant effect on kidney function while on tofacitinib (choice D).

10. A 47-year-old man with ankylosing spondylitis presents to his Primary Care Physician's office for a routine physical. He has not seen his PCP in multiple years. He also has a history of GERD and osteoarthritis. For his ankylosing spondylitis, his symptoms have been well controlled on Etanercept for many years.

    Which of the following is the most important screening measure?

    A. Depression screen
    B. Colonoscopy
    C. Lipid panel
    D. DEXA scan

    Correct answer: C
    Explanation: Patients with a history of SpA have an increased risk for cardiovascular disease. Appropriate screening and monitoring must be performed to help minimize cardiovascular risk factors. While this 47 year old male does not have traditional risk factors for cardiovascular disease (coronary artery disease, diabetes, hyperlipidemia, etc.), his history of ankylosing spondylitis puts him at increased risk. He has not had a physical with blood work in years, and the most appropriate screening would be a lipid panel (choice C) to stratify risk and determine if statin therapy is indicated. There is no physiologic reason for a depression screen (choice A) beyond routine primary care practices. A colonoscopy (choice B) is not indicated until the age of 50 unless there is a history of colon cancer in a first-degree relative or the patient is experiencing GI symptoms (diarrhea, hematochezia, etc.). There is no indication for DEXA screening (choice D) in this 47-year-old male that does not appear to have a history of risk factors for osteoporosis.

11. A 54-year-old man with ankylosing spondylitis presents for routine follow-up with his rheumatologist. His joint symptoms are currently well controlled on adalimumab monotherapy. Routine labs are unremarkable.

    Which of the following should be addressed in an appropriate review of systems?

    A. Eye pain or redness
    B. Pain in the Achille's tendons
    C. Changes in bowel habits
    D. All of the above

    Correct answer: D

Explanation: SpA is a spectrum of disease, and numerous extra-articular manifestations can occur. This male currently has well-controlled ankylosing spondylitis, but it is important to assess for the development of comorbidities. An appropriate review of systems includes questions screening for uveitis (choice A), enthesitis (choice B), IBD-associated symptoms (choice C), as well as other comorbidities such as CVD, obesity, diabetes, dyspnea, and depression

12. A 64-year-old man with PsA presents for follow-up several months after being his initial diagnosis. He has failed naproxen and meloxicam with appropriate length trials. On examination, he has diffuse psoriatic plaques and synovitis in his DIPs and PIPs. His other comorbidities include well-controlled type 2 diabetes, coronary artery disease, and heart failure with an ejection fraction of 25%.

    Which of the following is the most appropriate therapeutic to prescribe?

    A. Adalimumab
    B. Secukinumab
    C. Indomethacin
    D. Etanercept

    Correct answer: B
    Explanation: This patient is presenting for follow-up evaluation after an appropriate trial of two separate NSAIDs and still presenting with active psoriatic arthritis. The next most appropriate step at this point is to escalate therapy to a biologic medication. It would not be appropriate to prescribe a third NSAID (choice C) due to already failing two other NSAIDs. When choosing an appropriate biologic therapy, it is important to consider other medical comorbidities that could complicate treatment. This patient has systolic heart failure with an ejection fraction of 25%, and there is a relative contraindication to TNF-inhibitors in the setting of advanced heart failure (choice A and D). Interleukin inhibitors such as secukinumab (choice B), ustekinumab, and ixekizumab are approved for the treatment of psoriatic arthritis, and would represent appropriate therapeutic options.

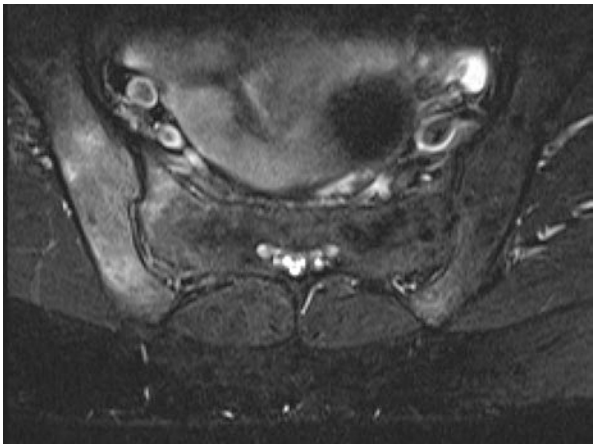
13. A 24-year-old woman presents for evaluation of persistent low back pain for the past 4 months. Symptoms are worse in the morning and result in approximately 90 minutes of morning stiffness. Nothing makes symptoms better or worse. Labs are remarkable for a normal ESR and CRP, and a negative HLA-B27. On examination the patient is nontoxic appearing, and there is tenderness to palpation in the bilateral SI joints. X-ray is obtained using the Ferguson view with normal appearing SI joints. MRI is ordered and demonstrated below.

    What is the most likely diagnosis?

    A. Mechanical back pain
    B. Osteitis condensans ilii
    C. Ankylosing spondylitis
    D. SI joint infection

    Correct answer: C

Explanation: This woman's clinical presentation with a 4-month history of inflammatory back pain is concerning for axial SpA. Laboratory testing is uninformative; ESR and CRP are infrequently elevated in SpA. The X-ray is unremarkable for any SI joint involvement, but an MRI is ordered to aid in diagnosis given the presence of inflammatory back pain. The MRI image is from a STIR sequence and demonstrates bilateral SI joint bone marrow edema, left side greater than right, suggestive of inflammation. The most likely diagnosis overall is ankylosing spondylitis (choice C). It is unlikely that this patient has simple mechanical back pain (choice A) as the presenting symptoms are



inflammatory in nature and the MRI demonstrates SI joint inflammation. Osteitis condensans ilii is a mimic of ankylosing spondylitis, but tends to occur in older females who are multiparous and have a triangular pattern on imaging. There is nothing in the question stem that would be concerning for SI joint infection (choice D), and the MRI makes it unlikely given the bilateral involvement of the SI joints.

14. A 54-year-old man presents to rheumatology with a complaint of back pain for the past 3 months. His pain is worse in the morning, with approximately 20–30 minutes of morning stiffness. He also has occasional arthralgias in the hands, knees, and ankles. Two weeks ago, the patient developed intermittent diarrhea and abdominal pain. The diarrhea is described as watery, without evidence of blood or mucus. He has lost approximately 8 pounds in the past week.

    On examination, he is nontoxic appearing with normal vital signs. There are multiple tender joints, but no synovitis. There is no tenderness to palpation in the bilateral SI joints.

    Lab results demonstrate evidence of an elevated ESR and CRP. HLA-B27 is negative. RF and CCP are negative. X-rays are performed and demonstrate no peripheral erosions and no evidence of SI joint inflammation.

Which of the following is the most likely diagnosis?

A. Ankylosing spondylitis
B. Seronegative RA
C. IBD-associated SpA
D. Whipple's disease

Correct answer: D
Explanation: This patient presents with low back pain and oligoarthritis for the past 3 months associated with watery diarrhea for 2 weeks and weight loss. The examination is notable for no synovitis and no tenderness in the SI joints despite it being the main presenting complaint. Laboratory workup is remarkable only for elevated inflammatory markers, and X-rays demonstrate no evidence of inflammatory arthritis or SpA. This question introduces a rare mimic of SpA (and other inflammatory arthridites), and is meant to be a case of Whipple's disease (choice D). Whipple's disease caused by *Tropheryma whipplei* can mimic SpA and rheumatoid arthritis. This is unlikely to be ankylosing spondylitis (choice A) given the age of the patient. This could potentially be seronegative RA (choice B), although the absence of synovitis on exam argues otherwise; however, the diarrhea and weight loss are clues that there may be another etiology. It would be unusual for this to be a presentation of IBD-associated SpA (choice C) given the lack of inflammatory symptoms and the presence of watery diarrhea, but it should be considered on the differential.

15. A 30 year-old man with HLA-B27+ AS returns to your office for follow-up of his disease. He has been on golimumab since his diagnosis nearly 10 years ago and states that he is feeling well. His exam is unchanged and BASDAI is 1. He recently got married and asks regarding the risk of his children having this disease. Which of the following are true?

A. 40% of individuals with the presence of an HLA-B27 allele and a first-degree relative will develop AS.
B. Male children will have an increased risk of AS compared to his female children.
C. Additional genes such as NOD2 (CARD15) increase the risk of developing AS.
D. All of the above.

Correct answer: A
Explanation: The question of disease inheritance is fairly common among patients with rheumatologic disease. Genetic studies have shown the strongest linkage between HLA-B27 and AS. Epidemiologic studies have shown that then incidence of HLA-B27 to be present in the overwhelming majority of cases, but only ~5% of individuals with this gene develop disease. The presence of HLA-B27 and a first-degree relative with AS increases the incidence of disease to 40% (choice A). Although, interestingly, there is an increased risk of AS if one's mother had disease compared to one's father, there is no difference in

risk of AS between male and female offspring (option B). While there are overlapping genetic risk loci between IBD and AS, NOD2/CARD15 is unique to Crohn's disease (choice C). Shared genetic risk loci between IBD and AS lie within the IL-17, IL-23, and TNF pathways.

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Chapter 9
Systemic Lupus Erythematosus (SLE)

Teja Kapoor and Pooja Mahadeshwar

Systemic Lupus Erythematosus Demographics and Epidemiology

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease characterized by the production of autoantibodies that lead to systemic inflammation and multi-organ involvement. It affects approximately 130 out of every 100,000 people in the United States [1]. Significant gender, racial, and ethnic disparities exist in SLE. There is a tenfold higher prevalence of SLE in women compared to men and a 2.3-fold higher prevalence of SLE in non-whites (including African American, Hispanic, Asian) compared to whites [2, 3]. In some cohorts, the prevalence of SLE in blacks can be as high as 1 in 537. The extent and severity of disease manifestations, while varying widely among individuals, also demonstrate racial disparities. Among SLE patients, those of the black race or Hispanic ethnicity have greater severity of disease activity, greater likelihood of renal involvement, and earlier age of disease onset [2, 3].

While chronic organ damage is the late result of uncontrolled inflammation and treatment side effects, infections in SLE patients present an early risk of major morbidity and mortality. Deregulation of the immune system in SLE and standard treatment with immunosuppression are two major factors that make SLE patients particularly at risk for infection.

A bimodal pattern of mortality is seen in SLE with early deaths caused by either the occurrence of infections or uncontrolled inflammation from the disease itself and late deaths resulting from cardiovascular disease or malignancies such as lym-

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phomas [4]. With the growth in treatment options, life expectancy of lupus patients has improved from a 4-year survival rate of 50% in the 1950s to a 15-year survival rate of 80% [4].

Role of Genetics in SLE

Genetics plays a significant role in the development of SLE. Studies on monozygotic and dizygotic twins demonstrate a hereditary predisposition for SLE. A monozygotic twin has a 25–50% risk of developing SLE, while a dizygotic twin has a 2–5% risk [4, 5]. Studies have demonstrated alterations in particular genes that increase the risk of autoimmunity and thus development of SLE. For example, whole genome scans of families that include multiple members with SLE have identified multiple loci, particularly in major histocompatibility complex (MHC) genes HLA-DR2 and HLA-DR3 that can improve self-antigen presentation to T-cells and B-cells [4, 5]. Deficiencies of the early complement system (C1q, C2, C4) can alter the clearance of apoptotic cellular debris, increase self-antigen presentation by reactive T-cells, and increased type I interferon production [4, 5]. Alleles, such as IRF5, IRF7, TNFAIP3, and TREX1, that lead to alterations in toll-like receptors and type I interferon production can increase activation of innate immunity [5].

Environmental Risk Factors for SLE

Environmental factors may also contribute to the development of SLE. Such factors may include a preceding viral infection, particularly Epstein-Barr virus (EBV). A case-control study involving children and young adults demonstrated the presence of anti-EBV antibodies in 99% of patients who developed SLE and the presence of EBV DNA in 100% of patients who developed SLE [4]. Ultraviolet radiation from sun exposure has also been known to activate and exacerbate skin manifestations of SLE [4].

SLE Classification Criteria

Classification criteria for SLE were developed primarily for research purposes in order to ensure the homogeneity of patients in clinical trials. SLE, however, is a heterogeneous disease that ranges widely in its clinical and serological manifestations. Though helpful in guiding diagnoses of SLE, use of the classification system as diagnostic criteria would limit the identification of patients with early disease or mild cases of SLE.

Widely used is the 1997 revised American College of Rheumatology classification criteria (Table 9.1), which requires that a patient meets at least 4 out of 11

Table 9.1 SLE classification criteria

American College of Rheumatology revised SLE classification criteria		Systemic Lupus International Collaborating Clinics (SLICC) criteria	
Classification as SLE requires 4 out of 11 criteria		Classification as SLE requires either 4 out of 17 criteria (including ≥1 clinical and ≥ 1 immunological) OR biopsy-confirmed lupus nephritis	
Criteria	*Definition*	*Criteria*	*Definition*
		Clinical criteria	
1. Malar rash	Erythematous rash in malar distribution, spares nasolabial folds, flat or raised, non-scarring	1. Acute cutaneous lupus erythematosus (ACLE)	Malar rash, photosensitive rash, or maculopapular lupus rash OR subacute cutaneous lupus manifestations (annular raised erythematous lesions with central areas of scaling)
2. Photosensitivity	Erythematous rash after sunlight exposure, in sun-exposed areas of body, non-scarring	2. Chronic cutaneous lupus erythematosus (CCLE)	Discoid lupus, lupus tumidus, lupus profundus (also known as lupus panniculitis), or chilblain lupus lesions
3. Discoid rash	Erythematous patches with central area of atrophy and depigmentation, scarring	3. Alopecia	Diffuse hair thinning, non-scarring
4. Oral ulcers	Painless oral (palate, buccal mucosa, tongue) or nasal ulcers	4. Oral or nasal ulcers	Painless ulcers on palate, buccal mucosa, tongue OR painless nasal ulcers
5. Arthritis	Tenderness, swelling, or effusion in at least 2 peripheral joints	5. Joint disease	At least 2 peripheral joints with synovitis (swelling or effusion) OR tenderness and morning stiffness ≥30 minutes
6. Serositis	Evidence of pleuritis (pleuritic-type chest pain, pleural friction rub, or pleural effusion) OR evidence of pericarditis (friction rub, pericardial effusion, or EKG changes consistent with pericarditis)	6. Serositis	Evidence of pleuritis (pleuritic-type chest pain for ≥1 day or pleural friction rub or pleural effusion) OR evidence of pericarditis (friction rub or pericardial effusion or EKG changes consistent with pericarditis)

(continued)

Table 9.1 (continued)

American College of Rheumatology revised SLE classification criteria		Systemic Lupus International Collaborating Clinics (SLICC) criteria	
7. Renal disorder	Proteinuria of ≥500 mg/24 hours (per urine protein/creatinine ratio or 24-hour urine protein) or ≥ 3+ on urine dipstick test OR presence of cellular casts (such as RBC, granular, tubular casts)	7. Renal	Proteinuria of ≥500 mg/24 hours (per urine protein/creatinine ratio or 24-hour urine protein) OR presence of RBC casts
8. Neurologic disorder	Seizures OR psychosis	8. Neurologic	Psychosis, seizures, mononeuritis multiplex, neuropathy OR acute confusional state
9. Hematologic disorder	Hemolytic anemia with reticulocytosis OR at least 2 occasions with leukopenia (WBC <4000/mm^3) OR at least 2 occasions with lymphopenia (lymphocytes <1000/mm^3) OR thrombocytopenia (platelets <100,000/mm^3)	9. Hemolytic anemia	Positive direct Coombs test
10. ANA	Abnormally elevated titer of ANA	10. Leukopenia or lymphopenia	At least 1 occasion of WBC <4000/mm^3 OR at least 1 occasion of lymphocytes <1000/mm^3
11. Immunologic disorder	Either positive anti-dsDNA OR positive anti-Sm OR positive antiphospholipid antibody (anticardiolipin, or lupus anticoagulant or false-positive RPR)	11. Thrombocytopenia	Platelets <100,000/mm^3

Table 9.1 (continued)

American College of Rheumatology revised SLE classification criteria	Systemic Lupus International Collaborating Clinics (SLICC) criteria	
	Immunologic criteria	
	1. ANA	Anti-nuclear antibody level above lab reference range
	2. Anti-dsDNA	Anti-dsDNA antibody level above lab reference range
	3. Anti-Sm	Presence of anti-Sm antibody
	4. Antiphospholipid antibody	Either positive lupus anticoagulant or false-positive RPR or medium to high titers of anticardiolipin antibody (either IgG, IgM, or IgA) or positive anti-beta-glycoprotein I antibody (either IgG, IgM, or IgA)
	5. Low complement	Low levels of C3, C4, or CH_{50}
	6. Direct Coombs test	Positive direct Coombs test without evidence of hemolytic anemia

criteria to be classified as having SLE. A newer classification system developed in 2012 is the Systemic Lupus International Collaborating Clinics (SLICC) criteria (Table 9.1), which requires that at least 4 out of 17 clinical and immunological criteria (including at least 1 clinical criterion and at least 1 immunological criterion) are met or that the patient has biopsy-proven lupus nephritis with either a positive anti-nuclear antibody (ANA) or a positive double-stranded DNA (dsDNA) to be classified as having SLE [6]. The SLICC criteria includes a wider range of SLE disease manifestations and has a similar specificity (96% versus 98%) and greater sensitivity (95% versus 90%) compared to the 1997 ACR criteria [7, 8].

Drug-Induced SLE

Medications may cause a condition with lupus-like symptoms referred to as drug-induced lupus. The most common inciting medications are hydralazine, procainamide, penicillamine, quinidine, minocycline, isoniazid, antitumor necrosis factor inhibitors, diltiazem, interferon-alpha, methyldopa, and chlorpromazine [4, 5].

Manifestations of drug-induced lupus are limited primarily to cutaneous and arthritic manifestations. Organ involvement such as lupus nephritis or neurological manifestations is very rare [4].

Autoantibodies in SLE

The anti-nuclear antibody is the hallmark laboratory test for SLE. Although 98% sensitive, it is not specific for SLE and can also be found in other autoimmune diseases such as hypothyroidism, hyperthyroidism, celiac disease, scleroderma, and dermatomyositis. Approximately 30% of normal healthy patients have a positive ANA test and do not develop SLE over time [9]. Autoantibodies (Table 9.2) can be detected as early as 10 years prior to the diagnosis of SLE [9].

Cutaneous Manifestations of SLE (See Fig. 9.1a–j)

The cutaneous manifestations of SLE can be subdivided into three categories which include acute cutaneous lupus erythematosus (ACLE), subacute cutaneous lupus erythematosus (SCLE), and chronic cutaneous lupus erythematosus (CCLE) lesions. The most common acute cutaneous lupus lesions include a malar rash ("butterfly rash") and photosensitive rash.

Table 9.2 Autoantibodies in SLE

Autoantibody substrate	Clinical utility
dsDNA (double-stranded DNA)	High specificity for SLE Correlates with disease activity
Sm	High specificity for SLE Does not correlate with disease activity
Ribosomal P proteins	High specificity for SLE Associated with neuropsychiatric manifestations
Histones	Associated with SLE and drug-induced lupus
Ro/SS-A	Associated with neonatal lupus (see Fig. 9.1e), photosensitvity, Sjogren's syndrome, subacute cutaneous lupus, and neuromyelitis optica (NMO)
La/SS-B	Associated with presence of anti-Ro/SS-A antibodies, neonatal lupus, and Sjogren's syndrome
Phospholipid (lupus anticoagulant, cardiolipin antibody, B2-glycoprotein 1)	Associated with hypercoagulable state and thrombosis, recurrent spontaneous abortions, and focal neurologic deficits
U1-RNP	Associated with mixed connective tissue disease (unless occurring with anti-Sm antibody)
Cell surface antigens of red blood cells, platelets, lymphocytes, neuronal cells	Hemolytic anemia, thrombocytopenia, lymphopenia, and diffuse neurologic deficits, respectively

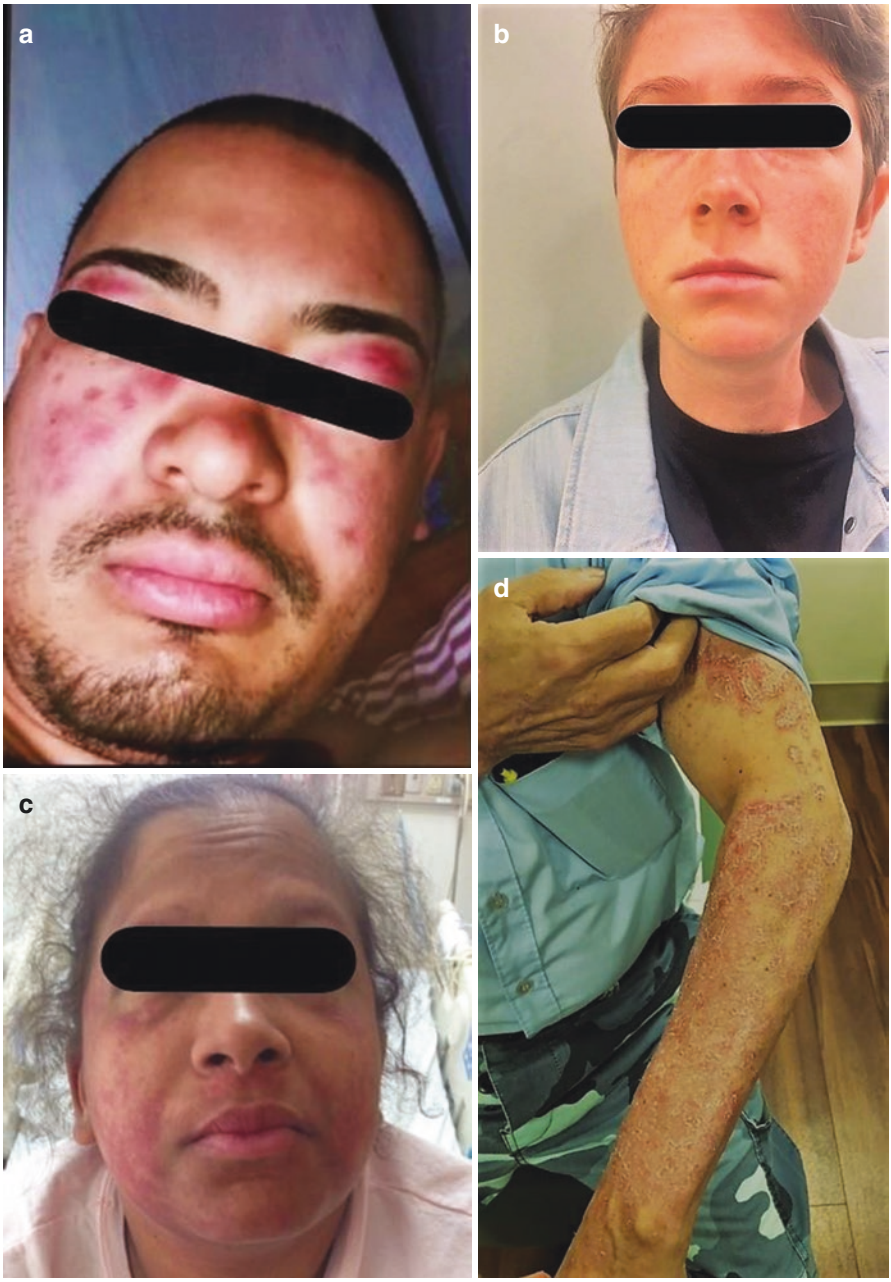

Fig. 9.1 Mucocutaneous manifestations of SLE. (**a**) Malar ("butterfly") rash 1. (**b**) Malar ("butterfly") rash 2. (**c**) Malar rash and photosensitive rash. (**d**) Subacute cutaneous lupus erythematosus (SCLE) rash. (**e**) Neonatal lupus rash. (**f**) Discoid rash of lip. (**g**) Discoid rash of ear. (**h**) Scarring discoid alopecia. (**i**) Small-vessel digital vasculitis. (**j**) Painless hard palate oral ulcer

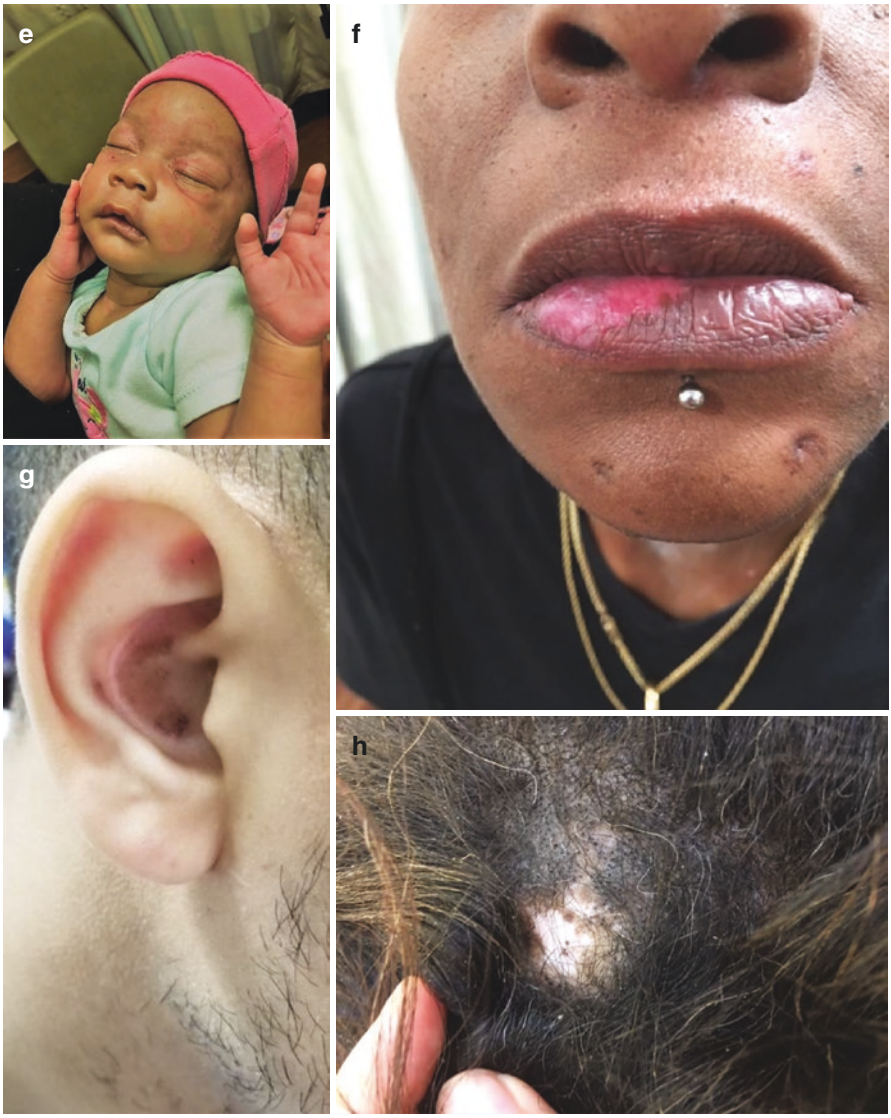

Fig. 9.1 (continued)

Fig. 9.1 (continued)

Malar Rash

A malar rash is one of the most common initial manifestations in SLE. It is a photosensitive erythematous rash that can be flat or raised, spares the nasolabial folds, and resolves without scarring. However, it must be differentiated from rosacea, dermatitis, and seborrhea [5] (see Fig. 9.1a–c).

Photosensitive Rash

Another common acute cutaneous rash is a photosensitive rash, which can occur in any sun-exposed region of the body. It is usually a flat maculopapular erythematous rash that resolves without scarring. It must be differentiated from medication-induced photosensitive rashes, such as those induced by hydrochlorothiazide and NSAIDs [5] (see Fig. 9.1c).

Subacute Cutaneous Lupus Erythematosus (SCLE)

Less common are SCLE rashes, which are annular raised erythematous lesions with areas of scaling in the center. These must be differentiated from medication-induced SCLE-like rashes, caused by terbinafine, hydrochlorothiazide, angiotensin-converting enzyme inhibitors, and calcium channel blockers [5] (see Fig. 9.1d).

Chronic Cutaneous Lupus Erythematosus (CCLE)

Chronic cutaneous lesions include discoid lupus, lupus tumidus, lupus profundus (also known as lupus panniculitis), and chilblain lupus lesions.

Discoid Rash

Discoid lesions are chronic scarring erythematous plaques or papules that have a central area of atrophy and depigmentation. They can occur on the face, neck, ears, and upper extremities. Skin biopsy will demonstrate inflammation and vacuolization at the junction between the dermis and epidermis ("interface dermatitis") with deposition of IgG, IgM, C3, and IgA ("positive lupus band test"). Discoid rash can occur in isolation without systemic manifestations of lupus. Approximately 10% of patients with discoid rash who are ANA negative eventually develop systemic lupus. The presence of a positive ANA test, discoid lesions on the trunk, or cytopenias increases the risk of developing SLE within the subsequent 5 years [5] (see Fig. 9.1f–h).

Lupus Tumidus

Lupus tumidus is a photosensitive rash that presents as red urticarial annular plaques with sharp raised borders and resolves without scarring. It tends to be more common in men. Biopsy would demonstrate a dense perivascular infiltrate that does not involve the dermal-epidermal junction interface and is negative upon immunofluorescence testing. It can occur in patients without systemic lupus, and only 10% of lupus tumidus patients have a positive ANA test [10].

Lupus Profundus (Lupus Panniculitis)

Lupus patients can develop chronic relapsing-remitting inflammation of the subcutaneous fat tissue, leading to deep painful firm nodules. The end result may be dented scars (lipodystrophy) of the fat tissue, caused by dense lymphocytic infiltration. The face is the most commonly affected area, but involvement of the upper arms, thighs, and breasts can also occur. Biopsy is critical to rule out subcutaneous lymphoma, which can have a similar presentation [5, 10].

Chilblain Lupus

This rare form of CCLE resembles frostbite, with its painful, violaceous plaques, and nodules in cold-exposed areas. Examination may reveal a mottled appearance over the fingers, with severe forms leading to digital ulcers. Nailfold capillary exam will show periungal capillary dilations. Biopsy shows epidermal atrophy, interface vacuolization, and perivascular mononuclear infiltrate. Smokers or patients with Raynaud's phenomenon are at higher risk for chilblain lupus. The majority of patients with chilblain lupus do not have other systemic manifestations of lupus, while approximately 20% of patients develop systemic lupus [10].

Oral or Nasal Ulcers

These ulcers are typically painless and may go unnoticed by the patient. They are commonly found on the upper hard palate, buccal mucosa, or nasal septum. Painful ulcers should raise concern for a herpes simplex infection [5] (see Fig. 9.1j).

Alopecia

Hair thinning or patchy hair loss is a common manifestation of SLE. Once the underlying SLE disease activity is controlled, alopecia typically begins to improve. It is usually non-scarring, unless it occurs in the setting of a surrounding discoid lesion [5] (see Fig. 9.1h).

Musculoskeletal Manifestations

Arthritis in SLE rarely leads to joint erosions and destruction. Patients tend to develop "Jaccoud arthropathy" which affects the tendons around the joints, causing tendon laxity. Patients can develop reversible ulnar deviation, swan-neck deformity, and MCP subluxation. Over time, however, the deformities can become fixed [5].

Serositis

Patients with SLE can develop pleuritis, pericarditis, or less commonly peritonitis. Moderate and severe serositis inflammation can also lead to accumulation of fluid such as pleural or pericardial effusions. Fluid aspiration reveals a sterile, inflammatory exudative fluid, with either a neutrophil or lymphocyte predominance [5, 11].

Cytopenias

There are a number of cytopenias that may present in SLE patients. The most common anemia is anemia of chronic disease, followed by iron-deficiency anemia and hemolytic anemia. Approximately 10% of SLE patients have a Coombs positive anti-erythrocyte antibody, usually of the warm-type IgG. Other causes of hemolytic anemia must be evaluated, including microangiopathic hemolytic anemia in the setting of APLS, medications, and infections. Red cell aplasia, involving serum IgG that inhibits erythrocyte formation in the bone marrow, is a rare cause of anemia in SLE [11].

Leukopenia in SLE is usually the result of peripheral consumption rather than bone marrow production of leukocytes. However, autoantibodies to leukocytes may form that inhibit granulocyte growth colony-forming units in the bone marrow leading to decreased bone marrow production [11].

Thrombocytopenia may be an isolated manifestation in SLE or may be a component of multisystem disease activity. Antibodies to platelets usually include either autoantibodies against thrombopoietin receptor (TPOR) or against glycoprotein IIb/IIIa (GPIIb/IIIa). Anti-TPOR-induced thrombocytopenia has a poorer response to immunosuppressants compared to anti-GPIIb/IIIa-induced thrombocytopenia. Thrombocytopenia may also occur in the setting of active APLS and is usually associated with hemolytic anemia. Other causes of thrombocytopenia include medications, infections, and hemolytic uremic syndrome/thrombotic thrombocytopenic purpura (HUS/TTP) which may coexist with active SLE. Although treatments differ, TTP-HUS requires plasmapheresis, while active SLE requires immunosuppressant therapy [11].

Rarely, patients with SLE may develop pancytopenia. Pancytopenia in SLE may be due to reversible myelofibrosis with bone marrow hypocellularity that may be

responsive to immunosuppressants. Other causes of pancytopenia include hemophagocytic syndrome/macrophage activation syndrome (HLH/MAS) or cytotoxic immunosuppressants [11].

Lupus Nephritis

Renal involvement in lupus patients is collectively described as "lupus nephritis" and can affect the glomeruli, tubules, interstitial tissue, and blood vessels. In 2004, the Society of Nephrology and Renal Pathology Society (ISN/RPS) classified lupus nephritis according to six classes (Table 9.3) based on glomerular pathology [5, 11].

Class I: Minimal Mesangial Lupus Nephritis

Light microscopy appears to show normal glomeruli. Immunofluorescence (IFA) and electron microscopy demonstrate immune deposits in the mesangium. Patients have normal urinalysis and normal serum creatinine. No treatment is required [5, 11].

Class II: Mesangial Proliferative Lupus Nephritis

Light microscopy will show increased hypercellularity in the mesangium. Electron microscopy and IFA will show immune deposits in the mesangium. Patients usually have near normal urinalysis and normal serum creatinine. Treatment is rarely

Table 9.3 ISN/RPS 2003 classification of lupus nephritis

Class	Class definition	Subclasses[b]
I	Minimal mesangial LN	
II	Mesangial proliferative LN	
III	Focal LN	III (A) III (A/C) III (C)
IV[a]	IV-S: Diffuse LN IV-G: Global LN	IV-S (A) IV-S (A/C) IV-S (C) IV-G (A) IV-G (C)
V	Membranous LN	
VI	Advanced sclerosing LN	

[a]Class IV lesions are further categorized into IV-S for segmental disease and IV-G for global disease

[b]Class III and Class IV lesions are further subclassified into active lesions (A), chronic lesions (C), or both (A/C)

required, but patients may benefit from an angiotensin-converting-enzyme inhibitor (ACE inhibitor) if there is elevated proteinuria >0.5 g/day [5, 11].

Class III: Focal Proliferative Lupus Nephritis

Histology demonstrates segmental lesions involving <50% of the glomeruli, with hypercellularity and immune complex deposition in the *subendothelial* space and mesangium. Patients present with increasing serum creatinine, proteinuria, hematuria, low complement levels, elevated dsDNA antibody, hypertension, and lower extremity edema. Immunosuppressive treatment is required, with high-dose steroids and either mycophenolate mofetil or cyclophosphamide. Without treatment, patients will progress to Class IV lupus nephritis [5, 11].

Class IV: Diffuse Proliferative Lupus Nephritis

Class IV lupus nephritis is a continuum of Class III LN that has extended to affect over 50% of the glomeruli. Class IV LN is further divided into Class IV-S and Class IV-G. Class IV-S is characterized by segmental lesions involving >50% of the glomeruli, and Class IV-G is defined by global glomerular lesions involving >50% of the glomeruli. There is also presence of basement membrane thickening, sclerosis of capillaries, as well as inflammatory infiltrate and areas of necrosis that lead to "crescent" formation. IFA microscopy reveals a "full house pattern" with IgG, IgM, IgA, C3, and C1q deposition in the *subendothelial* space. Patients will present similarly to Class III LN and require similar treatment [5, 11].

Class V: Membranous Lupus Nephritis

Histology will demonstrate global or segmental immune deposits in the *subepithelial* space. Patients usually present with significant proteinuria, minimal hematuria, and normal serum creatinine, complements, and anti-dsDNA levels. Treatment usually requires only ACE inhibitors, but may require immunosuppressants if there is extensive proteinuria [5, 11].

Class VI: Advanced Sclerosing Lupus Nephritis

Patients with sclerosis of 90% or more of their glomeruli are classified as having Class VI LN. There is no significantly active glomerular disease, and thus immunosuppression is avoided. These patients are prepared for or are undergoing renal replacement therapy [5, 11].

Indications for Renal Biopsy

Renal biopsy is indicated for:

1. Proteinuria of ≥1 gm/day
2. Proteinuria of ≥0.5 gm/day with hematuria and red cell casts
3. Unexplained increasing serum creatinine [5, 11]

Neuropsychiatric Lupus

The prevalence of neuropsychiatric manifestations of SLE (NPSLE) is estimated to be between 25% and 80% depending on the cohort. The ACR has 19 case definitions for NPSLE. The mechanisms for NPSLE involve anti-neuronal antibodies, APLS antibodies, thrombosis, vasculitis, non-inflammatory vasculopathy, cytokine production, and oxidative stress. Patients with diffuse CNS manifestations will demonstrate a lumbar puncture with inflammatory CSF, elevated IgG levels, oligoclonal bands, and anti-neuronal antibodies. SLE patients with significant psychiatric manifestations, such as severe depression or psychosis, may demonstrate anti-ribosomal P antibodies in the serum. Patients with more focal CNS deficits are more likely to have thromboembolic events and should be evaluated with MRI brain, serum APLS antibodies, and an echocardiogram [5, 11].

An N-methyl-D-aspartate receptor (NMDAR) antibody is a type of dsDNA antibody that interacts with the glutamate receptor and can be associated with neurocognitive dysfunction [5, 11].

Patients with Sjogren's syndrome and SSA/Ro antibodies may have anti-aquaporin-4 antibodies that can lead to neuromyelitis optica (NMO). The NMO antibodies can cause transverse myelitis and optic neuritis [5, 11].

Pregnancy and Reproductive Effects of SLE

Fertility is not affected by lupus. Fertility may be affected by alkylating medications such as cyclophosphamide, which can increase ovarian failure in older patients in a dose-dependent manner. Premature gonadal failure may be also seen in male SLE patients with cumulative doses of cyclophosphamide [5, 11].

The SELENA trial was a randomized controlled trial of 183 SLE patients who received either oral contraceptives or placebo, with no increase in lupus flares, thrombosis, or adverse events. These patients, however, had low SLE disease activity and did not have high titer APLS antibodies. A study using combination

estrogen-progestin post-menopausal hormonal therapy demonstrated an increase in mild lupus flares and increased risk for thrombosis in APLS patients. Progesterone-containing contraceptives appear to be safe in SLE patients, including those with APLS, but may lead to a reduction in bone mass with prolonged usage [11].

Outcomes in pregnancy are improved in patients who have had inactive lupus 6 months prior to conception. Hydroxychloroquine has shown to decrease SLE flares during pregnancy. Patients with SSA (Ro) and SSB (La) antibodies are at risk for developing neonatal Lupus, with heart block as the most feared complication. Preventive treatment with aspirin 81 mg daily is recommended for all SLE patients to reduce the rate of preeclampsia and recurrent miscarriages, based on data extrapolated in non-SLE high-risk groups.

Medications in SLE

Medication choice depends on the severity and type of SLE manifestations.

Mild disease, such as rash, arthritis, and serositis, may be treated with NSAIDs, hydroxychloroquine, low-dose prednisone (<0.5 mg/kg/day), methotrexate, or leflunomide.

Moderate disease, such as extensive rash, severe arthritis, and severe serositis, or serologically active disease may respond to mycophenolate mofetil, azathioprine, and belimumab.

Patients with severe life-threatening disease would benefit from the same medications used for mild or moderate disease, but treatment will also include rituximab, cyclophosphamide, or IVIG (Table 9.4).

Table 9.4 SLE medications

Treatment	Indication	Mechanism of action
Immunosuppressive or anti-inflammatory		
NSAIDs	Treats mild SLE manifestations	Inhibition of cyclooxygenase, leading to a decrease in production of prostaglandins. Other mechanisms include inhibition of neutrophil aggregation, adhesion, and release of enzymes, and inhibition of NF-kB and cytokine production
Anti-malarial (hydroxychloroquine)	Treats and can prevent mild SLE manifestations	A base that accumulates and increases the pH of acidic lysosomes. This leads to disruption of antigen processing and a decrease of IL-1, IL-6, and interferons

Table 9.4 (continued)

Treatment	Indication	Mechanism of action
Corticosteroids (prednisone or IV methylprednisolone)	Treats mild, moderate, or severe SLE manifestations	Numerous mechanisms, including: Binding to intracellular receptors and blocking pro-inflammatory genes for interleukin-1, NF-kB High doses (prednisone >100 mg/day) intercalate into cellular membrane and reduces calcium and sodium transport across membrane, thereby reducing inflammation Decreases prostaglandin production and interferes with macrophages' and neutrophils' phagocytosis and cytokine production Inhibits T-helper cells and Th17 cytokine production
Cyclophosphamide	Treats severe SLE manifestations	DNA alkylating agent which cross-links and causes breaks in DNA, therefore leading to decreased DNA synthesis and cellular apoptosis, particularly in rapidly dividing cells such as B-lymphocytes
Mycophenolate mofetil (MMF)	Treats moderate to severe SLE manifestations	Inhibits the enzyme inosine-5′-monophosphate dehydrogenase (IMPDH), which is necessary for T-lymphocytes and B-lymphocytes to generate the nucleotide guanosine, therefore inhibiting lymphocyte proliferation and migration
Azathioprine	Treats moderate to severe SLE manifestations	A thiopurine nucleotide which incorporates into nucleic acids, leading to decreased production of purine nucleotides and decreased cellular proliferation
Methotrexate	Treats mild to moderate SLE manifestations	Inhibits AICAR transformylase, leading to increase in adenosine, which inhibits neutrophil function. Can also inhibit purine synthesis by inhibiting dihydrofolate reductase and thereby decreasing metabolically active folate
Immune cell-targeted therapy		
Anti-CD20 (rituximab)	Treats moderate to severe SLE manifestations	A chimeric mouse-human monoclonal antibody that binds CD20 antigen on B-cells, leading to B-cell elimination. Plasma cells are preserved
Belimumab	Treats moderate to severe SLE manifestations	A human monoclonal antibody to B-lymphocyte stimulatory molecule (BLYSS)/B-cell activating factor (BAFF), which promotes the survival, growth, and maturation of B-cells

Summary

- There are gender and racial disparities in SLE, with a greater prevalence in women and non-whites.
- Mortality in the first 5 years of SLE diagnosis is due to the disease itself or infections.
- Mortality after 10 years of SLE diagnosis is due to cardiovascular disease or malignancy. SLE patients are at risk for premature cardiovascular disease.
- Monozygotic twin studies have demonstrated that the genetic component to SLE can be as high as 50%.
- Environmental risk, including EBV and UV radiation, can also be a risk factor for SLE.
- There are two classifications currently in use for SLE, including the 1997 revised ACR criteria and the SLICC criteria, with the latter having greater sensitivity but less specificity.
- Drug-induced lupus usually manifests with cutaneous and arthritic manifestations and can occur with hydralazine, procainamide, penicillamine, quinidine, minocycline, isoniazid, antitumor necrosis factor inhibitors, diltiazem, interferon-alpha, methyldopa, and chlorpromazine. NSAIDs and thiazide diuretics can cause a photosensitive rash in SLE patients.
- ANA is 98% sensitive for SLE, but is not specific. Almost 30% of normal healthy patients can have a positive ANA. Patients may develop a positive ANA and other autoantibodies as early as 10 years prior to onset of SLE.
- Cutaneous manifestations of SLE include malar rash, photosensitive rash, SCLE, discoid rash, lupus profundus, chilblain lupus, and oral-nasal ulcers.
- Other manifestations include a nonerosive, nondeforming Jaccoud arthropathy, serositis, alopecia, cytopenias, lupus nephritis, and neuropsychiatric lupus.
- Indications for renal biopsy include proteinuria of at least 1 gram per day, proteinuria of at least 0.5 gram per day with hematuria and red blood cell cast, or an unexplained increase serum creatinine.
- There are six classes of lupus nephritis. Class I (minimal mesangial) and Class II (diffuse mesangial) LN are usually asymptomatic and do not require treatment.
- Class III (focal proliferative LN) and Class IV (diffuse proliferative LN) have subendothelial immune complex deposits with either <50% of glomeruli involved (Class III) or ≥ 50% glomeruli involved (Class IV LN). Class III and IV LN require aggressive immunosuppression with high-dose steroids (1 mg/kg/day–1000 mg/day) with either mycophenolate mofetil or cyclophosphamide to prevent progression to end-stage renal disease.
- Class V (membranous nephritis) has subepithelial immune complex deposits and is usually treated with ACE inhibitors. Immunosuppressants may be added for Class V LN that do not respond to ACE inhibitors alone.
- In Class VI LN (diffuse sclerosis LN), patients have ≥90% sclerosing of their kidneys with no lupus disease activity. The risk for immunosuppression outweighs any benefit.

- The ACR has 19 case definitions for NPSLE. Anti-neuronal antibodies are associated with diffuse CNS manifestation. Anti-ribosomal P antibodies are involved with severe psychiatric manifestations. Antiphospholipid antibodies are associated with focal CNS deficits. N-methyl-D-aspartate receptor (NMDAR) antibody is a type of dsDNA antibody that can be associated with neurocognitive dysfunction. Anti-aquaporin-4 antibodies may lead to neuromyelitis optica (NMO), which can lead to transverse myelitis and optic neuritis.
- Fertility is not affected by lupus. Treatment with cyclophosphamide may cause premature gonadal failure in both males and females and is associated with total cumulative cyclophosphamide dose. Estrogen-containing oral contraceptives are safe in SLE patients with no or low-disease activity and those who do not have APLS. Hydroxychloroquine has shown to decrease SLE flares during pregnancy, and data suggests that it may lessen the risk for neonatal lupus in SSA- or SSB-positive mothers. Aspirin 81 mg/day is recommended for SLE patients to possibly reduce preeclampsia risk, based on studies performed in other high-risk pregnancy groups.

20 Multiple-Choice Questions

1. A 36-year-old woman was diagnosed with SLE 4 years ago with malar rash, polyarthritis, +ANA, +dsDNA, and lupus nephritis Class IV treated with six doses of monthly intravenous cyclophosphamide. She now remains in remission on mycophenolate mofetil and hydroxychloroquine for maintenance therapy. She is admitted for 2 weeks of progressively worsening dyspnea on exertion with pleuritic chest pain. Patient denies fevers, chills, cough, or sick contacts. Exam is unremarkable, and vital signs are normal with oxygen saturation of 100% on room air. Labs show normal CBC, complements, inflammatory markers, dsDNA, and urine tests. Electrocardiogram shows normal sinus rhythm. Echocardiogram is unremarkable. Chest radiograph and high-resolution computerized tomography demonstrates an elevated left hemidiaphragm, but otherwise normal lung parenchyma. Pulmonary function tests (PFTs) show a restrictive pattern with reduced diffusion capacity.

   What is the most likely cause of this patient's condition?

   A. Pulmonary hypertension
   B. Diffuse alveolar hemorrhage
   C. Interstitial lung disease
   D. Shrinking lung syndrome

   Correct answer: D
   Shrinking lung syndrome is a rare pulmonary manifestation of SLE caused by diaphragmatic myopathy or phrenic neuropathy. It is characterized by dyspnea, elevated hemidiaphragm, restrictive pattern on pulmonary function tests, and

pleuritic chest pain. All other causes of restrictive lung disease must be excluded including interstitial lung disease, pulmonary hypertension, pulmonary fibrosis, and obesity.

Choice A is incorrect given normal echocardiogram and normal pulmonary vessels on CTA chest, although pulmonary hypertension can present with normal lung parenchyma and reduced lung disease pattern on PFTs.

Diffuse alveolar hemorrhage (choice B) is unlikely given normal hemoglobin and normal parenchyma on chest imaging.

Although interstitial lung disease (choice C) can present with a restrictive lung pattern on PFTs, it is unlikely for the patient to have normal parenchyma on lung imaging without signs of ground glass opacities or fibrosis.

References [12, 13]

2. A 23-year-old woman with SLE presents to your office for follow-up. She was diagnosed based on malar rash, painless oral hard palate ulcers, Class III lupus nephritis, +ANA, and antiphospholipid antibody syndrome with lupus anticoagulant and history of deep venous thrombosis. Her lupus is in remission on mycophenolate mofetil and hydroxychloroquine. She is on long-term anticoagulation. She plans to become sexually active and is asking about birth control options.

   Which of the following is recommended?

   A. Estrogen and progesterone oral contraceptives
   B. Progesterone-only containing oral contraceptive
   C. Barrier methods with condoms
   D. Spermicides

   Correct answer: B

   Progesterone-only containing oral contraceptives are the safest and most effective method of birth control in this patient.

   Estrogen and progesterone oral contraceptives (choice A) would place this patient with antiphospholipid syndrome at higher risk for blood clots. Although the SELENA trial demonstrated that estrogen- and progesterone-containing OCPs were safe in SLE patients without increasing their risk for SLE flares, patients with APLS were excluded.

   Barrier methods with condoms (choice C) and spermicides (choice D) have only an 85% and 71% efficacy in preventing pregnancy, respectively.

   References [14, 15]

3. A 22-year-old woman with SLE develops new-onset left eye redness, severe pain, photophobia, and tearing. She also has small vesicular blisters over her left eye and on the tip of the nose. All of the following contribute to the development of the rash *except*:

   A. Active SLE disease
   B. Lymphopenia
   C. High-dose glucocorticoids
   D. Hydroxychloroquine use

Correct answer: D

This SLE patient has developed Hutchinson's sign of herpes zoster ophthalmicus, which manifests as a unilateral painful vesicular rash in the dermatomal distribution of the trigeminal nerve. The rash occurs after reactivation of latent varicella zoster virus. SLE patients of all ages are at particular risk for shingles due to SLE itself (choice A), lymphopenia (choice B), immunosuppressants, and high-dose glucocorticoid use (choice C). Hydroxychloroquine has shown to have a protective effect against infectious complications in SLE patients (choice D).

References [16, 17]

4. Which of the following histological features on renal biopsy of a patient with lupus nephritis would support the further use of immunosuppressive therapy?

   A. Interstitial fibrosis
   B. Cellular crescents
   C. Fibrous crescents
   D. Glomerular sclerosis

   Correct answer: B

   Cellular crescents are markers of disease activity on renal histology in lupus nephritis and would support the use of further immunosuppression. Interstitial fibrosis (choice A), fibrous crescents (choice C), and glomerular sclerosis (choice D) are markers of chronic lesions. Other markers of active nephritis on histology include cellular proliferation, fibrinoid necrosis, and hyaline thrombi.

   References [5, 18]

5. A 29-year-old woman with SLE presents for follow-up and is found to be at 8 weeks' gestation. She is concerned about how her lupus may affect her pregnancy. Which of the following medications has the most supportive evidence for improving pregnancy outcomes in lupus patients?

   A. Hydroxychloroquine
   B. Aspirin 81 mg daily
   C. Aspirin 325 mg daily
   D. Azathioprine

   Correct answer: A

   Hydroxychloroquine has shown to improve outcomes in pregnancy. Discontinuation of hydroxychloroquine increases the risk of lupus flares during pregnancy. Active lupus during pregnancy can lead to miscarriage, stillbirth, preterm birth, preeclampsia, and eclampsia. Hydroxychloroquine use is considered safe in pregnancy and is not associated with birth defects. Data regarding the role of hydroxychloroquine in preventing cardiac manifestations of neonatal lupus is still unclear, but studies suggest that maternal use of hydroxychloroquine may decrease the risk of congenital heart block in infants of mothers with anti-Ro antibody.

   The US Preventative Task Force recommends the use of low-dose aspirin (choice B) in pregnant women at high risk for preeclampsia or preterm delivery, including SLE patients. Although preeclampsia risk reduction by low-dose aspi-

rin (ASA) was demonstrated in other high-risk groups, there is no trial evidence for the use of low-dose ASA in preventing preeclampsia in SLE patients.

High-dose ASA (choice C) has been associated with reduced birth weight and complications with fetal heart and lung development.

Azathioprine (choice D) is considered safe in lupus pregnancy. In a study of 87 lupus patients exposed to azathioprine versus 91 SLE patients with no exposure, there was no difference in the rate of live births, spontaneous abortions, mean birth weights, weeks of gestation, and low birth weight between the two groups.

References [19–21]

6. A 21-year-old woman presents for evaluation of diffuse polyarthralgias involving the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints, malar rash, fatigue, and elevated ANA. She has a history of acne, which is treated with minocycline, and vitamin D deficiency treated with vitamin D supplementation. Physical exam is significant for bilateral joint tenderness in the 1st–5th MCP joints and 2nd–5th PIPs and an erythematous macular rash on the cheeks that spares her nasolabial folds. Laboratory results include the following:

Laboratory test	Results	Reference range
Antinuclear antibody titer	1:160	1:40 or less
Anti-histone antibody titer	1:256	Less than 1:16
Anti-double-stranded DNA antibody	15 IU/mL	0–7 IU/mL
C3 complement	123 mg/Dl	100–233 mg/dL
C4 complement	17 mg/dL	14–48 mg/dL
Anti-perinuclear anti-neutrophil cytoplasmic antibody (pANCA)	1:160	<1:20
Anti-myeloperoxidase antibody (MPO antibody)	<1:10	<1:10

What is the best next step?

A. Begin prednisone
B. Begin hydroxychloroquine
C. Discontinue minocycline
D. Begin methotrexate

Correct answer: C

This patient has arthritis, malar rash, +ANA, and + dsDNA, which are concerning for SLE. However, she also has anti-histone antibodies and elevated p-ANCA titers, but negative MPO antibodies, which point to drug-induced lupus. Minocycline, a medication used to treat acne, may cause drug-induced lupus. Minocycline-induced lupus may be associated with anti-histone antibodies in 40% of patients and is frequently associated with a + p-ANCA with negative MPO antibodies. Complements are usually normal. Some patients with drug-induced lupus may also develop anti-dsDNA antibodies. Manifestations are usually limited to skin and arthritis, and patients are unlikely to develop organ involvement.

Answer choices A, B, or D may be appropriate medications for SLE patients without concern for drug-induced etiology.

References [5]

7. A 37-year-old man presents with hyperpigmented skin lesions over his scalp with areas of erythema around the borders. The patient also has central scarring alopecia. Labs reveal a + ANA 1:80, normal complements, and normal dsDNA, Smith, U1RNP, SSA, and SSB antibodies. Biopsy of the skin lesion shows hyperkeratosis with keratin-filled follicles, vacuolar degeneration of keratinocytes, and inflammatory dermal infiltrates, with a positive lupus band. He was diagnosed with discoid lupus and started on hydroxychloroquine. He began to have lightening of the surrounding erythema with hydroxychloroquine, but 9 months later began to develop enlargement of one of his scalp discoid lesions along with new left periarticular lymph node enlargement. He sees his dermatologist, who performs a repeat biopsy of the skin lesion.

   What is the most likely finding on the repeat biopsy?

   A. Bacterial infection
   B. Persistent discoid lupus activity
   C. IgG4
   D. Squamous cell carcinoma

   Correct answer: D
   Squamous cell carcinoma can arise from discoid lesions. They can appear as enlarging, refractory lesions, which can metastasize to local lymph nodes.

   Bacterial infection (choice A) would present with a demarcated skin erythema and warmth consistent with cellulitis. Persistent discoid lupus (choice B) would be less likely to present with local unilateral lymph node enlargement. IgG4 (choice C) has not been known to develop from discoid lesions.

   References [10, 22, 23]

8. A 40-year-old man with SLE presents with new-onset proteinuria of 1.5 grams in 24 hours, lower extremity edema, and hypertension. He undergoes a renal biopsy. Histology demonstrates segmental immune deposits in the subepithelial space. What is the next best step?

   A. Observation
   B. Begin steroids
   C. Begin an ACE inhibitor
   D. Begin mycophenolate mofetil

   Correct answer: C
   The patient has findings consistent with Class V membranous lupus nephritis on biopsy. The next best step in treatment would be to start an ACE inhibitor.

   Steroids (choice B) and mycophenolate mofetil (choice D) are typically reserved for aggressive forms of Class V lupus nephritis, Class III focal proliferative lupus nephritis, or Class IV diffuse proliferative lupus nephritis. Class III and Class IV lupus nephritis would present with *subendothelial* immune com-

plex deposits and require treatment with steroids (choice B) and mycophenolate mofetil (choice D). Patients with Class I minimal mesangial nephritis or Class II mesangial proliferative lupus nephritis can be observed without intervention (choice A).

9. A 25-year-old woman presents with active SLE, manifested by photosensitive rash, moderate pericardial effusion, small-vessel cutaneous vasculitis on the palms, and low-grade fevers. Exam is notable for a young woman with an erythematous macular rash throughout her face and in a V-shaped distribution across her anterior chest. She has small vasculitic lesions on her palms and distant heart sounds on auscultation. Patient also appears to have diffuse soft tissue edema and a non-tender distended abdomen with a mild fluid wave. She has been complaining more recently of watery diarrhea. Workup was negative for infections. Lab results reveal +ANA 1:1280, low albumin of 1.5 g/dL (normal range, 3.5–5.5 g/dL), low C3 and C4 complements, and otherwise normal urinalysis and normal LFTs. What would be the most likely finding upon further testing?

   A. Positive stool alpha-1 antitrypsin
   B. Positive hydrogen breath test for lactose intolerance
   C. Positive serum tissue transglutaminase antibody
   D. Elevated TSH, with undetectable free T4

   Correct answer: A

   Protein-losing enteropathy is a rare but well-reported manifestation of SLE. It should be considered in any active lupus patient with unexplained hypoalbuminemia, edema, ascites, pleural effusions, or pericardial effusions. Patients can also have diarrhea, abdominal pain, nausea, and vomiting. Diagnosis involves stool testing for alpha-1 antitrypsin (correct choice A) or Tc-(99 m) albumin scintigraphy. A 24-hour urine protein is normal and usually measured to be less than 0.5 g/day. Approximately 44% of patients may have mucosal thickening visible on colonoscopy, while 52% have no abnormalities. Histology may reveal inflammatory cell infiltrate, lymphangiectasia, mucosal atrophy or vasculitis, and edema of the GI mucosa in 80% of patients. Patients respond to steroids and immunosuppressants.

   Lactose intolerance (choice B) may explain the patient's diarrhea, but would not explain the hypoalbuminemia.

   Serum tissue transglutaminase (choice C) would be positive in celiac disease, a GI hypersensitivity to wheat protein gluten. Celiac disease can lead to diarrhea and malabsorption.

   Patients with severe hypothyroidism, such as those with myxedema coma, can be associated with hypoalbuminemia. Constipation is more common than diarrhea in severe hypothyroidism.

   References [24]

10. A 37-year-old man presents with several months of progressive fatigue, malaise, painless oral ulcers, and diffuse alopecia. He was admitted after presenting with 3 hours of paraparesis. Examination revealed absent knee and ankle reflexes, absent plantar reflex, and decreased sensation at the T4 level.

    All of the following can be associated with the patient's underlying condition, EXCEPT:

    A. Longitudinal spinal cord involvement
    B. Neuromyelitis optica (NMO) antibodies
    C. Antiphospholipid antibodies
    D. Single level of spinal cord involvement

    Correct answer: D
    Transverse myelitis (TM) is a rare manifestation that can occur in 1–1.5% of neuropsychiatric SLE (NPSLE) patients. Transverse myelitis may even present as the first initial manifestation in SLE. Thoracic cord involvement is the most frequent spinal cord region affected. Unlike multiple sclerosis which may be limited to only a few levels of the spinal cord (choice D), lupus-transverse myelitis is associated with *longitudinal* cord involvement. Transverse myelitis may be associated with the presence of antiphospholipid antibodies (choice C), which can be found in up to 45% of TM patients, and the presence of neuromyelitis optica (NMO) antibodies (choice B), which can be found in up to 25% of TM patients. Although studies are limited, patients treated with a combination of pulse-dose glucocorticoids and cyclophosphamide demonstrate improved outcomes.

    Reference [25]

11. Each of the following is a risk factor for premature ovarian failure in SLE patients on cyclophosphamide, EXCEPT:

    A. Cumulative cyclophosphamide dose
    B. Methotrexate use
    C. Older patient age
    D. Lack of gonadotropin-releasing hormone (GnRH) analog prior to cyclophosphamide

    Correct answer: B
    Methotrexate use is associated with fetal teratogenicity but is not associated with premature ovarian failure.

    Cumulative cyclophosphamide dose (choice A) and older patient age (choice C) is associated with greater risk for premature ovarian failure in SLE patients treated with cyclophosphamide. A case-control study demonstrated that cyclophosphamide-induced premature ovarian failure occurred in 5% of patients treated with GnRH analog, compared to 20% of age-matched and cumulative cyclophosphamide dose-matched controls who were not treated with GnRH analog (matched odds ratio 0.09, $P < 0.05$).

    Reference [26]

12. The risk of hemorrhagic cystitis and bladder cancer with cyclophosphamide treatment increases with all of the following EXCEPT:

A. Cumulative cyclophosphamide dose
B. Cigarette smoking
C. Mesna and IV hydration
D. BK virus infection

Correct answer: C

Acrolein is a metabolic product of cyclophosphamide. Accumulation of acrolein in the bladder can lead to hemorrhagic cystitis and bladder cancer. Cumulative cyclophosphamide dose (choice A), such as using IV monthly cyclophosphamide rather than daily oral cyclophosphamide, as well as cigarette smoking (choice B), which contains a significant amount of acrolein, increases the risk for hemorrhagic cystitis and bladder cancer.

BK virus infection (choice D) of the bladder can also increase the risk for hemorrhagic cystitis and bladder cancer.

Mesna (choice C) is a sulfhydryl compound that is filtered through the kidneys and into the urine. Once it accumulates in the bladder, it can directly bind and neutralize acrolein. Oncology studies with ifosfamide has demonstrated that the use of intravenous hydration and intravenous mesna can lower the risk of hemorrhagic cystitis and bladder cancer.

Reference [5, 27, 28]

13–16. Match the medication to its drug mechanism.

Medication	Mechanism of action
13. Cyclophosphamide	A. Inhibits the enzyme inosine-5′-monophosphate dehydrogenase (IMPDH), which is necessary for T-lymphocytes and B-lymphocytes to generate the nucleotide guanosine, and therefore inhibits lymphocyte proliferation and migration
14. Mycophenolate mofetil	B. A thiopurine nucleotide which incorporates into nucleic acids, leading to decreased production of purine nucleotides and decreased cellular proliferation
15. Azathioprine	C. A base that accumulates and increases the pH of acidic lysosomes. This leads to disruption of antigen processing and a decrease in IL-1, IL-6, and interferons
16. Hydroxychloroquine	D. DNA alkylating agent that cross-links and causes breaks in DNA, therefore leading to decreased DNA synthesis and cellular apoptosis, particularly in rapidly dividing cells such as B-lymphocytes

Correct answers:

13. D
14. A
15. B
16. C

Reference [5]

17. A 43-year-old female smoker with SLE presents with skin lesions over her fingers. Examination reveals violaceous raised mottled macules over the distal fingers, which worsen with cold exposure.

    The above describes which type of skin manifestation?

    A. Chilblain lupus
    B. Lupus tumidus
    C. Lupus pernio
    D. Lupus profundus

    Correct answer: A

    Chilblain lupus presents with painful, violaceous plaques, and nodules in cold-exposed areas of the fingers. In severe cases, patients can develop digital ulcers. Nailfold capillary exam shows periungal capillary dilations. Smoking and Raynaud's phenomenon increases the risk for developing chilblain lupus.

    Lupus tumidus (choice B) is a photosensitive urticarial raised rash that typically occurs on the chest, abdomen, or back and resolves without scarring.

    Lupus pernio (choice C) is a misnomer and manifests in sarcoidosis patients rather than lupus patients. It presents as a chronic raised indurated skin lesion that is often purplish in color. It is seen on the nose, forehead, ears, cheeks, and lips.

    Lupus profundus (also known as lupus panniculitis) is caused by chronic inflammation of the subcutaneous fat tissue due to dense lymphocytic infiltration (choice D).

    References [10]

18. Which of the following is *not* a risk factor associated with hydroxychloroquine retinal toxicity?

    A. Renal dysfunction
    B. Dosing according to ideal body weight
    C. Liver dysfunction
    D. Hydroxychloroquine use of greater than 5 years

    Correct answer: B

    Hydroxychloroquine retinopathy occurs in approximately 1–2% of patients using hydroxychloroquine. Patients at higher risk of hydroxychloroquine retinopathy are those who have used hydroxychloroquine for over 5 years (choice D) or who have renal (choice A) or liver (choice C) dysfunction. Patients at higher risk for retinopathy should be evaluated by an ophthalmologist on a yearly basis. Dosing according to ideal body weight reduces the risk for hydroxychloroquine retinopathy (choice B).

    Reference [5]

For questions 19–20, use the possible answer choices listed below:

1. Cardiovascular disease
2. Active SLE disease
3. Malignancy
4. Infections

19. What are the most common causes of death in lupus patients within the *first* 5 years of their lupus diagnosis?

    A. 1 and 2
    B. 3 and 4
    C. 1 and 3
    D. 2 and 4

    Correct answer: D
    There is a bimodal pattern of death in SLE patients. Death in the first 5 years of the disease is primarily due to either active SLE itself or due to infections in the setting of immunosuppressive treatment of SLE.
    Reference [5]

20. What are the most common causes of death that occur in lupus patients at least 10 years *after* diagnosis of lupus?

    A. 1 and 2
    B. 3 and 4
    C. 1 and 3
    D. 2 and 4

    Correct answer: C
    The two most common causes of death seen in SLE patients after 10 years of disease are cardiovascular disease and malignancy. Cardiovascular risk is two- to eightfold higher in SLE patients. Risk of malignancy such as lymphoma is fivefold higher in SLE patients.
    Reference [5]

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Chapter 10
Sjögren's Syndrome

Anna Rapti, Nikolaos Marketos, and Clio P. Mavragani

Introduction

SS is a female-dominated [1], autoimmune disorder of unknown etiology and diverse phenotypical expression. Xerostomia and keratoconjunctivitis sicca (due to lymphocytic infiltration of salivary and lacrimal glands, respectively) are considered to be the clinical hallmarks, while B-cell hyperactivity is thought to be the pathophysiological cornerstone. Genetic susceptibility and environmental triggers are combined in ways yet to be defined, leading to innate and subsequently adaptive immunity over-activation [2–5]. For most patients, the disease runs an indolent course with sicca symptoms being the main complaint, along with musculoarticular pain and potentially disabling fatigue [6, 7]. However, one third of SS patients develop extraglandular manifestations, and a small percentage of them, but considerably higher compared to the one related with other systemic autoimmune disorders, proceed to develop lymphoma. Therefore, SS provides a unique study model of malignant turn in inflammatory background, caused by an autoimmune disease [8, 9]. Early prognostic tools and better understanding of the different etiopathogenetic pathways leading to divergent disease phenotypes are challenging but also the key to development of effective treatment and improvement of quality of life for these patients.

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Epidemiology – Definition

SS is encountered in approximately 0.5% of the general population, making it the second most common systemic autoimmune disease after rheumatoid arthritis. Women are affected at a 9:1 ratio in comparison to men, usually between the ages of 40 and 60 years [1, 10].

Primary and Secondary SS

SS has been traditionally classified into primary and secondary depending on whether it occurs alone or in the context of another systemic autoimmune disease (systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), scleroderma, dermatomyositis) [10]. However, it has been increasingly appreciated that this classification is rather confusing since secondary forms of the disease encompass entities with distinct genetic, clinical, and serological profiles. Therefore, the replacement of the term "secondary" by the phrase "SS-associated disease" has been proposed by several investigators [11, 12].

Etiopathogenesis

SS is a disease of so far unknown etiology. Stress, as well as environmental, genetic, and epigenetic factors, seems to interact in pathogenesis (Fig. 10.1).

Fig. 10.1 A model of potential contribution of different factors in SS pathogenesis

Higher prevalence of SS around menopause fueled the hypothesis of estrogen deficiency as a possible disease mechanism. Murine experiments have shown that estrogens inhibit the IFNγ-induced expression of adhesion molecule-1 and exhibit a protective role regarding autoimmune lesions in salivary and lacrimal glands [13]. Ovariectomy led to increase of apoptotic epithelial cells in salivary glands, associated with α-fodrin cleavage, in other murine models [14]. Moreover, increased number and impact of stressful events prior to disease onset in association with inadequate coping mechanisms, coupled with a chronically suppressed hypothalamic-pituitary-adrenal axis [15], potentially leads to defective anti-inflammatory mechanisms, thus promoting an exacerbated immune response. As in many autoimmune diseases, viruses such as Coxsackie, CMV, retroviruses, HCV, and Epstein-Barr have been previously viewed as initial triggers for SS [1, 16]. Endogenous triggers, such as long interspersed nuclear element 1 (LINE-1; L1) [17, 18], have been recently shown to be over-expressed in salivary glands of SS patients possibly as a result of defective methylation [19], leading to increased production of type I interferons and B-cell activation [3–5]. The increased familial aggregation of SS and other autoimmune diseases supports the notion that genetic background is a significant contributor in disease pathogenesis and that shared susceptibility gene variants plus common environmental stimuli are the basis for a wide range of autoimmune manifestations [20–24]. Indeed, this predisposing genetic basis seems to involve genes inside and outside the MHC locus implicated in the IFN signaling pathway, others that regulate B-cell function and antibody production, as well as the apoptotic and inflammatory genes in NF-kB pathway [4, 25] (Table 10.1). Nowadays, deregulation of epigenetic mechanisms and intestinal microbial dysbiosis attract increasing attention as potential culprits in disease onset [26–28].

The observation that lymphocytes infiltrating exocrine glands and parenchymal organs surround epithelia suggests a central role of the epithelial cell in the formation and further organization of characteristic immunopathological lesions in SS [29]. Especially, salivary gland epithelial cells have been investigated and found to

Table 10.1 Association of non-MHC class genes with SS susceptibility according to distinct pathogenetic pathways

	Type I and II IFN pathways	B-cell activation	NF-κB
Genes/ chromosomes	IRF5/Chr7	BLK-FAM167A/Chr8	TNFAIP3/chr6
	IRF5/TNPO3/Chr7	CXCR5/Chr11	TNIP1/Chr5
	STAT4/Chr2	BAFF/Chr13	LTA/LTB/TNF gene clusters
	IL12A/Chr3	GTF2I/chr7	BAFF-R/Chr22
	NCR3/NKp30/Chr6	EBF1/Chr5	

IRF5 interferon regulatory factor 5; *TNPO3* transportin 3; *STAT4* signal transducer and activator of transcription 4; *IL12A* interleukin 12A; *NCR3/NKp30* natural cytotoxicity triggering receptor 3/ natural killer protein 30; *BLK-FAM167A* B-lymphocyte kinase/family with sequence similarity 167, member A; *CXCR5* chemokine (C-X-C motif) receptor 5; *BAFF* B-cell activating factor; *GTF2I* general transcription factor 2I; *EBF1* early B-cell factor 1; *TNFAIP3* tumor necrosis factor-alpha-induced protein 3; *TNIP1* TNFAIP3-interacting protein 1; *LTA/LTB/TNF* lymphotoxin gene A, lymphotoxin gene B, tumor necrosis factor; *BAFF-R* B-cell activating factor receptor

undergo increased apoptosis [30], leading to release of autoantigens (such as Ro/SSA and La/SSB) which in turn drive the production of disease-specific autoantibodies. The immunocomplexes that are generated through this process result in type I interferon (IFN) production by plasmacytoid dendritic cells (PDCs) in individuals with genetic predisposition. Subsequently, type I IFN can reinforce epithelial activation and BAFF overexpression, as well as autoantibody production. The complex role of activated epithelia as antigen-presenting cells and cells secreting chemokines and cytokines or expressing chemotactic molecules places them at the center of the immunological process. Epithelial cells ultimately contribute to further aggregation of inflammatory cells, activation of lymphocytes (both T and B), and autoantibody production, thus closing the vicious circle of autoimmunity. This series of events can possibly culminate in extensive tissue damage and even B-cell monoclonal expansion [4, 31–35]. Therefore, the term "autoimmune epithelitis," stressing the key role and active involvement of epithelial cells, has been fairly proposed to describe SS [36].

Diagnosis and Differential Diagnosis

Thorough patient history and meticulous clinical examination of all systems are of utmost importance [10]. Family history should also be recorded, as familial clustering of cases with SS and other autoimmune conditions has been recorded [20–25]. Classification criteria are commonly used in order to establish SS diagnosis, with the latest revision having taken place in 2016 by the American/European Consensus Group (Table 10.2) [37]. Differential diagnosis is summarized schematically in Table 10.3 [37–41].

Diagnostic Tests

Laboratory Tests

Routine laboratory tests (full blood count, renal and liver function tests, serum protein electrophoresis plus immunofixation in case of hypergammaglobulinemia, erythrocyte sedimentation rate, C-reactive protein, urine analysis) and immunologic markers (rheumatoid factor, anti-nuclear antibodies, complement levels, antibodies against the cytoplasmic antigens SSA/Ro and SSB/La, cryoglobulins, anti-thyroid autoantibodies) are included in the laboratory evaluation of suspected SS [42–44]. Testing for viruses (HCV, HIV, HTLV-1) and IgG4 levels is carried out for differential diagnosis purposes, and other targeted autoantibodies or supplementary laboratory tests can be requested, according to specific clinical manifestations [38–46]. A schematic presentation of associations between specific autoantibodies detected in SS patients and disease phenotypical characteristics is shown in Table 10.4 [46–63].

Table 10.2 2016 American College of Rheumatology/European League Against Rheumatism classification criteria for primary SS. The classification of pSS applies to any individual who meets the inclusion criteria (a), does not have any of the conditions listed as exclusion criteria (b), and has a score of at least 4 when the weights from the five selected criteria items are summed (c). Several changes from 2002 AECG classification criteria were made. Subjective ocular or oral symptoms are now considered a prerequisite, rather than criteria contributing to the total score as they were before. Sialography and scintigraphy have been omitted, and a higher threshold for the ocular staining score has been implemented. The list of exclusion criteria was revisited, as the newly identified IgG4-related disease was added and lymphoma was removed, while more accurate techniques are required to rule out known, confounding entities (PCR confirmation of active hepatitis C). Finally, anti-SSB/La autoantibodies positivity was concluded to have no diagnostic value in the absence of anti-SSA/Ro and was therefore withdrawn. To be noted that patients on anticholinergic drugs should be objectively evaluated for their sicca symptoms after a sufficient time of these medications has elapsed

(a) Inclusion criteria
Positive response to at least 1 of the following questions:
1. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
2. Do you have a recurrent sensation of sand or gravel in the eyes?
3. Do you use tear substitutes more than 3 times a day?
4. Have you had a daily feeling of dry mouth for more than 3 months?
5. Do you frequently drink liquids to aid in swallowing dry food?
or
Suspicion of Sjögren's syndrome from the ESSDAI questionnaire (at least 1 domain with a positive item)

(b) Exclusion criteria
1. History of head and neck radiation treatment 2. Active hepatitis C infection 3. AIDS 4. Sarcoidosis 5. Amyloidosis 6. Graft-versus-host disease 7. IgG4-related disease

(c)

Criteria items	Weighted score	SS classification
Labial salivary gland with focal lymphocytic sialadenitis and focus score ≥ 1 foci/4 mm^2	3	Score ≥ 4
Anti-Ro/SSA positivity	3	
Ocular staining score ≥ 5 (or van Bijsterveld score ≥ 4) in at least one eye	1	
Positive Schirmer's test (≤5 mm/5 min in at least one eye)	1	
Unstimulated whole saliva flow rate ≤ 0.1 ml/min	1	

Table 10.3 SS differential diagnosis. Other causes of sicca symptoms and processes infiltrating the exocrine glands need to be ruled out in order to reach the correct diagnosis. IgG4-related disease is a newly identified entity, added in the exclusion criteria list of the recently reviewed American/European Consensus SS classification criteria. It is a multi-organ, immune-mediated condition that has unified several diseases once considered to be individual. It includes Mikulicz disease (sialo/dacryo-adenitis and salivary/lacrimal gland enlargement), Küttner tumor, Riedel's thyroiditis, orbital inflammatory pseudotumor, pituitary hypophysitis, and hypertrophic pachymeningitis in the head and neck region, as well as autoimmune pancreatitis, interstitial pneumonitis, interstitial nephritis, prostatitis, retroperitoneal fibrosis, and inflammatory aortic aneurysm. Elevated serum IgG4 levels (≥135 mg/dl) and infiltration of abundant IgG4-positive plasma cells into affected organs help with differential diagnosis

Sicca symptoms (xerophthalmia and/or xerostomia)	Lymphocytic infiltration of exocrine glands	Non-lymphocytic infiltration of exocrine glands
Use of medications *Antihypertensives, antihistamines, antidepressants, isotretinoin, etc.* Previous head and neck radiation Diabetes mellitus Vitamin A deficiency Any functional or anatomical defect of the eyelid Chronic blepharitis, chronic conjunctivitis, or another chronic eye inflammation Psychogenic	Chronic viral infections *Hepatitis C, AIDS, HTLV-1* IgG4-related disease Chronic graft-versus-host disease Lymphoma	Granulomatous diseases *Sarcoidosis, tuberculosis, leprosy, syphilis* Metabolic infiltration *Hyperlipoproteinemia, diabetes mellitus, amyloidosis, hemochromatosis*

Salivary Gland Biopsy

Minor salivary gland biopsy (MSGB) (Fig. 10.2) displays a crucial role for diagnosis, prognosis, and risk stratification [64, 65]. According to American/European Consensus SS classification criteria of 2016, diagnosis cannot be established without a positive MSGB or positive anti-SSA/Ro antibodies [37]. Moreover, intense lymphocytic infiltration has been identified as an independent histopathological risk factor for NHL development [66], which is the leading cause of excess mortality in SS patients [67–69].

The presence of a lymphocytic infiltrate of ≥50 lymphocytes per 4 mm^2 of glandular parenchyma, usually located in the periductal area, is considered a positive focus score. The average number of these lymphocytic aggregates per 4 mm^2 of salivary gland tissue is the focus score (Fig. 10.3) [64]. Despite the fact that only focus score appears in the American/European consensus criteria, Tarpley score (measure of glandular architecture derangement) is also commonly used [65, 70]. Another important histopathological feature is the presence of germinal center (GC)-like structures (Fig. 10.4). The latter have been associated with higher focus score, higher frequency of extraglandular manifestations, hypergammaglobulinemia, increased RF levels, and higher prevalence of positive anti-SSA/Ro and/or anti-SSB/La autoantibodies. The presence of GC-like structures has

Table 10.4 Prevalence of specific autoantibodies in SS patients and correlation with clinical manifestations, other serological features, and disease outcomes. This table includes traditional autoantibodies for disease classification, autoantibodies identified from murine models, and autoantibodies typically associated with other autoimmune diseases. The hoped-for result of as early as possible diagnosis has recently led to the marketing of a new diagnostic kit (Sjö® test). The cumulative sensitivity of traditional (ANA, RF, anti-SSA/Ro, anti-SSB/La) and novel (anti-CA VI, anti-SP-1, anti-PSP) antibodies of Sjö® panel has been estimated to be 91.8%, whereas the sensitivities for anti-SSA/SSB alone and for the novel biomarkers alone were found to be 74.9% and 49.8%, respectively. Additionally, the cumulative specificity for the complete Sjö® panel was estimated at 79.8%. Further potential biomarkers currently under investigation are anti-kallikrein antibodies, antibodies against carbamylated proteins, and antibodies against TRIM38 proteins, among others (not shown in the table)

Type of autoantibodies	Prevalence of autoantibody positivity in pSS patients	Clinical correlation/significance
Anti-Ro/SSA Anti-La/SSB	33–74% 23–52%	Usually associated with female sex, younger age at diagnosis, more prominent lymphocytic infiltrate of the exocrine glands, and potentially a higher prevalence of extraglandular manifestations Attention needed in case of pregnancy, due to potential congenital heart block of the baby (complete heart block occurring in approximately 2% of cases)
Anti-nuclear antibodies (ANA)	59–85%	Associated with female gender, younger age at diagnosis, parotid gland enlargement, extraglandular manifestations, cytopenia, hypergammaglobulinemia, as well as increased frequency of RF, anti-Ro/SSA, anti-La/SSB, and antiphospholipid antibodies positivity
Rheumatoid factor (RF)	36–74%	Linked to earlier disease onset, female predominance, positive salivary gland biopsy, more frequent extraglandular features, and higher use of corticosteroids, among others Also, increased frequency of anti-La/SSB, anti-Ro/SSA, cryoglobulins, and ANA positivity, as well as low C3/C4 and hypergammaglobulinemia
Cryoglobulins	9–15%	One of the indisputable risk factors for non-Hodgkin's lymphoma development and SS-related death. Also, linked to earlier disease onset, higher frequency of extraglandular features (vasculitis, renal involvement, peripheral neuropathy, Raynaud's phenomenon) and cytopenia, as well as higher prevalence of parotid gland enlargement
Anti-thyroperoxidase antibodies (anti-TPO) Anti-thyroglobulin antibodies (anti-TG)	11–45% 3–100%	Autoimmune thyroid disease prevalence in SS seems to be 10–30% Furthermore, SS prevalence in already diagnosed autoimmune thyroid disease has been reported to be 3–32% (10 times higher probability of SS in autoimmune thyroid disease than in the general population) Sicca symptoms are even more frequent in the context of autoimmune thyroid disease (37% of patients develop xerostomia and 23% isolated keratoconjunctivitis sicca) Autoimmune thyroid disease-associated SS is linked to milder SS phenotype, but also to greater risk of developing further autoimmune diseases (such as autoimmune liver and inflammatory bowel diseases), requiring closer follow-up

(continued)

Table 10.4 (continued)

Type of autoantibodies	Prevalence of autoantibody positivity in pSS patients	Clinical correlation/significance
Antibodies against cyclic citrullinated peptides (anti-CCP)	3–10%	Anti-CCP-positive pSS patients do not seem to have major clinical differences from anti-CCP-negative individuals, but there is a possible association with nonerosive arthritis
Anti-mitochondrial antibodies (AMA)	1.7–27% Depending on laboratory technique for detection; indirect immunofluorescence, Western blot, or ELISA	Specific for primary biliary cirrhosis (PBC) Also, higher prevalence of Raynaud's phenomenon, peripheral neuropathy, hypergammaglobulinemia, and high ESR Valuable for separating patients with autoimmune liver involvement from those with chronic viral liver disease
Anti-smooth muscle antibodies (ASMA)	30–62%	Autoimmune hepatitis (only 1.7–4% in pSS patients)
Anti-centromere antibodies (ACA, comprising of CENP-A, CENP-B, and CENP-C)	3.7–27%	Overlapping features between SS and systemic sclerosis (SSc) Up to 40% of the ACA-positive pSS patients can progress to systemic sclerosis Associated with delayed disease onset, but increased frequency of keratoconjunctivitis sicca, Raynaud's phenomenon, peripheral neuropathy, and lymphoma Lower frequency of anti-Ro/La antibodies and higher prevalence of other coexisting autoimmune disorders, such as PBC SS patients usually recognize CENP-C alone, whereas recognition of both CENP-B and CENP-C is more frequent in SSc
Antibodies against carbonic anhydrase (anti-CA; 13 known isoenzymes)	12.5–20.8%	Anti-CA II antibodies linked to renal involvement and particularly distal renal tubular acidosis Anti-CA VI and anti-CA XIII antibodies have also been shown to correlate with urine pH and inversely with serum sodium levels (cross-reactivity between anti-CA VI and anti-CA XIII is a possible scenario, as CA VI is the only isoenzyme secreted in saliva and expressed in the parotid and submandibular glands, but not in the kidney) Anti-CA VI is considered a novel, early SS biomarker, included in commercially available Sjö® diagnostic panel. It is the most prevalent novel autoantibody of the kit among both SS and non-SS dry eye patients (52% and 43%, respectively). Anti-CA VI positivity has been linked to more severe xerophthalmia, presence of xerostomia, younger age, and negative MSGB

Type of autoantibodies	Prevalence of autoantibody positivity in pSS patients	Clinical correlation/significance
Antibodies to 21-hydroxylase (anti-21[OH])	17.50%	Anti-21[OH] positivity was not linked to overt adrenal insufficiency, but it was associated with adrenal hyporesponsiveness and evidence of more prominent B-cell activation in MSG tissue samples Decreased prevalence of subjective xerophthalmia and increased frequency of leukopenia were also noted for anti-21[OH]-positive SS individuals
Anti-muscarinic receptor antibodies	62.2–81.8%	Associated with cytopenia and higher ESSDAI scores Could partially account for the salivary gland hypofunction, the gastroesophageal symptoms, and the bladder smooth muscle hyperresponsiveness, observed in pSS patients
Antibodies against citrullinated alpha-enolase peptides (anti- CEP-1)	60% of anti-citrullinated protein antibodies (ACPA)-positive pSS patients Less than 10% of unselected pSS patients	Associated with higher urine pH levels at first evaluation (linked to distal renal tubular acidosis, nephrocalcinosis, and impaired bone health)
Antibodies against salivary protein 1 (anti-SP-1)	52% of SS patients 19% of SS patients with negative anti-Ro/anti-La	Antibodies against murine SP-1 (no known human protein analogue) seem to identify targets in human parotid glands Anti-SP-1 antibodies are considered novel, early SS biomarkers, included in commercially available Sjö® diagnostic panel Patients with lower focus scores in MSGB tend to be tested positive for anti-SP-1 more often than those with higher focus scores (who generally test positive for anti-Ro/anti-La). Especially patients expressing only anti-SP-1 antibodies (no anti-Ro/anti-La) have low or negative MSGB focus score Anti-SP-1 can also be used as a marker to separate SS-associated RA from RA not complicated with SS
Antibodies against parotid secretory protein (anti-PSP)	18%	PSP is a protein involved in the binding and clearance of infectious agents Anti-PSP is considered a novel, early SS biomarker, included in commercially available Sjö® diagnostic panel Can also be positive in non-SS dry eye disease and rarely in RA and healthy controls
Anti-α-fodrin antibodies	29% of pSS patients, but 47% of SLE patients Almost 2 times more prevalent in non-SS sicca than SS patients	Anti-α-fodrin antibodies serum concentrations have been associated with the degree of lymphocytic infiltration in salivary glands Usually found in early disease stages Most probably not useful for SS diagnostic purposes

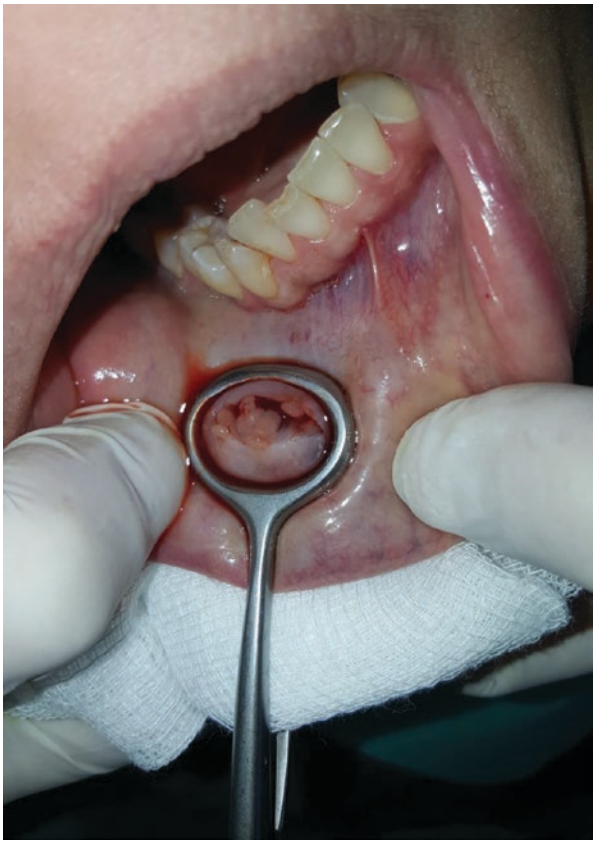

Fig. 10.2 Minor salivary gland (labial) biopsy. The procedure is simple and well-tolerated and can be done under local anesthesia on an outpatient basis. Usually 4–6 minor salivary gland lobules need to be sampled, in order for the tissue to be considered representative. Several different surgical approaches have been suggested in an effort to minimize complications. Most frequent adverse events reported in literature include temporary localized pain and bleeding, and only rarely there have been cases with persistent hypoesthesia of the lower lip (Photograph courtesy of E. Piperi, Assistant Professor in Department of Oral Pathology, School of Dentistry, UoA)

also been suggested to confer increased risk for lymphoma development. However, the contradicting results on GC-like structures significance from various studies – possibly due to poor definition on one hand and under-detection in H&E staining on the other – underline the need for uniform criteria and further research [65, 70–73].

The advantages of MSGB include easy accessibility, avoidance of skin incisions, and local anesthesia. Parotid biopsy is reserved only to rule out lymphoma in case of persistent parotid enlargement [74, 75]. MSGB sensitivity and specificity are considered to be higher than 75% and 90%, respectively [64, 76, 77].

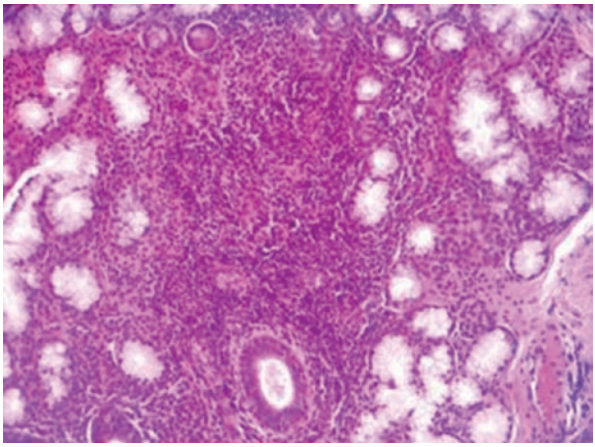

Fig. 10.3 Minor salivary gland biopsy with high focus score (Hematoxylin & Eosin staining)

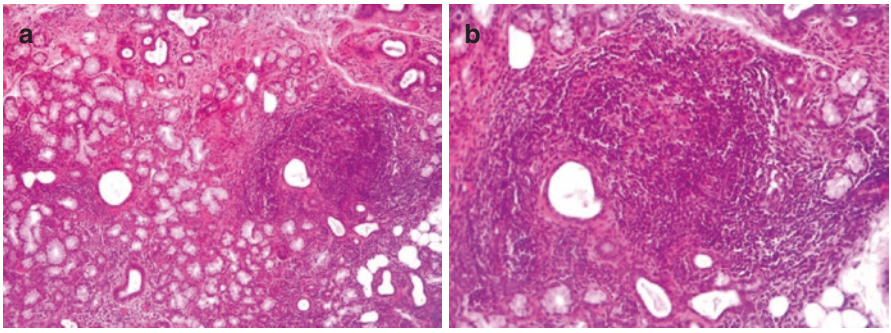

Fig. 10.4 Minor salivary gland biopsy with MALT development and germinal center-like formation in ×100 (**a**) and ×200 (**b**) magnification (Hematoxylin & Eosin staining). GC-like structures are tertiary ectopic lymphoid structures, and they are considered an advanced histopathologic lesion, previously correlated with future lymphomagenesis, extraglandular manifestations, and earlier diagnosis. However, their role in lymphomagenesis is still questioned, since more recent research has failed to demonstrate such a correlation. The prevalence of GC-like structures in SS patients is ranging from 18% to 59% according to different studies

Oral Involvement Assessment Tests

The objective evaluation of xerostomia and oral involvement in SS, except for the generally accepted MSGB, remains a challenge [75, 78]. The easiest, most common, and affordable way to assess major and minor salivary gland secretory capacity is the measurement of salivary flow or sialometry. Unstimulated whole saliva flow rate equal to or below 0.1 ml/min is considered abnormal (0.3–0.4 ml/min are expected for healthy individuals) [75].

Sialography may be used to demonstrate the morphology of the ducts, while scintigraphy can assess the salivary gland functionality. The nonspecific results of

both techniques and the involvement of radiation for the latter have led to their removal from the most recent SS classification criteria [75, 79].

Ultrasound (US), being noninvasive, inexpensive, and radiation-free, is drawing a lot of attention for the purposes of major salivary gland imaging. Multiple studies have shown good agreement and comparable results between salivary gland ultrasound and sialography and even diagnostic superiority compared to scintigraphy [80].

In addition to its value as a diagnostic tool, the prognostic value of ultrasound has also been explored. Increased parenchymal dyshomogeneity scores of major salivary glands have been found to correlate with SSA, SSB, ANA, RF, higher levels of IgG, salivary gland enlargement, cutaneous vasculitis and/or purpura, GC-like structures in salivary gland biopsy, CD4 T-cell lymphopenia, Raynaud's phenomenon, and disease activity scores. Last but not least, there is some evidence that ultrasonographic images of salivary glands change in response to treatment (rituximab versus placebo) for SS [80].

Elastography is an added feature to the classic US modality, which can increase sensitivity compared to B-mode US alone and differentiate between SS patients and sicca controls [81].

Ocular Tests

Mainly aqueous deficiency but also meibomian gland dysfunction and neuropathic pain contribute to increased tear evaporation rate, reduced tear film stability, and ocular discomfort in SS patients [82].

Keratoconjunctivitis sicca (KCS) symptoms can be quantified using patient questionnaires, like the Ocular Surface Disease Index (OSDI). The main available objective tests are Schirmer's test (Fig. 10.5), ocular surface dye staining (Fig. 10.6), and tear breakup time (TBUT) [82–84]. Among those, only the first two are included in the latest classification criteria [37].

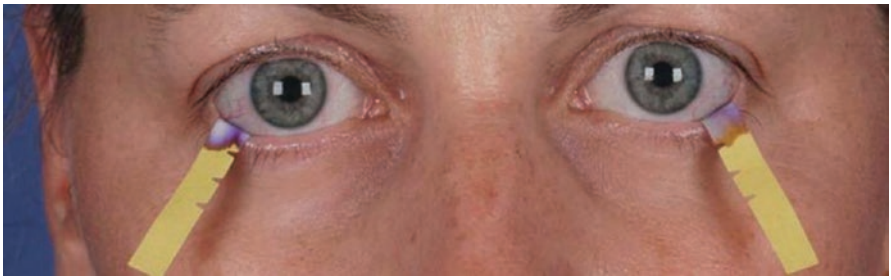

Fig. 10.5 Schirmer's test involves the measured wetting of a standardized paper strip, placed over the inferior eyelid, over a certain period of time. It is usually performed without anesthesia, and the test is considered positive when at most 5 mm of the paper are wetted in 5 min time. The cutoff point is lower (<3 mm) when the test is performed under anesthesia, as in this case we measure the basal/non-reflex tear production (Permission to re-produce kindly granted by Messmer [40])

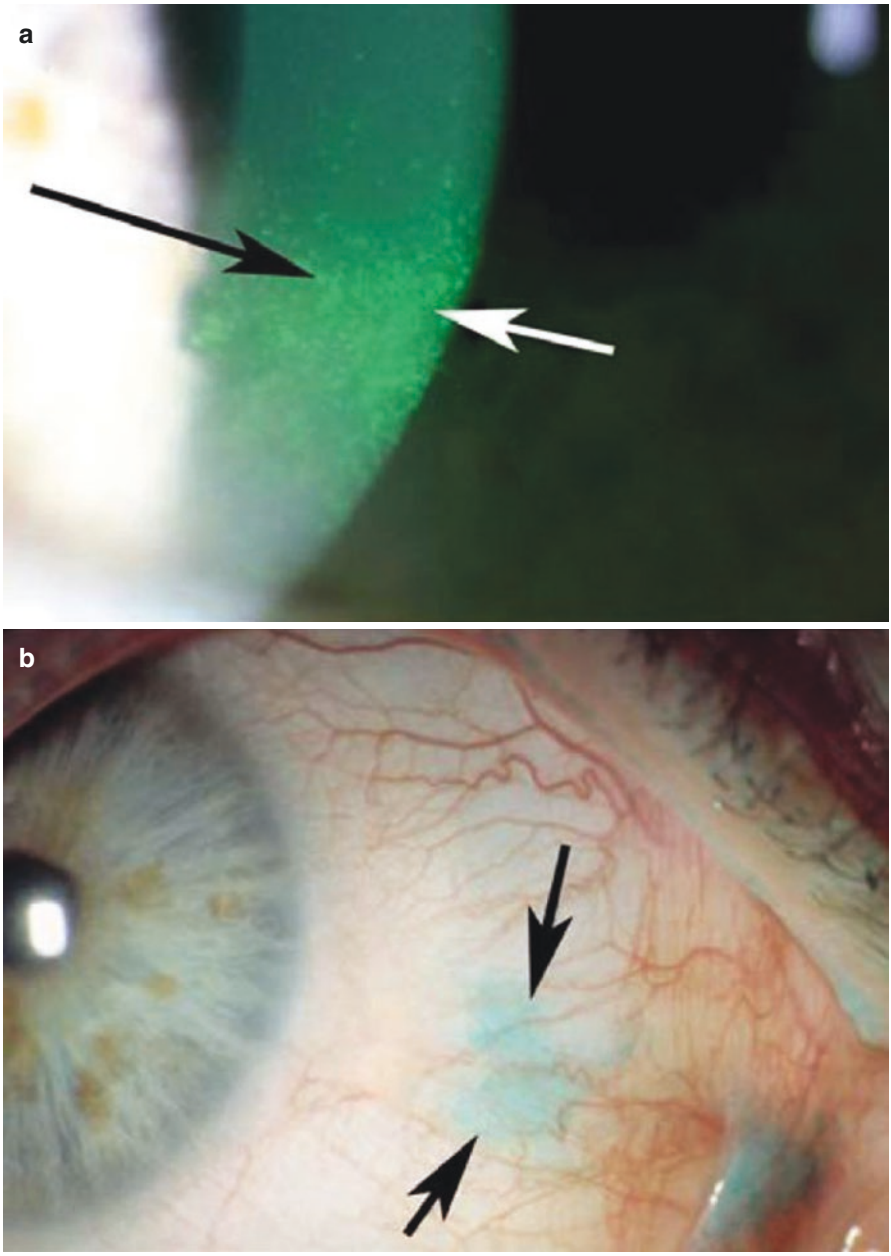

Fig. 10.6 Staining of the ocular surface in dry eye disease. Fluorescein better stains the cornea (**a**), while lissamine green (LG) is preferred for the conjunctiva (**b**). LG tends to be used nowadays instead of rose bengal (RB), due to improved toxicity and tolerance profile, given their similar staining properties. Both RB and LG bind to corneal epithelial cells that are uncoated by mucin or other proteins, and these damaged areas are easily observed under slit lamp examination. However, both dyes seem to correlate poorly to symptom severity as stated by patients in relevant questionnaires (Permission to re-produce kindly granted by Messmer [40])

Disease Activity Indexes

There are two indexes, introduced by European League Against Rheumatism (EULAR), which are used to assess SS activity from the patient's and the clinician's point of view. The first one is the EULAR Sjögren's Syndrome Patient Report Index (ESSPRI), which consists of three visual-analogue scales measuring severity of sicca symptoms, fatigue, and pain [85]. The second one is the EULAR Sjögren's Syndrome Disease Activity Index (ESSDAI), which assesses the activity in 12 different domains representing organ systems. Since its introduction, ESSDAI has become the gold standard in terms of disease activity assessment because it serves as point of reference among physicians; it is widely used in randomized controlled trials as outcome measure and has been correlated with biomarkers and lymphoma development risk [42, 43].

Clinical Manifestations and Disease Management

SS can manifest with a plethora of clinical signs and symptoms, frequently vague and definitely not pathognomonic, often resulting in diagnostic delays [86]. Oral and ocular dryness, sometimes accompanied by xeroderma, upper respiratory desiccation, and vaginal dryness with subsequent dyspareunia are among the most common complaints [10]. Extraglandular manifestations (Fig. 10.7) occur in at least one third of individuals and can schematically be divided into three groups: nonspecific, periepithelial, and immune complexes mediated [6, 87–94]. The disease often runs a benign, indolent course with the exception of severe systemic complications causing excess morbidity and most importantly lymphoma, which is one of the main causes of mortality in SS [42, 67].

With regard to management, pilocarpine is usually initiated in an effort to alleviate ocular discomfort and difficulty in everyday life caused by lack of saliva, but residual lacrimal and salivary gland function is a prerequisite in order to be effective [95, 96]. SS patients must be informed on the rare side effects of pilocarpine, such as excessive sweating, nausea, diarrhea, and palpitations; for this reason, progressive dose escalation is recommended. Natural tears and lubricants for ocular use, as well as artificial saliva and oral solutions with chlorhexidine, are frequently used by patients and recommended by ophthalmologists and dentists, respectively [97]. Interestingly, in contrast to other systemic autoimmune diseases with high inflammatory load, SS-related sicca complaints do not respond to immunosuppressive treatment [98]. Mild aerobic exercise is recommended for fatigue [99], while disease-modifying antirheumatic drugs (DMARDs) are reserved for extraglandular manifestations [100–103]. The rare cases of aggressive lymphomas are managed with cytotoxic drugs [104–106]. Tables 10.5 and 10.6 display the array of clinical manifestations and the recommended treatment options in SS patients [107–120].

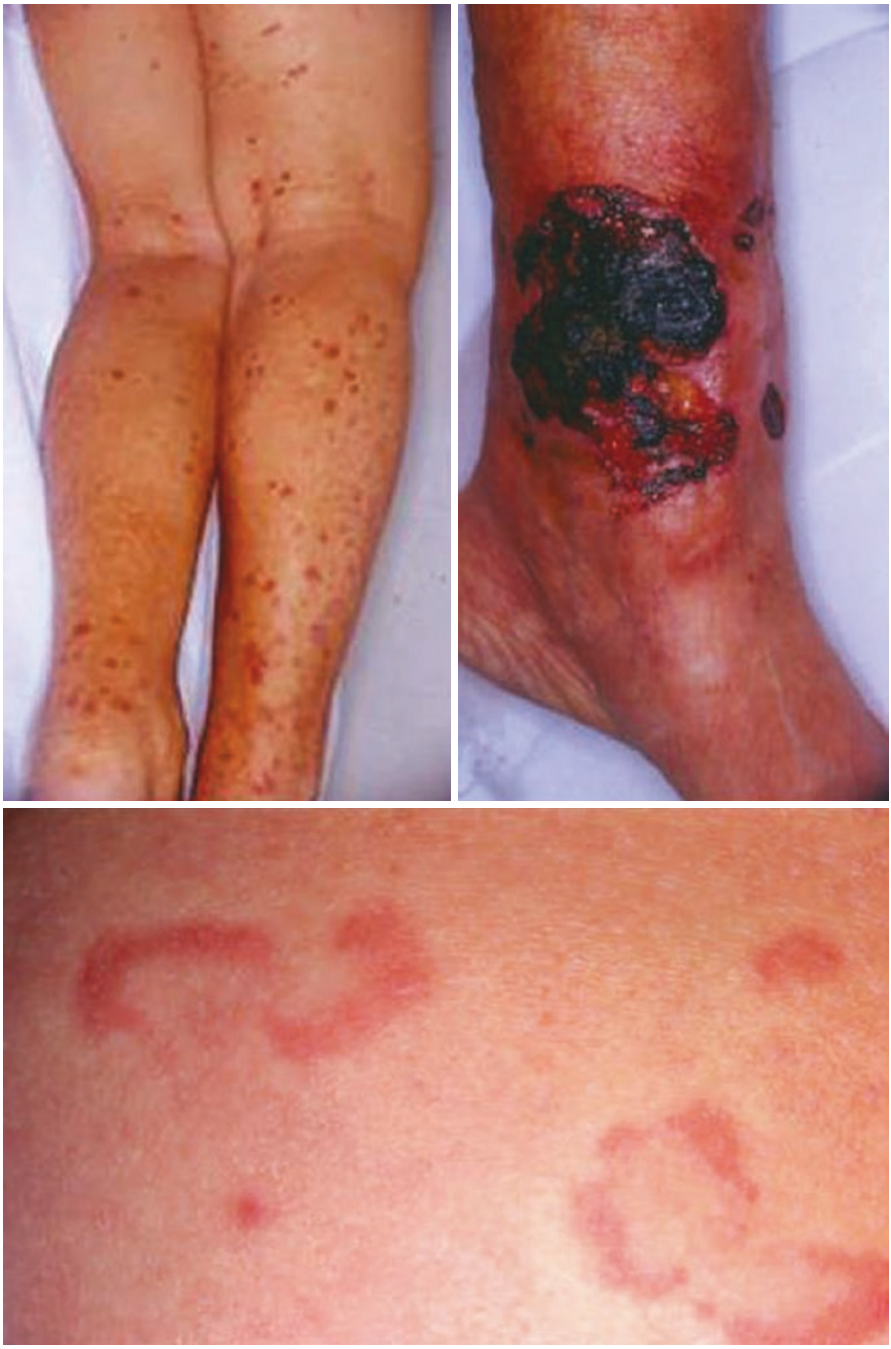

Fig. 10.7 Extraglandular features of SS. *Top left*: Palpable purpura in the lower extremities. *Top right*: Multiple necrotic cutaneous ulcers of the lower extremities in a patient with SS and cryoglobulinemia. *Bottom*: Annular urticarial lesions of the trunk (Permission to re-produce kindly granted by Hile et al. [148])

Table 10.5 Glandular manifestations and their treatment in SS patients

Organ involvement	Symptoms and signs	Therapeutic approach
Ocular	Irregularity of the corneal image, irritation, redness, photosensitivity	*No MG damage* (aqueous deficiency) Stop offending drugs, environmental changes, artificial tears, gels, ointments Ω3 suppl., CIS collyrium (0.05%) pulse steroids, punctal plugs, secretagogues, moisture chamber spectacles Topical autologous serum, contact lenses, permanent punctal occlusion Systemic anti-inflammatory medication, eyelid surgery *MG damage* (evaporative) Stop offending drugs, environment modification, lipid-rich tear substitutes, warm compress, massage CIS: 2–2.5 mg/kg/d, topical steroids, AZI, DXC, secretagogues, punctal plugs, moisture chamber spectacles Topical autologous serum, contact lenses Eyelid surgery
Oral	Dryness, caries, angular cheilitis Salivary gland enlargement	Dental fluorination, masticatory stimulation, chlorhexidine Pilocarpine hydrochloride: max 20 mg/d in divided doses Cevimeline hydrochloride: max 30 mg × 3 CS, 0.25–0.5 mg/kg/d for 10–15 d
Pancreatic	Recurrent autoimmune pancreatitis (5%)	AZA 2–3 mg/kg/d, RTX, pancreatic enzymes
Vaginal	Dyspareunia	Lubricants

MG meibomian gland, *CIS* cyclosporine, *AZI* azithromycin, *DXC* doxycycline, *CS* corticosteroids

Lymphomagenesis and Lymphoproliferation

SS is unique among autoimmune diseases as for malignant transformation risk. Those patients seem to have a 10–44-fold greater risk of developing lymphoma compared to general population, whereas systemic lupus erythematosus patients and rheumatoid arthritis patients only have a seven-fold and four-fold greater risk, respectively [67, 121]. In other words, 2.7–9.8% of SS patients are diagnosed with non-Hodgkin lymphoma (NHL) and that risk increases by 2.2% per year of age [78, 122].

Mucosa-associated lymphoid tissue (MALT) lymphomas represent 60% of cases [67]. Most common sites are the salivary glands, especially the parotid and submandibular glands, but other mucosal sites of MALT lymphoma development include the orbits, nasopharynx, stomach, thyroid, and lung [78]. Other subtypes of lymphoma found in these patients are the diffuse large B-cell lymphoma (DLBCL) and the nodal marginal zone lymphoma (NMZL), which – together with MALT – account for more than 90% of total SS-associated lymphoma cases [67].

Multiple research studies have been focusing their efforts on correlating clinical, serological, and histopathological features with risk of lymphomagenesis [66, 72, 123–126], and an attempt has also been made to formulate a predictive score for

Table 10.6 Extraglandular manifestations and their treatment in SS patients

Organ involvement	Symptoms and signs	Therapeutic approach
Nonspecific		
Musculoskeletal	Myalgias, arthralgias, Jaccoud arthropathy, rare arthritis	HCQ, MTX, or combination of both, small dose CS < 15mg qd
Raynaud's phenomenon	Cold-related color skin changes	Vasodilators, especially calcium channel blockers
Fatigue (35–50%)	Increased need for resting hours, disruption of sleep patterns	Nordic (active) walking, HCQ in some cases RTX
Periepithelial		
Bronchi (10–20%) Small airway disease (13%) ILD (17%)	Mild to moderate dyspnea and dry cough, xerotrachea	Bronchodilators AZA, RTX
Autoimmune cholangitis	LFTs abnormalities, jaundice	RTX UDCA, AZA
Renal/bladder (4–30%) Tubulo-interstitial nephritis Interstitial cystitis (0.3%)	Hypokalemic hyperchloremic distal renal tubular acidosis/ nephrocalcinosis Pollakiuria, nycturia, urinary urgency, pelvic or suprapubic pain	Urine alkalization (bicarbonate, electrolyte supplements) CS CS, CIS, surgical intervention
Immune complex-mediated disease		
Skin vasculitis Vasculitis in 5% Purpura – palpable in 5% Annular erythema	Cryoglobulinemia	CYC, AZA RTX for necrotizing vasculitis (cycles of 2gr q15 days interval/6 months)
Glomerulonephritis(rare)	Membranous or membranoproliferative	CS, RTX, CYC
Neuropathy (20%) Peripheral neuropathy CNS	Peripheral sensorimotor neuropathy or pure sensory neuropathy Motor neuropathy/ganglionopathy Mononeuritis multiplex Small fiber neuropathy MS-like	CS, 0.5–1 mg/kg, and IVIGs, RTX CS, 0.5–1 mg/kg, and CYC/ AZA, 2–3 mg/kg/d Anticholinergics, antidepressants, gabapentinoids CS, PE, RTX
Low-grade lymphoma *Disseminated lymphoma*		Wait and watch policy R-CHOP = if diffuse large B cell

HCQ hydroxychloroquine (5 mg/kg qd), *MTX* methotrexate 2.5–3 mg/15 kg qw), *CS* corticosteroids, *RTX* rituximab (cycles of 2gr q15 days interval/6 months), *AZA* azathioprine (2–3 mg/kg qd), *UDCA* ursodesoxycholic acid, *CIS* cyclosporine (2–2.5 mg/kg qd), *CYC* cyclophosphamide (750 mg–1 g/m^2), *IVIGs* intravenous immunoglobulins, *R-CHOP* rituximab-(c)yclophosphamide, (h)ydroxydaunorubicin, (o)ncovin (vincristine), (p)rednisone

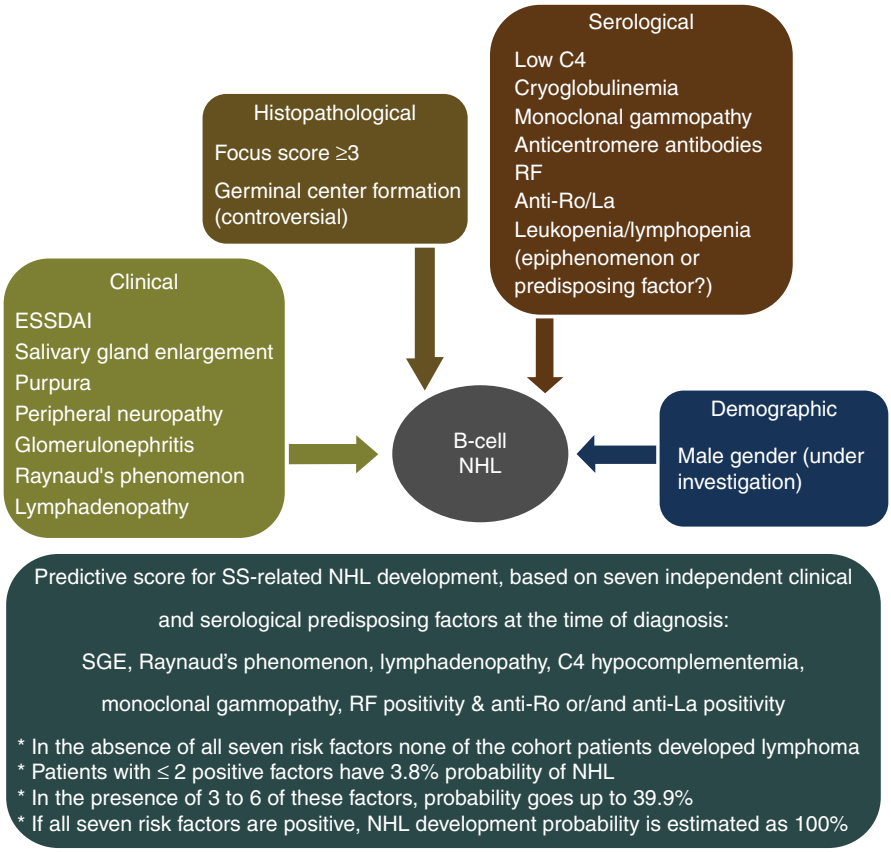

Fig. 10.8 Risk factors for lymphomagenesis in SS, as identified by various studies over the last years and a predictive score formula based on seven of them. Relevant information is gathered at the time of disease diagnosis and correlates with disease outcome, even years later, leading to the conclusion that early risk stratification is feasible for those patients. SGE salivary gland enlargement

SS-related NHL development based on data collected at the time of diagnosis [123] (Fig. 10.8). However, the molecular etiopathogenetic aspects of malignant transformation still remain largely elusive and ill-defined.

Current belief on etiopathogenesis of lymphoma focuses on four interrelated axes: chronic inflammation, B-cell activation, defective immunosurveillance, and epigenetic alterations [4, 104]. Focus score of at least 3 in MSGBs of SS patients has been identified as an independent and important predicting factor for NHL development, and the use of this threshold has a positive predictive value of 16% and a negative predictive value of 98% for that kind of malignant transformation [66]. Furthermore, the activation of P2X7 receptor-NLRP3 inflammasome complex (with subsequent increase of pro-inflammatory cytokines IL-18 and IL-1β serum levels, among others) correlates with lymphocytic infiltration severity, ESSDAI

scores, and lymphoproliferation risk. The hypothesis of inflammasome activation secondary to increased accumulation of proinflammatory nucleic acid shreds, ineffectively degraded and cleared, has recently been supported [127, 128].

Another factor promoting chronic inflammation seems to be IFNγ, as the mRNA levels in MSGBs have been associated with a higher degree of lymphocytic infiltration, shown to be a predisposing factor for lymphomagenesis [129]. Moreover, a functional variant of TNFAIP3 gene (rs2230926), encoding the A20 protein, leads to unopposed NF-κB pathway activation and is therefore involved in inflammatory process perpetuation, B-cell survival, and more aggressive disease phenotype with earlier disease onset and increased lymphoproliferation risk [130].

B-cell activating factor (BAFF), produced by various immune cells but also by the salivary epithelial cells and regulated by both type I and II IFNs, is of utmost importance for the maturation, proliferation, and survival of B cells. BAFF levels are found increased in SS patients' serum with a history of lymphoma, and high levels persist for years after treatment and remission [4, 131, 132]. Another equally important observation is the association of specific BAFF polymorphisms with SS-related lymphomagenesis and in particular the significantly different prevalence of the protective AA genotype of the rs12583006 polymorphism, as well as of the protective haplotypes TACAC and TACC and of the risk haplotype TTTC in SS patients prone to NHL development (high risk determined by the presence of adverse predictors), compared to low-risk individuals [133]. Additionally, a specific mutation (His159Tyr) of BAFF receptor (BAFF-R) is of interest, as it has been identified in more than two thirds of SS-associated MALT lymphoma. This mutation, leading to NF-kB pathway activation, was linked to earlier development of lymphoma or adverse immunological features (hypergammaglobulinemia and positive RF) [78, 134].

Finally, Fms-like tyrosine kinase 3 ligand (Flt-3 l) is a protein that acts as a cytokine and a growth factor, activating Flt-3 (or CD135) on the surface of hematopoietic progenitor cells, and therefore considered to be a mediator of B-cell survival. Higher levels of Flt-3l are strongly associated with history of lymphoma, detectable years before malignant transformation, and not affected by treatment [135].

The vicious circle of autoreactive B-cell chronic stimulation and immunocomplexes formation might finally lead to the favorable, monoclonal expansion of rheumatoid factor (RF)-reactive B cells and to the lymphomatous transformation, under defective immunosurveillance [4]. As a matter of fact, IFNα mRNA levels in MSGBs seem to strongly correlate with the expression of pro-apoptotic molecules (tumor suppressor gene p53 and auto-antigen Ro52, with the latter negatively regulating the anti-apoptotic B-cell lymphoma 2 (Bcl-2) gene) [132]. Moreover, decreased prevalence of a specific TREX1 variant (rs11797 AA genotype) in SS-related non-MALT cases was observed. This variant was shown to associate with higher mRNA IFNα levels in SS salivary gland tissues [136].

Further oncogenic mechanisms, likely to contribute to malignant turn in SS, are the over-expression of Bcl-2 due to a translocation involving chromosomes 14 and 18, leading to inhibition of apoptosis and increased B-cell survival. Apart from IFNα effect on p53 levels, specific mutations of this tumor suppressor gene were described 20 years ago in MSGBs from SS-associated NHL cases [4, 132, 137].

Epigenetic changes, involving methylating enzymes and transcription of non-coding micro-RNAs, are also implicated in lymphomagenesis [138]. MiR200b miRNAs, which regulate the expression of oncogenes and tumor suppressor genes, have been found to be downregulated in MSGBs with advanced lymphocytic infiltration and MALT lymphoma [139]. Especially miR200b-5p strongly discriminates SS patients who already have or will develop NHL from the rest of them or from sicca controls [140]. As for methylating enzymes, DNA methyltransferase (DNMT)3B and methyl-CpG-binding protein 2 (MeCP2) have been found decreased in SS-lymphoma patients [141], while methylene-tetrahydrofolate reductase (MTHFR) gene variants, leading to defective methylation and impaired stability of DNA, have lately been suggested as susceptibility factors for non-MALT lymphoma [142].

It becomes clear that the multifactorial process of lymphomagenesis is rather complicated, and the finely tuned balance between opposing forces can become deranged and lead to adverse outcomes. An example of that is the IFNγ/IFNα mRNA ratio in MSGBs, which has emerged as a histopathological biomarker for the prediction of in situ lymphoma development [132].

SS-related hematological malignancies are correlated with an eightfold higher mortality risk compared to general population [69], and one in five deaths of SS is attributable to lymphoma [68]. Follow-up every 6 months is recommended for high-risk patients. Overall, NHL 5-year survival is estimated at approximately 92%, but higher disease activity is linked to higher possibility of relapse and death [143–145]. Wait and watch strategy is suitable for MALT lymphomas localized in the salivary glands, while rituximab and chemotherapy are employed in case of disseminated or aggressive disease [106, 146, 147, 149].

Multiple-Choice Questions

1. Which of the following clinical features would set Sjögren's syndrome (SS) on top of your differential diagnosis list?

   A. A 60-year-old man with polyarthritis of the small joints of the hands, morning stiffness of >1h, and low-grade evening fever
   B. A 30-year-old woman with fatigue, hair loss, sun sensitivity of the skin, pleurisy, and oral aphthae
   C. A 50-year-old woman with ocular and oral dryness, fatigue, arthralgias of the hands and feet, and purpura
   D. A 45-year-old woman with known depression and use of relevant medication, fatigue, low-grade fever, appetite loss, and weight loss
   E. An 85-year-old woman otherwise in good health complaining for dry eyes, dry mouth, constipation, and fatigue

   Correct answer: C

Feedback:

A. Rheumatoid arthritis. Typical presentation with polyarthritis of small joints, morning stiffness.
B. Systemic lupus erythematosus presentation.
C. Sjögren's typical presentation.
D. Depression most probable; other causes must be excluded.
E. Age-related fatigue and dryness. Late onset of symptoms – autoimmune disease of lower probability.

2. Which of the following are currently believed to be implicated in disease pathogenesis?

A. UV light
B. Genes
C. Stress
D. Surgery
E. Androgens
F. All of the above
G. A + B + C + E

Correct answer: G
Feedback: All these factors except previous surgery are currently implicated.

3. Which are the main identified pathways of SS pathogenesis?

A. IFNγ
B. B-cell hyperactivity
C. NF-κB
D. All of the above
E. None of the above

Correct answer: D
Feedback: All of the above pathways are considered viable for disease pathogenesis.

4. Which of the following medications would you prescribe to a patient with ocular dryness due to pSS?
Multiple answers eligible

A. Methotrexate
B. Pilocarpine
C. Hydroxychloroquine
D. Cevimeline
E. Etanercept
F. Oral cyclosporine
G. Ocular drops of cyclosporine
H. Infliximab

Correct answer: B, D, G

Feedback:
A, C. Methotrexate and hydroxychloroquine are used for musculoskeletal manifestations, despite inadequate data.
E. TNFα inhibitors have not shown encouraging results so far.
F. Oral cyclosporine is reserved for resistant pulmonary disease, but topical treatment has been used effectively in ocular symptoms of SS.

5. Which of the following medications would worsen a patient's established SS symptoms?

   A. Artificial tears
   B. Artificial saliva
   C. Methylcellulose inserts
   D. Amitriptyline

   Correct answer: D
   Feedback: Amitriptyline is known to exacerbate oral dryness.

6. What treatment modalities would you employ to alleviate fatigue in an SS patient?
   Multiple answers eligible

   A. Corticosteroids
   B. Azathioprine
   C. Hydroxychloroquine
   D. NSAIDs
   E. Serotonin uptake inhibitors
   F. Methotrexate
   G. Pregabalin
   H. Anti-TNF agents
   I. IVIG
   J. Aerobic exercise

   Correct answer: J
   Feedback:
   A, B, C, F, H. Corticosteroids have no effect on these nonspecific symptoms nor have immunomodulatory drugs as azathioprine, hydroxychloroquine, methotrexate, or TNF inhibitors.
   J. According to guidelines only aerobic exercise is effective.

7. What treatment would you suggest to manage the same patient's oral dryness?
   Multiple answers eligible

   A. Bromhexine
   B. Pilocarpine
   C. Hydroxychloroquine
   D. Cevimeline
   E. Sugar-free fluoride-containing chewing gums
   F. Etanercept
   G. Methotrexate
   H. Infliximab

I. Regular water drinking
J. Avoidance of drying air heating systems

Correct answer: B, D, E, F, I, J
Feedback: Pilocarpine, cevimeline, chewing gums that are sugar-free, frequent water intake, and avoiding air heating may alleviate symptoms. The rest of medication on this list has no proven effect on oral dryness.

8. You prescribed pilocarpine, and 1 week later the patient is back at the office with new complaints. Which of the following could be attributable to this medication?
Multiple answers eligible

A. Constipation
B. Glaucoma
C. Acute urinary retention
D. Nausea
E. Excessive sweating
F. Diarrhea
G. Urinary infection
H. Neuropathy
I. Palpitations

Correct answer: D, E, F, I
Feedback: Constipation, glaucoma, and acute urinary retention are side effects of inhibitors of cholinergic synapses and not of agonists like pilocarpine. Urinary infection and neuropathy are not side effects of pilocarpine.

9. Which is the most likely cause of recurrent renal colic in this patient?

A. Nephrocalcinosis in the setting of distal tubular acidosis
B. Nephrocalcinosis in the setting of proximal tubular acidosis
C. Hyperparathyroidism
D. Hyperoxaluria

Correct answer: A
Feedback: Despite the fact that both hyperparathyroidism and hyperoxaluria are valid causes, nephrocalcinosis in the setting of distal and not proximal tubular acidosis seems to be the most likely cause of renal colic in the setting of SS.

10. Among the following different therapeutic strategies for SS-associated low-grade lymphoma management, which one is advised?
A. Local radiotherapy
B. Wait and watch policy
C. IV immunoglobulin
D. Combination immunochemotherapy (rituximab and CHOP)
E. Mycophenolate mofetil

Correct answer: B
Feedback: Wait and watch policy is the recommended policy. IV Ig and mycophenolate mofetil have no place on lymphoma treatment. Combination therapy

(rituximab and CHOP) is indicated in diffuse B-cell lymphomas. Current data do not support the use of radiotherapy for localized low-grade MALT lymphomas.

11. Which of the following features have been associated with increased risk for lymphoproliferation in SS?
Multiple answers eligible

A. Parotid gland enlargement
B. Positive anti-TPO/anti-TG
C. Low C4 levels
D. Distal renal tubular acidosis
E. Fibromyalgia
F. Hypergammaglobulinemia

Correct answers: A, C, F
Feedback:
B. Autoimmune thyroiditis commonly coexists with SS, and it can also be responsible for sicca symptoms without SS, but does not evoke increased risk for lymphoma.
D. Glomerulonephritis (and not distal renal tubular acidosis) confers susceptibility to lymphoma.
E. Not linked to lymphoma, but correlated with SS-associated fatigue.

12. Which of the following conditions presenting with sicca symptoms can mimic SS?
Multiple answers eligible

A. Vitamin D deficiency
B. Wilson's disease
C. Graft versus host disease
D. Hepatitis B
E. Nonsteroid anti-inflammatory medications
F. Sarcoidosis

Correct answers: C, F
Feedback:
A. Vitamin A deficiency would be the correct answer.
B. Hemochromatosis and not Wilson's disease can cause sicca symptoms.
D. Hepatitis C would be the correct answer.
E. No relevant correlation with sicca symptoms, but commonly used to alleviate joint pain.

13. A 56-year-old woman is presenting with Raynaud's phenomenon. When asked, she also admits having dry eyes over the last year and feeling tired during the last 3 months. Routine laboratory tests are nonsignificant, ANA are positive, and anti-SSA/Ro antibodies are negative. The patient was eventually classified as SS. For which of the following tests has our patient definitely been tested positive?

A. Unstimulated salivary flow rate
B. Lissamine green ocular staining

C. Minor salivary gland biopsy
D. Schirmer's test
E. Anti-SSB/La antibodies
F. Tear breakup time

Correct answer: C
Feedback: According to the new classification criteria of 2016, SS cannot be verified unless at least anti-Ro antibodies or MSGB is positive. Since anti-Ro antibodies are negative in our case, MSGB is definitely positive (focus score ≥ 1), along with at least one other positive test among unstimulated salivary flow rate, Schirmer's test, and ocular staining.

14. Which of the following patients fulfill the American/European SS classification criteria of 2016?

A. A 43-year-old woman with total unstimulated salivary flow of 1 ml/15 min, positive ANA, positive anti-TPO/anti-TG, and Schirmer's test of 4 mm in 5 min in both eyes
B. A 42-year-old woman, regular blood donor up to recently, with new-onset xerophthalmia and arthralgias, positive anti-SSA/Ro antibodies, positive anti-CCP, and focus score of 1 in MSGB
C. A 50-year-old man with tracheostomy, complaining of sicca symptoms, fatigue, and diffuse musculoarticular pain, with unstimulated salivary flow of 0.5 ml/15 min
D. A 64-year-old woman with total unstimulated salivary flow of 0.5 ml/15 min, positive anti-SSA/Ro and anti-SSB/La antibodies, positive ACA and MALT lymphoma from minor salivary gland biopsy
E. A 60-year-old man with xerophthalmia, xerostomia, chronic dry cough, abnormal objective ocular tests, intense lymphocytic infiltration in MSGB, salivary gland enlargement, subclinical jaundice, and bilateral hydronephrosis
F. A 26-year-old woman, recently treated for Chlamydia infection, presenting with sicca symptoms and fatigue, with Schirmer's test of 3 mm and 4 mm (in 5 min) in the right and left eye, respectively, and an initial assessment of the MSGB showing lymphocytic infiltration

Correct answers: B, D
Feedback:

A. Score of 2 according to criteria. Autoimmune thyroiditis could account for sicca symptoms. Further tests needed.
B. Recently tested for hepatitis and HIV since she is a blood donor. Score of 6 according to criteria. Anti-CCP presence does not exclude SS diagnosis (anti-CCP-positive SS).
C. History on previous head and neck radiation should be recorded, as suspicion of treated laryngeal cancer is raised (presence of tracheostomy). Not fulfilling criteria.

D. Score of 7 according to criteria, since MSGB with MALT is considered positive. Lymphoma is no longer an exclusion criterion, and ACA-positive SS patients are known to be at increased risk for lymphoma.
E. Suspicion of IgG4-related disease. Need more information on MSGB and serum IgG4 levels.
F. This young woman recently had a sexually transmitted disease, so HIV and HCV infection need to be ruled out before classifying her as SS. More information on the MSGB would also be helpful, as CD8+ lymphocytes are usually the ones infiltrating salivary glands in HIV infection (in contrast to predominant CD4+ lymphocytes in SS).

15. Which of the following set of features describing different female SS patients confers the highest predicted risk for NHL?

A. Distal renal tubular acidosis, positive RF, photosensitive rash, filamentary keratitis, reduced unstimulated salivary flow rate, and dental caries
B. Raynaud's phenomenon, livedo reticularis, parotid gland enlargement, lymphadenopathy, positive anti-TPO, and positive anti-TG
C. Arthralgias, fatigue, abnormal ocular staining test, reduced unstimulated salivary flow, positive anti-SSA/Ro antibodies, and positive anti-CCP
D. Monoclonal gammopathy, positive RF, positive anti-SSA/Ro, low C4 levels, lymphadenopathy, submandibular gland enlargement, and Raynaud's phenomenon
E. Monoclonal gammopathy, positive anti-SSA/Ro and anti-SSB/La antibodies, elevated γGT, C3 and C4 hypocomplementemia, positive anti-thyroid antibodies, lymphadenopathy, and Raynaud's phenomenon

Correct answer: D
Feedback: Selection of the correct answer is based on the predictive score tool for SS-associated lymphoma, as seen in Fig. 10.8.

A. One positive factor only (3.8% probability of NHL).
B. Three positive adverse features (39.9% probability of NHL).
C. One positive factor only (3.8% probability of NHL).
D. All seven identified independent predicting factors are met, which means 100% probability of developing lymphoma.
E. Five positive predisposing factors (39.9% probability of NHL).

16. Which of the following sentences are true?

A. Ultrasound of major salivary glands has replaced sialography and scintigraphy in recently revised SS classification criteria (2016).
B. Type I interferon signature is more prominent in SS-associated lymphoma cases.
C. Epithelial cells in salivary glands have an active role in SS etiopathogenesis.
D. BAFF levels in patients' serum closely follow lymphoma flares and remissions and may therefore be used for follow-up.

E. MTHFR gene variants have been found to confer increased risk for MALT lymphomas in the context of SS.
F. MALT lymphomas localized in the salivary glands should ideally be monitored closely, without need for immediate treatment.

Correct answers: C, F
Feedback:
A. Not included in criteria yet but promising results and potential future role in diagnosis.
B. IFNγ (IFN type II) is more prominent in lymphoma.
D. BAFF levels are found elevated even years after lymphoma remission.
E. MTHFR gene variants are linked to some cases of non-MALT lymphomas.

17. Which of the following diagnostic tests does not have a place in high-risk SS patients monitoring for MALT lymphoma?

A. CT chest
B. CT abdomen
C. Colonoscopy
D. Upper GI endoscopy
E. Serum protein electrophoresis and immunofixation
F. Routine laboratory panel, including LDH and β2 microglobulin

Correct answer: C
Feedback:
A, B. CTs are commonly used for diagnosis or follow-up of MALT lymphoma in patients with severe adverse predictors or relevant history.
C. MALT lymphoma is not found in the bowel; thus, colonoscopy is an unnecessary test.
D. Stomach is a common site for the development of MALT lymphoma.
E. Protein electrophoresis and immunofixation might show hypergammaglobulinemia and monoclonality, which could mean malignant transformation in some cases.
F. Routine laboratory tests are necessary in follow-up anyway and rise in LDH or β2 microglobulin could be linked to lymphoma development or reappearance after treatment.

18. Which of the following tests would you recommend as the next diagnostic step for a patient complaining about xerostomia/xerophthalmia, who is reluctant to undergo MSGB and has a positive anti-SSA/Ro result?

A. Sialography
B. Scintigraphy
C. Major salivary gland ultrasound
D. Rose bengal ocular staining
E. Unstimulated salivary flow
F. Tear breakup time

Correct answer: E

Feedback:
A, B. Sialography and scintigraphy are no longer included in SS classification criteria (2016).
C. Ultrasound is not included in SS classification criteria, despite showing promising results.
D, E. Since anti-Ro are positive (3 points), 1 more point for SS classification is required, meaning either an abnormal, objective ocular test or unstimulated salivary flow rate measurement. The latter is the easiest and cheapest way to reach diagnosis. Furthermore, lissamine green is preferred over rose bengal for ocular staining, nowadays, since it is less irritant.
F. TBUT is not included in SS classification criteria, despite being commonly used to objectify ocular dryness.

19. Which of the following etiopathogenetic events have been proven to contribute to SS-related lymphoma development?
Multiple answers eligible

A. Persistent stimulation of autoreactive B cells
B. Chromosomal translocations
C. Coxsakievirus infection
D. Epstein-Barr virus infection
E. p53 mutations
F. BAFF polymorphisms

Correct answers: A, B, E, F
Feedback:

A. True.
B. Over-expression of Bcl-2, for example, is due to a translocation involving chromosomes 14 and 18.
C, D. These viruses have been suggested as possible triggering factors for SS etiopathogenesis, but not proven to contribute to disease onset or associated lymphoma development.
E. True.
F. True.

20. Which of the following sentences is true?

A. Secondary SS is diagnosed when sicca symptoms appear in the context of hepatitis C or HIV infection.
B. Germinal center-like structures are well-defined formations in MSGBs of SS patients, associated with late disease onset.
C. Males are not affected by SS as much as women, and even if they do, they present with milder symptoms.
D. MSGBs only have a place in SS diagnosis, and if classification criteria are met anyway, patients should not undergo this invasive procedure.
E. Ocular staining score and TBUT can be used interchangeably to objectify ocular involvement in SS, according to the latest classification criteria of 2016.

F. SS classification criteria cannot be used in patients who do not experience oral and/or ocular dryness, since sicca symptoms are considered to be the disease hallmark.
G. SS is one of the most common systemic autoimmune diseases, accompanied by the highest risk for lymphoma development among them.

Correct answer: G
Feedback:

A. Active hepatitis C and HIV infection are among exclusion criteria. The term "secondary" has previously been used to describe sicca symptoms occurring in the context of another systemic autoimmune disease and tends to be replaced nowadays by the more accurate "SS-associated disease."
B. There is lack of uniform criteria for the identification of GC-like structures in MSGBs, and their documented association with more severe disease generally leads to earlier disease diagnosis.
C. Male SS patients have been suggested to present with more severe disease phenotype, despite being fewer than women.
D. MSGBs histopathological characteristics have a major prognostic value and are therefore also used in patients' risk stratification.
E. TBUT is not included in SS classification criteria of 2016.
F. Patients scoring in at least one domain of ESSDAI (having systemic involvement) are now also considered for SS diagnosis according to the latest classification criteria, even in the absence of sicca symptoms.

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Chapter 11
Systemic Sclerosis (Scleroderma)

Lazaros I. Sakkas

Introduction

Systemic sclerosis (SSc) is a rare and complex systemic disease characterized by fibrosis involving the skin and internal organs, autoantibodies (autoAbs), and microvasculopathy (Raynaud's phenomenon [RP] and fibrointimal proliferation) that cause organ damage and curtail survival. SSc is a rare disease. In a recent study from the UK, prevalence of SSc was 307 per million and incidence 19.4/million/year with incidence 4.7 times higher in women than men and peak age of onset 55–69 years [1]. In the European SSc registry, the mean age at onset of RP was 42 years and of non-RP was 46 years [2], and 3–4 years earlier in African American patients [3]. Localized scleroderma (morphea, linear scleroderma) is confined to skin and subcutaneous tissues.

Pathogenesis

The etiology of SSc is not known. Limited data from twin studies indicate that environmental factors play a major role in the development of SSc. These include exposure to silica, heavy metals (mercury), and vinyl chloride, use of drugs (bleomycin, pentazocine), and infectious agents (cytomegalovirus, Epstein-Barr virus). Histology reveals the three cardinal features of SSc, obliterative microvasculopathy, deposition of collagen and other extracellular matrix (ECM) molecules, and inflammation. The pathogenesis of SSc is incompletely understood (Table 11.1).

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Table 11.1 Cells implicated in SSc pathogenesis

Cell	Pathogenic effects
Fibroblasts	Produce collagen and other extracellular matrix molecules
Adipocytes, endothelial cells, epithelial cells	Undergo transition to myofibroblasts expressing a smooth actin and producing collagen
T cells	Are oligoclonal-indicative of antigen-driven proliferation in skin lesions Produce pro-fibrotic IL-4, IL-13 cytokines Anti-maternal graft-versus-host disease may operate in some cases
B cells	Are activated (hyper-express CD19) Activate fibroblast to collagen production through cell contact Plasma cells produce antibodies that promote fibrosis Produce cytokines promoting fibrosis IL-10-producing regulatory B cells are decreased
Innate cells	Promote fibrosis through Toll-like receptors(TLRs), such as TLR4

Fibroblasts, T cells, B cells, and innate cells are involved in SSc pathogenesis. Epithelial cells, endothelial cells, and adipocytes can undergo transition to myofibroblasts, expressing α-smooth muscle actin and producing collagen [4]. Anti-maternal graft-versus-host disease may operate in some cases. TGFβ is the master fibrogenic factor in SSc. The Wnt/β-catenin pathway is also involved in fibrogenesis [5–7].

Clinical Manifestations and Assessment Tools

Cutaneous and Musculoskeletal Manifestations

Raynaud's phenomenon (*RP*) may appear years before other SSc manifestations. RP, along with the fibrointimal proliferation of digital arteries, may lead to digital ulcers (DUs). DU, a loss of epithelialization, occurs in nearly 50% of patients and may lead to secondary infection, gangrene, and *acro-osteolysis*. *Skin thickening* usually begins as puffy fingers (the first non-RP skin change) that gradually evolves into skin tightness and extends proximally. Skin thickening of the face diminishes the mouth aperture. Based on the extent of skin involvement, SSc is divided into limited cutaneous SSc (lcSSc) and diffuse cutaneous SSc (dcSSc), with lcSSc being more common (59%) than dcSSc (37%). The skin may have a salt and pepper appearance from hypopigmentation/hyperpigmentation changes. In the final atrophic stage, skin softens. Arthralgias and or arthritides are common, usually in small hand joints, and flexion contractures may develop from severe skin thickening. *Tendon friction rubs* are associated with dcSSc, scleroderma renal crisis (SRC), cardiac, and gastrointestinal complications and reduced survival [8]. *Calcinosis* of skin and subcutaneous tissues is more frequent in lcSSc (45%) than dcSSc (15%). It may be extensive and may cause skin ulceration and secondary infection. *Telangiectasias* are common and are commonly found on the face, lips, hands, and

chest. In the late atrophic skin stage of SSc, telangiectasias may be the only skin sign of SSc. Histology is dominated by the deposition of collagen, proteoglycans, and other extracellular matrix (ECM) molecules in the dermis which encase sweat glands and replace subcutaneous adipose tissue. Mononuclear cell infiltrates consisting of T cells, macrophages, and few B cells, eosinophils and mast cells appear early and gradually disappear as disease progresses. In small arteries there is fibrointimal proliferation.

Assessment Typical SSc nailfold capillaroscopy reveals dilated (giant) capillary loops, hemorrhages, and capillary loss. Skin thickening is assessed by the modified Rodnan skin score (mRSS).

Pulmonary Manifestations

Two main entities occur in SSc, interstitial lung disease (ILD) and pulmonary arterial hypertension (PAH). Other, much less frequent manifestations are pleuritis, endobronchial telangiectasias with hemoptysis, and cryptogenic organizing pneumonia.

ILD

Patients with ILD are asymptomatic at first but gradually develop dyspnea on exertion and dry cough. ILD is an early manifestation of SSc, is more common in dcSSc than lcSSc, and is associated with anti-topoisomerase I Abs (ATA) [9]. ILD can cause secondary pulmonary hypertension (ILD-PH). It is most commonly nonspecific interstitial pneumonia (NSIP) with mononuclear cell infiltrates and uniform distribution of fibrosis, and less commonly usual interstitial pneumonia (UIP) with scattered fibroblastic foci. ILD is a major cause of death with survival 58% at 10 years [10].

Assessment Pulmonary function tests (PFTs) with spirometry and diffusing capacity for carbon monoxide (DLCO) are routinely used for screening and follow-up in ILD. PFTs typically show a restrictive pattern. DLCO is reduced. High resolution computed tomography (HRCT) of the chest is the best test to detect ILD and reveals thickening of interlobular septa, honeycomb pattern, traction bronchiectasis, and alveolitis (ground glass opacities) [11]. Lung ultrasound can also detect lung fibrosis.

Pulmonary Hypertension

PH is the main prognostic factor for survival in SSc. Precapillary pulmonary hypertension (PH) in SSc is pulmonary arterial hypertension (PAH) and PH associated with ILD (ILD-PH) which is less responsive to treatment. PAH is defined by

right-sided heart catheterization as mean pulmonary arterial pressure ≥25 mmHg and normal pulmonary artery wedge pressure (≤15 mmHg) in the absence of significant ILD (only mild ILD on HRCT and FVC >70% of predicted value). PAH is associated with decreased of vasodilatory mediators, NO, and prostacyclin (PGI) and increased vasoconstriction mediator endothelin-1 (ET-1). Factors associated with increased risk for PAH include FVC(percentage)/DLCO(percentage) ratio of predictive values >1.60, anticentromere antibodies (ACA), telangiectasias, NT proBNP >300 ng/L, pericardial effusion, right axis deviation on ECG, TR jet velocity >2.8 m/s, 6 min walk distance (6 MWD) <440 min. Reduction of nailfold capillary density correlates with severity of PAH. Patients with PAH have dyspnea on exertion, but as the condition worsens, signs of right-sided heart failure develop. FVC(percentage)/DLCO(percentage) ratio of predictive values >1.6 is predictive of PAH. DLCO <45% of predictive value is associated with poor outcome. SSc-PAH carries a poor prognosis and a worse prognosis than idiopathic PAH but ILD-PH carries the worst prognosis.

Assessment Echocardiography, ECG, serum N-terminal pro-brain natriuretic peptide (NT proBNP) levels, FVC(percentage)/DLCO(percentage), 6 MWD, telangiectasias, and ACA are used to detect PAH early and stratify risks. Right-sided heart catheterization is the gold standard and used to confirm PAH. Cardiac MRI is also a useful method in evaluating PAH. The DETECT algorithm helps detect candidates for right heart catheterization [12]. The 2015 guidelines for the diagnosis and treatment of PAH stratified patients to low, intermediate, and high risk [13]. The low-risk group has (a) WHO functional classes I and II; (b) 6 MWD >440 min; (c) NT proBNP levels <300 ng/L; (d) echocardiography, right atrial area <18 cm^2, no pericardial effusion; and (e) hemodynamics, right atrial pressure (RAP) <8 mmHg, cardiac index (CI) ≥2.5 L/min/m^2, and venous oxygen saturation (SvO_2) >65%.

Risk stratification is very important. The 5-year mortality in patients with PAH and low-risk profile at baseline and follow-up was <10%, whereas patients with high-risk profile at baseline and follow-up had a 1-year mortality around 30% [14]. The 1-, 2-, and 3-year survival of SSc-PAH patients were 93%, 88%, and 75%, respectively [15].

Cardiac Manifestations

Cardiac manifestations include pericardial effusion, left or right diastolic dysfunction, right-sided heart failure from pulmonary hypertension, and arrhythmias. Takotsubo cardiomyopathy is rarely reported. Pericardial effusion is more frequent in dcSSc than lcSSc. Fibrinous pericarditis also develops. Arrhythmias may be caused by fibrosis of the conduction system and are more frequent in dcSSc than lcSSc. Postmortem studies reveal inflammatory infiltrates and fibrosis of the myocardium. Contraction band necrosis with patchy fibrosis may also be observed.

Assessment Echocardiography is the method of choice for evaluating cardiac function, chamber size, and wall motion abnormalities. Tissue Doppler echocardiography, cardiac MRI, single-photon emission tomography (SPECT), and thallium scanning may also be used. Two-dimensional echocardiography is the method of choice to detect pericardial effusion. ECG and Holter monitoring are used to detect cardiac arrhythmias [9].

Gastrointestinal Tract (GIT) Manifestations

The entire GIT can be affected with equal frequency in dcSSc and lcSSc. Fibrosis, smooth muscle atrophy, and autoAbs against muscarinic M3 receptor all contribute to GIT dysmotility. Dry mouth may be due to fibrosis or Sjogren's syndrome. Esophageal involvement occurs in nearly all patients and often is the first non-RP manifestation. Lower esophageal sphincter pressure is reduced and leads to gastroesophageal reflex, esophagitis, stricture, and dysphagia. There is delayed gastric emptying, and there may be vascular ectasia (watermelon stomach) which can cause bleeding. Intestinal involvement is reported in 23% of patients but by specific tests it occurs in up to 88% of patients. Intestinal dysmotility causes post-prandial bloating and constipation and may cause pseudo-obstruction (around 5% of patients). Stasis causes small intestinal bacterial overgrowth (SIBO) which in turn causes diarrhea, malabsorption, malnutrition, and oxalate nephropathy. Wide mouthed diverticula at the antimesenteric aspect of large bowel may occur. Anorectal involvement is very frequent (50–70% of patients) and may cause rectal incontinence in 24% of patients.

Assessment Barium esophagography is used to detect esophageal dysmotility. Esophageal manometry is used to detect lower esophageal sphincter pressure as an early esophageal involvement. Small intestinal hypomotility is assessed by the lactulose hydrogen breath test which allows estimation of oral-cecal transit time and the detection of SIBO. SIBO can also be detected by calprotectin levels but the gold test for SIBO is culture of jejunal fluid. Malabsorption is assessed by the malnutrition universal screening tool (MUST) to detect nutritional status, and by measurement of serum vitamin B12, folic acid, 25(OH) D, and prothrombin time [16].

Scleroderma Renal Crisis (SRC)

SRC is characterized by marked increase in blood pressure and rapidly progressive renal failure with or without thrombotic microangiopathy. The latter manifests with thrombocytopenia and intravascular hemolytic anemia. Normotensive SRC may occasionally occur. SRC most frequently occurs in dcSSc during the first 4 years of the disease. Risk factors include anti-RNA polymerase III (anti-RNAp3)

antibodies, and use of prednisolone >7.5 mg/day, or cyclosporine. Histology shows changes of malignant hypertension in small arteries. Stenosis of interlobular and arcuate renal arteries activates the renin-angiotensin system. SRC has a poor outcome [17].

Diagnosis

The new 2013 EULAR/ACR criteria for the classification of SSc help diagnose SSc early [18] (Table 11.2). AutoAbs help in diagnosis and management. Antinuclear Abs are present in nearly all patients. Anti-topo I Abs are associated with dcSSc (present in 59%) and ILD. ACA are associated with lcSSc (present in 48%) and inversely correlated with ILD. Anti-RNAp3 Abs are associated with dcSSc, SRC, and malignancies concomitant to SSc onset [19]. Anti-fibrillarin (U3RNP) Abs are more frequent in African Americans and associated with PAH and reduced survival. Anti-Th/To Abs are associated with worst survival in lcSSc. In a suspected case, nailfold capillaroscopy, and SSc-related autoAbs, antinuclear antibodies (ANA), anti-topoisomerase I (formerly Scl70), anticentromere, and RNA polymerase III antibodies are requested. Line blot assays allow the detection of multiple autoantibodies related to SSc.

The European scleroderma trials and research (EUSTAR) group, proposed and validated a 0–10 scale SSc activity index with six items, skin worsening during the previous month as evaluated by the patient, tendon friction rubs, DUs, mRSS, CRP, and DLCO. A score ≥2.5 identified active/very active disease [20]. The differential diagnosis includes various sclerotic disorders.

Table 11.2 The 2013 EULAR/ACR criteria for the classification of SSc

Item	Score
1. Skin thickening proximal to metacarpophalangeal joints	9
2. Skin thickening of fingers (use the maximum score)	
Puffy fingers	2
Skin thickening distal to metacarpophalangeal joints	4
Fingertip ulcers	2
Fingertip pitting scar	2
3. Telangiectasias	2
4. Abnormal nailfold capillaroscopy	2
5. Pulmonary arterial hypertension and/or interstitial lung disease	2
6. Raynaud's phenomenon	3
7. SSc-related autoantibodies (anticentromere, anti-topoisomerase I, anti-RNA polymerase III Abs) (score 1 for each antibody)	3 (maximum)

A total score ≥9 defines definite SSc [18]

Scleredema Scleredema is a skin mucin deposition disorder (produced by epithelial cells and fibroblasts) in the skin. It is associated with acute respiratory infection mostly due to streptococcus, diabetes mellitus, and monoclonal gammopathy of unknown significance (MGUS). It manifests with woody induration of skin that begins in the neck and back, and spares hands and feet. There is no Raynaud's phenomenon, nailfold capillaroscopy changes, or SSc-related autoAbs, and no internal organ involvement [21]. Skin biopsy shows mucin deposition (stain with Asian blue or colloidal iron) in the dermis between collagen bundles without spindle fibroblasts.

Scleromyxedema Scleromyxedema (papular mucinosis or lichen myxedematosus) is a systemic mucin deposition disorder. It affects middle-aged persons and is associated with MGUS, and rarely with multiple myeloma. It manifests with waxy firm papules closely spaced, often pruritic, and skin thickening in SSc-like distribution. The mid-back is frequently involved, unlike SSc. There is internal organ involvement and, frequently, destructive polyarthritis. Unlike SSc, there is no Raynaud's phenomenon nor telangiectasias. Skin biopsy shows mucin deposition in the dermis, fragmented elastic fibers, spindle fibroblasts, and small perivascular chronic inflammatory infiltrates. Diagnosis is based on clinical manifestations, skin biopsy, absence of thyroid disease, presence of monoclonal gammopathy [22].

Nephrogenic Systemic Fibrosis (NSF) NSF occurs within days to months following exposure to particular gadolinium-based contrast agents in patients with renal impairment (eGFR <30 mL/min/1.73 m^2 or on dialysis). It affects skin and internal organs. Skin changes are mostly in extremities, nearly never in face and include marked induration/peau d'orange, patterned plaques, cobblestone pattern, and joint contractures. There are no SSc-related autoAbs, no RP, no dilated loops on nailfold capillaroscopy.

Sclerodermatous Chronic Graft-Versus-Host Disease (scGVHD) scGVHD occurs after allogeneic hematopoietic cell transplantation (HSCT) and affects skin subcutaneous tissues and fascia. There is no internal organ involvement, RP, and no nailfold dilated loops or capillary loss.

Eosinophilic Fasciitis (EF) EF causes symmetrical induration of the skin sparing hands and face. It is associated with hematological malignancies. The skin may have a pea d'orange appearance and the groove sign, a depression along superficial veins of extremities. Peripheral eosinophilia and serum aldolase may be elevated. EF lacks SSc-related autoAbs and nailfold capillaroscopy changes. Skin biopsy encompassing fascia shows thickening of fascia and eosinophilic infiltrates.

Prognosis

SSc has a high mortality rate. In a recent study from the UK, survival at 1, 5, and 10 years was 94%, 80%, and 66%, respectively [1]. In a multinational cohort, life

years lost were 22 in women and 26 in men, and mortality in patients with dcSSc was 24% at 8 years of disease onset [23]. PAH and ILD are the primary SSc-related cause of death today [23, 24]. There is an increased risk of cancer in SSc [25].

Treatment

Optimal care of patients with SSc requires a multidisciplinary effort. Since vasculopathy, immune system activation, and fibrosis contribute to pathogenesis of the disease, at present, treatment of SSc depends on organs/tissues involved [9, 26, 27]. Systemic immunosuppressants may be considered in early dcSSc, as they improved skin score and tended to improve survival at 24 months in an observational study [28].

Raynaud's Phenomenon Dihydropyridine-type calcium blockers (nifedipine 10–20 mg thrice daily) are the first choice followed by phosphodiesterase (PDE)-5 inhibitors (sildenafil, tadalafil, vardenafil). The prostanoid iloprost may be used intravenously (IV) in severe cases.

DUs Iloprost IV (0.5–2 ng/kg/min for 6–8 hours per day for 1–3 days every month) is effective in healing ulcers and may prevent the development of new ulcers. Endothelin (ET)-1 receptor antagonists (ERAs; bosentan) may prevent the development of new DUs.

Skin and Musculoskeletal Disease Methotrexate improves skin score and arthalgia or arthritis. Mycophenolate mofetil (MMF) may also be considered.

ILD Cyclophosphamide, orally or IV monthly pulses, improves symptoms and slightly improves FVC, but not DLCO. MMF or rituximab may be considered. HSCT improved skin score, FVC, and event-free survival. However, HSCT is associated with high risk of early mortality and viral infections and should be considered only in selected patients at risk of organ failure.

PAH The sooner the initiation of treatment, the better the survival [15]. Drugs that inhibit the endothelin (ET)-1 pathway (ET receptor antagonists, ERAs: bosentan, ambrisentan, macitentan) and drugs that augment the nitric oxide pathway (PDE-5 inhibitors [sildenafil, tadalafil], and guanylate cyclase stimulator [riociguat]) improve symptoms and hemodynamic measurements. Selexipag, a new oral non-prostanoid, selective prostacyclin IP receptor agonist, alone or in combination with ERA and/or PDE-5 inhibitor, reduced by 40% a composite morbidity/mortality end point. Parenteral prostanoids are used in severe cases. Epoprostenol via continuous IV infusion and other prostacyclin analogues (iloprost by IV infusion, treprostinil by subcutaneous infusion) improve symptoms and hemodynamic measurements [13].

Combination therapy may be used sequentially or upfront. Combination of PDE-5 inhibitor with riociguat is contraindicated as it causes hypotension. Supporting measures include diuretics in patients with right heart failure, and oxygen in patients with SaO_2 <91%. To optimize treatment efficacy and improve survival, early detection of PAH and institution of therapy is of paramount importance. For patients with WHO class III or IV despite optimal medical therapy, lung transplantation is advised.

Gastrointestinal Tract (GIT) All patients should be on proton-pump inhibitors. A pro-motility drug may help in gastro-esophageal reflex. For diarrhea, low-fat diet and avoidance of lactose- or fructose-containing items are advised. If recurrent, antibiotics for 10 days per month for 3–4 months is recommended. For constipation, prucalopride, a selective 5-HT4 receptor agonist, may help. Parenteral alimentation is used in severe malnutrition [16].

Scleroderma Renal Crisis ACE inhibitors improved survival in patients with SRC and should form the basis of treatment. Avoid medium-high dose steroids and cyclosporine [17]. Treatment of SSc is summarized in Table 11.3.

Table 11.3 Treatment of SSc based on manifestations

Manifestation	Treatment
Raynaud's phenomenon	1st choice: dihydropyridine-type calcium blockers (nifedipine 10–20 mg × 3/day 2nd choice: phosphodiesterase (PDE)-5 inhibitors (sildenafil, tadalafil, vardenafil) The prostanoid iloprost IV in severe cases
Digital ulcers	Iloprost IV infusion (0.5–2 ng/kg/min) for 6–8 hours per day for 1–5 days every month PDE-inhibitors (bosentan) may prevent new DUs
Skin and musculoskeletal manifestations	Methotrexate is beneficial for skin tightness and arthralgias
Interstitial lung disease	Cyclophosphamide orally or IV pulses Mycophenolate mofetil, rituximab Hematopoietic stem cell transplantation in severe cases
Pulmonary arterial hypertension	Endothelin-1 receptor antagonists, PDE-5 inhibitors are used sequentially or upfront combination. Selexipag is used alone or in combination with ERA or PDE-5 inhibitor Prostanoids IV in severe cases
Gastrointestinal manifestations	Proton-pump inhibitor Antibiotics for 10 days every month in recurrent diarrhea Prucalopride for constipation Parenteral nutrition for severe malnutrition
Scleroderma renal crisis	Angiotensin-converting enzyme inhibitors-based anti-hypertensive drugs

Questions

1. In a patient with SSc-PAH and functional WHO class II, you recommend:

   A. Upfront combination of ambrisentan with sildenafil
   B. Upfront combination of selexipag with macitentan
   C. Upfront combination of sildenafil with riociguat
   D. All of the above
   E. Only A and B

   Correct answer: E
   Upfront combination of an ERA or selexipag and a PDE-5 inhibitor is recommended. PDE-5 inhibitor and riociguat both increase the NO pathway and their combination is contraindicated as it may cause hypotension.
2. Systemic sclerosis-associated interstitial lung disease:

   A. Is associated with anti-topoisomerase I antibodies
   B. Is associated with increased IL-10+regulatory B cells
   C. Occurs most frequently in long-standing diffuse cutaneous SSc
   D. All of the above
   E. Only A and C

   Correct answer: A
   IL-10+ regulatory B cells are decreased in SSc particularly ILD-SSc. ILD occurs early in the course of SSc.
3. For the vasculopathic manifestations of SSc, it is true that:

   A. Scleroderma renal crisis occurs most often in limited cutaneous SSc
   B. Loss of nailfold capillary density correlates with severity of PAH
   C. PAH and ILD-associated PH are equally responsive to drug treatment
   D. Only A and B
   E. Only A and C

   Correct answer: B
   Scleroderma renal crisis (SRC) occurs most commonly in diffuse cutaneous SSc during the first 4 years. ILD-associated PH responds worse than PAH to drug treatment.
4. In a patient with scleroderma renal crisis, you will most likely see:

   A. Increase serum lactate dehydrogenase levels
   B. Normal-increased serum haptoglobin levels
   C. Positive anticentromere antibodies
   D. All of the above
   E. Only A and B

   Correct answer: A
   Scleroderma renal crisis (SRC) may have intravascular hemolytic anemia, that means increased serum LDH, decreased-to-absent serum haptoglobin. SRC most commonly occurs in diffuse cutaneous SSc, and is associated with decreased frequency of anticentromere antibodies.

5. In the pathogenesis of systemic sclerosis it is true that:

   A. T cells in skin lesion are polyclonal
   B. T cells are likely to produce Th2 cytokines
   C. Regulatory B cells producing IL-10 are increased
   D. Only A and B
   E. Only B and C

   Correct answer: B
   T cells in skin lesions are oligoclonal, indicative of antigen-driven T cell proliferation. T cells in SSc are of Th2 type producing IL-4 and IL-13. Regulatory B cells producing IL-10 are decreased in SSc.
6. In a patient with systemic sclerosis, it is true that:

   A. Tendon friction rubs are associated with limited cutaneous systemic sclerosis
   B. Telangiectasias are found more frequently in lower extremities than the upper extremities
   C. Puffy hands and esophageal involvement are the earliest signs of the disease
   D. All of the above
   E. Only B and C

   Correct answer: C
   Tendon friction rubs are associated with diffuse cutaneous SSc and internal organ involvement. Telangiectasias are most frequent in the face, lips, hands, and upper part of trunk.
7. In a patient with systemic sclerosis

   A. DLCO and FVC decrease proportionally in pulmonary arterial hypertension
   B. DLCO decreases disproportionally relative to FVC in ILD-associated pulmonary hypertension
   C. serum NT proBNP levels are increased in both PAH and ILD-associated pulmonary hypertension
   D. Only A and C
   E. Only B and C

   Correct answer: C
   DLCO and FVC decrease proportionally in ILD-associated PH. DLCO decreases disproportionally relative to FVC in PAH.
8. A patient with scleredema is expected to have

   A. Skin induration in hands and feet
   B. Internal organ involvement
   C. No Raynaud's phenomenon
   D. All the above
   E. Only A and B

   Correct answer: C
   Scleredema is a mucin deposition disease confined to the skin but it spares hands and feet.

9. A patient with scleromyxedema is expected to have

   A. No internal organ involvement
   B. Skin changes in SSc-like distribution
   C. Telangiectasias in SSc-like distribution
   D. Only A and B
   E. Only A and C

   Correct answer: B
   Scleromyxedema is a systemic mucin deposition disease with internal organ involvement. There is an SSc-like distribution of skin lesions, but no telangiectasias.

10. In the differential diagnosis of systemic sclerosis, it is true that:

   A. Nephrogenic systemic sclerosis only develops in patients on dialysis
   B. Eosinophilic fasciitis is associated with hematological malignancies
   C. Sclerodermatous graft-versus-host disease usually develops after homologous hematopoietic cell transplantation
   D. All the above
   E. Only A and B

   Correct answer: B
   Nephrogenic systemic sclerosis develops in patients with eGFR <30 mL/min/1.73 m^2 or on dialysis. Sclerodermatous graft-versus-host disease most frequently develops after allogeneic hematopoietic cell transplantation.

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Chapter 12
Vasculitis

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Introduction

The systemic vasculitides are a heterogeneous group of inflammatory diseases that share the pathogenic feature of inflammation focused in the wall of blood vessels. The vasculitides are categorized according to the caliber of the blood vessels involved, with large-vessel disease (such as Takayasu's) affecting the aorta and great vessels, while small-vessel disease (such as ANCA-associated vasculitis) mediates damage in the smallest capillaries of the lungs and kidneys. Because nearly every organ system in the body can be affected by vasculitic syndromes, the clinical approach to a case of suspected vasculitis involves recognition of typical patterns of organ involvement associated with each specific vasculitic entity and the assimilation of key laboratory, radiographic, and histologic findings to secure a diagnosis. In this chapter, we will summarize the clinical syndromes associated with each form of vasculitis, review diagnostic studies that assist in their identification, and summarize the current approaches to immunosuppressive treatment.

Diagnostic Approach

Vasculitis is often raised as a diagnostic consideration in patients with multi-organ disease and/or active inflammatory markers of unclear etiology. When considering a diagnosis of vasculitis, clinicians ought to consider several important questions [1]:

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1. Is this a true vasculitis, or a condition that mimics vasculitis?
2. If this is vasculitis, is it a primary vasculitis, or secondary to another underlying cause?
3. What is the extent of organ involvement present?
4. What specific type of vasculitis is this most likely to be?
5. How do I confirm the diagnosis of the suspected vasculitis?

The so-called vasculitis mimics include a variety of diagnoses capable of generating a clinical presentation similar to that of a systemic vasculitis, but whose pathogenesis is not due to primary inflammation within the walls of blood vessels. While the general elements of their presentation may appear quite similar to the vasculitides, careful assessment of the appropriate clinical data can help discriminate genuine vasculitides from these mimics. The vasculitis mimics include various types of infections (endocarditis, angioinvasive aspergillosis), thrombotic disorders (antiphospholipid antibody syndrome, thrombotic thrombocytopenic purpura, sickle cell disease), embolization (from atrial myxoma or cholesterol emboli from atheroma), noninflammatory vessel wall disorders (fibromuscular dysplasia, amyloidosis, scurvy), and vasospasm due to ergotism and other exposures. The list of vasculitis mimics with regards to more isolated or single-organ findings is even broader, such as is the case with malignancy or infections that cause cavitary lung lesions like those seen in granulomatosis with polyangiitis, or conditions such as reversible vasoconstriction syndrome that can mirror the findings of central nervous system vasculitis.

Histology

The diagnosis of vasculitis is made based on tissue histopathology in concert with the appropriate clinical presentation for the disease in question. While not necessarily available in the assessment of all suspected cases of vasculitis, tissue histopathology can be enormously helpful in accurately identifying the diagnosis of vasculitis. Thus, there are several key phrases that help to identify typical findings of vasculitis seen on histopathologic analysis of tissue. These include:

1. Infiltration of the vessel wall by immune cells
2. Fibrinoid necrosis of blood vessel walls
3. Leukocytoclasis

Since the mechanism of tissue and organ damage in vasculitis is due to sequential inflammation and necrosis of blood vessels leading to impairment of blood flow and perfusion, the nature of this vessel inflammation is of significant consequence. It is essential to identify what type of cellular infiltrate is present, such as with regards to the presence of neutrophils, lymphocytes, mononuclear cells, giant cells, or other leukocytes. The composition of the inflammatory cellular infiltrate in vasculitis is independent of the caliber of vessel involved, and mixed cellular infiltrates are common.

Fibrinoid necrosis describes the accumulation of proteinaceous material in the tissue matrix in a pattern that resembles fibrin. This finding can be seen with type III hypersensitivity immune reactions involving blood vessels in vasculitis, but can also be observed in cases of pre-eclampsia, malignant hypertension, and acute transplant rejection.

The breakup of nuclei of dying cells (also known as karyorrhexis) results in the pathologic finding known as nuclear dust. The presence of such nuclear debris, coupled with inflammatory infiltrate of blood vessels and deposition of fibrin within a vessel lumen or wall, can provide strong evidence for the presence of a vasculitis. Indeed, such findings in small vessels and with neutrophils as the cellular infiltrate are essentially the definition of leukocytoclastic vasculitis, and the presence of nuclear dust may in fact precede the accumulation of fibrin.

Taken together, the findings noted above can help to identify the presence of a vasculitic process and allow the physician to identify which specific vasculitis may be at play. For instance, polyarteritis nodosa, granulomatosis with polyangiitis, and eosinophilic granulomatosis with polyangiitis are all forms of necrotizing vasculitis that may demonstrate mixed cellular infiltrates, but granulomatosis with polyangiitis and eosinophilic granulomatosis with polyangiitis may also (as the names imply) demonstrate granulomatous inflammation and, in the case of the latter, involve prominent eosinophilic infiltrate.

Immunofluorescent staining for immune complex deposition (complement components and immunoglobulin isotypes) is an additional histologic technique that adds valuable information to the evaluation of suspected vasculitides, in particular the small-vessel vasculitides. This method permits the discrimination of pauci-immune vasculitis (e.g., ANCA), where minimal or no immune complex deposition is expected, from other causes of small-vessel vasculitis associated with positive immunofluorescent staining, such as HSP (characterized by IgA deposits) and cryoglobulinemia. Immunofluorescent staining should be obtained in the analysis of cutaneous vasculitis and glomerulonephritis, and may be valuable in other tissue sites in specific clinical scenarios as well.

Imaging

Specific imaging studies may be of help in the diagnosis of vasculitis and understanding the nature and degree of vessel and organ involvement. Imaging modalities that have traditionally been of significant use with respect to vasculitis include Doppler ultrasound, conventional angiography, computed tomography angiography, and magnetic resonance angiography. MRI/MRA is a noninvasive procedure of particular utility, as it can identify both vessel wall edema (as seen in aortitis) and luminal abnormalities (such as subclavian stenosis). This imaging modality can be valuable in a number of clinical scenarios, such as when there is a clinical history concerning for giant cell arteritis but negative temporal artery biopsy. However, it is important to note that artifactual findings, such as subclavian pseudostenosis, can

confound the picture and must be taken into account. PET/CT is an alternative technique that is now being used to identify large-vessel vasculitis by showing FDG avidity in blood vessels, thus indicating active disease. More recent research on PET/CT has indicated that this modality may have the potential to indicate signs of active disease in patients who otherwise appear to be in clinical remission based on history, exam, and laboratory studies [2].

Secondary Causes of Vasculitis

The term "secondary vasculitis" refers to a vasculitis syndrome that occurs in the context of an underlying disease or disorder. The causes of secondary vasculitis can be broken down into the categories of systemic rheumatic diseases, infections, drugs/medications, and cancer.

Among rheumatic diseases, rheumatoid arthritis, systemic lupus erythematosus, Sjogren's syndrome, and, to a lesser extent, scleroderma and inflammatory myopathies may be associated with secondary forms of vasculitis.

Rheumatoid vasculitis is fairly uncommon and, when it does occur, is more often seen in middle-aged male smokers with high-titer rheumatoid factor. Manifestations of the systemic vasculitis associated with rheumatoid arthritis may include nail fold infarcts, skin rash due to leukocytoclastic or lymphocytic vasculitis, and mononeuritis multiplex associated with neurovascular involvement. Small-vessel vasculitis may be complicated by microvascular thrombosis, and, rarely, leg ulcerations or gangrene can occur. The incidence of rheumatoid vasculitis has decreased with the advent of disease-specific drugs and immunotherapy with tumor necrosis factor inhibitors and anti-B cell therapy.

With regard to systemic lupus erythematosus (SLE), it is important to note that vasculopathy associated with inflammatory and noninflammatory occlusive disease can be seen and can precede the appearance of other clinical signs of SLE. Indeed, vasculopathy in SLE can further be broken down into the categories of vascular deposits of immune complexes, noninflammatory necrotic vasculopathy, thrombotic microangiopathy, and true lupus vasculitis. It is of great importance to evaluate for the presence of antiphospholipid antibodies in patients with SLE and vaso-occlusive disease. Cutaneous findings of SLE-associated vasculitis may include purpura, and small-vessel involvement of the kidneys, heart, brain, pulmonary alveoli, and gastrointestinal tract may occur. Leukocytoclastic vasculitis, cryoglobulinemic vasculitis, and systemic vasculitis following the pattern seen with polyarteritis nodosa are among the most common forms of lupus vasculitides.

In primary Sjogren's syndrome, vascular inflammation can result from hyperglobulinemia and immune complex deposition, or in the setting of cryoglobulinemia. With Sjogren's syndrome-associated cutaneous vasculitis, there is more often small- versus medium-vessel involvement, leukocytoclastic versus mononuclear vasculitis, and an association with a higher prevalence of extraglandular and other immunologic features of the disease. Small-vessel vasculitis may manifest as palpable purpura, urticarial lesions, or erythematosus maculopapules, while life-threatening

vasculitis is frequently associated with concurrent cryoglobulinemia. The presence of cutaneous vasculitis is an important marker of patients with more severe disease, including an increased risk of lymphoma.

In patients with systemic sclerosis, the distinction between occlusive and inflammatory vasculopathy can be clinically challenging and may require histopathologic analysis of tissue. These patients are often found to have decreased circulating levels of vasodilators (nitric oxide synthetase, prostacycline) and increased levels of vasoconstrictors (endothelin-1, vascular endothelial growth factor), thereby leading to intimal proliferation, luminal narrowing, and tissue hypoxia resulting in endothelial dysfunction and damage. Inflammatory vasculitis is less commonly encountered than noninflammatory vasculopathy in these patients, though a multitude of conditions that include ANCA-associated vasculitis, large-vessel vasculitis, Behçet's disease, and relapsing polychondritis have been reported to co-occur in a minority of patients with scleroderma.

Certain infections may play an interesting role in the development of vasculitis. Such is the case of polyarteritis nodosa associated with hepatitis B infection, when there is deposition of immune complexes formed from viral antigens and antibodies responsible for activation of the classic complement pathway and for neutrophil recruitment. Similarly, hepatitis C-associated cryoglobulinemia is a well-known phenomenon, and possible associations between hepatitis B and HIV with the development of cryoglobulinemia may exist as well. Tuberculous and syphilitic aortitis are well established conditions, and there is evidence that direct endothelial cell invasion may be the main pathogenic process accounting for vasculitis in infections caused by CMV, herpes simplex, rickettsiae, fungi, and bacteria. Additional work is needed to better understand the mechanisms underlying the development of primary vasculitides in the context of infection.

Drug-induced vasculitis is thought to be an immune complex-mediated process, and innumerable classes of drug have been reported as potential causes of vasculitis, most frequently with cutaneous manifestations. Among the most common culprits of drug-induced vasculitis are propylthiouracil, hydralazine, minocycline, allopurinol, D-penicillamine, sulfasalazine, penicillins, cephalosporins, and levamisole-contaminated cocaine. Drug-induced vasculitis cannot easily be differentiated from primary vasculitis, but this condition should be suspected when vasculitis manifests after a new drug exposure and when observing regression of the vasculitis after withdrawal of the potential offending agent. Urine drug screening should be considered in patients presenting with new vasculitic lesions of the face and ears.

A multitude of paraneoplastic vasculitides have been reported in the literature. Vasculitis due to myelodysplastic syndromes and other hematologic malignancies most frequently affects cutaneous vessels, but large-vessel vasculitis (in the form of giant cell arteritis and Takayasu's arteritis) and medium-vessel vasculitis (in the form of granulomatosis with polyangiitis and polyarteritis nodosa) have been described as well. Paraneoplastic vasculitis can be the initial manifestation of an occult malignancy. In addition to hematologic malignancies, tumors of the lung, gastrointestinal tract, and urinary tract can also be associated with the development of vasculitis, most frequently a leukocytoclastic vasculitis.

Primary Vasculitides

The primary vasculitides are a group of inflammatory diseases that mediate organ damage through primary inflammation within the walls of blood vessels. The primary vasculitides tend to affect blood vessels of specific size and are, therefore, organized according the caliber of involved blood vessels.

Large-Vessel Vasculitis

Giant Cell Arteritis (GCA)

Giant cell arteritis is a large-vessel vasculitis that occurs almost exclusively in adults over the age of 50, with a predominance among Caucasian women. Typical symptoms include headache, tongue and/or jaw claudication, scalp tenderness, fever, weight loss, vision change, and diplopia. There is also frequent co-occurrence with polymyalgia rheumatic, with up to 50% of patients with GCA manifesting signs of this condition. The systemic manifestations of GCA and PMR appear to result from production of pro-inflammatory cytokines derived from macrophages, such as tumor necrosis factor, interleukin (IL)-1, and IL6. Interferon-γ expression has also been shown in temporal artery biopsy samples from GCA patients. While nonspecific laboratory findings indicative of inflammation—elevated erythrocyte sedimentation rate and C-reactive protein, anemia, thrombocytopenia, hypoalbuminemia, elevated ferritin—support a diagnosis of GCA, it is the positive temporal artery biopsy, with vasculitis characterized by mononuclear predominant cellular infiltration or granulomatous inflammation usually with multinucleated cells, that serves as the gold standard for histopathologic diagnosis (Fig. 12.1). While corticosteroids have been the mainstay of treatment of GCA for many decades, methotrexate dosed at 7.5–15 mg weekly has been established in a series of randomized controlled trials as an effective steroid-sparing adjunct. More recently, randomized, placebo-controlled studies demonstrated that sustained steroid-free remission of GCA at 52 weeks could be achieved in patients treated with weekly or every other week tocilizumab, a humanized monoclonal antibody against IL6, and prednisone taper compared to those treated with placebo and prednisone taper; these patients also received significantly less total prednisone than patients in the placebo groups and the number of adverse events were similar across all groups [2, 3]. The findings are biologically plausible with respect to the role IL6 seems to play in the disease, and this study supported the Food and Drug Administration's approval of the medication in August 2017 for the treatment of GCA.

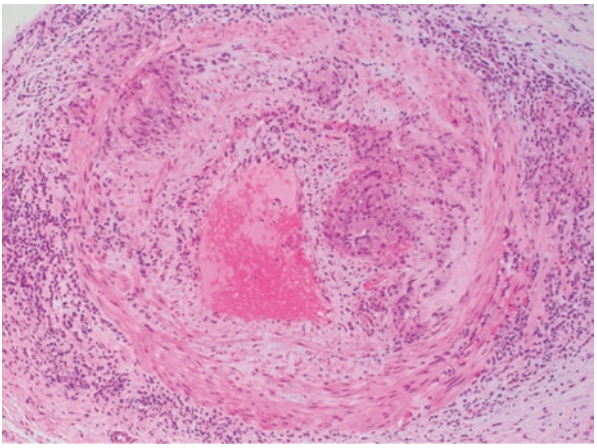

Fig. 12.1 Giant cell arteritis. The wall of this muscular artery is diffusely involved by granulomatous inflammation, including scattered multinucleated giant cells, with significant loss of the muscular media and internal elastic lamina due to the vasculitis. (Photo courtesy of Dr. Charles Eberhart, Johns Hopkins University School of Medicine, Department of Pathology)

Takayasu's Arteritis

Takayasu's arteritis is a large-vessel vasculitis that predominantly affects women under the age of 40, with an increased prevalence among individuals of Asian descent. There are two general phases to the condition: the systemic phase and the occlusive phase. The systemic phase may manifest with fever, fatigue, weight loss, and other nonspecific constitutional symptoms, while the occlusive phase reflects symptomatic ischemia due to arterial stenoses, such as with claudication pain in the limbs, vision loss, headache, or unequal or absent pulses in the upper extremities. Takayasu's arteritis is thought to start at the aortic annulus and progress from there, with autopsy studies rarely finding arteritis that is confined only to the aorta and its branches. Takayasu's arteritis appears to involve cell-mediated immunity, with Th1 CD4+ lymphocytes supporting granuloma formation via interferon-γ and HLA-DR+ circulating T lymphocytes that appear to be sensitized against aortal antigens [4]. The 1990 American College of Rheumatology (ACR) Classification Criteria for Takayasu's arteritis include disease onset before the age of 40, arteriographic narrowing of the entire aorta documented with CT angiography, decreased brachial pulse in at least one brachial artery, and a difference of >10 mm Hg in systolic blood pressure between both arms [5]; a minimum of three of six possible criteria are required for classification, and, though the diagnosis is supported by a history of elevated acute phase reactants at presentation, normal values do not exclude the diagnosis [6]. CT angiography and magnetic resonance angiography are the preferred imaging modalities for diagnosing Takayasu's arteritis. Reasonable initial treatment of the disease per EULAR treatment guidelines includes prednisone initially at 1 mg/kg/day up to 60 mg daily, maintained for at least 1 month, followed

by a gradual prolonged taper [7]. Immunosuppressive adjunctive therapy aside from glucocorticoids is also strongly recommended because of a propensity for Takayasu's arteritis to remain subclinically active even on glucocorticoids, with the possibility of relapse of the disease with steroid monotherapy; indeed, roughly 50% of patients with successfully induced remission suffer from relapse of disease [8]. Azathioprine 2 mg/kg daily or methotrexate 20–25 mg weekly can be used as steroid-sparing agents and, for refractory cases, alternative steroid-sparing adjuncts include anti-TNF agents or cyclophosphamide.

Cogan's Syndrome

Cogan's syndrome is a chronic inflammatory disease of unclear origin that manifests with ocular, vestibuloauditory, and vasculitic findings. These may include interstitial keratitis, episcleritis, uveitis, or other orbital inflammation; sensorineural hearing loss, tinnitus, or vertigo; and, in 10–30% of patients, aortitis or other similarly significant vasculitis. Atypical cases of Cogan's syndrome have been reported to involve the cardiovascular, neurologic, and gastrointestinal systems as well. Research has focused on the possible underlying autoimmune etiology of the condition, including the identification of an immunodominant peptide that shows similarity with autoantigens such as SSA/Ro and with the reovirus III major core protein lambda 1 and also shows similarity with the cell-density enhanced protein tyrosine phosphatase-1 (DEP-1/CD148), which is expressed on the sensory epithelia of the inner ear and on endothelial cells [9]. Treatment of Cogan's syndrome depends on the type of organ involvement and the severity of disease. Keratitis, episcleritis, and anterior uveitis can typically be treated with topical prednisone acetate for several weeks. Deeper ocular inflammation and vestibuloauditory symptoms should be treated with at least prednisone 1 mg/kg daily and typically for at least 2–6 months. Some clinicians may also choose to add cyclophosphamide, methotrexate, cyclosporine, or infliximab for recalcitrant cases.

Behçet's Disease

Oral aphthosis, along with genital aphthosis, is a hallmark feature of Behçet's disease, though recurrent oral aphthosis in and of itself has a long differential that includes certain vitamin deficiencies, herpes simplex and other infectious etiologies, autoimmune blistering diseases such as IgA pemphigus or pemphigus vulgaris, drug-induced causes, or paraneoplastic phenomena. Celiac Disease and inflammatory bowel disease can also present with aphthous-like ulcerated lesions. The International Study Group for Behçet's Disease identified recurrent oral ulceration as the required criterion for diagnosis, with patients also needing at least two of the following minor criteria to indicate a diagnosis of Behçet's disease: recurrent

genital ulceration; characteristic inflammatory eye disease such as anterior or posterior uveitis, retinal vasculitis, or cells in the vitreous; characteristic skin lesions such as erythema nodosum; or positive pathergy test (hyper-reactivity of the skin to minor trauma) [10]. Research has identified a strong genetic underpinning in Behçet's disease of the MHC-related allele HLA-B51/B5, and carriage of this allele has been shown to predominate in men and be associated with a higher prevalence of genital, ocular, and skin manifestations and with a lower prevalence of gastrointestinal manifestations [11]. Behçet's disease is unusual among the vasculitides as it has been shown to affect small, medium, and large vessels and can also involve the central nervous system. Venous thromboembolism can also occur in Behçet's disease, and there is some discussion in the literature as to whether immunosuppression without anticoagulation is sufficient to prevent recurrence of this manifestation [12]. Colchicine, dapsone, azathioprine, apremilast, thalidomide, and interferon have all been used in the treatment of mucocutaneous manifestations of Behçet's disease, while azathioprine, methotrexate, and cyclosporine have been used for ocular manifestations. Cyclophosphamide, anti-TNF agents, and chlorambucil have been used for refractory, severe central nervous system disease or life-threatening complications of Behçet's disease.

Medium-Vessel Vasculitis

Polyarteritis Nodosa

Polyarteritis nodosa (PAN) is a necrotizing arteritis of medium or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules. The disease is not associated with antineutrophil cytoplasmic antibodies (ANCA). Hepatitis B infection is commonly associated with PAN and is present in 20–30% of cases [13]. Clinical presentations are heterogeneous, with end-organ effects resulting from perfusion defects caused by the vasculitis. Common symptoms include constitutional symptoms, weight loss, myalgias, arthralgias, and skin abnormalities such as necrotizing purpura or subcutaneous nodules, while peripheral nerve involvement including mononeuritis multiplex is also common and is seen in roughly 80% of cases [14]. Involvement of the gastrointestinal, cardiac, genitourinary, and renal systems is seen as well. Mortality over a mean follow-up period of 6 years has been estimated at 25%, with one third of deaths being due to uncontrolled or relapsed vasculitis [15]. There are no specific biomarkers for PAN, and it is reasonable to screen for hepatitis B (HBV) and hepatitis C (HCV), human immunodeficiency virus (HIV), and parvovirus B19 to exclude the presence of these infections. Testing for ANCA, Proteinase 3 (PR3) antibodies, Myeloperoxidase (MPO) antibodies, cryoglobulins, and rheumatoid factor also should be obtained to exclude the differential diagnoses of ANCA-associated small-vessel vasculitis and cryoglobulinemic vasculitis. Serologic screening and

surveillance for end-organ involvement and damage with creatine kinase levels, troponin, liver function and renal function testing, spot urine protein:creatinine ratio, and urinalysis is important in disease management. Acute phase reactants should be followed to monitor disease activity and response to treatment. Conventional dye angiography can be used to assess for medium-vessel microaneurysms, stenoses, and luminal irregularities. In general, conventional angiography is the imaging gold standard for PAN since neither CT nor MRI angiography offer comparable sensitivity. Treatment selection should be based on HBV status, mortality risk as predicted by the Five-Factor Score, and the severity and degree of organ involvement [14]. For patients with HBV infection, lamivudine is the preferred antiviral agent of choice, with plasma exchange on a background of prednisone until HBeAb seroconversion occurs. For non-HBV cases with a Five-Factor Score > 0, which corresponds to a poorer prognosis and increased 5-year mortality, a combination of steroids and cyclophosphamide induction followed by azathioprine maintenance may be used. Plasma exchange has not been shown to be beneficial for non-HBV cases of PAN.

Kawasaki Disease

The most common systemic vasculitis among children worldwide is Kawasaki disease, a vasculitis that affects medium caliber vessels. Kawasaki disease occurs most frequently in children under the age of 5. While Kawasaki disease can affect children of all ethnicities, its highest prevalence is found in Asian populations, particularly Japanese children. Kawasaki disease typically presents with acute onset fevers and acute phase reactant elevation without an infectious source. Additional features may include cervical lymphadenopathy, generalized or palmoplantar rash, lesions of the mucus membranes (including strawberry tongue) and ocular disease including conjunctivitis and uveitis. The most feared complication of KD is cardiac disease: myocarditis in the early phase of the disease, and coronary artery aneurysms which develop in later stages. For this reason, echocardiography is a mandatory diagnostic study in the evaluation of suspected cases of Kawasaki disease and is performed serially to monitor for the development of aneurysms in confirmed cases. Ophthalmologic exam should also be obtained due to the high prevalence of uveitis. Additional studies should be undertaken to exclude infectious etiologies with similar presentations, including scarlet fever, parvovirus and herpesviruses, and other inflammatory conditions (JIA, periodic fever syndromes). Once the diagnosis of Kawasaki disease is made, therapy with IVIG is standardly implemented. The implementation of IVIG early in the disease course has demonstrated significant benefit in reducing the risk of coronary artery aneurysms [16] Additional therapies considered in refractory or severe Kawasaki disease include aspirin, glucocorticoids, and repeat courses of IVIG. With timely diagnosis and treatment, Kawasaki disease can be limited to a monophasic illness with minimal long-term sequelae in many patients.

Small-Vessel Vasculitis

Granulomatosis with Polyangiitis (GPA)

Granulomatosis with polyangiitis, formerly known as Wegener's granulomatosis, is an ANCA-associated necrotizing vasculitis with granulomatous inflammation, predominantly affecting small to medium vessels and usually involving the upper and lower respiratory tracts. The varied clinical presentations of GPA are driven by the presence of granulomatous inflammation that can manifest as orbital pseudotumor, chronic sinusitis, Eustachian tube dysfunction, subglottic stenosis, and cavitary pulmonary lesions, or by the small- or medium-vessel vasculitis, which can result in pulmonary hemorrhage, glomerulonephritis, palpable purpura or mononeuritis multiplex. Abnormalities of the upper airway, including chronic rhinitis with or without nasal crusting, epistaxis, chronic sinusitis, and serous otitis, are typically the earliest presenting features and are estimated to be present in over 90% of cases [17]. Anti-PR3 antibody positivity with a C-ANCA pattern by indirect immunofluorescence microscopy has a high specificity and positive predictive value for GPA, but the absence of ANCA or PR3 does not exclude the diagnosis, and isolated granulomatous disease of the upper or lower respiratory tract in particular has a propensity to be associated with PR3 and C-ANCA negativity. PR3-ANCA is thought to be present in 80–95% of GPA cases, with the remaining 5–20% exhibiting atypical MPO-ANCA positivity or no ANCA [18]. GPA can be divided into the categories of limited disease, which tends to be characterized by predominance of necrotizing granulomatous manifestations, and severe disease, which is disease threatening the function of life or a vital organ, usually secondary to the vasculitis. The term "limited" may be misleading since patients with non-life-threatening forms of GPA often suffer from chronic morbidity and can require several years of continuous immunosuppression to adequately treat the mass lesions associated with this form of GPA. In general, patients with limited GPA are treated with an antimetabolite agent such as methotrexate, azathioprine, mycophenolate mofetil, or leflunomide. Rituximab may have a role for patients who have been refractory to this class of agents or are intolerant of these drugs. Patients with severe GPA should be treated with induction with pulse intravenous methylprednisolone 1000 mg daily for 3 days, thereafter converted to oral prednisone, used in conjunction with cyclophosphamide or rituximab. Concurrent cyclophosphamide as an induction agent can be given either orally at 2 mg/kg daily to a maximum dose of 200 mg daily for 6 months or as a series of IV pulses of 15 mg/kg to a maximum of 1.2 grams initially every 2 weeks for the first three pulses, followed by spacing to every 3 weeks for the next 3–6 pulses [19]. As an alternative to cyclophosphamide induction, rituximab is FDA-approved for induction in patients and should be administered according to the RAVE trial protocol at a dose of 375 mg/m^2 weekly for 4 weeks [20]. Among patients with the severe forms of ANCA-associated vasculitis, rituximab is commonly considered to be the treatment of choice for younger patients (who are concerned about preserving fertility), older patients (who may not be able to tolerate

traditional cytotoxic agents), or patients who have previously been treated with cyclophosphamide. Remission induction with cyclophosphamide should be followed by 18–24 months of immunosuppressive therapy in accordance with the 2008 EUVAS Management Guidelines [19]. Azathioprine 2 mg/kg daily is preferred, but options may also include methotrexate 20–25 mg per week if creatinine is <1.5 mg/dL, mycophenolate mofetil 1000 mg twice daily, or leflunomide 20–30 mg daily as second-line options. Rituximab can also be used as a long-term maintenance agent.

Microscopic Polyangiitis (MPA)

Microscopic polyangiitis is a necrotizing vasculitis with few or no immune deposits that predominantly affects small vessels, but without the presence of necrotizing granulomas that is characteristic of GPA. The initial presentation of MPA typically is characterized by a long prodromal phase dominated by marked constitutional symptoms followed by rapidly progressive necrotizing glomerulonephritis presenting as a nephritic syndrome. Glomerulonephritis is present in roughly 80% of cases at diagnosis, but pulmonary involvement is less common, occurring in about 10–30% of patients [21]. Another important distinguishing feature of MPA from GPA is that fever is the presenting feature in 80% of cases of MPA, but is an initial feature in only of 20–25% of cases of GPA. Anti-MPO antibody positivity with a P-ANCA pattern by indirect immunofluorescence microscopy has a high specificity and positive predictive value for MPA, but the absence of ANCA or MPO does not exclude the diagnosis. Although MPA and GPA can appear similar in many aspects of presentation, more detailed analyses of pathophysiology indicate key differences in these conditions. While both anti-MPO and anti-PR3 antibodies can activate neutrophils in vitro, the evidence for in vivo pathogenicity of anti-MPO is more robust than that for PR3-ANCA. A recent genome-wide association study of patients with ANCA-associated vasculitides demonstrated a significant association of PR3-ANCA and human leukocyte antigen-DP and the genes encoding α1-antitrypsin and PR3 while MPO-ANCA were significantly associated with human leukocyte antigen-DQ [22]. Nevertheless, similar to GPA, MPA can be categorized as limited or severe disease, and the treatment modalities are quite similar, including pulse methylprednisolone converted to oral prednisone and used in conjunction with cyclophosphamide or rituximab for induction for severe disease. Azathioprine, methotrexate, mycophenolate mofetil, leflunomide, rituximab, and, though with significant potential side effects form long-term use, cyclophosphamide can be used for maintenance therapy.

Eosinophilic Granulomatosis with Polyangiitis (EGPA)

Eosinophilic granulomatosis with polyangiitis, formerly known as Churg-Strauss syndrome, is an ANCA-associated, eosinophilic necrotizing vasculitis affecting

predominantly small to medium vessels that is associated with asthma and peripheral and tissue eosinophilia. Diagnosis of eosinophilic granulomatosis with polyangiitis is supported by a history asthma, peripheral eosinophilia with an absolute eosinophil count >1500/mm^2 and biopsy showing evidence of necrotizing granulomas and eosinophilic small-vessel vasculitis. Asthma is the defining clinical feature of EGPA, being present in >90% of patients at diagnosis and preceding the onset of vasculitis in roughly 80% of cases [23]. EGPA is typically divided into three phases of the disease: the allergic phase, with occurrence of asthma, allergic rhinitis, and sinusitis; the eosinophilic phase, in which eosinophilic organ infiltration (e.g., lungs, heart, and gastrointestinal system) occurs; and the vasculitic phase, with purpura, peripheral neuropathy, and constitutional symptoms. ANCA-positive patients are at increased risk for otolaryngologic involvement (usually sinusitis); neurologic complications including peripheral neuropathy and mononeuritis multiplex; renal involvement (typically an interstitial nephritis rather than glomerulonephritis). An unusual feature of neurologic involvement in EGPA is the occurrence of bilateral wrist or foot drop in patients, which is not typically seen in individuals with other small- or medium-vessel vasculitides. Similar to the approach for GPA and MPA described above, corticosteroids with cyclophosphamide or rituximab are classically used for remission induction, while azathioprine and methotrexate are some of the main therapeutic options for remission maintenance in EGPA. Interestingly, IL5 plays a central role in regulating eosinophil proliferation, maturation, and differentiation and is present at increased levels in patients with eosinophilic granulomatosis with polyangiitis, indicating that this cytokine may be important in disease pathogenesis [24]. In 2017, a multicenter, double-blind, parallel-group, randomized phase 3 clinical trial of 136 participants demonstrated that treatment with mepolizumab, an anti-IL5 monoclonal antibody that binds to IL5 and prevents its interaction with its receptor on the eosinophil surface, resulted in significantly more weeks in remission and a higher proportion of participants in remission than did placebo, thereby allowing for reduced glucocorticoid use [25]. On the strength of this and other trials, the FDA approved mepolizumab in December 2017 for the treatment of EGPA, though it is important to note that the dose of the medication used in the trial was 300 mg administered every 4 weeks, as opposed to the 100 mg dose every 4 weeks typically used in asthma without concurrent EGPA.

Henoch-Schonlein Purpura

Henoch-Schonlein purpura (HSP) is a small-vessel vasculitis that is more common in children than in adults, is typically self-limited, and is notable for histology demonstrating IgA deposition in the walls of involved blood vessels. While monophasic in children, it can be relapsing in adults and may result in renal failure and gut ischemia. Purpura not due to thrombocytopenia should raise suspicion for this condition, as should concomitant arthritis, abdominal pain, and glomerulonephritis. From the pediatric literature, there is little evidence that

immunosuppression is effective in the treatment of renal disease. For the cutaneous lesions of the condition, and possibly for the gastrointestinal symptoms as well, dapsone is often first-line therapy once glucose-6-phosphate dehydrogenase deficiency has been ruled out, given the possibility of significant hemolysis due to dapsone in such patients. Patients should be counseled that cutaneous vasculitis can be stimulated by activities that promote circulation to the lower extremities, including exercise, heat, and alcohol. Pressure stockings can be very effective for the treatment of the cutaneous manifestations of HSP and should be worn as much as possible, especially with regard to periods of activities such as those noted above. HSP is associated with a risk of renal insufficiency that remains even after initial recovery of renal function, thus routine monitoring of renal function should continue over a patient's lifetime.

Single Organ Vasculitis

The Chapel Hill Consensus Conference definition for single-organ vasculitis defines this entity as "vasculitis in arteries or veins of any size in a single-organ that has no features that indicate that it is a limited expression of a systemic vasculitis." Importantly, this definition is one that relies on vigorous exclusion of primary or secondary systemic rheumatic causes. When diagnosed, single-organ vasculitis by definition does not evolve into systemic vasculitis. Importantly, though, workup often reveals secondary non-rheumatic cause for the vasculitis such as cancer, environmental exposures, or infection.

Most available knowledge regarding single-organ vasculitis is based on small case series that have appeared in the literature over the last several decades [26]. Any organ system can be involved, but the most common targets are often skin, central and peripheral nervous system, muscle, gastrointestinal organs, the urogenital tract, breasts, and the eyes. In contrast, other visceral organs including the heart, liver, lungs, and the kidneys have never been established to be targets of single-organ vasculitis. The clinical presentation is a consequence of the specific end-organ that is involved. In general, however, constitutional symptoms are infrequently seen, acute phase reactants are usually normal to only slightly elevated, and the prognosis is often benign. The vasculitis itself is thought to follow a monophasic course in most cases. That being said, there is currently little evidence-based data to guide management of this group of vasculitides. Most experience with treatment has been based on retrospective series, and there are no randomized placebo-controlled trials of intervention for single-organ vasculitis to date.

High-Yield Review of Vasculitis

Key Points on Systemic Vasculitis

- Systemic vasculitides share the pathogenic feature of inflammation focused in the walls of blood vessels.
- Primary vasculitides are categorized according to the caliber of the blood vessels involved.
- Secondary vasculitis can be due to underlying connective tissue disease, infection, drug-induced, or paraneoplastic causes.
- Commonly used imaging modalities in suspected vasculitis include Doppler ultrasound, conventional angiography, computed tomography angiography, magnetic resonance angiography, and positron emission tomography.
- Diagnosis of vasculitis is made based on tissue histopathology in concert with the appropriate clinical presentation.
- Typical histologic findings of vasculitis include infiltration of the vessel wall by immune cells, fibrinoid necrosis of blood vessel walls, and leukocytoclasis.

Clinical Pearls on Primary Vasculitides

- Giant cell arteritis occurs almost exclusively in adults over the age of 50, with a predominance among Caucasian women.
- Takayasu's arteritis predominantly affects women under the age of 40, with an increased prevalence among individuals of Asian descent.
- Cogan's syndrome typically involves ocular, vestibuloauditory, and vasculitic findings.
- Hepatitis B infection is commonly associated with polyarteritis nodosa.
- The most feared complication of Kawasaki disease is cardiac disease, with myocarditis in the early phase of the disease and coronary artery aneurysms in later stages.
- Anti-PR3 antibody positivity with a C-ANCA pattern by indirect immunofluorescence microscopy has a high specificity and positive predictive value for granulomatosis with polyangiitis, but the absence of ANCA or PR3 does not exclude the diagnosis.
- Microscopic polyangiitis has a similar presentation as granulomatosis with polyangiitis but without the presence of necrotizing granulomas.
- An unusual feature of neurologic involvement in eosinophilic granulomatosis with polyangiitis is the occurrence of bilateral wrist or foot drop in patients, which is not typically seen in individuals with other small- or medium-vessel vasculitides.
- Henoch-Schonlein purpura is often monophasic in children but can be relapsing in adults and may result in renal failure and gut ischemia.

Questions

1. A 67-year-old Caucasian male presents with 5 weeks of headache lateralized to the right temporal region. He has also suffered recurrent fevers, myalgias, and an unintentional 10 lbs. weight loss. Two days ago, he suffered an episode of several hours of vision loss in the right eye.

   Examination is notable for tenderness to palpation and hair thinning over the right temporal region. There is also weakness of the proximal muscles of the shoulder girdle. Lab work is notable for ESR 78 mm/hour and CRP 3.4 mg/dL.

   Which of the following is a reasonable molecular target of therapy in this patient?

   A. TNF-α
   B. Il-4
   C. C5a
   D. IL-6

   Correct answer: D
   The patient has giant cell arteritis with polymyalgia rheumatica. IL-6 is a key T-cell cytokine mediator in this disease process. Tocilizumab, which targets the IL-6 axis, received the Food and Drug Administration's approval in August 2017 for the treatment of GCA.
2. A 28-year-old Puerto Rican male presents to the ER after tripping while descending stairs in his home. He endorses feeling unwell also for the past 2 weeks with subjective fever, chills, malaise, abdominal pain, and an unintentional five-pound weight loss. He has also noted right testicular pain.

   Examination is notable for mild diffuse tenderness to palpation of the abdomen. A right foot drop is present. 1+ bipedal edema is present. The lower extremities are also notable for livedo reticularis.

   A medium-vessel systemic vasculitis is suspected. Conventional angiography reveals multiple microaneurysms of the intrahepatic and intrarenal arteries. Fusiform aneurysms and occlusive lesions throughout the superior mesenteric arterial distribution including of the hepatic and splenic branches are also noted.

   Which of the following viral infections has NOT been associated with this systemic vasculitis?

   A. HIV
   B. Hepatitis B
   C. Zika virus
   D. Parvovirus B19

   Correct answer: C
   The patient has polyarteritis nodosa, a medium-vessel vasculitis. He presents with typical features including constitutional symptoms, livedo reticularis, and mononeuritis multiplex. The abdominal symptoms are from vasculitic involvement of the intra-abdominal medium vessels. HIV, parvovirus B19, and hepatitis B all have been reported in association with polyarteritis nodosa.

3. A 24-year-old Asian female presents to her primary care provider for a routine annual health physical. She has no significant prior medical history. Except for numbness and recurrent episodes of her left arm "falling asleep" several times in the last 2 months, she has no specific complaints. Interestingly, these episodes of numbness seem to occur after activity. She regularly participates in Zumba classes, but stopped going for the past 2 weeks to avoid provoking her left arm symptoms. She is left-handed.

   She has an unremarkable routine 10-system exam. CMP, CBC, ESR, CRP, urinalysis, and urine pregnancy screening are also unremarkable.

   Which diagnostic test is most likely to establish her diagnosis?

   A. EMG/NCS
   B. Chest CT angiography
   C. ANA screening
   D. Urine drug testing

   Correct answer: B
   The patient's presentation is most concerning for Takayasu arteritis. CT angiography and magnetic resonance angiography are the preferred imaging modalities for diagnosing Takayasu's arteritis.
4. A 22-year-old Caucasian female presents for evaluation of a recurrent nodular rash with burning pain on the bilateral lower extremities. She has not experienced any similar rash in the past, though she does have recurrent nodulocystic acne controlled with topical retinoids and minocycline. She does not smoke and denies any use of illicit drugs.

   Her examination revealed multiple violaceous, tender, subcutaneous nodular lesions ranging in diameter from 0.5 cm to 1 cm over the bilateral lower legs. The overlying skin was mildly warm but nontender.

   A short course of oral steroids led to remission for her lesions for roughly 1 week. However, the lesions recurred after stopping steroids. She also noticed new bilateral ankle pain, stiffness, and swelling. The rest of her exam was unremarkable.

   Lab work was significant for pANCA positive in 1:640 titer. Follow-up ELISA for MPO and PR3 was negative. Urine studies, chest X-ray, and sinus CT scans were unremarkable. A urine drug screen was negative.

   A skin biopsy of one of the nodules around the ankle revealed a necrotizing granulomatous vasculitis with neutrophil-predominant infiltration of medium- and small-sized arterial walls.

   Which of the following is most reasonable next step?

   A. Start rituximab.
   B. Discontinue her minocycline acne therapy.
   C. Start methotrexate.
   D. Maintain the patient on long-term low-dose prednisone (5 mg/d).

   Correct answer: B

The patient's presentation and her atypical (e.g., negative PR3 and MPO) high-titer pANCA in particular are highly suspicious for a drug-induced vasculitis. Minocycline is a known cause of drug-induced vasculitis.

5. A 54-year-old male presents for evaluation of fever, sinusitis with purulent crusting nasal discharge, and generalized malaise for the past 6 months. His symptoms have been refractory to multiple courses of oral antibiotics. He denies any shortness of breath, numbness or tingling, focal weakness, or skin lesions.

   Examination is notable for an anterior nasal septal perforation, nasal crusting with clots, and an early saddle nose deformity. Lungs are clear to auscultation. Skin and neurologic examinations are unremarkable.

   A cANCA is positive in 1:640 titer, and PR3 is positive. Renal parameters are unremarkable. A chest X-ray is clear. Sinus CT shows chronic pan-sinusitis.

   Aside from oral steroids, which of the following is the most appropriate therapy?

   A. Rituximab
   B. Hydroxychloroquine
   C. Colchicine
   D. Methotrexate

   Correct answer: D
   The patient has limited GPA. For limited GPA, Methotrexate is appropriate first-line therapy for both induction and remission maintenance. Rituximab is generally reserved for severe/generalized disease and as salvage therapy for treatment-refractory limited disease. Colchicine and hydroxychloroquine are immunomodulatory agents that have no established role in the treatment of GPA.

6. A 29-year-old female presents to the ER because of acute onset right-sided weakness and slurred speech. She is accompanied by her husband, who reports that the patient had been feeling unwell with subjective fevers, chills, malaise, and diffuse myalgias for the preceding week. She has no significant medical history otherwise and takes no medications or herbal supplements.

   Initial examination confirms a dense right-sided hemiparesis and prominent left facial droop. A bruit is auscultated over the left neck. A non-contrast head CT reveals an acute left MCA territory infarction. Reperfusion therapy with tPA is given, but with no improvement in her neurologic features over the next 48 hours.

   CBC is notable for a leukocytosis of 12.7 with neutrophil predominance. CMP reveals an elevated creatinine of 1.7. Acute phase reactants are elevated with ESR 89 mm/hour and CRP 3.7 mg/dL.

   CT angiographic is significant for focal stenotic lesions of the left subclavian, left common carotid and right renal arteries. There is also aortic root dilatation.

Echocardiography is negative for valvular vegetations, but shows diffuse global hypokinesis with a left-sided ejection fraction of 37%.

In addition to IV systemic steroids, induction with cyclophosphamide is discussed, but the patient and her husband adamantly refuse because of concerns about long-term fertility.

Aside from continuing systemic steroids, which of the following is a reasonable therapy?

A. IVIG
B. Azathioprine
C. Infliximab
D. Rituximab

Correct answer: C
The patient has suffered a stroke in the setting of newly diagnosed Takayasu arteritis. Because of severe life-threatening end-organ involvement, induction with cyclophosphamide or an anti-TNF agent is preferred. The patient, however, has declined cyclophosphamide because of concern about the impact of long-term fertility. Anti-TNF agents are not teratogenic, but the passive transfer of drug before delivery has consequences for the timing of newborn vaccinations that should be discussed in coordination with an obstetrician and pediatrician.

7. A 5-year-old boy is brought to the pediatric ER for evaluation of chest pain. His parents note that he also has been suffering from fevers to 102 degrees Fahrenheit and a painful tongue that has made eating difficult. He has no known sick contacts.

   Examination is notable for a maculopapular rash over the trunk and extremities, desquamation of the skin over the palms and fingertips, and bilateral conjunctivitis.

   ECG reveals ST elevations in leads II, III, and aVF. A stat echocardiogram reveals an ejection fraction of 39%.

   Which of the following should be initiated at this time?

   A. IV systemic steroids
   B. Rituximab
   C. Cyclophosphamide
   D. IVIG

   Correct answer: D
   The patient has Kawasaki disease with typical mucocutaneous features and evidence of a myocardial infarction due to coronary artery involvement. IVIG together with aspirin is first-line therapy.

8. A 37-year-old woman is referred for evaluation of abdominal pain and abnormal CTA findings. She describes postprandial epigastric pain ongoing for the past 3 months, but denies any associated constitutional symptoms.

   Examination is notable only for abdominal tenderness. Laboratory findings have included mild anemia with normal renal and hepatic function. ESR is 7 mm/hour and CRP 0.1 mg/dL.

CTA demonstrates serial stenotic and aneurysmal lesions of the celiac artery, creating a "beads on a string" appearance. All other vascular territories in the thorax and abdomen are normal.

What is the most likely diagnosis?

A. Polyarteritis nodosa
B. Segmental arterial mediolysis
C. Antiphospholipid syndrome
D. Thromboangiitis obliterans

Correct answer: B
Segmental arterial mediolysis is a noninflammatory vasculopathy that commonly affects the abdominal vasculature. The lack of acute phase reactant elevation and the isolated distribution in the celiac artery are keys to differentiating this diagnosis from polyarteritis nodosa. Antiphospholipid syndrome would be more likely to involve multiple vascular territories with occlusive rather than aneurysmal lesions. Thromboangiitis obliterans is not known to affect the visceral arterial system.

9. A 19-year-old male presents to the emergency department with purpuric skin lesions. He reports that the lesions developed over the past week and have been progressive.

Exam reveals retiform purpura involving the ears, cheeks, and nose. A nasal septal defect is also noted.

Chest X-ray and renal function parameters are normal.

Which of the following studies would you order next?

A. Urine drug screen
B. MRA of the abdomen
C. Anti-DNA antibodies
D. Paroxysmal nocturnal hemoglobinuria flow cytometry assay

Correct answer: A
This patient's presentation is suggestive of levamisole-induced vasculitis. Levamisole is an antihelminthic agent that is frequently identified as an adulterant in cocaine. The patient's nasal septal defect is a clue to the possibility of cocaine use. MRA of the abdomen would not add relevant information, and the patient's presentation is not suggestive of SLE. While PNH is associated with thrombosis, the finding of necrotic lesions on the face without any indication of visceral thrombosis would be unusual.

10. A 34-year-old woman presents for evaluation of purpuric skin lesions. For the past 6 months, she has noticed crops of coalescing purpuric lesions on the lower legs. She denies any sensory or motor deficits in the extremities. Review of systems is notable for prominent sicca symptoms. She has experienced painless swelling in the vicinity of her parotid glands for the past year, and the parotids are enlarged with palpable nodularity on exam.

Initial laboratory studies demonstrate high-titer anti-SSA, anti-SSB, and rheumatoid factor. Labial salivary gland biopsy demonstrates focal lymphocytic sialadenitis with a high focus score (5.4), and several germinal centers are noted.

Which of the following studies should be obtained next?

A. Salivary scintigraphy
B. Anti-CCP antibodies
C. EMG/NCS
D. Ultrasound guided parotid biopsy

Correct answer: D
This patient's presentation is consistent with primary Sjogren's syndrome, diagnosed on the basis of autoantibody positivity and labial salivary gland biopsy findings. The skin lesions are compatible with LCV, likely due to cryoglobulinemia. The reported major salivary gland enlargement is concerning for the presence of B cell (MALT) lymphoma. She should therefore be evaluated with major salivary gland imaging and biopsy. The other studies are of lesser priority in this patient's evaluation.

11. A 68-year-old woman with PMR returns for follow-up. 3 months ago, she presented with aching soreness of the upper arms, shoulders and back, and elevated acute phase reactants. Initial treatment with 15 mg prednisone daily led to rapid resolution of her symptoms. She has since tapered her dose to 5 mg daily.

She notes that for the past 2 weeks, she has had difficulty chewing food due to soreness in her jaw. She has also noticed tenderness of her scalp when laying her head on a pillow at night. Yesterday she experienced diplopia which lasted for several hours before spontaneously resolving.

Which is the most appropriate next step in this patient's management?

A. Referral to headache specialist.
B. Referral to ophthalmologist.
C. Addition of gabapentin 300 mg three times daily.
D. Increase prednisone to 60 mg daily.

Correct answer: D
This patient with recently diagnosed PMR is now presenting with signs of GCA, including jaw claudication, scalp tenderness, and visual disturbance. This is concerning for the risk of impending visual loss, and she should therefore be treated with high-dose glucocorticoid immediately, while being referred for temporal artery biopsy. Ophthalmology exam is indicated, but steroids should not be withheld while this referral is pending.

12. A 17-year-old male presents with 2 weeks of periumbilical pain and nausea. A purpuric rash has also appeared on the lower extremities. He describes aching and stiffness in the small joints of his hands as well as his knees.

Laboratory parameters are notable for mild anemia, ESR 85 mm/hour, and UA with 2 + RBC and 3 + protein.

A biopsy of a skin lesion is most likely to demonstrate what finding on immunofluorescent staining?

A. Intercellular IgG staining
B. Linear basement membrane zone staining of IgG and C3
C. IgA deposition
D. Minimal staining (pauci-immune)

Correct answer: C
This young male patient is presenting with typical findings of Henoch-Schonlein purpura, including abdominal pain, proteinuria, and purpuric skin lesions. HSP is mediated by IgA immune complex deposition, which can be visualized by immunofluorescent staining on skin biopsy.

13. A 27-year-old Turkish male with a history of recurrent oral and genital ulcers presents to the emergency department with hemoptysis. He gives additional history of recurrent uveitis treated with intermitted steroids and chronic pain in the knees, wrists, and hands. He has not received chronic immunomodulatory therapy and is not followed by a rheumatologist. For the past 24 hours he has been coughing up blood.

Which of the following is likely to be identified with additional studies?

A. Cavitary lung nodules
B. Pulmonary artery aneurysms
C. Mediastinal lymphadenopathy
D. Perforated gastric ulcer

Correct answer: B
This patient fits a diagnosis of Behcet's disease with oral and genital ulcers, uveitis, and arthritis. His presentation with hemoptysis is worrisome for a feared complication of Behcet's: pulmonary artery aneurysms.

14. A 72-year-old man presents for evaluation of aortitis. Over the past 3 months, he has experienced night sweats, fevers, and a 10-pound weight loss. Three days ago he presented to the emergency department where he was found to have highly elevated acute phase reactants. An MRI demonstrated thickening and enhancement of the wall of the thoracic aorta. A temporal artery biopsy was negative.

In addition to constitutional symptoms, he reports hearing loss as well as ringing in his ears over the past 3 months. For the past 2 weeks he has experienced pain and photophobia in his left eye. An ophthalmology exam performed today revealed signs of interstitial keratitis.

What is the most likely diagnosis?

A. Cogan's syndrome
B. Giant cell arteritis
C. Evans syndrome
D. Sweet's syndrome

Correct answer: A

Cogan's syndrome is a systemic vasculitis which characteristically affects the eyes and vestibuloauditory system. Cogan's syndrome can cause vasculitis in other vessels, including aortitis. Interstitial keratitis is the hallmark ocular finding and clue to this case. While GCA can manifest with symptoms involving the same organs, the negative temporal artery biopsy and specific finding of interstitial keratitis make Cogan's syndrome more likely than GCA. Evans and Sweet's are hematologic and dermatologic conditions, respectively.

15. A 43-year-old woman presents for evaluation of an orbital mass identified by her ophthalmologist. Over the past 2 months she has noticed diplopia and pain involving the left eye, leading to an MRI that showed a mass lesion in the left orbit. She has a history of recalcitrant sinusitis which has been increasingly problematic over the past year.

    Examination reveals proptosis of the left eye, crusting of the nasal mucosa, and a nasal septal perforation. Laboratory parameters include normal renal and hepatic function, ESR 52 mm/hour, and negative ANCA testing. Chest CT demonstrates several pulmonary nodules of moderate size, one of which shows signs of cavitation. Biopsy of the orbital mass demonstrates granumolatous inflammation and geographic necrosis. Microbial stains including AFB are negative.

    Which of the following is the most likely diagnosis?

    A. Sarcoidosis
    B. GPA
    C. Thyroid eye disease
    D. IgG4 related disease

    Correct answer: B
    This patient's presentation with sinusitis, orbital inflammatory disease, and pulmonary nodules is compatible with several diagnoses, including limited GPA. The histopathology confirms GPA as the etiology, despite negative ANCA testing which is more common in the limited form of GPA. While sarcoidosis, autoimmune thyroid disease, and IgG4RD can all cause orbital mass lesions, the histologic findings described here are not compatible with these diagnoses and instead implicate GPA as the diagnosis.

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Chapter 13
Inflammatory Myopathies

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Idiopathic inflammatory myopathies (IIM) are a heterogeneous group of autoimmune syndromes characterized by chronic muscle weakness and skeletal muscle inflammation of unknown etiology. The incidence is approximately five cases/100,000 persons-years, and the annual prevalence can range between 15 and 33/100,000 persons. While skeletal muscle is the main target, IIM are a systemic disease and can affect the skin, lungs, and joints as well. They are characterized by the presence of autoantibodies in the majority of cases and respond to immunosuppression.

There are four distinct types of myositis based on muscle biopsy findings: dermatomyositis (DM), polymyositis (PM), immune-mediated necrotizing myopathy (IMNM), and inclusion body myositis (IBM).

Epidemiology

Of the four distinct types of myositis, DM and PM rank highest in prevalence at 5–22 per 100,000. Next is IMNM with a prevalence of 9–14 per 100,000, leaving IBM as the rarest form of IIM with a prevalence of 0.9–1.49 per 100,000. However, with better recognition of IBM, the prevalence is on the rise, and when subcategorized by age, IBM is the most common myopathy over the age of 50.

Age and gender also vary with the type of myositis, with DM/PM having a female predominance of 2:1, IBM having a male predominance, and IMNM having no gender bias. In regard to age, IMNM and DM/PM have similar peak incidences between ages 40 and 50, while IBM patients typically present later in life

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at a peak age of onset of 60. Notably subgroups within IMNM, including anti-SRP and non-statin exposure HMGCR patients, have earlier disease onset with a peak around 40.

Clinical Presentation

Dermatomyositis

Patients with DM usually present with cutaneous and/or muscular manifestations evolving over weeks to months. Characteristic skin rash can predate, present concurrently, or develop after muscle weakness is established, and one characteristic can prevail over the other. When Bohan and Peter proposed the first set of criteria in 1975, definite DM was established based on a combination of muscle involvement and characteristic skin rash, which both had to be present for a definite diagnosis. However, it was soon realized that there were patients with the characteristic rash and little or no clinically apparent muscle weakness. These patients would now be classified as *amyopathic DM* or *hypomyopathic DM*, if they had no signs or evidence of hypoclinical muscle involvement, like elevated CPK, MRI findings of muscle edema, EMG abnormalities, and/or muscle biopsy findings. There is significant heterogeneity in clinical presentations creating a diagnostic challenge.

Skin Findings

There is a wide spectrum of skin findings that can occur in patients with DM, and it may be difficult to differentiate from rashes observed in other rheumatic diseases. The pathognomonic skin rashes of DM include the Gottron's sign and the Heliotrope rash. *Gottron's sign* is a lichenoid violaceous lesion located typically over the extensor surface of MCPs, PIPs, and DIPs. These lesions can be also present on the extensor surface of other joints, such as elbows, knees, and toes. The term *Gottron's papules* is used for raised lesions. *Heliotrope rash* is an erythematous or purplish discoloration of the eyelids due to vascular dilatation and may be associated with periorbital edema. While these rashes are specific for DM, quite often patients may present with a diffuse erythematous rash involving any area of the body. Patients may have a *malar rash*, similar to the one observed in lupus, but it is usually flat and extends over the nasolabial folds. An erythematous rash may affect the posterior neck and shoulders (*shawl sign*), anterior neck and chest (*V-sign*), or lateral thighs (*Holster sign*). Patients can present with *periungual erythema* due to dilated capillary loops. *Nailfold capillary changes*, such as enlargement of capillary loops, decreased density, hemorrhages, and microvascular disarrangement, have been identified by capillaroscopy similarly to scleroderma, with or without the presence

of Raynaud's phenomenon. *Mechanic's hands*, hyperkeratotic fissures of the lateral side of digits, are more commonly found in patients with anti-synthetase syndrome. Another important feature of cutaneous manifestations of IIM is *pruritus*, which can severely impact the quality of life.

Calcinosis cutis is the subcutaneous deposition of calcium in skin and subcutaneous tissues. New lesions can be surrounded by erythematous discoloration of the overlying skin and can ulcerate with a milk-like discharge. Depending on their location severe debilitation may occur. *Calcinosis cutis* is more commonly seen in juvenile dermatomyositis (44–70%) but can be also observed in 20% of adult-onset DM as well. There is a particular association with anti-NXP2 autoantibodies and can appear within 8 years of disease onset.

Cutaneous punctuate ulcers are a distinguishing feature of patients with anti-MDA-5 autoantibodies. These patients may also present with hyperkeratotic *papules* over the palmar surface of the MCP and IP joints, as opposed to Gottron's papules. Oral lesions and/or *oral pain* is another uncommon feature that can present in these patients.

An *ovoid palatal patch* on the posterior hard palate has been recently observed to be highly associated with TIF1γ dermatomyositis and concurrent cancer diagnosis. The lesion is a symmetric arcuate erythematous patch across the midline that does not ulcerate. Pathological findings reveal interface dermatitis with increased dermal mucin.

Muscle Findings

Patients with IIM usually present with subacute to insidious onset of progressive symmetric proximal muscle weakness. Acute onset of weakness has been described in few cases, more commonly in IMNM, and can be misdiagnosed as rhabdomyolysis. However, the symptoms of weakness do not improve with hydration and persist with time. Patients complain of difficulty getting up from the chair, climbing up stairs, or raising their arms above their heads. Physical exam reveals weakness of arm and hip flexors (deltoids and iliopsoas muscles, respectively). Weakness of triceps, biceps, hamstrings, and quadriceps signifies extensive muscle disease.

Red Flags

Due to the wide range of causes for muscle weakness, specific red flags should alert you to other etiologies.

Distal muscle weakness is not common and should raise the possibility of an alternative diagnosis including IBM. Patients with IBM may have asymmetric weakness with distal muscle groups such as finger flexors, wrist flexors, ankle

dorsiflexors, and triceps targeted first. Because of distal muscle weakness, *falls* are a subsequent consequence.

As noted above, *asymmetric weakness* is uncommon and should prompt a secondary workup. Additional findings such as facial involvement and scapular winging should elicit a similar response. Facial weakness such as obicularis occuli weakness can be seen in IBM or genetic muscle diseases, like facioscapulohumeral muscular dystrophy (FSHD). Furthermore *oculobulbar symptoms* are commonly seen in neuromuscular disorders such as Myasthenia Gravis. *Scapular winging* can be seen in genetic muscular dystrophies such as limb-girdle muscular dystrophy (LGMD) and facioscapulohumeral dystrophy (FSHD), while *camptocormia*, i.e., paraspinous muscle weakness leading to a stooped position, may be seen in advanced cases of IIM and should also raise a red flag. But also alert for other possible conditions such as IBM, myasthenia gravis, and amyotrophic lateral sclerosis.

Lack of response to immunosuppression should also raise a red flag. IBM can commonly be mistaken for PM, so when muscle weakness progresses despite implementation of therapeutic interventions, diagnosis of IMM should be reconsidered.

A comparison between IBM and PM/IMNM is included in Table 13.1.

Table 13.1 Comparison of PM/IMNM to IBM

Characteristics	PM/IMNM	IBM
Age	Variable	>50
Sex	F ≥ M	M > F
Muscle weakness pattern	Symmetric Proximal	Asymmetric Predominantly distal
Muscle groups most commonly involved	Deltoids, hip flexors	Finger flexors, quadriceps
Other organ involvement	Lung, joints, skin/no	Neuropathy
Association with other diseases	Overlap	Sjögren's syndrome HIV
Autoantibodies	MSA	Anti-NT5c1A
EMG/NCS	Myopathic	Myopathic and neuropathic
Muscle biopsy	Primary inflammation (CD8+ T cells), MHC I upregulation/ necrosis, degeneration and regeneration, sparse inflammatory cells	Primary inflammation (CD8+ T cells), MHC-I upregulation, rimmed vacuoles, protein aggregates, cytochrome oxidase-deficient fibers
Response to immunosuppression	Yes	No

PM polymyositis, *IMNM* immune-mediated necrotizing myopathy, *M* male, *F* female, *MSA* myositis-specific antibody, *anti-NT5c1A* anti-cytosolic 5′-nucleotidase 1A antibody

Interstitial Lung Disease (ILD)

Interstitial lung disease is often associated with antisynthetase syndrome with a prevalence of 70% in that subgroup. CT radiographic imaging is useful in differentiating nonspecific interstitial pneumonia (NSIP), usual interstitial pneumonia (UIP), and cryptogenic organizing pneumonia (COP). With imaging some form of chronicity can be gleaned, as ground glass opacities are typically associated with acute inflammation and honey-combing is a sign of chronic fibrotic disease. Since radiographic findings are so characteristic for ILD a bronchoscopy and biopsy are typically not needed. The exception would be a bronchoscopy and BAL to rule out an indolent infection or malignancy.

Pulmonary function testing (PFT) can be helpful as ILD is a restrictive disorder (decreased vital capacity, decreased DLCO, but preserved FEV1/FVC ratio). PFTs reliability is highly dependent on patient participation and the facility performing the test. However, if used properly PFTs can be a great screening tool for diagnosis and progression. Notably, an isolated low DLCO can be a sign of ILD but other etiologies should be investigated such as anemia and PAH. PAH should be a concern especially with overlap patients with scleroderma.

Heart

Cardiac involvement in IIM is rare and typically limited to arrhythmias and myocarditis. To screen for myocardial involvement, a troponin test and/or BNP will be more helpful, since CK-MB is typically already elevated in IIM due to muscle injury.

Gastrointestinal Disease

Esophageal dysmotility is quite common with a prevalence of 10–30%. This is due to weakness of striated muscles located in the upper one-third of the esophagus and/or the oropharyngeal muscles. This results in symptoms of dysphagia, reflux, and aspiration. Diagnosis is based on barium swallow evaluation, and patients can benefit from speech therapy and/or esophageal dilatation in more advanced cases. Intestinal perforation can be a rare complication of DM and is usually associated with the presence of anti-NXP2 antibodies. Besides surgical intervention, immunosuppression is required in these cases.

Malignancy

The association of IIM with malignancy has been described since the beginning of the twentieth century. Cancer-associated myositis is defined as the development of

malignancy within 3 years of the diagnosis of IIM. The standardized incident ratio (SIR) varies from 2.17 to 6.5 in DM and 1.7 to 2.2 for PM. Risk factors include male sex, older age, disease resistant to treatment, or rapidly progressive disease and elevated inflammatory markers. The most significant prognostic factor though is the presence of the myositis-specific antibodies anti-Tif1γ, anti-NXP2, and anti-SAE. Newer studies indicate an increased risk for anti-HMGCR and anti-SRP, although the risk could vary depending on the geographical location. Nevertheless, all newly diagnosed patients should be screened for malignancy.

Overlap Myositis

Inflammatory Arthritis Inflammatory arthritis is common among IIM patients, and treatment should be organ specific (i.e., methotrexate, rituximab, tofacitinib, etc). Antisynthetase syndrome presenting with inflammatory arthritis and ILD can be mistaken initially for seronegative rheumatoid arthritis. Rarely patients with Rheumatoid Arthritis (RA) will develop a true myositis. Notably patients with RA have been found to have nodular myositis on autopsy with focal accumulations of necrosis and inflammation.

Scleroderma Patients with the autoantibodies anti-Ku and anti-PM/Scl often have associated scleroderma features.

Mixed connective tissue disease (MCTD) This diagnosis is defined by a positive anti-RNP autoantibody with overlapping features of myositis, lupus, and scleroderma. A common shared clinical feature is Raynaud's phenomenon.

Systemic Lupus Erythematosus (SLE) While musculoskeletal complaints are common in SLE, actual myositis is relatively uncommon. Medication side effects should be investigated as glucocorticoids and antimalarial drugs can cause a drug-induced myopathy.

Laboratory Findings

While no laboratory findings are specific for the wide range of myositis subtypes, elevated muscle enzymes are often the first indication for an IIM.

Elevated muscle enzymes include creatine phosphokinase (CK), aldolase, AST, ALT, and CPK MB in various combinations. Notably, amyopathic causes of myopathy are not accompanied by elevated muscle enzymes. Additionally patients may present with elevated aldolase but normal CK, as a sign of fasciitis. DM may occur with normal CK levels despite muscle weakness, whereas IMNM are associated with highly elevated CK serum levels, that commonly reflects disease activity.

Of note, while renal complications are common due to elevated CK levels in rhabdomyolysis, this is often not seen with elevated CK levels in IIM. We rarely see rhabdomyolysis in IIM due to the insidious onset of the autoimmune process, but patients should be closely monitored for myoglobinemia.

While elevated ESR is a common finding in other autoimmune conditions, IIM are not characterized by elevated inflammatory markers.

Due to the wide differential diagnosis for muscle weakness, additional laboratory test including thyroid axis evaluation, infectious agents such as HIV and hepatitis, and electrolytes (Magnesium, Calcium, Phosphorus, and Vitamin D) should be performed at diagnosis.

Autoantibodies

As we learn more about IIM and the various subtypes, there is a strong association between autoantibodies and distinct clinical phenotypes. Roughly 60–70% of patients with IIM have a known autoantibody. However, autoantibodies not only contribute to IIM diagnosis limiting the need of invasive diagnostic procedures but may also define patients' subgroups, indicate patients with increased risk of malignancy, support prediction of outcomes based on their clinical presentation, and guide treatment in specific cases. Notably, a negative ANA should not preclude further autoantibody evaluation, as many myositis-associated antibodies are cytoplasmic. A full summary of common myositis antibodies is presented in Table 13.2.

Due to the association of malignancy with certain antibody profile, including anti-NXP2, anti-TIF1γ, anti-SRP, and anti-HMGCR, a screening exam including chest/abdominal/pelvic CT or PET-CT is often recommended at diagnosis. Age-appropriate cancer screening recommendations should be also tightly enforced.

Imaging Studies

While certain cases of IIM can be diagnosed without imaging studies, the use of MRI can be helpful in determining the degree of inflammation, chronicity of disease, and guide direct biopsies if needed.

If available, non-contrast MRI with fat suppression or short tau inversion recovery (STIR) is the imaging of choice. With active inflammation, T2-weighted fat suppressed images will show enhancement of the musculature and occasionally fascia, which indicates edema. Conversely with chronic disease, T1-weighted images will demonstrate fatty replacement, which indicates irreversible damage. With imaging, biopsies can be directed to the muscle groups with the most inflammation increasing the yield of making an IIM diagnosis.

Imaging studies to evaluate soft tissue calcifications include X-rays and CT scans, which may be more readily available than MRI.

Table 13.2 Myositis antibodies

Autoantibody	Autoantigen	Clinical feature	Cancer associated
Antisynthetase antibodies			
Anti-Jo-1	Histidyl t-RNA synthetase	Mechanic hands, Raynaud's, arthritis, ILD	
Anti-EJ	Glycyl t-RNA synthetase	Mechanic hands, Raynaud's, arthritis, ILD	
Anti-OJ	Isoleucyl t-RNA synthetase	Mechanic hands, Raynaud's, arthritis, ILD	
Anti-Pl-7	Threonyl t-RNA synthetase	Mechanic hands, Raynaud's, arthritis, ILD	
Anti-Pl-12	Alanyl t-RNA synthetase	Predominant ILD	
Anti-KS	Asparaginyl t-RNA synthetase	Mechanic hands, Raynaud's, arthritis, ILD	
Anti-Ha	Tyrosyl t-RNA synthetase	Mechanic hands, Raynaud's, arthritis, ILD	
Anti-Zo	Phenylalanyl t-RNA synthetase	Mechanic hands, Raynaud's, arthritis, ILD	
Dermatomyositis specific antibodies			
Anti-Mi-2	DNA helicase	Rash and muscle symptoms, treatment responsive	
Anti-NXP2	Nuclear matrix protein	Calcinosis, dysphagia, intestinal perforation, common in juvenile population	Yes
Anti-TIF1γ	Transcriptional intermediary factor 1-gamma	Ovoid palatal patch	Yes
Anti-MDA5	Melanoma differentiation-associated gene 5	Amyopathic, dorsal punctate ulcers, palmar hyperkeratotic papules, pneumomediastinum, and rapidly progressive ILD	
Anti-SAE	Small ubiquitin like modifier activating enzyme	Amyopathic, can progress to myositis/dysphagia, and rare ILD	Yes
IMNM specific antibodies			
Anti-SRP	Signal recognition particle	Necrotizing myopathy, myocarditis, dysphagia, severe myopathy, with very high CK	Yes
Anti-HMGCR	HMG CoA reductase	Necrotizing myopathy, with and without statin exposure, with very high CK	Yes
IBM specific antibodies			
Anti-5-NT1A	Cytosolic 5′-nuclerotidase 1A	Distal weakness	
Overlap antibodies			
Anti-Pm/Scl	PM/Scl-75/100 protein	Scleroderma/myositis overlap	
Anti-RNP	Ribonucleoprotein complex	Mixed connective tissue disease	
Anti-Ro	Ro/SSA	Associated with antisynthetase syndromes	
Anti-La	La/SSB	Associated with antisynthetase syndrome	
Anti-Ku	Ku complex (DNA repair)	Scleroderma/myositis overlap	

EMG/NCS

During the initial evaluation of weakness, it is important to distinguish between a neuropathic or myopathic etiology. While physical exam findings can be helpful, EMG/NCS may play a critical role in this differentiation. Typically NCS should be normal in IIM, but neuropathic changes can be seen in IBM.

While not very specific (33%), EMG does have high sensitivity of 85% regarding IIM. Therefore, a normal EMG is unusual in IIM. IIM is characterized by irritable myopathy. In these cases we are looking for insertional and spontaneous fibrillations/sharp waves, low amplitude/short duration polyphasic motor unit action potentials (MUAP), and complex repetitive discharges. Due to low specificity, these findings typically suggest an autoimmune cause but may be found also in other myopathic conditions.

Muscle Biopsy

While muscle biopsies are not required for the diagnosis of IIM, especially when patients have stereotypical DM skin findings, they can be helpful in equivocal cases. Notably as we better understand the tight association between antibody and clinical phenotype/subtype, the utility of a biopsy is limited.

Until that time, muscle biopsies are still helpful. Choosing the correct muscle group for biopsy is crucial as many factors may affect the yields of the exam. We typically prefer biopsies of the deltoid or quadriceps avoiding the side that the EMG (if done) was performed, as needle insertion may cause local inflammation, artifacts, and muscle weakness due to high likelihood of extensive fatty replacement. MRI imaging may help to narrow down the muscle group that is most inflamed (increased T2 STIR enhancement) and to avoid muscle groups that have fatty infiltration. Of note, if fascial enhancement is noted on MRI, sampling of the overlaying fascia, in addition to the muscle, is recommended.

While the pathological feature of IIM is not often specific, the finding of perifasciular atrophy is pathognomonic for DM. This is caused by a complement-mediated process affecting the microvasculature of the perimysium and perifasicular endomysium, resulting in an inflammatory infiltrate and eventual atrophy. Conversely, PM avoids the vasculature and targets the myocytes resulting in focal endomysial infiltrates that surround the non-necrotic muscle fibers (primary inflammation). With DM/PM there is an upregulation of MHC Class I antigens on the muscle fibers. This is different from IMNM, which predominately has muscle necrosis and regeneration, myophagocytosis, and minimal lymphocytic infiltrates. Finally in IBM, biopsies may show primary inflammation, upregulation of MHC Class I antigens, amyloid deposits or tubulofilaments on electron microscopy, and red rimmed vacuoles on Gomori trichrome stain. While previously believed to be highly specific, red-rimmed vacuoles may be observed in other myopathic conditions other than IBM.

Skin Biopsy

The pathological findings of DM skin lesions are akin to SLE skin lesions, as both are characterized by interface dermatitis. Interface dermatitis under the microscope is described as a perivascular lymphocytic infiltrate of the dermis with mild atrophy of the epidermis and vacuolar changes in the basal keratinocyte layer. Immunofluorescence is also similar with both complement and immunoglobulin deposition along the dermal-epidermal junction.

As noted above the ovoid hard palate lesions also share the pathological findings seen in the skin with interface dermatitis.

Differential Diagnosis

Due to the wide breath of causes for myopathy, a detailed understanding of the differential is important to make the right diagnosis. A full list of etiologies of myopathy is outlined in Table 13.3.

Table 13.3 Differential diagnosis

Inflammatory/autoimmune	Idiopathic inflammatory myopathies Overlap syndromes (SLE, MCTD, scleroderma) Sarcoidosis Chronic Graft versus Host Disease (GVHD)
Drug and toxins	Statins Steroids Colchicine AZT Antimalarials (esp. Cholorquine) Alcohol Cocaine Amiodarone D-penicillamine
Metabolic/electrolyte disturbances	Glycogen storage disease Abnormal lipid metabolism Mitochondrial myopathies Nutritional deficiencies (Vitamin D) Electrolyte disorders Amyloidosis
Infectious	HIV Respiratory viral illness (adenovirus, influenza) Lyme disease Toxoplasmosis/Trichinella Staphylococcus/streptococcus (cause of pyomyositis)
Neuromuscular	Myasthenia gravis Lambert-Eaton Muscular dystrophies Amyotrophic lateral sclerosis (ALS)
Endocrine	Altered thyroid axis Hyperparathyroid Cushing's disease Diabetes (diabetic amyotrophy or diabetic muscle infarction)

Treatment

With the exception of IBM, IIM is typically responsive to immunosuppression. Measurements of treatment efficacy include increase of muscle strength, changes in extent of skin rash, and/or improvement of PFTs. While CK levels can be an indicator for muscle destruction, especially in IMNM, they do not always correlate significantly with disease activity in DM. Thus, isolated changes of CK are not adequate to guide treatment, but the overall clinical judgment.

Patients are often treated with a tiered approach initiating steroids 1 mg/kg/day, with IV pulse methylprednisolone 1000 mg/day for a total of 3 days reserved for life-threatening conditions (respiratory failure or dysphagia). Subsequently, steroids are tapered while a disease-modifying agent (DMARD) is concomitantly started, such as methotrexate, azathioprine, or mycophenolate mofetil. The choice of agent can be guided based on extramuscular manifestations. Methotrexate is commonly avoided in IIM complicated with lung disease, due to the potential side effect of pneumonitis. Mycophenolate mofetil is preferred in severe skin disease, although evidence is based mostly on case-series. While hydroxychloroquine is a mild agent and is used with success in SLE, it is generally avoided in DM given the reported risk of worsening of the skin rash.

Refractory disease (steroid dependent) or severe cases often require further addition of immunosuppressive agents, like combination of azathioprine and methotrexate, IVIG, or rituximab. Rarely, cyclophosphamide can be used in life-threatening cases. Clinical experience has noted that IMNM often requires IVIG when anti-HMGCR autoantibodies are present, and rituximab in anti-SRP positive IMNM. Case reports/series have noted benefit of tacrolimus and IVIG in MDA5-related DM, and tofacitinib in refractory DM.

Patients with a diagnosis of IBM, not only do they not respond to immunosuppression, but treatment could actually lead to faster progression of the disease. Therefore, there is no role for immunosuppressive agents, and the only helpful therapeutic intervention remains physical therapy, whose goal is to halt the disease progression.

Questions

1. A 30-year-old female with no past medical history or prior medications, presented with 3-month history of weakness. On presentation, she was noted to have a CK of 30,000 U/L. A subsequent MRI was notable for edema of proximal lower extremities on STIR imaging, while muscle biopsy showed necrosis, upregulation of MHC class I, and lack of predominant inflammatory cells. She was started on immunosuppression with steroids and mycophenolate with improvement of her muscle strength, but CK elevation persisted.

What is the next step?

A. Refer to neurology, as this is not an inflammatory myopathy.
B. Consider further serological testing.
C. Consider a metabolic myopathy.
D. Re-biopsy the patient.

Correct answer: B
The patient has evidence of immune-mediated necrotizing myopathy, as evident by muscle weakness, elevated CPK, and muscle biopsy. The patient has improved clinically, but her CPK remains elevated, which we commonly see in IMNM. Would consider checking anti-HMGCR antibody for statin-naive IMNM or anti-SRP antibodies, as antibody specificity could guide subsequent treatment plan. There is no need to refer to neurology for genetic or metabolic myopathy, as the patient has shown improvement with immunosuppression. Repeat muscle biopsy would not offer any additional information and would probably only show improvement of the pathology.

2. A 25-year-old female medical student is learning rheumatology in class. After her course she is worried about a photosensitive rash. She was seen by dermatology with a skin biopsy notable for interface dermatitis. At that time, she denied any focal weakness.

   What would be the next step?

   A. Treat for DM.
   B. Perform cancer screening due to the association of cancer and DM.
   C. Obtain serological testing for SLE.
   D. Defer management to dermatology, as this is the only manifestation of disease.

   Correct answer: C
   The skin pathology for SLE and DM are very similar. It is important to rule out systemic SLE before starting treatment. While hydroxychloroquine is first-line treatment for SLE, it might cause rash exacerbation in DM, so we initiate it with caution.

3. A 45-year-old SLE patient, who has been treated with hydroxychloroquine and mycophenolate, is found to have elevated CK and CK-MB. Her workup included an echocardiogram, which revealed ejection fraction of 30%, but a subsequent cardiac MRI did not show delayed enhancement. Due to her increased risk of accelerated cardiovascular disease, a heart catheterization was also performed which was negative.

   What is the next best step?

   A. Start goal-directed therapy for heart failure.
   B. Place on transplant list for a heart.
   C. Start steroids.
   D. Obtain heart biopsy.

   Correct answer: D

Hydroxychloroquine is a rare cause of myopathy and neuropathy. It can present at any time in therapy but most commonly after prolonged use, and it does not seem to be dose-dependent. Cardiomyopathy can be either due to muscle involvement or abnormalities of the conduction system. Biopsy to look for acid phosphatase-positive vacuoles and granules is imperative, as this could be a drug-induced phenomenon requiring the discontinuation of the offending agent. Improvement is not always guaranteed and symptomatic treatment is recommended.

4. A 45-year-old man with past medical history of gout and hyperlipidemia presents for evaluation of frequent falls in the last few months. He was very active until few years ago when he started having difficulty reaching objects above his head or lifting heavy objects. He later developed difficulty swallowing as well, although he denies any choking episodes so far, and noticed that he cannot whistle anymore. His current medications include colchicine and atorvastatin. The patient walks with a high stepping gait. He has some weakness of his orbicularis oris. He has muscle weakness of his thigh flexors. He cannot flex his shoulders above 120 degrees, but he is able to resist the examiner's strength at that position. He also has left greater than right ankle dorsiflexion weakness. He does not have any weakness of finger flexion. Reflexes are 1+ throughout. Babinski's reflex is negative. Laboratory studies show elevated creatine phosphokinase and aldolase levels.

   Muscle biopsy demonstrates small muscle fibers, occasional necrotic muscle fibers, endomysial CD8+ T cells, and MHC class I upregulation.

   What is the next best step?

   A. Start prednisone 60 mg daily.
   B. Stop the colchicine and atorvastatin and re-evaluate.
   C. Refer to neuromuscular specialist.
   D. Perform EMG/NCS.
   E. Perform brain MRI.

   Correct answer: C

   The patient most likely has FSHD and needs to be evaluated by a neuromuscular specialist. Immunosuppressive treatment is the appropriate next step if the patient had IIM. However, given the asymmetrical muscle weakness, and facial muscle involvement, the patient has an alternate diagnosis. Endomysial inflammation and upregulation of MHC class I, while common in IIM, can be present in other conditions as well, like IBM or genetic muscle disease.

   While both colchicine and statin are myotoxic medications, symmetric muscle weakness would be more common and would not expect MHC I upregulation on muscle biopsy.

   EMG/NCS is helpful in differentiating neurologic from muscular diseases, but the patient's physical exam and muscle biopsy findings are adequate to rule out nerve involvement. Similarly, no brain lesion could explain the patient's constellation of symptoms, so brain MRI would not be of priority.

The patient most likely has facioscapulohumeral dystrophy. Although the majority of patients present with symptoms within the first decades of their lives, FSH can also present later in life. Patients often have face and scapular involvement, as well as proximal upper and lower extremity weakness. Foot drop is common and can be unilateral. The fact that the patient can lift their arms up to 120 degrees and resist to examiner's strength implies that he has scapular weakness and cannot stabilize the shoulder to the torso, i.e., scapular winging. While most of his symptoms could also be seen in IBM, the young age of disease onset, the presence of scapular winging, and lack of finger flexor weakness (which is one of the major clinical findings for IBM) should alert us for an alternate diagnosis.

5. A 70-year-old female with history of COPD, hypertension, diabetes, and hyperlipidemia presents to the emergency room with complaints of diffuse muscle weakness and tea-colored urine. Her symptoms started a day ago with exertional fatigue, diffuse muscle aches, swelling, and weakness. She decided to call the ambulance when her urine changed color. She denies any difficulty breathing but just recovered from an upper respiratory infection, for which she was prescribed a Z-pack.

   The physical examination is remarkable for 3/5 muscle strength in proximal and distal upper and lower extremities. Rest of examination is unremarkable. Her laboratory studies revealed an elevated CPK 15,000 U/L, serum creatinine 2.0 mg/dL, positive urine myoglobin. She was treated for rhabdomyolysis with IV fluids. A week later, her CPK decreased to 3000 U/L and her creatinine to 0.9 mg/dL. The patient, although felt somewhat better, continued to have myalgias, and her muscle strength was 4/5.

   What is the next best step?

   A. EMG/NCS.
   B. Muscle biopsy.
   C. Check anti-HMGCR titers.
   D. Check a viral panel (HBV, HCV, HIV).
   E. Discharge the patient and follow up with her PCP.

   Correct answer: E

   The patient most likely had drug-induced rhabdomyolysis due to the combination of statins with macrolides that preceded this event. The fact that the CPK decreased and her muscle strength is improving without the use of immunosuppression points to the fact that this is most likely not an immune-mediated myopathy. An EMG/NCS at the acute phase of rhabdomyolysis and statin toxicity would also show irritable myopathy, and a muscle biopsy at this point would show necrosis (with a difference of lack of MHC class I upregulation). Therefore, any testing for IIM should be deferred for at least 1 month after an episode of rhabdomyolysis. Similarly, we would defer checking anti-HMGCR antibodies as an outpatient, if the patient does not improve or worsens. While viral infections can cause myopathy, it is uncommon to cause rhabdomyolysis,

and given the patient's demographics would not be on the top of our differential at this point.

6. A 42-year-old female with no significant past medical history has been complaining of a skin rash developing the last few weeks. She denies any changes in the detergents or the beauty products she has been using. She also has been complaining of increased sensitivity of her gums and some difficulty climbing up the stairs. On her physical exam, she has erythematous papules over her knuckles, elbows, and knees. She also has tender papules over the creases of her palms, diffuse palmar erythema, and periungual erythema. She has 4/5 muscle strength of her hip flexors, but rest of examination is 5/5. Labs revealed some mild increase in her CPK.

   What is the most likely complication of her disease?

   A. Dysphagia
   B. Pneumomediastinum
   C. Bowel perforation
   D. Rhabdomyolysis
   E. Camptocormia

   Correct answer: B
   The patient has dermatomyositis based on the elevated CPK, proximal muscle weakness, and typical skin rash (Gottron's papules). Additional details of oral sensitivity and papules at the palmar creases point toward a diagnosis of anti-MDA5 associated dermatomyositis. Anti-MDA5-positive DM patients have usually amyopathic or hypomyopathic DM, increased risk of oral pain or ulcers, arthritis, skin ulcerations, and tender palmar papules. These patients have high mortality due to increased risk of rapidly progressive ILD and pneumomediastinum. Therefore, these patients need to be recognized early and be initiated on aggressive immunosuppression. Dysphagia and bowel perforation are more commonly seen with anti-NXP2 DM.

7. A 35-year-old male with no significant past medical history presents for evaluation of subacute onset proximal muscle weakness and skin rash. He is complaining that he has difficulty getting up from a chair or reaching above his head. He feels that he has difficulty keeping his head high, and it gets worse the more he tries. He is also complaining of occasional double vision and dysphagia. His physical exam is consistent with 4/5 hip flexor and deltoid muscle weakness. His neck flexor is 3/5, but he does not have any facial weakness. His skin examination is significant for heliotrope rash and Gottron's sign. He is found to have elevated CPK, and his EMG is consistent with irritable myopathy. He is diagnosed with dermatomyositis, and he is started on prednisone 60 mg. One day later, he is calling complaining of worsening of his muscle weakness.

   What is the next best step?

   A. Start pulse steroids and cyclophosphamide.
   B. Perform a muscle biopsy.

C. Refer him to ophthalmology for evaluation of diplopia.
D. Perform a single fiber EMG.
E. Stop all treatment, as the patient most likely has IBM.

Correct answer: D
The patient most likely has a combination of dermatomyositis and myasthenia gravis. He is complaining of occasional double vision, which is a red flag indicative of an alternative diagnosis. Facial muscle involvement can be seen in genetic muscle disease, inclusion body myositis, myasthenia gravis, or other neuromuscular diseases. Given the fact that he does not have any facial muscle weakness on exam, the diagnoses of genetic muscle disease or IBM are less likely, as the weakness should be present at all times. Additionally, IBM is not commonly seen in this age group. Myasthenia gravis is an autoimmune disease secondary to antibodies against nicotinic acetylcholine receptors at the neuromuscular junction. Patients with myasthenia gravis have activity-induced weakness and are worse at the end of the day. They commonly have diplopia, ptosis, dysphagia, or dysarthria, before developing weakness of larger muscle groups. Treatment is immunosuppression, but high doses of steroids can paradoxically cause exacerbation of the symptoms, so most specialists start with low dose of prednisone. While serologic evaluation is usually the first step in evaluation, single fiber EMG is the most sensitive test, followed by repetitive nerve stimulation and anti-AChR antibodies.

8. A 45-year-old female is evaluated for progressive muscle weakness. The patient states that she has noticed that over the last year she has stopped many of her outdoor activities due to fatigue and weakness. She has been progressively getting weaker to the point that she cannot climb up stairs without holding on the rail. Her physical exam reveals proximal muscle weakness. Her EMG/NCS showed mild myopathic pattern, and her muscle biopsy revealed necrotizing myopathy without lymphocytic infiltrates. Her laboratory work is shown below.

Laboratory test	Result	Reference range
Aldolase, serum	10.5 IU/L	<8.2 IU/L
Antinuclear antibody	1:160	Greater than 1:40 is abnormal
Creatine kinase, serum	2583 IU/L	24–170 IU/L
Creatinine, serum	0.6 mg/dL	0.7–1.5 mg/dL
TSH	1.5 mIU/L	0.4–5.0 mIU/L
Free T4	0.2 ng/dL	0.7–1.9 ng/dL

What is the next best step?

A. Start prednisone 60 mg.
B. Send for anti-HMGCR and anti-SRP antibodies.
C. Perform muscle MRI.
D. Start levothyroxine.
E. Start hydroxychloroquine.

Correct answer: D

The patient has evidence of necrotizing myopathy with proximal muscle weakness, elevated CPK, myopathic EMG, and muscle biopsy. While IIM is possible, we need to rule out other etiologies. The patient has normal TSH but undetectable free T4, consistent with secondary hypothyroidism. The patient most likely has necrotizing myopathy secondary to hypothyroidism. If there is no improvement of her symptoms despite adequate thyroid replacement, then we need to further evaluate for IIM with anti-HMGCR and anti-SRP antibodies. There is no need to start immunosuppression at this point, before ruling out thyroid-associated myopathy. A muscle MRI would show muscle edema, as indicated by the physical exam, elevated CPK, positive EMG, and muscle biopsy. Therefore, muscle MRI would not give us any additional information. The patient does have positive ANA, but that is not adequate to start hydroxychloroquine treatment.

9. A 70-year-old female was diagnosed 2 months ago with dermatomyositis, based on proximal muscle weakness, elevated CPK, irritable myopathy on EMG, and characteristic skin rash (Gottron's sign, heliotrope sign). The diagnosis was supported by positive anti-TIF1g antibody. She was placed on tapering doses of steroids and mycophenolate with improvement of her disease. One year later, she presents with worsening of muscle weakness and her skin rash, associated with weight loss 20 pounds over the last 6 months and new onset nonproductive cough. She is started on prednisone again, but there is no response. Her labs are significant for elevated inflammatory markers and microcytic anemia.

   What is the most likely cause for this patient's presentation?

   A. Infection
   B. Flare of dermatomyositis
   C. New onset interstitial lung disease
   D. Malignancy
   E. Medication toxicity

   Correct answer: D

   Anti-TIF1g associated dermatomyositis is associated with an increased risk of cancer and has to be in the differential at all times. While all of the options above are possible, the slowly progressive weight loss, elevated inflammatory markers, and microcytic anemia should alert for the possibility of malignancy, and all newly diagnosed patients should be screened with chest/abdomen/pelvis CT, along with age-appropriate screening.

10. A 75-year-old male was diagnosed with polymyositis a year ago. His symptoms included progressive muscle weakness, elevated CPK, irritable myopathy on EMG, and evidence of primary inflammation on muscle biopsy of his quadriceps. He did not have any evidence of skin rash, arthritis, or interstitial lung disease. He was started on prednisone and azathioprine with improvement of his CPK. However, he has been unable to be tapered off prednisone due to slowly progressive muscle weakness. He is now admitted to the hospital after

an episode of fall, as his "left knee buckled." Inpatient team is asking the help of rheumatology consult for further management.

What is the most important step for this patient's management?

A. Chest/abdomen/pelvis CT to rule out malignancy
B. Methylprednisolone 1 gr daily for 3 days
C. Repeat muscle biopsy
D. Muscle MRI
E. Physical exam

Correct answer: E

The patient most likely has inclusion body myositis. Demographics (male sex, age), lack of extramuscular manifestations that would be associated with IIM, and lack of clinical improvement with immunosuppression are all red flags for an alternate diagnosis. Improvement of CPK with steroids is not indicative of disease response, as we can see that even with genetic muscle diseases. The patient most likely had a fall secondary to quadriceps weakness, leading to knee buckling, commonly seen in IBM. Physical exam is the most important diagnostic step for IBM, looking for asymmetric muscle weakness, finger flexor and quadriceps weakness, and facial involvement.

High Yield Facts

- IIM diagnosis is based on a combination of history, physical exam, muscle/skin biopsy, EMG, muscle MRI, and autoantibodies.
- There are four distinct types of myositis based on muscle biopsy findings: DM, PM, IMNM, and IBM.
- IBM is the most common myopathy over the age of 50 years old, is male predominant, and does not respond to immunosuppression.
- Amyopathic/hypomyopathic DM is characterized by the presence of DM pathognomonic rash without any evidence of muscle involvement.
- ~70% of patients with IIM have a myositis autoantibody.
- Myositis-specific autoantibodies can aid in IIM diagnosis, defining clinical presentations, indicate increased risk of malignancy, and potentially guide treatment.
- Distal or asymmetric muscle weakness, oculobulbar symptoms, scapular winging, and lack of response to immunosuppression should alert the physician for an alternate diagnosis.

Chapter 14
Osteoporosis

Aaroop Haridas and Seth Mark Berney

History

The term osteoporosis originated in France, in 1833, when Jean Martin Lobstein, a French pathologist, used the term to describe the histologic appearance of aged human bone.

In the 1960s, with the availability of bone densitometry, the association between osteoporosis and certain fractures was confirmed.

Definitions

Osteopenia refers to systemic low bone density or bone mass (matrix) with normal mineralization, resulting in increased bone fragility and risk of fracture.

Osteoporosis represents the extreme of osteopenia with very low bone density/bone mass (matrix) with normal mineralization, resulting in significantly increased bone fragility and risk of fracture. In 1994, an expert panel of the World Health Organization (WHO) established the most widely used definition of osteoporosis as "a state in which the bone mineral density (BMD) in women falls more than 2.5

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standard deviations below the young adult mean" [1]. However, as the data only included measurements of postmenopausal women and men older than 50 years, these definitions are only used for those populations. For premenopausal females and males less than 50 years of age, the Z score is used.

Osteomalacia is the progressive loss of calcium and phosphorus from bones with normal bone matrix resulting in increased bone fragility and risk of fracture.

Fragility Fractures are those that occur spontaneously or after minimal trauma, defined as falling from a standing height or less. Osteoporotic patients are prone to all fractures.

FRAX (Fracture Risk Assessment) tool—The FRAX tool is a computer algorithm to evaluate the 10-year probability of fracture, based on individual patient characteristics that integrate the patients clinical risk factors with bone mineral density (BMD) at the femoral neck [2].

Incidence and Prevalence

Osteoporosis is the most common metabolic bone disease and affects more than 200 million people worldwide. According to statistics from the International Osteoporosis Foundation, 1 in 3 women over the age of 50 years and 1 in 5 men will experience osteoporotic fractures worldwide [1]. Additionally, osteoporosis causes more than 8.9 million fractures annually, resulting in an osteoporotic fracture every 3 seconds. Every osteoporotic fracture predicts subsequent fractures.

Natural Course of Osteoporosis [3]

Postmenopausal women progressively lose bone which follows a linear pattern at the hip and a quadratic pattern at the spine, with loss rates decreasing in older age. The rate of bone loss increases for the first 3 years post-menopause and then slows down, but without treatment never stops. In contrast, premenopausal women also experience bone loss but at a much slower rate.

Morbidity and Mortality

In the United States alone, more than 1.5 million osteoporotic fractures occur annually, including 250,000 hip, 250,000 wrist, and 500,000 vertebral fractures. Twenty percent of those with a hip fracture die, 25% are confined to long-term facilities and

50% of patients are unable to ambulate independently and require long-term care. Osteoporotic fractures result in a decreased quality of life, increased disability-adjusted life span and big financial burden to health insurance systems.

Economic Burden

Osteoporosis-related fractures cost patients, their families and the healthcare system approximately $19 billion annually [4] with projected costs by 2040 of $50 billion annually in the United States.

Bone Physiology

Bone constantly undergoes remodeling, during which osteoclasts resorb bone and osteoblasts produce new bone. Numerous metabolic changes, systemic and local inflammatory diseases can modify osteoblast and osteoclast number and activity, changing bone turnover, and resulting in either a net increase or decrease in BMD.

RANKL/RANK/OPG Pathway

RANK Ligand (RANKL) (a protein produced by osteoblasts) binds to its receptor, RANK, on osteoclasts which stimulates osteoclast maturation, survival, and subsequent bone resorption.

Osteoprotegerin (OPG) (also a protein produced by osteoblasts) blocks the activity of RANKL. RANKL expression is increased by parathyroid hormone, cytokines (TNF-α, IL-1, IL-11) and glucocorticoids. RANKL expression is decreased by estrogen and cytokines (TGF-β, IL-4) [5].

Etiology of Osteoporosis

Osteoporosis results from lifestyle changes, medical conditions (including gonadal failure, i.e., menopause) or medications. Ninety-five percent of osteoporosis in women result from menopause complicated by other risk factors, listed below.

Endocrine abnormalities	Cushing's syndrome, hyperthyroidism, hypogonadism hyperparathyroidism, hypercalciuria, hyperprolactinemia, Panhypopituitarism, diabetes, androgen insensitivity
Hematological disorders	Multiple myeloma, leukemia, lymphoma, systemic mastocytosis, hemophilia, thalassemia, monoclonal gammopathies
Rheumatologic	Rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and other systemic inflammatory diseases
Gastrointestinal disorders	Gastric bypass, gastrectomy, IBD, primary biliary cirrhosis, celiac disease, pancreatitis
Renal	Renal failure, renal tubular acidosis
Pulmonary	Chronic respiratory diseases
Neurologic diseases	Epilepsy, multiple sclerosis, parkinsonism, muscular dystrophy, stroke, spinal cord injury
Genetic disease	Glycogen storage diseases, hemochromatosis homocystinuria, porphyria, Menke syndrome, Riley-Day syndrome, cystic fibrosis, homocystinuria, hypophosphatemia, Gaucher's disease Osteogenesis imperfecta, Ehlers-Danlos syndrome, Marfan syndrome
High-risk medications	Long-term steroids (≥5 mg/day prednisone or equivalent for ≥3 months), phenytoin and carbamazepine [6], heparin, gonadotropin-releasing hormone agonists, lithium, aromatase inhibitors, aluminum (in antacids), cancer chemotherapeutic drugs, depomedroxyprogesterone [7], proton pump inhibitors, tamoxifen (premenopausal use) [8], thiazolidinediones, thyroid hormones (in excess)

Risk Factors for Osteoporosis

Genetics and lifestyle risk factors contribute to the development of osteoporosis. A maternal history of hip fracture is associated with a twofold increased risk of a hip fracture in the patient. A prior fracture is associated with an 86% increased risk of any fracture. A long hip axis length may contribute to increased fracture risk; conversely, a short hip axis length may protect. Other protective factors include weight bearing exercise, African American ethnicity, a balanced diet with adequate amounts of calcium and vitamin D.

Non-modifiable risk factors of low bone mass	Modifiable risk factors of low bone mass
Advancing age	Low calcium or vitamin D intake
Race (white/Asian)	Sedentary lifestyle
Female gender	Cigarette smoking
Early menopause and late menarche	Lack of sunlight exposure
Slender build (<127 pounds)	Estrogen deficiency
Family history of hip fragility fracture	Alcohol excess or caffeine excess
Dementia	Glucocorticoid therapy
	Fracture after the age of 50 years
	Neurologic disorder
	Inability to stand from a chair without using arms
	Self-evaluation of health as fair to poor

Osteoporosis in Men [9]

This has become a significant health concern. Fractures in men increase dramatically after age 70, typically beginning 5–10 years later in life than women. The incidence of hip fracture is one-third to one-half of that in women. Hip and spine fractures are more prevalent in men older than 70 years. Men are less likely than women to be treated with antiresorptive therapy after a hip fracture. This is likely multifactorial in etiology, but provider ignorance and clinical inertia appears contributory. Severe hypogonadism from androgen deprivation therapy for prostate cancer is common in elderly men, as is hypogonadism, alcohol abuse, smoking, gastrointestinal and hepatic disorders and malabsorption.

Clinical Features of Osteoporosis

Osteoporosis has no clinical manifestations until a patient experiences a fracture.

Loss of height (>1.5 inch), localized spinal pain (indicative of fracture), accentuated kyphosis (Dowager's hump), or vertebral compression fracture on a chest radiograph may be seen. Almost all non–spine-related fractures occur as a result of trauma and have the acute signs and symptoms of a fracture. However osteoporotic vertebral fractures frequently do not result from overt trauma, leading to a delayed diagnosis.

Evaluation of Osteopenia/Osteoporosis

A clinical evaluation for osteoporosis consists of a careful history and physical examination to identify features of osteoporosis, as well as conditions that contribute to its development, including a height assessment, followed by the measurement of the patient's bone mineral density and a lab evaluation for the contributory conditions.

Basic lab evaluation
Serum creatinine, albumin, calcium, phosphorous, alkaline phosphatase levels
Serum 25-hydroxy vitamin D level
Serum thyroid stimulating hormone
Serum testosterone levels in men
Celiac disease antibody testing (if white with symptoms or low 25-OH vitamin D level)
24-hour urinary calcium level
Additional testing if the basic evaluation does not elucidate the cause
Serum protein electrophoresis if over the age of 50 years with undiagnosed anemia
Serum parathyroid hormone level
Bone biopsy under calcified sections with double tetracycline label
Serum biochemical markers of bone turnover
Urinary free cortisol

Methods of Evaluating Bone Mineral Density

Radiographs

Osteopenia/Osteoporosis on radiographs in the absence of fracture is a very subjective observation, and this terminology is frequently misused. Conventional X-ray techniques are insensitive in the evaluation of bone density at any skeletal site because 30–40% bone must be lost before it is radiologically evident.

Single Photon Absorptiometry of the Radius or Heel

This involves determining the mineral content of bone by measuring the absorption of a monochromatic, low energy photon beam, produced by a radioactive source (iodine-125 or americium-241). However, disadvantages include the fact that the object of study might consist of only two materials with different absorption coefficients. Also, the radioactive source needs to be replaced after a certain period.

Quantitative CT Scan (QCT) of the Lumbar Spine

QCT is a true bone density measured in g/cm^3, and it can analyze the trabecular and cortical compartments of bone unlike DEXA. Unfortunately, the disadvantages include lower precision, a higher dose of ionizing radiation, lesser availability and complex scanner operation when compared to DEXA. Additionally, most large epidemiological osteoporosis studies with fracture endpoints have not used QCT measurements.

Calcaneal Ultrasound (Quantitative Ultrasound/QUS)

QUS employs high-frequency sound waves to determine bone density, and QUS correlates with the BMD measured by DEXA. QUS could discriminate subjects with and without a fracture history and predict risk for future fracture. Therefore, QUS is convenient and provides information on bone microarchitecture as well as BMD. However as numerous QUS devices have been developed by many manufactures, each with its own designed logarithm for the calculation and interpretation of QUS indices, inter-device comparison of the results of bone health assessment is not possible. Furthermore, the precision of QUS is reported to be poorer compared to DEXA.

Dual Energy X-Ray Absorptiometry (DEXA)

This is currently the gold standard for measuring bone mineral density and determining whether someone has normal/osteopenic or osteoporotic bone. Its advantages include a low radiation exposure of 1–5 micro Sieverts and short procedure time of less than 20 minutes. Also, it does not require a complex scanner operation and has lower cost compared with QCT.

The disadvantages of DEXA include its inability to capture three-dimensional bone microarchitecture; the bone mineral density values obtained with dual X-ray absorptiometry do not represent true volumetric bone mineral density, but a projected areal bone mineral density and DEXA cannot distinguish between increased bone mineral density values arising from thicker bones and those arising from increased tissue mineral density (such as from osteophytes). Hence DEXA may give falsely high BMD values in those with bone-forming pathologies such as osteoarthritis and spondyloarthropathies and in patients who have had orthopedic or neurologic surgery. DEXA scans can be distorted by aortic calcification, soft-tissue calcification and other artifacts in older individuals.

According to the guidelines of the Scientific Advisory Board of the National Osteoporosis Foundation, bone densitometry using DEXA is useful in determining which patients might benefit from bone protective therapy [10].

- T-score: the number of SD (standard deviations) the patient is below or above the mean value for young (30 years old) normal subjects (peak bone mass) but is used only for postmenopausal women and men >50 years of age. This is a good predictor of the fracture risk.
- Z-score: defines how the bone mineral density (BMD) compares to age matched controls and is used for premenopausal women and men <50 years old.
- Absolute BMD: This is expressed in g/cm^2. This is the value needed to calculate changes in BMD, and whether those changes are significant.

The World Health Organization Criteria for Osteoporosis [11]

For postmenopausal women and men >50 years of age

Diagnostic criteria	Classification
$T \geq -1$	Normal
$T = -1$ to -2.5	Osteopenia(low bone mass)
$T \geq -2.5$	Osteoporosis
Osteoporosis + fracture	Severe or established osteoporosis

For premenopausal women and men <50 years of age

A Z-score of < -2.0 is interpreted as “bone density which is below the expected range for age.”

A Z-score of > −2.0 is interpreted as "bone density which is within the expected range for age."

Because very small changes in a patient's bone mass may be significant, and the BMD is reported to the thousandth decimal place, the BMD is used to determine whether a patient's bone density has significantly changed when compared with a prior DEXA.

To assess response to therapy, the follow-up DXAs must be performed on the same machine as the prior scan or on a machine with which it was cross calibrated, to avoid or minimize intermachine variability. The Least Significant Change (standard error) is the amount that is considered a statistically significant difference, when compared with a prior timepoint. The National Osteoporosis Foundation recommends treatment for all people who have a lumbar spine, hip or femoral neck T-score of −2.5 or lower. For people who have a bone density between −1 and −2.5, the National Osteoporosis Foundation recommends performing a Fracture Risk Assessment (FRAX), which provides a 10-year risk of a hip fracture or a major osteoporotic fracture. At least two different locations must be tested: spine, right hip, left hip or nondominant mid shaft radius (especially if the patient has a cortical bone disorder such as hyperparathyroidism). Additionally, the spine measurement must contain at least two contiguous vertebrae. Because osteoporosis is a systemic disease, the lowest T score found determines the patient's single diagnosis.

Clinical Indications for Measuring a Patient's Bone Mineral Density

According to the International Society of Clinical Densitometry in 2004:

1. All postmenopausal women <65 years who have one or more additional risk factors for osteoporosis (besides menopause)
2. All women >65 years and men >70 years regardless of additional risk factors
3. Adults with bone fragility fractures
4. Adults with a condition associated with low bone mass or bone los
5. Anyone being considered for therapy for osteoporosis
6. Anyone being treated with bone anti-osteoporotic therapy to monitor treatment effect
7. Anyone not receiving therapy in whom evidence of bone loss would lead to treatment

Fracture Risk Assessment (FRAX) https://www.shef.ac.uk/FRAX/tool [2]

The clinical risk factors included in the FRAX program include:

1. Age
2. Sex
3. Weight
4. Height
5. Previous fragility fracture
6. Parental hip fracture
7. Current smoking
8. Current glucocorticoid use (≥5 mg prednisone for 3 months or more)
9. Rheumatoid arthritis
10. Secondary causes of osteoporosis, i.e., myeloproliferative disorders, chronic kidney disease, chronic liver disease, etc.
11. Alcohol intake of 3 or more units/day (a unit of alcohol is equivalent to a glass of beer [285 mL], an ounce [30 mL] of spirits, or a medium-sized glass of wine [120 mL])

These risk factors are added to the femoral neck BMD in the FRAX equation to calculate the 10-year fracture risk. *In the United States, either a 10-year risk of hip fracture of 3% or more or a major osteoporotic fracture of 20% or more is the threshold to recommend treatment.* The fracture risk threshold for treatment is individualized by country, so it is important to enter the country in which the patient resides into the formula.

Treatment of Low Bone Mineral Density, Osteopenia, and Osteoporosis

The decision to initiate a bone-active agent for those with low bone mass is based on the patient's risk stratification using the WHO FRAX tool, the lowest T-score value, and history of a fragility fracture.

The patients risk may be stratified as either:

- Low risk: FRAX 10-year risk for a major osteoporotic fracture of <10%
- Medium risk: FRAX 10-year risk of 10–20%
- High risk: FRAX 10-year risk >20%, or a T-score below −2.5 at any site, independently or along with a history of a previous fragility fracture

Non-pharmacologic Interventions to Prevent Low Bone Mass or Fractures

- Physical therapy—structured weight bearing exercise programs and gait training to improve coordination.
- Interventions to prevent falls and resulting fractures.

- Maintaining ideal body weight (there is no evidence that interventions aimed at gaining or losing weight in thin and obese persons, respectively, can reduce fracture risk).
- Discontinue tobacco and excessive alcohol use.
- Address modifiable risk factors including polypharmacy and environmental hazards.
- Hip protectors, walking aids, safety aids at home (home safety check).

Pharmacologic Interventions

Vitamin D and calcium supplementation guidelines according to the National Osteoporosis Foundation (NOF) [12]

	Daily calcium intake	Daily vitamin D intake
Women <50 years	1000 mg	400–800 IU
Women >50 years	1200 mg	800–1000 IU
Men 51–70 years	1000 mg	800–1000 IU
Men >71 years	1200 mg	800–1000 IU

In addition to calcium and vitamin D, pharmacological interventions are broadly divided into two categories, based on their net result as anti-resorptive and anabolic agents. Anabolic agents stimulate bone formation thereby increasing BMD-Teriparatide (Forteo). Strontium ranelate is not approved by the FDA. Anti-resorptive therapies (bisphosphonates, estrogen and selective estrogen receptor modulators, denosumab) reduce bone resorption thereby preserving bone mineral density (BMD).

Bisphosphonates

Alendronate, risedronate and ibandronate are oral formulations. Zoledronic acid, ibandronate and pamidronate are intravenous formulations. Although it was the first bisphosphonate used for osteoporosis, etidronate is not FDA approved for osteoporosis in the United States. Pamidronate is also not specifically approved for osteoporosis by the FDA. Oral bisphosphonates are poorly absorbed from GI tract and carry a risk of esophagitis. Weekly, monthly and yearly dosing improve patient compliance. Rare risks include atypical femur fractures and osteonecrosis of the jaw. Due to the potential of atypical femur fractures, many authorities recommend a two-year drug holiday after 5 years for oral bisphosphonates and after 3–5 years for zoledronic acid.

Contraindications to bisphosphonates include pregnancy, chronic kidney disease stage 4 or 5, low serum calcium (<8.5 mg/dl in the presence of a normal albumin), osteomalacia, vitamin D deficiency (until it is corrected), pre-existing esophageal conditions such as Barret's esophagus, and patients who cannot stay upright for an hour, after taking the oral medication. A 25(OH) vitamin D level > 40 ng/ml has been associated with a more favorable response to bisphosphonate therapy [13].

After ingesting an oral bisphosphonate, the patient should be instructed to consume a tall glass of plain water and maintain an upright posture for 30 minutes. The side effects of nausea, dyspepsia, abdominal pain and gastritis are not significantly different between alendronate, risedronate or ibandronate and placebo.

Side effects of bisphosphonates include esophagitis (oral bisphosphonates), musculoskeletal pain (both oral and IV forms), an acute phase reaction consisting of fever, myalgia, and arthralgia for IV bisphosphonates, hypocalcemia for IV bisphosphonates, esophageal cancer which could be secondary to nonadherence to prescribing directions and resulting esophagitis, rare osteonecrosis of the jaw, and sub trochanteric fractures (the association of which have been questioned).

Denosumab

A monoclonal antibody which binds to and prevents RANKL from binding to RANK. It inhibits osteoclast formation, function and survival. Can be used in patients with renal dysfunction but not in hypocalcemia. The dosage is 60 mg subcutaneous every 6 months. Side effects reported in clinical trials include infections of the skin, GI tract, urinary system, ear, endocarditis [14] musculoskeletal pain and rash.

Teriparatide

Stimulates net bone formation when given subcutaneous. Its side effects include nausea, dizziness, headaches, muscle cramps, and hypercalcemia. Teriparatide is approved by the US Food and Drug Administration (FDA) to treat men and women with osteoporosis for up to 2 years. It is administered 20 mcg subcutaneous daily. Based on the first 7 years of the Osteosarcoma Surveillance Study (a 15-year study), there does not appear to be a causal association between teriparatide treatment and osteosarcoma in humans [15].

Calcitonin

Calcitonin prevents bone resorption and is administered intranasally or subcutaneous. Calcitonin at doses of 200 IU/ day stabilizes and may produce a short-term increase in bone density at the lumbar spine. However, the effect on nonvertebral fractures was not significant. But calcitonin diminishes bone pain in osteoporotic vertebral fractures; thus, its niche appears to be decrease pain in acute osteoporotic fractures.

FDA-Approved Agents for Osteoporosis

A. *Anti-resorptive agents that lower the risk of spine, hip and non-vertebral fractures (first line agents)*

   1. Alendronate (Fosamax)
   2. Risedronate (Actonel)
   3. Zoledronic acid (one infusion may last for more than 6 years) (Reclast)
   4. Denosumab (Anti–RANKL antibody) (Prolia) no drug holiday

B. *Anti-resorptive agents that lower the risk of spine fractures but now show evidence effects on the risk for hip or non-vertebral fractures (second line agents)*

   1. Calcitonin (Miacalcin, Fortical)
   2. Ibandronate (Boniva)
   3. Raloxifene (Evista)

C. *Anabolic agents that lower the risk of spine and non-vertebral fractures*

   1. Teriparatide (PTH, Forteo)
   2. Abaloparatide (PTHrP, Tymlos)

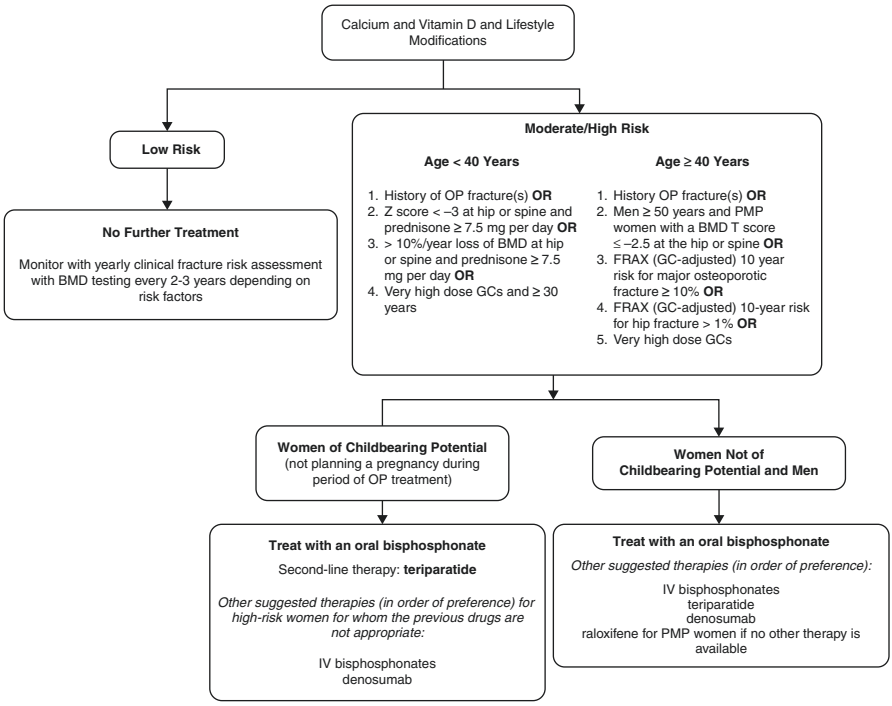
Guidelines for Glucocorticoid-Induced Osteoporosis (GIOP)

Etiology

Bone loss occurs within 6–12 months of the start of steroids, due to glucocorticoid-induced increased osteoclast activity, urinary Ca excretion and decreased osteoblast activity, GI calcium absorption, and estrogen and testosterone levels.

No dose of prednisone is safe for bone mineral density. In fact, prednisone doses as low as 2.5 mg/day orally or even intraarticular triamcinolone suppresses osteocalcin, a serum marker of bone formation, and increases the risk of fracture. The increased risk for fractures during GC treatment appears to be dose-dependent. If glucocorticoid (GC) treatment is >7.5 mg/day, the FRAX risk increases by 1.15 for major osteoporotic fracture and 1.2 for hip fracture.

American College of Rheumatology Guidelines for Glucocorticoid-Induced Osteoporosis Prevention and Treatment [16]



(Very high-dose glucocorticoid (GC) treatment was defined as treatment with prednisone >30 mg/day and a cumulative dose of 5 gm in the past year)

Guidelines for Premenopausal Women with Childbearing Potential Who Have Had a Previous Fragility Fracture

There are no tools to estimate the absolute fracture risk in children or adults <40 years of age.

The ACR Voting Panel designated men and women <40 years of age to be at moderate risk if they were expected to continue prednisone treatment at >7.5 mg/day for 6 months and had either 1) a hip or spine BMD Z score of < −3 or 2) a rapid decline in hip or spine BMD (equivalent to >10% in 1 year) during GC treatment [16].

Guidelines for Patients on Intermittent Pulses of Intravenous Glucocorticoids and Inhaled Steroids

Specific guidelines for prevention and treatment of GIOP in patients receiving intermittent pulse glucocorticoids (>1 gm) without daily therapy are lacking, though the

American College of Rheumatology recommendations include treatment with an oral or IV bisphosphonate or teriparatide or denosumab, in those who have received >5 gm of prednisone equivalent in the last 1 year [16].

Effectiveness of Pharmacological Therapy

Risk reductions of between 30% and 70% have been demonstrated for vertebral fractures, 15–20% for non-vertebral fractures and up to 40% for hip fracture [17].

Reassessment of Risk [18]

The optimal interval for repeating Dual-energy X-ray Absorptiometry (DXA) scans is unknown.

Because the changes in bone density over short intervals are often small, frequent testing (e.g. <2 years) is unnecessary in most patients. Recent evidence suggests that healthy women age 67 and older with normal bone mass may not need additional DXA testing for up to 10 years if their osteoporosis risk factors do not significantly change. In all adults and children who continue GC treatment, a risk reassessment should be performed every 12 months [16].

In clinical practice, any patient with a T-score below −1.5 and a loss of 4% or more of their BMD after 1 year on glucocorticoids should be treated with a bone preserving agent.

Patient Education

Education of patients to obtain resources to prevent falls and fractures is available at the National Osteoporosis Foundation website. https://www.nof.org/patients/

High-Yield Review Points

1. Osteopenia refers to systemic low bone mass with normal mineralization, resulting in increased bone fragility and risk of fracture.
2. The WHO defines osteoporosis as a state in which the bone mineral density in women that falls more than 2.5 standard deviations below the young adult mean.
3. Osteomalacia is the progressive loss of calcium and phosphorus from bones with normal bone matrix resulting in increased bone fragility and risk of fracture.
4. Fragility Fractures are those that occur spontaneously or after minimal trauma.

5. FRAX (Fracture Risk Assessment) tool is a computer algorithm to evaluate the 10-year probability of fracture, based on individual patient characteristics that integrate the patients clinical risk factors with bone mineral density at the femoral neck.
6. Bone constantly undergoes remodeling in a person's lifetime, during which osteoclasts resorb bone and osteoblasts produce new bone.
7. RANK Ligand, produced by osteoblasts, binds to RANK on osteoclasts which stimulates bone resorption. Osteoprotegerin produced by osteoblasts blocks the activity of RANKL.
8. A maternal history of hip fracture is associated with a two-fold increased risk of a hip fracture. A prior fracture is associated with an 86% increased risk of any fracture.
9. Dual Energy X-ray Absorptiometry (DEXA) is the gold standard for measuring bone mineral density.
10. According to the WHO, for postmenopausal women and men >50 years of age, a T score more than −1 is considered normal bone density, T score of −1 to −2 is considered osteopenia, and a T score less than −2.5 is osteoporosis.
11. For premenopausal women and men <50 years of age, the Z score is used. A Z-score of < −2.0 is interpreted as "bone density below the expected range for age," and a Z-score of > −2.0 is interpreted as "bone density within the expected range for age."
12. In the United States, either a 10-year risk of hip fracture of 3% or more or a major osteoporotic fracture of 20% or more is the threshold to recommend treatment.
13. Alendronate, risedronate, and ibandronate are oral bisphosphonates, and zoledronic acid, ibandronate, and pamidronate are intravenous formulations.
14. Denosumab is monoclonal antibody which binds to RANKL and prevents it from binding to RANK. It inhibits osteoclast formation and can be used in those with renal dysfunction.
15. Teriparatide given subcutaneous is anabolic and stimulates bone formation.
16. Calcitonin decreases pain in acute vertebral osteoporotic fractures.
17. Contraindications to bisphosphonates are pregnancy, chronic kidney disease stage 4 or 5, low serum calcium, osteomalacia, uncorrected vitamin D deficiency, Barrett's esophagus and patients who cannot stay upright for an hour, after taking the oral medication.
18. Bone loss occurs within 6 months of the start of steroids. There is no bone safe dose of prednisone.

Questions

1. A 68-year-old woman who takes alendronate 70 mg weekly for 2 years and calcium and vitamin D returns for a routine clinic appointment. In the past year, she experienced one vertebral compression fracture. DEXA reveals a T score of −3.0 in the hip and −3.2 in the spine, and a significant decrease in the BMD compared with the DEXA from 2 years ago. What is the next step in management?

   A. Add teriparatide
   B. Wear a hip protector
   C. Replace alendronate with risedronate
   D. Stop alendronate and start teriparatide
   E. Add Raloxifene to alendronate

   The correct answer is D.
   Teaching point—choice of osteoporotic therapy.
   Discussion
   This patient has osteoporosis and has received appropriate first line management with a bisphosphonate. However, she has experienced progressive bone loss and a fracture. As the bone loss is significant and progressive, this warrants treatment with a therapy with a different mechanism of action. Teriparatide is useful in those with severe osteoporosis who fail a bisphosphonate. There is no evidence that the addition of an anabolic agent to a bisphosphonate will decrease fracture risk.
   In randomized control trials, hip protectors have not been shown to reduce hip fractures.
   Raloxifene is a selective estrogen receptor modulator (SERM) that suppresses bone resorption and improves bone density. However, it is has not been shown to reduce fractures in combination with a bisphosphonate. Additional correct answers could have been to replace alendronate with IV ibandronate or zoledronic acid or subcutaneous denosumab. However, these options were not offered.
2. A 75-year-old woman developed back pain 4 weeks ago, which has progressively worsened and unresponsive to acetaminophen and ibuprofen. Her physical examination is unremarkable except for mid back midline vertebral tenderness on palpation with muscle spasm. A lateral spine radiograph reveals a non-displaced T 10 compression fracture.
   Which of the following may provide early relief of her bone pain?

   A. Cyclobenzaprine
   B. Alendronate
   C. Thoracolumbar orthoses (TLO) brace
   D. Calcitonin
   E. Vertebroplasty

   The correct answer is D.

Teaching point—management of acute compression fracture.
Discussion
This patient presents with an acute vertebral compression fracture. While many patients experience relief with acetaminophen or an NSAID, when pain persists, intranasal calcitonin could significantly reduce pain from vertebral compression fractures.
Muscle relaxants do not help pain from vertebral fractures, without an accompanying component of muscle spasm.
Additionally, while popular, no evidence exists supporting the use of back braces for acute pain relief. A bisphosphonate is useful for long-term treatment of osteoporosis but would not help for acute pain relief. Prospective trials have demonstrated no efficacy for vertebroplasty in acute pain relief.

3. A 65-year-old woman underwent a DEXA scan. Her lab testing including renal function, electrolytes, TSH, and vitamin D levels are normal. Results of the DEXA scan are:

	Bone density (g/cm^2)	Young adult (T score)	Age matched (Z score)
Lumbar spine L1-L4 (average)	0.924	−2.4	−0.7
Total proximal femur			
Left	0.638	−2.8	−1.8
Right	0.740	−2.1	−1.2
Mean	0.690	−2.7	−1.4

What is the next step in management?

A. Diagnose osteoporosis and discuss treatment
B. Diagnose osteopenia and discuss management
C. Calculate the FRAX score and decide whether to treat
D. Reassure the patient, that she has a normal bone density, because her Z scores are normal
E. Recommend OTC calcium and vitamin D, and advice follow up in 6 months.

The correct answer is A.
Teaching point—diagnosis of osteoporosis.
Discussion
The World Health Organization and the International Society for Clinical Densitometry define osteopenia as a T score −1.1 to −2.4 and osteoporosis as a T score less than −2.5.
Because she meets criteria for osteoporosis, she deserves treatment.
FRAX tool is only to guide management in patients with osteopenia and not been on any osteoporosis therapy. Z scores are useful for fracture risk estimation in premenopausal women, men younger than 50 years or in children.

4. A 75-year-old man with a history of fracture after falling from a standing position, diabetes, atrial fibrillation, GERD, and hypothyroidism presents for a follow-up visit. His medications include metformin, Xarelto, omeprazole and levothyroxine. What is the strongest risk factor for osteoporosis in this patient?

   A. Anticoagulation
   B. Omeprazole use
   C. Diabetes
   D. Prior fracture
   E. Hypothyroidism

   The correct answer is D.
   Teaching point—risk factor for fracture.
   Discussion
   History of a prior fragility fracture is the strongest risk factor and is predictive of a future osteoporotic fracture.
   While the use of a proton pump inhibitor, diabetes, hypothyroidism, anticoagulation and elderly age are all risk factors that predispose to osteoporosis, they do not predict subsequent fractures as strongly as a prior fracture.
5. A 60-year-old woman with current alcohol and tobacco abuse and a T4 compression fracture is evaluated in her primary care provider's office. A dual-energy X-ray absorptiometry (DEXA) scan showed a right hip T-score of −2.4 and vertebral T-score of −3.0. She has taken alendronate, calcium and vitamin D since then. On physical examination, she has thoracic kyphosis. Laboratory studies show normal calcium level and 25-hydroxy-vitamin D levels. A basic metabolic panel is normal. Repeat DEXA shows a stable bone mineral density. In addition to recommending alcohol cessation, what medication change would you make at this time?

   A. Add denosumab
   B. Stop alendronate
   C. Replace alendronate with teriparatide
   D. No change in current treatment.

   The correct answer is D.
   Teaching point—management of follow-up osteoporosis.
   Discussion
   After recommending complete tobacco and alcohol cessation, this patient should continue alendronate. She has documented osteoporosis and is at high risk for subsequent fractures due to multiple risk factors, including a prior fracture. Her bone mineral density (BMD) has stabilized on an oral bisphosphonate, which is the goal.
   A drug holiday is indicated for patients who have been on bisphosphonates for 3 to 5 years, have had no progression of the disease, and have minimal risk factors for additional fractures. This patient has multiple risk factors for fractures; hence, a drug holiday is not appropriate.

6. A 44-year-old woman with a history of Adult Onset Stills disease, tobacco abuse and status post total hysterectomy with bilateral salpingo-oopherectomy presents for follow-up evaluation. She has required prednisone 7.5 mg/day for the last 7 months to control worsening joint swelling in the hands and wrists. In addition to prednisone, she takes methotrexate 20 mg orally weekly, leflunomide 20 mg orally daily and sulfasalazine 1000 mg oral twice a day.

   On physical examination, she has active synovitis of multiple pips and mcp joints bilaterally. Her dual X-ray absorptiometry (DEXA) scan shows a T-score of −1.6. Her Fracture Risk Assessment Tool (FRAX) score shows a 10-year glucocorticoid-adjusted risk of hip fracture of 2%. In addition to smoking cessation and initiation of calcium and vitamin D, according to the 2017 guideline of the American College of Rheumatology, which of the following is the most appropriate action to prevent osteoporosis in this patient?

   A. Denosumab
   B. Teriparatide
   C. Alendronate
   D. Intravenous bisphosphonate therapy

   The correct answer is C.
   Teaching point—management of glucocorticoid-induced osteoporosis.
   Discussion
   The most appropriate treatment for this woman is initiation of an oral bisphosphonate.
   The American College of Rheumatology guidelines in 2017 are a helpful tool, to guide the prevention of glucocorticoid-induced osteopenia and osteoporosis.
   Initial GC-induced osteoporosis prevention involves lifestyle modifications, weight-bearing exercise, smoking cessation, and treatment with calcium (800–1000 mg/day) and vitamin D (600–800 IU/day). These preventive strategies should be used in patients who are under the age of 40 or have a low risk of fracture.
   In adults who are 40 years or older with a moderate or high risk of fracture, oral bisphosphonate therapy is recommended in addition to calcium and vitamin D and lifestyle modifications. According to the guidelines, this patient, who has a glucocorticoid adjusted Fracture Risk Assessment Tool (FRAX) score of 2% and has a moderate (>1% and < 3%) 10-year risk of hip fracture, should be treated with an oral bisphosphonate.
   The current guidelines place any patient taking prednisone ≥2.5 mg for ≥3 months at risk for osteoporosis. A clinical fracture risk assessment should be performed within 6 months of the initiation of long-term glucocorticoids. For adults aged more than 40 years, an initial assessment should include FRAX scoring for risk assessment. Bone mineral density screening should be obtained for adults younger than 40 years of age who have additional risk factors within 6 months of therapy initiation. Clinical risk fracture reassessment should then be performed annually in patients continuing steroid therapy. Intravenous

bisphosphonates are not indicated unless patients cannot tolerate oral bisphosphonates or are non-compliant.

7. A 50-year-old postmenopausal woman with a history of anorexia nervosa is evaluated for a new-patient visit. Her current BMI is 16. She has otherwise been healthy and currently feels well. She never smoked. Her family history is significant for a fragility fracture in her father. Her medications are over-the-counter calcium and vitamin D supplements.

   Her physical examination is normal. Results of laboratory studies reveal a serum calcium level of 9.0 mg/dL and 25-hydroxyvitamin D level of 50 ng/mL; TSH is 2.0. A dual-energy X-ray absorptiometry (DEXA) scan shows T-scores of −1.6 in the femoral neck and −1.6 in the lumbar spine. Her 10-year fracture risk using the Fracture Risk Assessment Tool (FRAX) is 5% for major osteoporotic fracture and 0.9% for hip fracture.

   Which of the following is the most appropriate management of this patient?

   A. Begin a SERM.
   B. Repeat DEXA scan in 2 years
   C. Replace calcium with cholecalciferol
   D. Start bisphosphonate therapy

   The correct answer is B.

   Teaching point—management of low bone mass in postmenopausal woman.

   Discussion

   Treatment for low bone mass in postmenopausal women involves lifestyle modification (weight-bearing exercises and avoidance of tobacco or excessive alcohol), vitamin D and calcium supplementation.

   As her bone density by DEXA is between −1 and −2.5, the need for pharmacologic therapy is based on the FRAX score—a 10-year estimated fracture risk (≥20% for a major osteoporotic fracture or ≥ 3% for hip fracture).

   A repeat dual-energy X-ray absorptiometry (DEXA) scan should be performed in 2 years in this patient with low bone mass and relatively low 10-year fracture risk.

   As she has a low BMI, she is at increased risk for osteoporosis. Additionally, her calcium and vitamin D levels are appropriate. Continuing lifestyle activities (such as maximizing weight-bearing exercise and avoidance of tobacco or excessive alcohol) is appropriate management of this patient.

   SERM (selective estrogen receptor modulator) like raloxifene are associated with an increased risk of thromboembolism and vasomotor symptoms. There is limited data supporting use of raloxifene for treating patients with low bone mass.

   Bisphosphonates are considered first-line therapy for osteoporosis, although they are not used routinely in women with low bone mass, unless the FRAX score suggests an increased risk.

8. A 36-year-old man presented to the physician's office with a 6-month history of lower back pain. There was no history of trauma or fall. He is an astronaut and

takes no medications or supplements, does not smoke or consume alcohol, or use recreational drugs.

His last visit in space about 1 year ago, for a duration of 3 months. He has never been on corticosteroids and has no history of prior fractures. He has tried a course of physical therapy for 6 weeks for his back, with worsening of back pain. Review of systems and physical examination are unremarkable, except for low back pain and tenderness on palpation at L4. On further testing, serum levels for luteinizing hormone (LH), follicle-stimulating hormone (FSH), TSH, free T4 and testosterone are normal. Complete blood count and a complete metabolic panel are normal.

Which of the following is the most appropriate next step for this patient?

A. Scheduled acetaminophen
B. Referral to pain management
C. Obtain a lumbar radiograph
D. Start bisphosphonate therapy

The correct answer is C.

Teaching point—obtain appropriate imaging in a patient with risk factors for bone loss and focal signs. Space travel is a risk factor for bone loss. It is unclear how to prevent this from occurring.

Discussion

When the effects of gravity on the longitudinal skeleton are removed, as with space travel or inactivity, bone resorption is greater than bone formation. This was demonstrated in patients who were on continuous bed rest. It was found that their urinary calcium increases rapidly and by the sixth week of bed rest, plateaus for several weeks, and then decreases but remains above the ambulatory baseline thereafter. This occurred even though the patients received vitamin D supplementation. Bone loss continues at this rate for at least 36 weeks. Attempts to prevent disuse osteoporosis with both mechanical and biochemical means, including exercise, skeletal compression, increased hydrostatic pressure to the lower body, supplemental calcium and phosphorus, calcitonin, or bisphosphonate use were not successful.

9. 76-year-old white male with a history of malleolus fracture during a skiing accident at age 60 years, left hip fracture at age 75, and hypothyroidism treated with 100 mcg of levothyroxine is seen at his primary care physician office for an evaluation. BMD by DEXA confirms osteoporosis, and he is started on therapy.

Which of the risk factors or mechanisms are thought to play an important role in the development of osteoporosis, by an estrogen independent mechanism?

A. Increased IFN-γ production
B. TGF-β down regulation
C. Age
D. Decreased IL 7 production

The correct answer is C.

Teaching point—recognize the importance of aging by itself, as a risk factor for the development of osteoporosis, which may operate through estrogen dependent and estrogen independent mechanisms.

Discussion

It is known that the underlying mechanisms of osteoporosis in older adults are different than those associated with estrogen deprivation. Markedly increased bone resorption leads to the initial fall in bone mineral density. With increasing age, there is also a significant reduction in bone formation. The exact mechanism of aging and its effect on the bone are not completely clear, but it plays an important role in the pathophysiology of age-related osteoporotic fractures.

A DEXA scan is useful to measure bone density but may not be able to measure age-related structural bone decline.

The loss of bone may be secondary to age-related changes in other organs and tissues, such as the ovary (estrogen deficiency), the adrenal gland (glucocorticoid excess or hyper-responsiveness), the kidney [loss of nephrons, reduced synthesis of calcitriol, calcium malabsorption, and secondary hyperparathyroidism], and muscle (sarcopenia, inactivity, reduced mechanical loading). However, additional age-related mechanisms intrinsic to the bone, like excessive accumulation of reactive oxygen species (ROS), contribute to age-related changes in many tissues including the bone.

Increased oxidative stress is strongly implicated in the biology of aging and the pathogenesis of age-related diseases. Recent evidence indicates that oxidative stress is a fundamental mechanism of the age-dependent decline of bone mass and strength and that loss of estrogens exaggerates the effects of aging on bone by decreasing defense against oxidative stress. The balance between the generation of reactive oxygen species versus defense against them is critical for bone homeostasis throughout life.

Estrogen deficiency up regulates IFN-γ production through TGF-β down regulation. Estrogen has a direct stimulatory effect on the production of this factor. TGF-β is a powerful inhibitor of T cell activation. Another mechanism by which estrogen regulates IFN-γ and TNF production is by repressing the production of IL-7, which is a potent inducer of bone destruction.

10. 32-year-old African American male referred to the bone clinic with recent onset of left knee pain for 7 days. He has a history of lactase deficiency and hence avoids all dairy products, SLE and biopsy proven lupus nephritis since the age of 20 years, has been on varying doses of prednisone (5–60 mg oral daily, for the last 10 years), post treatment with IV cyclophosphamide for lupus nephritis, and osteonecrosis of bilateral femoral heads. BMD by DEXA revealed.

Radial diaphysis T score	−2.0
Distal radius T score	−3.4
L3 lateral T score	−2.7
Lumbar L1–L4 T score	−3.5

He has no history of fractures, metal of both femoral heads, preempts interpretation of the hip BMD

Which of the following medications are not known to worsen bone loss?

A. Prednisone
B. Hydroxychloroquine
C. Cyclophosphomide
D. Both B and C

The correct answer is B.

Teaching point—hydroxychloroquine appears to protect against low BMD in patients with SLE, who are treated with corticosteroids.

Discussion.

In a study evaluating risk factors for low bone mineral density in patients with systemic lupus erythematosus (SLE), the following factors were found to be significantly related to lower BMD—Caucasian race, increased number of pregnancies, postmenopausal status, higher SLE damage index, and higher cumulative corticosteroid dose. An unexpected finding was that taking Hydroxychloroquine was the only factor associated with higher BMD of the hip and spine. Hydroxychloroquine has been shown to suppress bone resorption in vitro possibly by inducing osteoclastic apoptosis and thus decreased bone resorption. However more data and studies are needed in this regard.

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Chapter 15
Crystal Arthritis

Anastasia Slobodnick, Michael Toprover, and Michael H. Pillinger

Gout

Gout is the most common crystal arthropathy, with a prevalence of approximately 3.9% in the United States [1]. Overall, gout is significantly more prevalent in men than women (ratio of 4–10:1), although prevalence tends to increase in women after menopause [2]. In both sexes, gout is associated with significant morbidity and mortality [3]. The links between gout and myriad other medical conditions, including cardiovascular disease, metabolic syndrome, renal disease, cancer, and diabetes, are being actively explored.

Risk Factors

Both genetic and environmental factors contribute to the onset of gout. Genome-wide association studies (GWAS) have identified variants in genes encoding urate transporters in the kidney (notably *SLC2A9* and *ABCG2*) and the gut (*ABCG2*) that are thought to contribute to hyperuricemia and therefore increased gout risk [4].

Multiple lifestyle factors are also associated with increased predisposition to gout [5]. A variety of foods and beverages have been associated with increased risk

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for hyperuricemia and gout flares, including alcohol, purine-rich foods such as red meat and shellfish, and fructose-sweetened beverages [6]. In addition, the use of certain medications, including diuretics, low-dose aspirin, cyclosporine, tacrolimus, nicotinic acid, and teriparatide, may promote hyperuricemia and therefore increase the risk for gout [6].

Pathophysiology

The mechanisms of inflammation that lead to acute gout flares center around monosodium urate (MSU) crystal formation and phagocytosis by macrophages, leading to activation of an inflammatory cascade. The sine qua non of MSU crystal formation is hyperuricemia, which results from either excessive production or inadequate excretion of urate, or both. Excessive urate production may be either primary, resulting from genetic aberrancies in enzymes involved in the purine synthesis and/or salvage pathways (e.g., Kelley-Seegmiller syndrome), or secondary, resulting from increased cell turnover, such as in myeloproliferative disorders or tumor lysis syndrome. In the kidney, urate is filtered by the glomerulus and simultaneously resorbed and secreted in the proximal tubule. Primary urate under-excretion may result from inherited defects of renal urate secretory transporters in the setting of otherwise normal renal function (e.g., ABCG2 defects). Among patients with hyperuricemia in the absence of secondary causes, approximately 90% are primary under-excreters, and 10% are primary overproducers [7]. Alternatively, secondary defects in renal uric acid excretion may occur in the setting of chronic kidney disease (i.e., glomerular dysfunction), use of certain medications (see the risk factors section), exposure to lead (saturnine gout), or as a response of the kidney to metabolic abnormalities such as lactic or ketoacidosis [8].

Once MSU crystals have formed and been phagocytosed by local tissue macrophages, they activate intracellular assembly of the NLRP3 inflammasome, a multiprotein complex that triggers the activation of caspase-1, leading to cleavage, activation, and secretion of 1L-1β (as well as IL-18). Secreted 1L-1β binds to IL-1 receptors in an autocrine and paracrine manner, inducing the release of additional pro-inflammatory cytokines, leading to local inflammation and systemic effects such as fever. Thus IL-1β plays a central role in the genesis of gouty inflammation. Among the cytokines secondarily produced in response to 1L-1β are IL-8, IL-17, IL-6, and CXCL8, which promote upregulation of adhesion molecule families of selectins and integrins on the luminal surface of endothelial cells, facilitating neutrophil adherence and recruitment into the synovium [9]. Concurrently MSU crystals have the ability to activate complement, directly stimulating neutrophils, and providing a signal gradient to attract them to the inflammatory site [10].

In addition to triggering the inflammatory response, MSU crystals stimulate negative feedback mechanisms that eventually lead to the resolution of a gout flare. Important mechanisms in inflammation resolution include the formation and release by neutrophils of neutrophil extracellular traps (NETs), structures composed of

DNA and associated proteins. While NETs initially promote further proinflammatory cytokine release, later in the inflammatory process they reverse their role and promote proinflammatory cytokine degradation, ultimately leading to resolution of the acute gout flare [8].

Clinical Presentation

In its early stages, gout is characterized by recurrent episodes of pain and swelling in one or a few joints, occasionally associated with systemic symptoms such as fever. The episodes are self-limited, with symptoms usually peaking in intensity within the first 24 hours after symptom onset, and resolving (even without treatment) after 5–10 days. Among men, at least 50% of initial gout flares occur in the first metatarsophalangeal joints, and 85% of gout flares occur in the lower extremities, although any joint in the body can be affected. Among women, the first MTP is involved less frequently, with the knee being another common site of first gouty flares. Over time, the attacks become more frequent, and smoldering chronic inflammation may persist between attacks [11]. After years of recurrent, untreated gout flares, patients may develop chronic tophaceous gout, characterized by granuloma-like masses composed of complexes of MSU crystals and NETs surrounded by macrophages, multinucleated giant cells, and fibroblasts.

Diagnosis

Making a diagnosis of gout requires the potential integration of clinical, laboratory, and radiographic components. These components are summarized in the 2015 American College of Rheumatology (ACR) gout classification criteria (Table 15.1), which have a reported sensitivity of 92% and specificity of 89% [12]. However, diagnosing gout as a chronic disease state must be distinguished from the diagnosis of an acute gout flare. Even in a patient with an established diagnosis of gout, the occurrence of an acute mono- or polyarticular arthritis requires the consideration of a range of alternative diagnoses, including a joint infection (a rheumatologic emergency), or a flare driven by an alternative type of crystal (see calcium crystals, below). Indeed, the coexistence of a gout flare with either of these other entities is a well-recognized occurrence. Definitive diagnosis of an acute gout flare therefore usually requires the aspiration and examination of synovial fluid, with the gold standard for an acute gout flare being the identification of MSU crystals along with inflammatory cells, mainly neutrophils, in the joint aspirate of a patient with acute arthritis, including evidence that some neutrophils are actively phagocytosing MSU crystals. MSU crystals are needle-shaped and negatively birefringent under polarized microscopy, making them easily recognizable. Even when MSU crystals are present, the possibility of a co-existing alternative etiology requires careful consideration [13].

Table 15.1 2015 ACR classification criteria for gout[a, b]

		Points
Clinical		
Pattern of joint or bursa involvement during past or present symptomatic episodes	Ankle or midfoot without first MTP joint	1
	First MTP joint involved	2
Number of typical characteristics (reported or observed erythema overlying affected joint, can't bear touch or pressure, difficulty walking and inability to use joint)	One characteristic	1
	Two characteristics	2
	Three characteristics	3
Time course of episodes (time to maximal pain <24 hours, resolution of symptoms in <14 days, complete resolution between symptomatic episodes)	One typical episode	1
	Recurrent typical episodes	2
Clinical evidence of tophus	Present	4
Laboratory		
Serum urate—ideally not on urate-lowering therapy and at least 4 weeks after the start of an acute flare	<4 mg/dL	−4
	6–8 mg/dL	2
	8–<10 mg/dL	3
	≥10 mg/dL	4
Synovial fluid analysis of symptomatic joint or bursa	MSU negative	−2
Imaging		
Double-contour sign on ultra sound or urate depositoin on dual-energy CT	Present	4
X-rays of hands and/or feet demonstrating at least 1 erosion	Present	4

Adapted from Neogi et al. [12]
[a]Entry criteria: at least one episode of swelling, pain, or tenderness in a peripheral joint or bursa
[b]Presence of MSU crystals in the synovial fluid of a symptomatic joint or bursa, or in a tophus, is sufficient for classification of gout without applying this criteria

Treatment

Treatment of an acute gout attack focuses on reducing the inflammation associated with gout flares, whereas chronic treatment of gout centers around lowering serum urate levels. The ACR offers guidelines for treatment of acute gout attacks, prophylaxis against repeat flares, and therapies for chronic treatment [14, 15] (Fig. 15.1). In the setting of an acute gout flare, patients may be treated with either monotherapy or combination therapy (depending on the severity of the attack and number of joints involved) using non-steroidal anti-inflammatory drugs (NSAIDs), oral steroids, colchicine, and/or intra-articular steroid injections. The choice of an anti-inflammatory agent is based on safety (e.g., consideration of patient comorbidities) as well as physician and patient preference. NSAIDs and oral steroids should not be used in combination. When the aforementioned agents are ineffective or contraindicated, biologic agents that block IL-1β activity, most notably anakinra, may be considered, although these are not FDA approved. If the patient is already using urate-lowering agents, these should not be discontinued during the acute flare as the resultant rise in urate may exacerbate the attack.

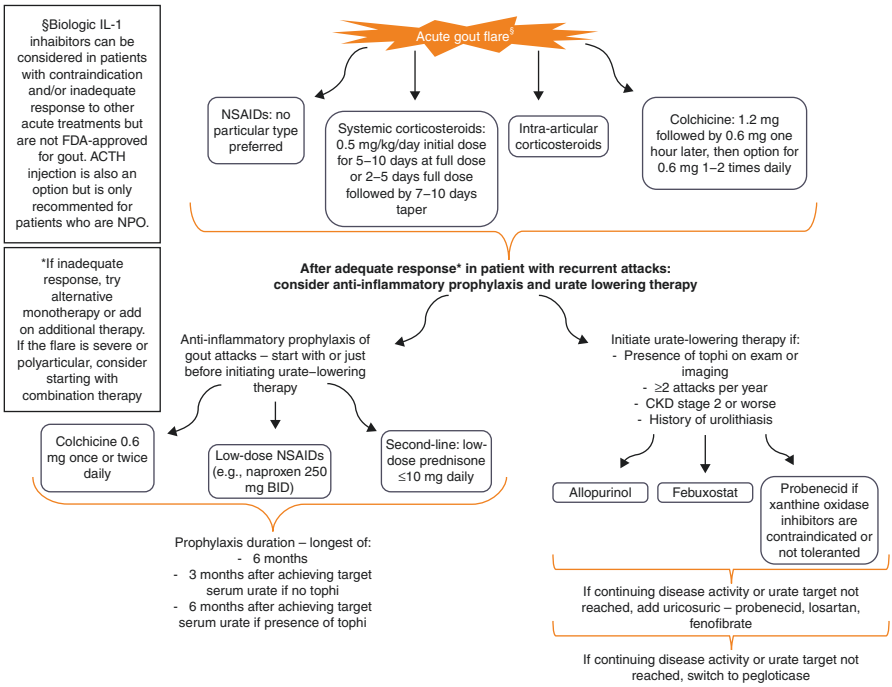

Fig. 15.1 American College of Rheumatology (ACR) guidelines for the management of gout. Summarized here are the ACR guidelines for treating gout, beginning with the management of acute flares and moving on to the indications for, and approaches to urate lowering. (For the complete guidelines, see *Khanna* et al [14, 15])

For patients with frequent attacks (>2/year), or who have had a single attack in the setting of chronic kidney disease or a history of tophi or renal stones, urate-lowering therapy (ULT) should be initiated. First-line options for ULT include the xanthine oxidase inhibitors allopurinol and febuxostat. A choice between these two agents may be made based on cost (allopurinol much cheaper), risk of potentially fatal allopurinol hypersensitivity syndrome (greatest among certain Asian populations who are HLA B58∗01-positive, requiring that these populations be checked for HLA type before starting allopurinol), and recent reports that use of allopurinol may be associated with reduced cardiovascular mortality relative to febuxostat [16]. The target serum urate level should be less than 6.0 mg/dL, or lower in the case of tophaceous gout (typically less than 5.0 mg/dL), or as needed to prevent attacks and resolve tophi. ULT should be started simultaneously with, or just after initiation of anti-inflammatory prophylactic colchicine or a low-dose NSAID (or low-dose steroids as a third-line agent), as ULT initiation has been found to paradoxically increase the risk of gout flares at the onset of therapy [17]. Prophylaxis is typically continued for at least 6–9 months. If both allopurinol and febuxostat are contraindicated or not tolerated by a particular patient, the uricosuric agent probenecid may be started instead. Probenecid or the alternative uricosuric lesinurad (not to be used as

monotherapy) may also be “added on” to xanthine oxidase inhibitor therapy if a patient has had an inadequate response to treatment. Losartan and fenofibrate also have ULT potential and may be added on to a xanthine oxidase inhibitor, particularly if they are also indicated for hypertension or cardiovascular disease. Finally, the highly potent uricase pegloticase may be considered in patients with refractory disease, or with a significant tophus burden.

Calcium Crystal Diseases

Calcium Pyrophosphate Deposition Disease

Calcium pyrophosphate crystal deposition (CPPD) is a broad term used to describe the varying presentations associated with the formation and deposition of calcium pyrophosphate dihydrate (CPP) crystals. In many cases, CPPD is asymptomatic, but in some patients CPPD can provoke an acute inflammatory arthritis. In other cases, patients can develop a more chronic arthritis reminiscent of either osteoarthritis (non-inflammatory) or rheumatoid arthritis (inflammatory). The prevalence of CPPD varies from 7% to 10% in different studies [18]. Of these, a significantly smaller percentage will have symptomatic disease.

Risk Factors

CPPD is idiopathic in most cases, with no apparent underlying condition. However, several factors have been associated with an increased risk for crystal deposition. CPPD risk tends to increase with age, being most common among individuals over 80 years old [18]. Hyperparathyroidism raises the risk of CPPD approximately threefold above that of the general population [19]. Other conditions associated with increased CPPD risk include gout (~2.5 times more likely), osteoarthritis (~2 times more likely), rheumatoid arthritis (~2 times more likely), hemochromatosis (~2 times more likely), hypomagnesemia (~1.25 times more likely), and osteoporosis (~1.25 times more likely) [19]. In contrast, certain medications, including proton pump inhibitors, thiazide diuretics, and loop diuretics, have been associated with a decreased risk of CPPD. Other conditions that have been inversely associated with CPPD include alcohol and tobacco abuse disorders, coronary artery disease, congestive heart failure, diabetes, and hypertension [19].

Pathophysiology

CPP crystals are formed within the cartilage, as a result of the interaction of inorganic pyrophosphate with calcium ions. Inorganic pyrophosphate is a breakdown product of extracellular ATP. Although most ATP is generated within chondrocytes,

it may be transported out into cartilage where ectonucleotidases enzymatically liberate pyrophosphate. Additionally, a membrane transport protein termed ANKH may directly secrete pyrophosphate from the chondrocytes into the extracellular milieu. Gain-of-function mutations of the ANKH protein have been seen in familial cases of CPPD, but ANKH up-regulation may also occur secondarily in the setting of cartilage damage [20]. Although CPPD crystals are formed from a combination of inorganic phosphate and calcium, the exact mechanism of crystal formation is not well understood.

Once CPPD crystals are liberated from the cartilage into the synovial fluid, they drive acute inflammation in a manner similar to that of MSU crystals. In vitro, CPPD and MSU crystals can be shown to have many similar effects, including activation of the NLRP3 inflammasome in macrophages [21].

Clinical Presentation

Most cases of CPPD are asymptomatic and are discovered incidentally when a radiograph of a joint shows CPPD deposition within the cartilage, the condition known as chondrocalcinosis. As noted earlier, however, CPPD may also present as an acute inflammatory arthritis, or as a chronic arthritis similar to osteoarthritis or rheumatoid arthritis.

Acute CPPD arthritis (colloquially known as pseudogout) usually presents as a rapid onset of mono- or oligoarticular pain but may rarely present with polyarticular involvement. The most common joint involved is the knee, followed by the wrist and the metacarpophalangeal joints [22]. In contrast to gout, bursal involvement is uncommon. Symptoms during an acute episode include pain, erythema, and swelling of the joint that occasionally spreads to the surrounding soft tissues [21]. Due to the inflammatory nature of the pain, patients may develop fevers, chills, and other constitutional symptoms. Occasionally, CPP crystals may deposit in the ligaments at the superior aspect of the dens in the cervical spine, which may intermittently cause acute pain (presumably relating to inflammatory flares) and may be seen on cervical computed tomography scans (crowned dens syndrome).

Symptoms of acute CPPD arthritis are similar to those of an acute gout attack. However, there are several notable features that may distinguish CPPD arthritis from a gout flare, including the fact that CPPD less commonly involves the first metatarsophalangeal joint. Acute CPPD arthritis is typically less severe than gout. On the other hand, whereas gout attacks usually resolve after a few days, acute CPPD arthritis may smolder for weeks to months if not adequately treated [21].

In contrast to acute CPPD arthritis, chronic CPPD arthritis may mimic osteoarthritis, with a mono- or polyarticular presentation. However, chronic CPPD arthritis generally affects different joints than those commonly affected in primary osteoarthritis, namely, the wrists, glenohumeral joints, metacarpophalangeal joints, the midfoot, or the hindfoot [21–23]. In these cases, the presumption is that cartilage damage from CPPD leads to osteoarthritis in atypical locations [22]. On the other hand, the presence of established osteoarthritis appears to promote the risk for

CPPD, including up-regulation of the ANKH protein in chondrocytes, suggesting that CPPD and OA can be reiterative processes. Patients with osteoarthritis as a phenotype of chronic CPPD arthritis may also develop acute flares, as well as severe articular destruction, out of proportion to that seen primary osteoarthritis. As noted above, in some cases, CPPD deposition may result in a smoldering polyarthritis similar to rheumatoid arthritis (pseudo-RA).

Diagnosis

As with gout, the gold standard for diagnosis of CPPD is identification of calcium pyrophosphate crystals within the synovial fluid of an affected joint. CPPD crystals are classically rhomboid-shaped, smaller than MSU crystals, and are weakly positively birefringent on polarized light microscopy [23]. They are often pale and may be missed without vigorous and persistent examination. As with gout, the presence of CPPD crystals does not preclude the simultaneous presence of other inflammatory arthritis, most commonly gout or joint infection [13].

Imaging of joints in CPPD often shows the presence of chondrocalcinosis. This can readily be seen on plain radiographs, computed tomography, and musculoskeletal ultrasound, where it presents as a hyperechoic dotted line *within* the cartilage, in contrast to the appearance of MSU, which is visible on ultrasound as a hyperechoic line *along the surface* of the cartilage ("double contour" sign) [21, 24].

Treatment

Acute CPPD arthritis is treated using many of the same anti-inflammatory medications as gout. In patients with mono-arthritis, intra-articular glucocorticoids are often an effective choice. In patients who have oligo- or polyarticular joint involvement, or who are not amenable to injections, treatment with oral colchicine at a daily dose of 0.6–1.2 mg, oral NSAIDs, or systemic glucocorticoids (oral, or intravenous) may be given [21]. As with gout, anti-IL-1β biologic therapy may be considered for refractory cases [25]. In contrast to gout, in which ULT can provide long-term management by preventing the formation of new crystals and promoting the dissolution of established ones, there are currently no medications available to remove or prevent the formation of CPP crystals, except perhaps in the rare cases of underlying metabolic diseases such as hyperparathyroidism. Thus, patients with frequent recurrent attacks may require chronic anti-inflammatory prophylaxis, most commonly with daily colchicine.

Similarly, there are no disease-modifying medications used in the treatment of primary chronic CPPD crystal arthritis. However, several studies report that use of intra-articular steroids, or the oral medications described, may provide pain relief and prevent recurrence [22]. As with acute CPPD arthritis, screening for and correcting underlying causes such as hyperparathyroidism may provide ameliorative opportunities, although such instances are rare.

Basic Calcium Phosphate

In clinical practice, basic calcium phosphate (BCP) crystals constitute three different types of calcium phosphate crystals, including carbonated-substituted hydroxyapatite, octacalcium phosphate, and tricalcium phosphate [22]. BCP crystals can cause two types of pathogenic syndromes affecting the musculoskeletal system, depending on where they deposit. If they infiltrate within the joint capsule, they may cause a severe destructive inflammatory arthritis. When found in the tissues around the joint, namely tendons, or bursae, they cause a calcific periarthritis. These presentations are not mutually exclusive, however. Rotator cuff calcification is common, with a prevalence of 2.7–7.3% in asymptomatic patients [26, 27].

Risk Factors

BCP crystal disease appears to be more common in women than men [28]. Risk factors that predispose to BCP crystal deposition include metabolic abnormalities, specifically elevated levels of circulating calcium or phosphate, calciphylaxis in end-stage renal disease, and familial hypophosphatasia (genetic deficiency in alkaline phosphatase activity leading to hyperphosphatemia) [29]. BCP crystal disease has also been described in patients with endocrinopathies including adult onset diabetes mellitus, hypothyroidism, and aberrant estrogen metabolism (menstrual disorders such as endometriosis, ovarian cysts, polycystic ovarian syndrome, or those with recurrent miscarriages) [30].

Pathophysiology

The formation of BCP crystals occurs in areas where there are elevated levels of extracellular calcium and phosphate along with conditions favorable to encourage mineralization of the crystals. When present, BCP crystals may promote production of matrix metalloproteinases and other substances associated with joint damage and erosion of connective tissue [31].

Clinical Presentation

BCP crystal deposition is often asymptomatic and discovered incidentally on x-rays. However, when BCP crystals infiltrate the soft tissues around a joint, they may cause calcific periarthritis, most commonly in the shoulder. Periarthritis is more common in women than men and usually occurs around or after age 50. The supraspinatus tendon is most frequently involved, followed by the infraspinatus tendon. The subscapularis and long biceps tendon are less frequently involved [32]. Other common locations for calcific periarthritis include the gluteus medius tendon and

the reflected head of the rectus femoris [33]. More than one tendon may be involved. Symptoms included chronic pain along with self-limited flares of acute inflammatory pain. Calcification may cause tendon tears or adhesive capsulitis [32].

BCP-associated arthritis occurs when the crystals deposit within the joint capsule or cartilage [33]. In these cases an acute self-limiting arthritis may ensue, with edema, erythema, and joint tenderness, along with decreased joint motion. BCP infiltration in the joint capsule of the shoulder may rarely be associated with Milwaukee shoulder, a rapidly destructive arthritis most prevalent in elderly women [32]. As with other acute crystal diseases, systemic signs, including fevers and chills, may be present.

Diagnosis

A definitive diagnosis of BCP disease is made by identifying the crystals. However, because of their small size and relatively amorphous structure, BCP crystals are not birefringent and are invisible under polarizing light microscopy. Based on their calcium content, the alizarin red S stain may be used to identify BCP crystals under light microscopy, where they will resemble reddish-orange clumps. Unfortunately, alizarin red S staining is neither sensitive nor specific as a test for BCP crystals, and is uncommonly performed by hospital labs. Other calcium-sensitive dyes have been used along with flow cytometry to identify the crystals but are costlier and less available. Similarly, electron microscopy may be used but is not available at most centers.

Imaging using x-rays may show erosions, severe joint degeneration, and soft tissue calcifications, the presence of which are usually presumed to represent BCP deposition. MRI and ultrasonography may show tissue destruction and ligament damage, but these are not specific for BCP disease.

Treatment

For calcific tendonitis most patients are treated conservatively with oral NSAIDs or acetaminophen, along with physical therapy to improve function. For acute BCP arthritis NSAIDS, oral steroids and/or colchicine may be tried, but data supporting these strategies is limited. In patients with more severe pain, or who fail oral therapy, intra-articular glucocorticoids may be used. If pain is resistant to injections, in cases of severe joint damage from Milwaukee shoulder surgery may be needed, up to and including joint replacement. At present, there are no available pharmacologic options to prevent or resolve BCP crystals, although managing underlying metabolic defects is always recommended.

Calcium Oxalate

Calcium oxalate crystals are a rare cause of inflammatory arthritis. The underlying cause for calcium oxalate arthritis is oxalosis, most commonly diagnosed as

hyperoxaluria [34]. Primary hyperoxalurias are a group of rare autosomal recessive diseases, with a prevalence of 0.8–2.9 in one million, that cause an abnormally increased conversion of glyoxylate to oxalate [35]. In contrast, secondary hyperoxaluria occurs due to increased intestinal absorption of dietary oxalate, most commonly as a consequence of diseases of fat malabsorption [36]. Oxalate is primarily excreted by the kidneys (raising the risk for oxalate kidney stones), but in both primary and secondary hyperoxaluria, the oxalate concentration exceeds the excretory capacity of the kidney, causing kidney failure and systemic buildup of oxalate, which may then deposit in various tissues of the body, including bones, tendons, cartilage, and joints. Oxalate arthritis is typically a symmetric, polyarticular disease with inflammatory joint effusions. The gold standard for diagnosis is microscopic identification of the crystals. Calcium oxalate crystals may be monohydrate or dihydrate. Monohydrate crystals are irregular squares or rods that look similar to CPP crystals, while the dihydrate crystals have a pathognomonic envelope-like or bipyramidal shape and are the most common ones seen. The crystals have variably positive birefringence and can also be stained with alizarin red S due to the calcium content. X-ray findings may show chondrocalcinosis, sclerosis, fractures, pseudofractures, subperiosteal resorption next to the oxalate deposits, and dense metaphyseal bands [34]. Treatment of the acute arthritis is similar to other inflammatory joint diseases with NSAIDs, colchicine, or steroids; treatment of hyperoxaluria requires dietary adjustment and management of the underlying cause, and in patients with primary hyperoxaluria, may require kidney and/or liver transplant [34].

Other Crystals

A number of other crystals can cause inflammation in joints. Perhaps most commonly seen, but uncommonly appreciated, are inflammatory reactions to *intraarticular corticosteroid crystals*. Most steroids are insoluble in lidocaine, and each forms their own unique and recognizable crystal structure. Injection of such steroids may therefore induce a transient acute inflammatory reaction, occurring within the first 24 hours and resolving with the dissolution of the crystals and the anti-inflammatory effect of the steroids themselves. Treatment is conservative, with NSAIDs and/or topical ice. *Cholesterol crystals* are characteristically reported in the joint or bursal fluid of individuals with rheumatoid arthritis, or occasionally other forms of inflammatory arthritis. Their presence is not typically associated with hyperlipidemia. Cholesterol crystals are negatively birefringent, plate-like, and notched. They are thought to have weak inflammatory potential; management addresses the primary underlying arthritis [37]. *Lipid liquid crystals* are positively birefringent lipid spherules that appear as Maltese crosses and stain positive with Sudan Black B. Their presence is associated with an acute inflammatory arthritis. Treatment with colchicine or NSAIDs has been reported to improve the arthritis [38].

Questions

1. A 59-year-old man presents for evaluation after his brother was hospitalized with an acute gout flare. The patient has not seen a doctor in 10 years but decided to come in because he is worried about his chances of developing a painful gout attack. He denies any past medical history and takes no medications other than an occasional aspirin for pain less than once a week. He actively smokes 0.5 packs of cigarettes daily and drinks 3–4 glasses of wine per week.

   Further workup demonstrates the following findings:

   - T 98.2 °F, BP 145/91 mm Hg, P 83/min and O_2 saturation 100% on room air
   - Physical exam: negative for tophi.

   Laboratory studies:

   - AST 23 U/L (Reference range 0–40 U/L)
   - ALT 21 U/L (Reference range 0–40 U/L)
   - Alkaline phosphatase 75 U/L (Reference range 40–150 U/L)
   - Total bilirubin 0.3 mg/dL (Reference range 0.2–1.2 mg/dL)
   - Albumin 4.1 g/dL (Reference range 3.5–5.2 g/dL)
   - Blood urea nitrogen 31 mg/dL (Reference range 7–20 mg/dL)
   - Creatinine 1.8 mg/dL (Reference range 0.8–1.2 mg/dL)

   Which one of the following features of this patient's case is most predictive for possible future development of gout?

   A. Aspirin use
   B. Chronic kidney disease
   C. Family history of gout in his brother
   D. Smoking history
   E. Wine intake

   Correct answer: B
   This patient's creatinine suggests that he has chronic kidney disease (CKD), probably secondary to hypertension, particularly since he has not had any medical follow-up in many years. CKD is considered an important risk factor for the development of gout, with studies demonstrating a 60% increase in gout risk for patients with chronic renal insufficiency.
   Low-dose aspirin use has been associated with decreased clearance of uric acid in the kidney. However, a study among healthy volunteers found no change in the renal clearance of urate after they were given a single dose of aspirin 100 mg. Given this patient's sporadic use of aspirin, it is unlikely that his aspirin use confers a greater risk of gout flare than his renal disease. Thus, choice A is incorrect.
   Studies of gout heritability suggest that gout arises from multiple factors, including a combination of multiple different genes, as well as environmental

contributors. A study from 2000 found a correlation of 0.19 for uric acid levels between siblings. Certain genetic polymorphisms have been found to increase risk for gout, particularly polymorphisms in the genes *SCLA2* and *ABCG2* encoding urate transporters in the kidney and gut, but the specific amount of risk conferred by these polymorphisms remains unclear. Because the impact of family history appears to be less potent than CKD, choice C is incorrect.

Tobacco use has not been associated with a higher risk for developing gout. Indeed, some studies suggest a possible lower risk of gout in patients who smoke, for unclear reasons. ACR nevertheless strongly recommends smoking cessation for all patients. Choice D is therefore incorrect.

While this patient does report regular alcohol use, a 2004 study utilizing the NHANES database did not find an increased risk for hyperuricemia among wine drinkers in the general population, as opposed to beer and liquor, both of which were associated with significantly increased serum uric acid levels. Other studies did find an association between wine drinking and increase risk for gout, but not at the level of wine consumption indicated here. Therefore Choice E is incorrect.

2. A 64-year-old Korean man presents for follow-up after experiencing an acute gout flare in his right 1st MTP joint during a recent hospitalization. Gout was confirmed by aspiration and microscopic examination for crystals, and he was treated with prednisone 30 mg with good response. He denies any history of prior gout flares. Today, he says he is feeling well, with minimal toe pain. Medical history is significant for chronic renal insufficiency, hypertension, coronary artery disease complicated by a myocardial infarction 1 year ago, and diabetes. Laboratory studies reveal the following:

   - Na 134 mmol/L (Reference range 134–146 mmol/L)
   - K 4.3 mmol/L (Reference range 3.6–5.2 mmol/L)
   - Cl 109 mmol/L (Reference range 98–108 mmol/L)
   - CO2 25 mmol/L (Reference range 22–29 mg/dL)
   - BUN 40 mg/dL (Reference range 7–20 mg/dL)
   - Cr 2.1 mg/dL (Reference range 0.8–1.2 mg/dL)
   - eGFR 38 ml/min/1.73m^2 (Reference range > 60 mL/min/1.73m^2)

   What would be the most appropriate next step in management?

   A. Initiate allopurinol
   B. Initiate febuxostat
   C. Initiate probenecid
   D. No management needed at this time
   E. Send HLA-B∗5801 testing

   Correct answer: E

   This patient has confirmed gout and stage 3 CKD. ACR guidelines recommend initiating urate-lowering therapy in patients with two or more attacks of gout in the prior year or after a single attack in patients with stage 3 or greater CKD,

tophi, or a history of renal stones. In this setting, allopurinol would be a reasonable first-line agent. However, ACR guidelines recommend HLA-B∗5801 testing before starting allopurinol in Korean patients with stage 3 or worse chronic kidney disease, as well as Han Chinese and Thai patients irrespective of renal function. These patients have a high prevalence of HLA-B∗5801 positivity, which conveys a high risk of potentially life-threatening allopurinol hypersensitivity. As this patient is Korean with stage 3B CKD, it is mandatory to assess HLA-B∗5801 status before deciding whether to institute allopurinol treatment.

While allopurinol would be a good and cost-effective first-line agent for this patient, it should not be started until HLA-B∗5801 has been assessed to be negative. Therefore choice A is incorrect.

Febuxostat is an alternative first-line option for urate-lowering therapy but is much more expensive than allopurinol. Additionally, some but not all studies suggest that patients taking allopurinol, particularly those with significant cardiovascular risk, may have lower risks of cardiovascular death than those taking febuxostat, an observation that is a current subject of active investigation. Until further evidence provides clarity, preferring allopurinol in high-risk cardiovascular patients is an appropriately prudent as well as cost-effective strategy, except in circumstances where allopurinol is not an option or has already been determined to be ineffective. Therefore choice B is incorrect.

Probenecid is considered an alternative first-line urate-lowering therapy for patients for whom a xanthine oxidase inhibitor is not an option. However, this patient's ability to use a xanthine oxidase inhibitor has not yet been ruled out. Moreover, probenecid's efficacy is markedly diminished in patients with creatinine clearances <50 mL/min, and it is not recommended in such cases. Therefore choice C is incorrect.

While urate-lowering therapy is not recommended in otherwise healthy adults after a first attack or in the setting of very rare gout attacks, it is recommended after even one attack in patients with stage 3 or greater CKD. Therefore this patient should be treated, and choice D is incorrect.

3. A 45-year-old man with tophaceous gout presents for his scheduled pegloticase infusion. He was initiated on pegloticase infusions 1.5 months ago, and his uric acid decreased from 9 mg/dL to 1.5 mg/dL 2 weeks after the first infusion. At his last infusion 2 weeks ago, his serum urate level was found to be 4.4 mg/dL. Today, he has bloodwork performed prior to pegloticase administration, and he is found to have the following:

   - Serum urate 6.1 mg/dL (Reference range 2.5–6.0 mg/dL)
   - Na 136 mmol/L (Reference range 134–146 mmol/L)
   - K 3.7 mmol/L (Reference range 3.6–5.2 mmol/L)
   - Cl 102 mmol/L (Reference range 98–109 mmol/L)
   - CO2 29 mmol/L (Reference range 22–29 mmol/L)
   - BUN 28 mg/dL (Reference range 7–20 mg/dL)
   - Cr 1.3 mg/dL (Reference range 0.8–1.2 mg/dL)

- WBC 5.3 × 10^3 /uL (Reference range 4.0–10.0 × 10^3/uL)
- Hgb 13.6 g/dL (Reference range 12–16 g/dL)
- Hct 40.1% (Reference 34–45%)
- Plt 356 × 10^3/uL (Reference range 150–400 × 10^3/uL)

Which of the following would be the best next step in management?

A. Hold pegloticase dose and check serum urate level again in 2 weeks.
B. Initiate allopurinol 100 mg daily.
C. Initiate lesinurad 200 mg daily.
D. Proceed with the administration of pegloticase.
E. Send glucose-6-phosphate-dehydrogenase enzyme test.

Correct answer: D

Pegloticase is a pegylated intravenous uricase that is recommended for patients with gout that has been refractory to more conventional urate-lowering therapy. It is highly effective in significantly lowering serum levels but is associated with a high rate of infusion reactions as well as tachyphylaxis, both thought mainly due to the development of anti-pegloticase antibodies. In order to reduce the risk of infusion reactions, the prescribing information for pegloticase recommends that patients have their serum urate levels evaluated prior to every infusion and that pegloticase be discontinued if a patient is observed to have two or more consecutive serum urate levels of >6 mg/dL (implying the development of antibodies). While this patient should be monitored carefully given his rising serum urate level at today's appointment, he has not yet had two consecutive levels >6 mg/dL. He can receive his pegloticase infusion today, but his serum urate level must be evaluated again prior to his next infusion in 2 weeks.

Because pegloticase should not be held at this time, choice A is incorrect.

Initiating allopurinol to reduce this patient's urate level might be effective but would interfere with the ability to evaluate the patient for the development of immunologic response to pegloticase (i.e., as rising serum urate level). In fact, co-treatment with pegloticase and another urate-lowering drug is contraindicated. Therefore, choice B is incorrect.

Lesinurad is a uricosuric agent which has been approved by the FDA for administration only in conjunction with a xanthine oxidase inhibitor, so this patient should not receive this medication. Moreover, there is no role for additional urate-lowering therapy in this patient at this time, as mentioned above. Therefore choice C is incorrect.

Individuals starting pegloticase should first be checked for glucose-6-phosphatase-dehydrogenase (G6PD) deficiency, since pegloticase generates a large oxidant load that can cause hemolysis in the setting of G6PD deficiency. However, this patient has not had any adverse hematologic effects since being initiated on pegloticase 1.5 months ago; even absent a prior test it is extremely unlikely that he is G6PD deficient and choice E is incorrect.

4. A 61-year-old man presents to your office for follow-up after a visit to the emergency department 5 days ago for an acute episode of pain and swelling in his right first MTP joint. He has a history of crystal-proven gout that was diagnosed 10 years ago, and since then he had had one episode of gout in his right first MTP joint, one episode in his left ankle, and a third episode in his left knee. His last gout flare was approximately 18 months ago. He is currently not taking any medications. On evaluation today, his exam is notable for minimal erythema and tenderness to palpation in his right first MTP joint, and no tophi. He denies pain with walking. His bloodwork is notable for the following:

   - Na 134 mmol/L (Reference range 134–146 mmol/L)
   - K 4.3 mmol/L (Reference range 3.6–5.2 mmol/L)
   - Cl 109 mmol/L (Reference range 98–109 mmol/L)
   - CO2 25 mmol/L (Reference range 22–29 mmol/L)
   - BUN 40 mg/dL (Reference range 7–20 mg/dL)
   - Cr 1.1 mg/dL (Reference range 0.8–1.2 mg/dL)
   - AST 35 U/L (Reference range 0–40 U/L)
   - ALT 33 U/L (Reference range 0–40 U/L)
   - Alkaline phosphatase 54 U/L (Reference range 40–150 U/L)
   - Total bilirubin 0.3 mg/dL (Reference range 0.2–1.2 mg/dL)
   - Serum Urate 7.2 mg/dL (Reference range 2.5–6.0 mg/dL)

   Which of the following would be the best next step in management?

   A. Give colchicine 1.2 mg once, followed by 0.6 mg 1 hour later, then every 12 hours.
   B. Inject the patient's right first MTP joint with corticosteroid.
   C. Prescribe colchicine 0.6 mg pills to take at home as needed.
   D. Start allopurinol 100 mg daily.
   E. Start prednisone 10 mg daily.

   Correct answer: C
   This patient with gout and occasional attacks has just recovered from his most recent attack and is feeling no pain. Although he still has some evidence of mild inflammation, since gout attacks are self-limited it is not necessary to treat him at this time. However, early treatment of the next attack (should it occur) is more effective than delayed treatment, particularly in the case of colchicine. Sending him home with a self-treatment option therefore represents good gout management. Other options for as-needed home use would include prednisone and NSAIDs, neither of which is offered as an option here.
   If anti-inflammatory treatment for his acute attack *were* needed, colchicine might be considered. The current ACR recommendations for acute gout treatment with colchicine are for patients to receive colchicine 1.2 mg as soon as possible at symptom onset, followed by an additional 0.6 mg 1 hour later, then to potentially continue colchicine 0.6 mg once or twice daily 12 hours later. However, colchicine is only recommended as an acute gout treatment if it can be started within 36 hours of treatment initiation, as the efficacy of colchicine

beyond this treatment window is unclear. Since this patient's gout symptoms first began 5 days ago, colchicine would be an incorrect choice even if acute treatment were needed. For multiple reasons, therefore, choice A is incorrect.
Since treatment of the asymptomatic residual inflammation of his current attack is not necessary, choices B (MTP injection) and E (prednisone) are both incorrect.
Allopurinol is a good choice for urate lowering in gout patients who require such treatment, and current ACR guidelines permit the initiation of urate-lowering therapy during a flare if the flare is being adequately treated with anti-inflammatories (a recommendation that remains somewhat controversial). The starting dose of allopurinol for patients with normal kidney function or CKD up to and including stage 3 is 100 mg. However, ACR guidelines do not recommend initiating urate-lowering treatment in patients who have had a single attack of gout, or fewer than two attacks in the past year in the absence of CKD, kidney stones, or tophi. This patient does not meet ACR criteria for initiation of urate-lowering therapy, and allopurinol should not be initiated. Therefore, choice D is incorrect.

5. A 58-year-old Han Chinese male with gout comes to your office seeking treatment advice. The patient was diagnosed with gout several years ago but has never been treated. He reports experiencing several attacks each year, each of which renders him incapacitated. Most of his attacks have been in his first MTP joint, but one was in his knee, at which time a joint aspiration confirmed the presence of negatively birefringent crystals. He has been tried on febuxostat in the past but experienced nausea and is unwilling to try the medicine again. Past medical history includes type 2 diabetes mellitus and mild chronic kidney disease. Current medications include rosiglitazone and low-dose aspirin daily. He denies any history of nephrolithiasis. Physical examination demonstrates no acute or chronic arthritis at the present time, and no tophi. Laboratory studies include

   - Serum urate 8.4 mg/dL (Reference range 2.5–6.0 mg/dL)
   - Serum creatinine 1.3 mg/dL (Reference range 0.8–1.2 mg/dL)
   - eGFR 66 ml/min/1.73m^2 (Reference range > 60 ml/min/1.73m^2)
   - HgB A1C 6.8%.
   - An HLA-B∗5801 test is positive.

   Which of the following is the next best treatment intervention for this patient?

   A. Discontinue aspirin.
   B. Initiate allopurinol, 50 mg daily, and titrate to target.
   C. Initiate lesinurad, 200 mg daily.
   D. Initiate losartan, 50 mg daily.
   E. Initiate probenecid, 500 mg daily, and titrate to target.

   Correct answer E
   American College of Rheumatology guidelines recommend a xanthine oxidase inhibitor, either allopurinol or febuxostat, as first-line therapy for urate lowering. When neither agent is an option, probenecid is recommended as the next

choice. Probenecid inhibits the renal tubule pump URAT1 to promote renal urate excretion. Probenecid should be started at 500 mg daily and then increased to achieve target urate or maximal permissible dose. Probenecid is not recommended for gout patients with a history of tophi or kidney stones and is not considered to be efficacious in the setting of eGFR less than 50 ml/min/1.73 m^2, but such features do not apply to this patient.

Low-dose aspirin has effects on the kidney that can reduce uric acid excretion and raise serum urate (in contrast, high-dose aspirin is urate lowering). ACR guidelines recommend considering whether non-essential medications that may raise urate can be discontinued or substituted with another agent (e.g., treating hypertension with losartan instead of hydrochlorthiazide). However, this 59-year-old male with cardiovascular risk (diabetes and CKD) meets US Preventive Services Task Force criteria for daily aspirin use. Since urate lowering can be accomplished even in the setting of aspirin use, aspirin should not be discontinued. Therefore choice A is incorrect.

While allopurinol is a first-line therapy for urate lowering in gout, the presence of HLA-B∗5801 renders patients at markedly increased (hundreds-fold) risk of allopurinol hypersensitivity syndrome, a potentially fatal illness. Because the gene is common in certain specific populations, HLA-B∗5801 testing is currently recommended prior to allopurinol use in Han Chinese (constituting more than 90% of all Chinese individuals) and Thai populations, and in Koreans with stage 3 CKD or worse. This patient was therefore appropriately tested for HLA-B∗5801 and, in the presence of this gene, should not receive allopurinol. Therefore choice B is incorrect.

Like probenecid, lesinurad inhibits URAT1 to promote renal urate excretion. Lesinurad is more potent than probenecid and can lower urate in patients with eGFR as low as 30 ml/min. However, lesinurad may promote transient or—much less commonly—permanent renal dysfunction when used as monotherapy and is therefore approved only as combination therapy with a xanthine oxidase inhibitor and only in patients with eGFR greater than 50 ml/min. While this patient's eGFR is not low enough to be a contraindication to use, he cannot take a xanthine oxidase inhibitor, and the use of lesinurad as monotherapy is not an acceptable option. Therefore choice C is incorrect.

Losartan is an angiotensin receptor blocker that has an incidental ability to inhibit URAT1 and can therefore lower serum urate. However, it is not as potent as probenecid or lesinurad. It is recommended as an off-label add-on to a xanthine oxidase inhibitor in individuals who have not achieved target serum urate when taking a xanthine oxidase inhibitor alone, particularly when such patients also need an anti-hypertensive agent. Losartan is therefore not a good option for this patient who does not have hypertension and needs a single agent, not an add-on agent. Therefore choice D is incorrect.

6. A 72-year-old male calls your office for advice about an acutely swollen and painful knee joint.

   The patient, who has a history of right knee osteoarthritis, was seen in your office for a routine visit the afternoon before. At that time, he was requesting a

corticosteroid knee injection preceding a vacation. You aspirated 20 cc of fluid from the knee. The synovial fluid aspirate was noteworthy for a white blood cell count of 1200/mm^3 (Reference range 0–200/mm^3), mainly neutrophils. No crystals were seen, and a gram stain was negative at the time. You injected 40 mg of triamcinolone hexacetonide, along with 3 cc of 1% lidocaine, which afforded the patient some immediate relief.

At approximately 3 AM, the patient was awakened by pain in the knee. He tossed and turned until morning, when he examined the knee and found that it was red and swollen. He took his temperature, which was 100.0 °F. Past medical history is noteworthy for diet-controlled type 2 diabetes mellitus. Laboratory studies from the day before demonstrated a normal complete blood count and serum chemistries.

Which of the following is the most appropriate action at this time?

A. Initiate ibuprofen, 800 mg three times daily.
B. Initiate vancomycin and ceftriaxone empirically.
C. No action.
D. Obtain serum urate level and erythrocyte sedimentation rate.
E. Re-aspirate the joint for white count, gram stain, and culture.

Correct answer: A

This patient has received an injection of triamcinolone hexacetonide for osteoarthritis. When viewed under a polarizing microscope, triamcinolone hexacetonide in synovial fluid appears as a rod-shaped negatively birefringent crystal and, like naturally occurring pathogenic crystals, has the ability to induce an acute inflammatory response. While different glucocorticoids form differently shaped crystals, all have the potential to elicit an inflammatory response. Such responses are reported to occur in about 2–25% of patients who receive steroid injections, may occasionally be severe (including low-grade fever, as in this patient), and may mimic other forms of inflammatory monoarthritis. Management is symptomatic; attacks resolve spontaneously when the crystals dissolve and the steroid medication exerts its anti-inflammatory effects. Common approaches to treatment include NSAIDs, colchicine, and topical ice. In this case, instructing the patient to take high-dose ibuprofen is an appropriate option.

Joint infection occurring after injection is a rare (between 1:750 and 1:10,000, based on several reports) but dreaded consequence of joint injection, possibly occurring even in the setting of meticulous sterile technique. However, the time to onset of symptomatic infection is delayed by several days, presumably owing to the time required for the infecting organism to achieve a clinically impactful population. Accordingly, infection in this patient whose flare began within hours is unlikely, and treatment with antibiotics in the absence of evidence of infection would be unnecessary at best. Therefore, B is an incorrect option.

If no action is taken in this patient, his inflammatory episode is likely to resolve within 24–48 hours. However, this patient is in distress, and not treating would only be a reasonable option if harm would be expected from treatment. Accordingly, C is an incorrect option.

Obtaining a serum urate and erythrocyte sedimentation rate will do the patient no harm but will also be of little or no clinical benefit. The erythrocyte sedimentation rate can be predicted to be elevated and will not help distinguish between etiologies of the joint swelling. Similarly, whether the serum urate is high or low will not provide any information on the etiology of the current attack. Therefore, choice D is incorrect.

Re-aspirating the joint for gram stain and culture would be an appropriate strategy if there were concern for infection, but as discussed above, the timing of onset of the attack (mere hours after the joint injection) makes an infection very unlikely, even in the setting of well-controlled diabetes. Moreover, the procedure will result in unnecessary discomfort and itself will convey the low but real risk for infection accompanying every joint procedure. If the patient's joint inflammation had occurred 48–96 hours after the joint injection, concern for infection would have been significant, and re-aspiration would have been imperative. In the current setting, choice E is incorrect.

7. You are called to consult on a 16-year-old male with a painful swollen elbow that he is unable to move. The patient has a history of kidney stones at age 13. His father died of complications of end-stage renal disease when he was 6 years old. You aspirate the joint and observe birefringent, bipyramidal crystals. The synovial fluid white blood cell count is 35,000/mm^3 (Reference range 0–200/mm^3), predominantly neutrophils, and gram stain is negative; culture is pending. Laboratory studies are noteworthy for an ESR of 43 mm/hour (Reference range < 20 mm/hour), a serum creatinine of 5.8 mg/dL (Reference range 0.8–1.2 mg/dL), and a normocytic, normochromic anemia.

   In addition to treating the patient with oral prednisone, which of the following is the most appropriate action at this time?

   A. Initiate dialysis.
   B. Initiate empiric antibiotics.
   C. Institute low-purine diet.
   D. Refer for hepatorenal transplantation.
   E. Refer for renal transplantation.

   Correct answer: A

   Early onset of renal stones and end-stage renal disease, along with the presence of bipyramidal crystals (classic for calcium oxalate) in the joint, are evidence of oxalosis, a late complication of hyperoxaluria that occurs when the kidneys can no longer excrete adequate amounts of oxalate to keep serum and tissue levels down. Primary forms of this condition are autosomal dominant, consistent with the report that this patient's father died of complications from end-stage renal disease at an early age. The presence of oxalosis indicates that this patient is at risk for potentially fatal systemic involvement of oxalate deposition, which requires early action. In addition to reducing the other harms of end-stage kidney disease, the use of dialysis can help clear the total body oxalate load and reduce risk, although dialysis is not as effective as renal oxalate

excretion, and kidney transplantation will likely be required in the future. In addition to dialysis, a low-oxalate diet is essential.

This patient's joint effusion demonstrates the presence of oxalate crystals and inflammation in the appropriate clinical setting, with a negative gram stain and a WBC count that is not intrinsically suspicious for infection (i.e., less than 50,000 WBCs/mm^3). Infection is therefore unlikely and empiric antibiotics are not warranted. Therefore, choice B is incorrect

A low purine diet would be useful for a patient with hyperuricemia and gout, since purines are metabolized to urate. In this case the problem is clearly oxalate, not urate, and a low purine diet would not be of value. Therefore, choice C is incorrect

In cases of primary genetic hyperoxaluria, as this one appears to be, management often requires renal transplantation, since dialysis may be inadequate to lower serum and tissue oxalate levels. In such cases, renal transplantation not only restores renal function but also promotes the removal of oxalate to control systemic disease. For Type I primary hyperoxaluria, in which excessive oxalate production is limited to the liver, combined hepatorenal transplantation is recommended, not only to restore renal function but also to normalize oxalate production. For Type II primary hyperoxaluria only renal transplantation is recommended, because oxalate production occurs in multiple tissues and is not significantly reduced by replacing the liver. In this patient, transplantation would be premature, since the efficacy of dialysis and diet are not yet established, and genetic testing will be required to determine which type of transplantation is warranted, if needed. Therefore, choices D and E are both incorrect.

Patients with secondary hyperoxaluria less commonly experience oxalosis and more commonly present with oxalate kidney stones and less severe renal impairment than is seen in primary hyperoxaluria. Secondary hyperoxaluria may be a result of diet alone, or more likely, of diet plus excess oxalate absorption from the gut that occurs in states of fat malabsorption such as Crohn's disease, gastric bypass, or short small bowel syndrome. In those cases, a low oxalate diet, plus changes to reduce fat malabsorption, may be sufficient management.

8. A 47-year-old female comes to your office complaining of left olecranon bursitis of recent onset. She reports a 10-year history of rheumatoid arthritis, currently managed with methotrexate 20 mg weekly, along with daily folic acid. On examination you confirm that her left olecranon bursa is enlarged and fluctuant, and mildly warm and erythematous. The elbow joint has full range of motion. Further examination demonstrates moderate bogginess of the MCP and PIP joints of the hands, bilaterally. Laboratory values are significant for an ESR of 42 mm/hour (Reference range < 20 mm/hour) and a positive rheumatoid factor. Complete blood count and basic metabolic panel are within normal limits. Aspiration of the bursa yields 10 cc of slightly cloudy yellow fluid. The bursal fluid WBC count is 22,000/mm^3 (Reference range 0–200/mm^3) (predominantly

neutrophils), and gram stain is negative. Under polarizing microscopy, you observe multiple birefringent, notched, plate-like crystals.

Which of the following is the most appropriate intervention at this time?

A. Aspirate elbow joint.
B. Initiate adalimumab.
C. Initiate lovastatin.
D. Initiate oral antibiotics.
E. Perform bursectomy.

Correct answer: B

This patient has cholesterol crystal-associated bursitis, a not uncommon finding in patients with rheumatoid arthritis. Cholesterol crystals may also be found in joints, and similar findings may less commonly occur in psoriatic arthritis, lupus, and Lyme arthritis. The reason for cholesterol crystal formation in systemic inflammatory arthritis is not fully known but appears to relate to a local phenomenon within the inflamed joint, as the phenomenon is not associated with hyperlipidemia. While cholesterol crystals are thought to be mildly inflammatory, in this case the presence of bursitis is indicative of inadequately treated rheumatoid arthritis, a presumption supported by the active symmetrical small joint synovitis of the patients hands. Management is therefore focused mainly on better treatment of the patient's rheumatoid arthritis; since she is already on maximal-dose methotrexate, adding adalimumab is a reasonable next intervention.

Aspirating the elbow joint would not be a useful strategy in this case (choice A). The elbow joint is asymptomatic and has full range of motion, suggesting it is uninvolved in the current problem, and is unlikely to be involved in the current clinical situation. Indeed, the elbow joint is not in communication with the olecranon bursa, and conditions affecting one rarely directly affect the other. Initiating lovastatin (choice C) would also not be a useful strategy; most cases of cholesterol crystal arthritis are unrelated to systemic hyperlipidemia and do not require therapeutic lipid lowering. Oral antibiotics (choice D) may be an acceptable treatment for an infected bursa (in contrast to infected joints which need intravenous antibiotics) but are not warranted here; the inflammation is local, the white count is only moderately elevated, the gram stain is negative, and the patient's rheumatoid arthritis/cholesterol crystal deposition are sufficient to account for the bursitis (though of course, sending and following up on fluid for culture constitutes proper medical practice). Bursectomy (choice E) is occasionally required for chronic refractory uncomfortable or painful olecranon bursitis, but that is not the clinical scenario here, and the current bursitis is likely to respond to rheumatoid arthritis treatment.

9. A 71-year-old female presents to your clinic complaining of pain in her right shoulder for the past 2 months. The shoulder hurts with movement, and pain also renders her unable to sleep on her right side. Acetaminophen 1000 mg afforded her no improvement. Her medical history includes adult-onset diabetes mellitus, hypertension, hypothyroidism, hyperlipidemia, coronary artery disease, and end-stage renal disease on dialysis for the past 4 years. Her current

medications include insulin, amlodipine, atorvastatin, and levothyroxine. On physical examination, she is afebrile with blood pressure of 148/86, and pulse of 92. Her heart and lung examinations are unremarkable. She has a normal arteriovenous fistula in her left forearm. Musculoskeletal examination is significant only for anterior fullness and diffuse tenderness in her right shoulder. The right shoulder is severely limited on active range of motion in all directions, and she is unable to lift her right arm above her head. Passive range of motion is slightly decreased in all directions, and she experiences significant pain upon abduction and elevation of the arm above her head. She denies any preceding trauma. Her left shoulder exam is normal. Laboratory studies include:

- White blood cell count: 4.6×10^3/uL (Reference range $4.0–10.0 \times 10^3$/uL)
- Hemoglobin: 8.2 g/dL (Reference range 12–16 g/dL)
- Platelet count: 218×10^3/uL (Reference range $150–400 \times 10^3$/uL)
- Potassium: 4.4 mmol/L (Reference range 3.5–5 mmol/L)
- Creatinine: 4.5 mg/dL (Reference range 0.8–1.2 mg/dL)
- Calcium 10.9 mg/dL (Reference range 8.4–10.2 mg/dL)
- Urate 4.2 mg/dL (Reference range 2.5–6.0 mg/dL)

Thyroid-stimulating hormone is within normal limits. Rheumatoid factor and CCP are negative.

An X-ray of her shoulder shows sclerosis and joint space narrowing of the glenohumeral and acromioclavicular joints, with calcification in the soft tissue around the humeral head and in the area of the rotator cuff tendons.

A joint fluid aspiration reveals a white cell count of 16,500 cells/mm^3, predominantly neutrophils. Gram stain shows no organisms, and cultures are negative. No crystals are seen under polarized light microscopy.

What is the most likely diagnosis?

A. Basic calcium phosphate arthritis
B. Calcium pyrophosphate deposition disease
C. Erosive osteoarthritis
D. Gout
E. Rheumatoid arthritis

Correct answer: A

This patient presents with an acute inflammatory monoarthritis affecting her shoulder, with calcific periarthritis, consistent with basic calcium phosphate arthritis, which most commonly affects the shoulder in women over the age of 50. Individuals with underlying metabolic abnormalities including hypercalcemia, end-stage renal disease, and endocrinopathies such as diabetes mellitus or hypothyroidism are particularly affected. Basic calcium phosphate crystals cannot be seen under polarized light microscopy but can be seen using electron microscopy and/or calcium staining with alizarin red S, neither of which is routinely done. When found in an acute setting with severe shoulder inflammation, tendinitis, and destructive arthritis, this condition is known as Milwaukee shoulder.

Choice B, calcium pyrophosphate deposition disease is incorrect. Although CPP crystals can cause an acute inflammatory arthritis affecting the shoulder with an inflammatory synovial fluid count, isolated shoulder involvement is not the most common presentation, tendons are less commonly affected than in basic calcium phosphate disease, and polarizing microscopy (especially in such a severe case) should have revealed positively birefringent rhomboid shaped crystals.

Choice C, erosive osteoarthritis, is incorrect. Erosive osteoarthritis is a condition that typically affects the distal interphalangeal and proximal interphalangeal joints of patients with hand osteoarthritis, causing inflammation and central joint erosions. Although basic calcium phosphate deposition may contribute to erosive osteoarthritis, the presentation in the shoulder is not consistent with such a diagnosis.

Choice D, gout, is incorrect. This patient, who is post-menopausal and has end-stage renal disease, may indeed be hyperuricemic and therefore susceptible to gout. However, a first attack in the shoulder would be uncommon, as would the duration of this condition in a first gouty attack. Most importantly, the absence of negatively birefringent needle-shaped crystals in the synovial fluid makes gout unlikely in this case.

Choice E, rheumatoid arthritis, is incorrect. Although rheumatoid arthritis can present later in life, and is more common among females, the lack of symmetrical small joint involvement of the hands, the monoarticular nature of the complaint, and the absence of RF and anti-CCP antibodies make rheumatoid arthritis unlikely.

10. A 52-year-old woman presents to your clinic with 5 days of severe neck pain. She denies any preceding trauma. She states that the pain is greatest in the back of her neck and that she has had trouble turning to look either left or right. The pain has continued to worsen over the past few days and did not improve with acetaminophen. Her past history is significant only for hypertension. On physical examination, she is afebrile with normal vital signs. She has decreased passive and active range of motion to a maximum of 30° in any direction, with increasing pain at the ends of the range. Her neurologic examination is normal. Laboratory studies, including complete blood count, basic metabolic profile, and creatinine, are all within normal limits. Her ESR is 51 mm/hour (normal range < 20 mm/hour), and her CRP is 1.60 mg/dL (normal: <0.8 mg/dL). An X-ray of her cervical spine shows a calcification slightly posterolateral to and abutting the odontoid process. An MRI showed a low signal intensity encircling the odontoid process.

    Which of the following is the best next treatment for this patient?

    A. Cervical epidural injection of corticosteroid
    B. Infliximab
    C. Isoniazid, rifampin, pyrazinamide, and ethambutol for 6 months
    D. Meloxicam
    E. Soft cervical collar with extra-strength acetaminophen

Correct answer: D

This patient most likely has crowned dens syndrome, a condition of calcification and crystal deposition around the odontoid process which can induce inflammation that most commonly causes neck pain, but may also cause headaches, fevers, and meningismus. Crowned dens syndrome is most commonly a consequence of calcium pyrophosphate deposition but may also be seen with basic calcium phosphate deposition. Diagnosis can be made by visualization of a crown-like calcified mass around the odontoid on x-ray. CT scans of the cervical spine may be more sensitive and specific and frequently show calcification of the transverse ligament. Biopsy of the mass is usually not needed but is diagnostic, typically revealing the crystals that cause the disease. First-line medications for crowned dens syndrome without acute neurologic complications are similar to any acute crystal disease—NSAIDs or colchicine—and most patients experience complete symptom resolution. Refractory cases may need oral prednisone, and if there is spinal cord compression, surgical debridement may be necessary.

This patient does not have evidence of spinal stenosis or foraminal narrowing to suggest degenerative joint disease requiring epidural injections. Therefore, choice A is incorrect.

Although spondyloarthropathy or rheumatoid arthritis may result in pannus that could be mistaken for the lesion of crowned dens syndrome, this patient has no peripheral joint involvement and has an acute inflammatory cause of her neck pain, consistent with crowned dens syndrome. Therefore, choice B is incorrect.

Although tuberculous spondylitis (Pott disease) may affect the cervical spine, it usually affects patients at high risk for tuberculosis and presents with a more subacute course with worsening pain which may eventually lead to destruction of the intervertebral joints and discs, leading to vertebral collapse and spinal compression. Therefore, choice C is incorrect.

This patient has an inflammatory condition and needs to be treated with anti-inflammatory therapy. While a soft cervical collar and acetaminophen would do no harm, they would be unlikely to adequately relieve her symptoms. Therefore, choice C is incorrect.

11. A 53-year-old man is referred to the rheumatologist for evaluation of chronic joint pains. He reports pain and swelling in his fingers, knees, and shoulders. His pain is chronic and does not wax and wane. He was recently seen by a community provider, who aspirated his knee and performed x-rays of his hands and knees, and he brings the reports with him today. He has been treating his pain with acetaminophen with modest relief but wants to know if there is anything better that he can do. His medical history is significant for diet-controlled diabetes mellitus. On physical examination, he is afebrile and hemodynamically stable. His musculoskeletal exam is significant for bony hypertrophy of the bilateral second and third metacarpophalangeal joints, along with mild warmth and minimal tenderness to palpation. He has bony hypertrophy of his knees with mild tenderness along the joint line and coarse crepitus. He complains of

pain with active and passive internal rotation of both shoulders, but has no edema or erythema of these joints, and has no pain over the acromioclavicular joint or evidence of impingement. A complete metabolic panel obtained the week before shows a creatinine of 1.1 mg/dL (Reference range 0.8–1.2 mg/dL), an AST of 72 U/L (Reference range 0–40 U/L), and an ALT of 68 U/L (Reference range 0–40 U/L).

Synovial fluid analysis from the knee aspiration the week before is as follows:

- 12,000 WBC/uL (Reference range 0–200/uL)
- 2000 RBC/uL (Reference range 0–50/uL)
- No organisms on gram stain with negative cultures
- Positively birefringent rhomboid crystals found in fluid

Hand X-rays: joint space narrowing along with hook-shaped osteophytes present in bilateral second MCP's, along with chondrocalcinosis of the triangular fibrocartilage above the ulnar styloid of the left hand. There is a subchondral cyst in the left third metacarpal head.

Knee X-rays: chondrocalcinosis with mild tricompartmental joint space narrowing and sclerosis

What is the most important next step in the assessment and management of this patient?

A. Continue acetaminophen and begin hand and knee exercises for osteoarthritis.
B. Order serum ferritin and transferrin saturation.
C. Order a serum urate level and start urate-lowering therapy together with colchicine.
D. Perform intra-articular corticosteroid injections of his tender joints.
E. Start celecoxib.

Correct answer: B

This patient is presenting with likely hereditary hemochromatosis based on the chronic arthritis, transaminitis, and diabetes. About one-third of patients with hereditary hemochromatosis arthropathy also have chondrocalcinosis, with CPPD crystals found in their synovial fluid. Classic joints affected in hemochromatosis (as well as CPPD arthritis) include the second and third metacarpophalangeal joints. Other joints frequently affected include the knees, shoulders, hips, and feet. Specific X-ray findings in hereditary hemochromatosis arthropathy include joint space narrowing and hook or beak-shaped osteophytes in the second or third metacarpophalangeal joints (along with CPPD deposition in some cases), as well as the presence of subchondral cysts and sclerosis indistinguishable from osteoarthritis. While not diagnostic, the presence of elevated transaminases and diabetes are also consistent with hemochromatosis involvement of the liver.

Even though the patient has joint space narrowing, osteophytes, and sclerosis on his X-rays, he clearly also has an inflammatory arthritis with CPPD crystals.

Additionally, osteoarthritis most frequently affects the distal interphalangeal or proximal interphalangeal joints and rarely affects the metacarpophalangeal joints. Thus, the patient has three joint diseases—osteoarthritis, CPPD arthritis, and hemochromatosis. Although the use of acetaminophen and occupational therapy may afford him transient relief, missing a diagnosis of hemochromatosis will put the patient at risk for additional long-term problems. Therefore, choice A would not be the most important action to take at this time.

The rhomboid-shaped, positively birefringent crystals seen in the synovial fluid are calcium pyrophosphate crystals. In contrast, urate crystals are negatively birefringent, needle-shaped crystals. Given lack of metatarsophalangeal or ankle/midfoot involvement, lack of episodic symptoms, and calcium pyrophosphate crystals, this patients presentation is not consistent with a gout attack and does not require gout assessment or treatment as an immediate activity. Therefore, choice C is incorrect.

This patient has chronic arthritis affecting multiple joints, with other findings compatible with hereditary hemochromatosis. Since corticosteroid injections are more appropriate and effective for mono- or oligo arthritis, their use here would be a secondary option at best. Therefore, choice D is incorrect.

Celecoxib treatment may provide him relief and is not contraindicated, but it is not the most important step at this time. Therefore, choice E is incorrect.

12. A 56-year-old man is referred to your office for management of recurrent episodes of pain and swelling that have variously affected the knees, wrists, and shoulders. He reports that each episode usually affects two or three of the aforementioned joints at a time. His most recent episode, which occurred about 3 weeks ago, affected his left knee and right wrist. Overall, the episodes occur roughly every few months and usually last up to 4 weeks before resolving. He started taking diclofenac during the last episode and believes that it greatly shortened the episode and improved his pain, and he continues to take it twice a day. On your examination today, he has no tender or swollen joints, although you notice Heberden's nodes on the second and fourth distal interphalangeal joint of his left hand. He also has bilateral knee crepitus. Labs reveal an ESR of 7 mm/hour (Reference range 0–22 mm/hour), a CRP of 0.2 mg/dL (Reference range 0–0.8 mg/dL), a creatinine of 0.9 mg/dL (Reference range 0.8–1.2 mg/dL), calcium of 11.3 mg/dL (Reference range 8.4–10.2 mg/dL), a normal thyroid stimulating hormone, a negative rheumatoid factor, and a serum urate of 4.5 mg/dL (Reference range 2.5–6.0 mg/dL). An ultrasound of his right knee shows linear and punctate hyperechoic densities within the hyaline cartilage.

    If you were to aspirate the fluid during his next attack, which would be the most likely finding?

    A. WBC 15,000 with neutrophil predominance and positively birefringent rhomboid-shaped crystals.
    B. WBC 41,000 with neutrophil predominance and negatively birefringent needle-shaped crystals

C. WBC 80,000 with neutrophil predominance and gram-positive cocci and no crystals
D. WBC 300 with lymphocytic predominance and variable positive birefringent envelope-shaped crystals
E. WBC 10,000 multinucleated giant cells, macrophages with phagocytized hemosiderin, and foam cells

Correct answer: A

This patient with an episodic inflammatory arthritis affecting the knees, wrists, and shoulders, with hypercalcemia on laboratory studies and a musculoskeletal ultrasound showing linear and punctate hyperechoic lesions in the hyaline cartilage that is pathognomonic for calcium pyrophosphate deposition. Given the setting of CPPD, and the recurrent nature and joints involved, acute CPPD arthritis is the most likely explanation for his flares. A moderately elevated WBC count and positively birefringent rhomboid crystals would be characteristic of this type of acute arthritis.

Although this patient has an episodic inflammatory arthritis that could be compatible with gout, the fact that he has a serum urate level within normal limits during an asymptomatic period, along with the lack of first MTP involvement in a male, would be uncharacteristic of gout. While the ultrasound findings do not rule out gout, neither to they provide any evidence for gout (i.e., tophi or "double contour" sign, or a hyperechoic continuous band over the superficial margin of the superior border of the articular cartilage). Therefore, choice B is incorrect.

A WBC count greater than 50,000/mm^3 would be most concerning for a septic joint and can occasionally be seen in gout; it is rarely seen in CPPD arthritis. Although infectious arthritis is always on the differential for inflammatory arthritis, this patient's recurrent arthritis with multiple joints involved, lack of systemic complaints, and lack of illness would be extremely atypical for joint infection. Therefore, choice C is incorrect.

The patient's episodes are clearly inflammatory, which would be inconsistent with a WBC that is in the normal range (as 300 is). Inflammatory effusions are defined as having at least 2000 WBC/mm^3. The patient in this case has an inflammatory arthritis and should have a synovial fluid white cell count between 2000 and 50,000 during an acute episode if inflammatory arthritis. Furthermore, positively birefringent envelope-shaped crystals would be pathognomonic for calcium oxalate crystals, not CPPD crystals. Therefore, choice D is incorrect.

Pigmented villonodular synovitis (PVN) is a condition of synovial thickening and overgrowth of unknown cause that most commonly affects the knees. Although it is benign (i.e., non-malignant) it can be invasive of bone and cause significant joint destruction. PVN can cause an inflammatory arthritis, with swelling that can be either episodic or continuous in nature. A joint aspiration would reveal bloody synovial fluid with multinucleated giant cells, macrophages that have phagocytized hemosiderin and foam cells. An ultrasound of this would reveal hypoechoic synovial proliferation and hypervascularity on

color Doppler. MRI can be used to demonstrate or rule out the presence of massive synovitis. While PVN could not be ruled out in this case without additional evaluation, its rarity, together with the established presence of CPPD to support an acute CPP arthritis, makes finding a synovial fluid consistent with PVN very unlikely. Therefore, choice E is incorrect.

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Chapter 16
Autoinflammatory Diseases

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High-Yield Review of Autoinflammatory Diseases
Key Points on Autoinflammatory Diseases

- Autoinflammatory diseases are a genetically heterogeneous group of rheumatic inflammatory diseases and are driven by abnormal activation of the innate immune system.
- Autoinflammatory diseases are distinct from systemic autoimmune diseases in that autoantibodies and antigen-specific T cells are generally absent in the former conditions.
- Autoinflammatory diseases compass monogenic and polygenic disorders, and molecular genetic analysis usually aids in the diagnosis.

Clinical Pearls on Autoinflammatory Diseases

- FMF is an autosomal recessive disorder generally, and patients have two copies of the *MEFV* mutations, but approximately 30% of patients carry only one copy and up to 20% of patients lack detectable mutations.
- CAPS has three subtypes that are caused by *NLRP3* mutations and is associated with inflammasome. Patients have good response to interleukin-1 inhibitors.

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- TRAPS is characterized by periorbital swelling and localized myalgia underlying rash.
- HIDS occurs in children and the disease onset is extremely rare in adults. Elevated IgD levels are not specific to the disease.
- NLRP12-AID and CAPS (FCAS1) share very similar phenotypes, and molecular analysis of *NLRP12* and *NLRP3* aids in the differentiation between the two diseases.
- NOD2-associated diseases include Blau syndrome, Crohn disease, and Yao syndrome, and they are distinct in clinical phenotypes and genotype.

Introduction

Autoinflammatory diseases (AIDs) are a genetically heterogeneous group of rheumatic diseases that are driven by abnormal activation of the innate immune system [1–3]. In its inception of this group of diseases, AIDs were defined to have recurrent episodes of fever and systemic inflammation without high titer of autoantibodies or high number of antigen-specific T lymphocytes. Most recently, AIDs have been defined as clinical disorders caused by defects or dysregulation of the innate immune system, characterized by recurrent or continuous inflammation (elevated acute-phase reactants) and by the lack of a primary pathogenic role of the adaptive immune system (autoreactive T cells or autoantibody production) [4, 5]. The prototypic AIDs are hereditary monogenic periodic fever syndromes, including familial Mediterranean fever (FMF), TNF receptor-associated periodic fever syndrome (TRAPS), mevalonate kinase deficiency (MKD) (formerly named as hyper-IgD with periodic fever syndrome), *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID) (formerly known as cryopyrin-associated periodic syndrome (CAPS)), and *NLRP12*-associated autoinflammatory disease (*NLRP12*-AID) [6]. With application of more advanced molecular techniques notably next-generation sequencing, the disease spectrum is rapidly expanding, including those associated with *PSMB8*, *ADA2*, *NLRC4*, and *NLRP1* genes as well. Monogenic AIDs are classified (Table 16.1).

Individual Disease

Familial Mediterranean Fever

Pathophysiology

Familial Mediterranean fever (FMF) is the most prevalent AID worldwide, which is characterized by recurrent episodes of fever and serosal inflammation. It is generally considered an autosomal recessive disorder, and the pathogenic mutations are

Table 16.1 The classification of autoinflammatory diseases

Monogenic periodic fever syndromes
FMF (familial Mediterranean fever)
MKD (mevalonate kinase deficiency)
NLRP3-AID (*NLRP3*-associated autoinflammatory disease)
TRAPS (TNF receptor-associated periodic fever syndrome)
NLRP12-AID (*NLRP12*-associated autoinflammatory disease)
NOD2-associated diseases
Blau syndrome
Crohn disease
Yao syndrome
PRAAS (proteasome-associated autoinflammatory disease)
DIRA (deficiency of the IL-1 receptor antagonist)
DITRA (deficiency of the IL-36 receptor antagonist)
PAPA (*PSTPIP1*-associated arthritis, pyoderma gangrenosum, and acne)
APLAID (*PLCG2*-associated antibody deficiency and immune dysregulation) syndrome
SAVI (STING-associated vasculopathy with onset in infancy)
DADA2 (ADA2 deficiency)
Schnitzler syndrome
CNO (chronic nonbacterial osteomyelitis)
Other rare AIDs

located in the *MEFV* gene on the chromosome 16. Four mutations, M694V, M694I, M680I, and V726A, account for most cases in the Mediterranean populations. The mutations in exon 10 of the *MEFV* gene tend to be associated with more severe disease as compared with variants found in exons 2 and 3. However, approximately 30% of patients who meet clinical diagnostic criteria for FMF have only one copy of *MEFV* mutations. Moreover, *MEFV* mutations are absent in up to 20% of patients who fulfill the clinical diagnostic criteria for FMF [7–9].

The *MEFV* gene, identified in 1997, encodes a protein of 781 amino acids, pyrin, which plays an important role in the innate immune system defending against external pathogens. In patients with FMF, the mutations in the *MEFV* gene result in the production of pyrin even in the absence of external triggers, leading to the formation of the NLRP3 inflammasome, which in turn causes the secretion of interleukin (IL)-1βand other inflammatory mediators, and eventually FMF attacks [7, 8].

Clinical Presentation

FMF mainly affects patients of Mediterranean descent, such as Turks, Armenians, North Africans, Jews, and Arabs, but it has also been reported in other parts of the world at a lower prevalence. Most patients experience the initial attack during early childhood, with 90% of patients exhibiting their first symptoms by the age of 20 years [7, 8].

FMF is characterized by recurrent attacks of fever and serositis resulting in abdominal and chest pain. The onset of symptoms is usually abrupt without consistent triggers. The disease attacks generally last fewer than 3 days before spontaneous resolution. Between attacks, irregular asymptomatic intervals range from weeks to years [7, 8].

1. Fever is present in almost all episodes, and the temperature usually rises to above 38°. Chills often herald the onset of fever, and the typical duration of fever only lasts between 12 h and 3 days.
2. More than 90% of the FMF patients have abdominal pain during attacks mostly as a result of sterile peritonitis. The pain is usually generalized, and guarding, rebound tenderness, and rigidity are often present. The abdominal pain is so severe that can mimic an acute surgical abdomen. Some patients also experience pleuritic chest pain which is usually unilateral. Concomitant pericarditis can also develop.
3. Other two common symptoms are joint pain which is usually mono- or oligoarticular affecting large joints (knee, ankle, hip, or wrist) and erysipelas-like skin changes which typically occur as a tender erythematous plaque in the lower extremities.
4. Sometimes, children with FMF can develop exertional myalgia of the lower limbs, and rarely, patients with M694V mutation may present with severe, debilitating "protracted febrile myalgia" lasting up to 8 weeks, which is thought to be due to vasculitis. Other rare manifestations also include acute scrotal swelling and tenderness and aseptic meningitis.
5. The laboratory tests during attacks demonstrate nonspecific systemic inflammation, including leukocytosis, neutrophilia, and elevated acute-phase reactants, such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), serum amyloid A (SAA), and fibrinogen. Mild to moderate, transient pleural, and pericardial effusion can be detected by imaging. Between attacks, persistent elevation of the acute-phase reactants may be present, and persistent proteinuria requires a renal biopsy to rule out amyloidosis.
6. Secondary (AA) amyloidosis is a major cause of mortality in FMF patients. Renal amyloidosis can present with nephrotic syndrome and gradually lead to end-stage renal disease. Amyloidosis can also involve other organs such as the liver, spleen, gastrointestinal tract, and heart. Colchicine treatment has markedly decreased the incidence of amyloidosis. Peritoneal adhesions leading to small bowel obstruction and infertility or subfertility are other long-term complications in the pre-colchicine era.
7. In addition, immunoglobulin A vasculitis, polyarteritis nodosa, Behçet's syndrome, and ankylosing spondylitis have higher prevalence among FMF patients.

Diagnosis

FMF is diagnosed based upon clinical ground, which can be supported but not excluded by genetic testing. Genetic testing is also performed to exclude other

hereditary periodic fever syndromes. The detection of biallelic pathogenic mutations in the *MEFV* gene confirms the diagnosis [9]. At present, the most widely used clinical diagnostic criteria were proposed by the Tel Hashomer Medical Center in Israel in 1997 [10]. Using this set of criteria, a diagnosis can be made with both a specificity and sensitivity of >95%. In this set of criteria, typical attacks are defined as recurrent (≥3 of the same type), febrile (rectal temperature of 38 °C or higher), and short (lasting between 12 h and 3 days). Incomplete attacks are defined as painful and recurrent attacks that differ from typical attacks in one or two features, as follows: (1) the temperature is normal or lower than 38 °C; (2) the attacks are longer or shorter than specified (but not shorter than 6 h or longer than a week); (3) no signs of peritonitis are recorded during the abdominal attacks; (4) the abdominal attacks are localized; (5) the arthritis is in joints other than those aforementioned. Attacks are not counted if they do not fit the definition of either typical or incomplete attacks. The requirements for the diagnosis of FMF are:

1. ≥1 major criteria
2. ≥2 minor criteria
3. 1 minor criterion plus ≥5 supportive criteria
4. 1 minor criterion plus ≥4 of the first 5 supportive criteria

The major differential diagnoses for FMF include other autoinflammatory periodic fever syndromes, such as TRAPS, CAPS, MKD, and periodic fevers with aphthous stomatitis, pharyngitis, and adenitis (PFAPA). These diseases all present with periodic or episodic fevers, but the durations of fever vary. The attacks of TRAPS typically last 1–3 weeks, CAPS 1–2 days, HIDS 3–7 days, and PFAPA 3–7 days with a true periodicity of 3–4 weeks. Genetic testing is used to help distinguish these diseases clearly. Systemic juvenile idiopathic arthritis or Still disease usually may be differentiated from FMF by its typical quotidian or persistent fever. The etiologies for fever of unknown origin, for instance, rheumatic diseases, infection, and malignancy, should also be considered and excluded based upon their specific clinical features [11].

Treatment

The initial treatment for FMF is daily oral colchicine at doses of 1–2 mg/day to prevent acute attacks and the development and progression of amyloidosis [11]. Compliance is very important for its efficacy. Colchicine should generally be started at a low dose and gradually increased as tolerated to minimize the gastrointestinal toxicities, such as diarrhea, cramping, and bloating. Dose adjustment is necessary in patients with renal or liver impairment. Higher dosage above 2 mg/day is rarely used for long periods because of intolerance.

Regular safety monitoring should include measurements of blood cell counts for leukopenia, urinalysis for proteinuria, serum chemistries, and the acute-phase reactants [11]. The efficacy of colchicine in FMF has been proven in several double-blind, placebo-controlled trials. It can induce a near cessation of FMF attacks in

about 70% of patients and provides at least some relief in more than 90%. In FMF patients with amyloidosis, colchicine could prevent the progression of nephrotic syndrome. Patients with elevated ESR, CRP, or SAA between attacks despite maximal colchicine are considered colchicine resistant because of the risk of amyloidosis.

For patients who are non-responders to colchicine (up to 15%) or those who are intolerant to colchicine (up to 5%), IL-1 inhibition is the preferred treatment. Concomitant colchicine at a tolerable dose should be given for the prevention of amyloidosis. Among the three IL-1 inhibitors, canakinumab, rilonacept, and anakinra, canakinumab is approved by FDA to treat the disease. TNF inhibitors or IL-6 receptor antagonist, tocilizumab, may be tried [11].

NLRP3-*Associated Autoinflammatory Disease*

Pathophysiology

NLRP3-associated autoinflammatory disease (*NLRP3*-AID), formerly known as cryopyrin-associated periodic syndromes (CAPS) or cryopyrinopathies [6], consists of a clinical continuum of three overlapping disorders of increasing severity, including familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), also known as chronic infantile neurologic cutaneous articular (CINCA) syndrome. All three cryopyrinopathies are caused by mutations in the *NLRP3* gene in chromosome 1, encoding a protein called cryopyrin (also known as NALP3, CIAS1, or PYPAF1). Thus, in 2018, it was proposed that a single name, *NLRP3*-associated autoinflammatory disease (*NLRP3*-AID), should be used, and adjectives mild, moderate, and severe phenotypes may be added instead of using the historical names FCAS, MWS, and NOMID/CINCA [6, 12, 13].

Cryopyrin belongs to the NOD-like receptor (NLR) family that is intracellular sensors of molecular danger signals. It serves as a scaffold for the assembly of the NLRP3 inflammasome, a multimolecular complex activating the protease, caspase-1, which cleaves pro-IL-1β and pro-IL-18 to their biologically active forms. Nearly 200 disease-causing mutations of the *NLRP3* gene have been reported in CAPS, and more than 75% of them are located in exon 3, which encodes the central regulatory NACHT domain of the cryopyrin protein. Point mutations in CAPS promote aberrant formation of the inflammasome and production of the active IL-1β, which leads to inappropriate inflammation. Phenotypic differences among the three cryopyrinopathies are thought to be caused by the different impact of mutations on the activity of the inflammasome, modulated by individual genetic background [12, 13].

Clinical Presentation [12, 13]

CAPS are rare autosomal dominant disorders with an incidence of 1/1,000,000 in the USA. The clinical features of the three subtypes of CAPS are described below.

FCAS, formerly known as familial cold autoinflammatory syndrome, is at the mildest end of the CAPS spectrum. The onset of symptoms typically occurs in early childhood, usually in the first year of life. FCAS flares are triggered by generalized cold exposure and present with a systemic inflammatory response including urticarial rash (100%), polyarthralgia (96%), and low-grade fever (93%). Patients may also experience conjunctivitis, which is rather distinctive among periodic fever syndromes, as well as fatigue, dizziness, headache, and nausea. Symptoms often develop within hours after cold exposure and last 12–48 h. FCAS rarely leads to secondary amyloidosis (<2%).

Muckle-Wells syndrome (MWS) is characterized by intermittent episodes of fever, urticarial rash, headache, conjunctivitis, and arthralgia/arthritis and may lead to severe sequelae such as progressive sensorineural hearing loss and renal amyloidosis. Febrile episodes are not typically precipitated by cold exposure. The self-limiting systemic inflammation may last between 12 h to days, and the intervals between attacks range from weeks to months. Patients who suffer from aseptic meningitis often complain of headache and may progress into increased intracranial pressure (ICP) with papilledema. Sensorineural hearing loss caused by chronic inflammation of inner ear typically develops in the late childhood or the early adulthood. Secondary amyloidosis has been described in 25–33% of untreated patients.

NOMID/CINCA is the most severe of the CAPS spectrum. In addition to the systemic symptoms similar to FCAS and MWS, such as urticarial rash, conjunctivitis, and fever, patients with NOMID/CINCA have characteristic abnormalities, including frontal bossing, protruding eyes, and saddle-shaped nose, generally manifesting at or near the time of birth. Focal exuberant cartilaginous proliferation at growth plates and epiphyses frequently leading to joint deformities is seen in up to 70% of patients, most commonly involving the epiphyses of the distal femur and proximal tibia and the patella. Chronic aseptic meningitis, presenting with irritability, headaches, nausea, and vomiting, can lead to increased ICP, papilledema, seizures, hydrocephalus, and cerebral atrophy. Other features include sensorineural hearing loss, uveitis, lymphadenopathy, hepatosplenomegaly, and arthralgia. NOMID/CINCA leads to growth retardation and cognitive disability and may cause premature death and secondary amyloidosis.

Laboratory findings in CAPS include leukocytosis with neutrophilia, thrombocytosis, and elevation of acute-phase reactants. Biopsies of urticarial rash show a marked perivascular infiltration of neutrophils, in contrast to the lymphocytic and eosinophilic infiltrate found in classical allergic urticaria. Lumbar punctures in patients with chronic meningitis may show increased ICP, neutrophilic leukocytosis, and elevation of protein. Radiographs of the long bones can demonstrate epiphyseal lesions.

Diagnosis

The diagnosis of CAPS should be suspected in patients with recurrent episodes of unexplained fever and/or urticarial rash, especially in patients with a positive family history. The diagnostic criteria for CAPS proposed by a multidisciplinary team of

international experts in 2017 require one mandatory criterion plus ≥two of six CAPS typical signs/symptoms [14]. In patients with typical manifestations, the presence of *NLRP3* mutations is confirmatory, but is not necessary to initiate therapy.

Treatment

Nearly all patients with CAPS respond dramatically to IL-1 blockade. Three IL-1 blocking agents are approved by the US Food and Drug Administration for the treatment of CAPS: anakinra, rilonacept, and canakinumab. Anakinra, an IL-1 receptor antagonist, is given subcutaneously on a daily basis. Rilonacept is a fusion protein consisting of a ligand-binding portion of the human IL-1 receptor linked to the Fc region of human IgG1. Rilonacept is given subcutaneously once a week. Canakinumab is a human anti-IL-1β monoclonal antibody, which is given subcutaneously every 8 weeks. Optimal treatment with these agents leads to complete resolution of symptoms in most cases [15].

NLRP12-*Associated Autoinflammatory Disease*

Pathophysiology

NLRP12-associated autoinflammatory disease (*NLRP12*-AID) is also known as familial cold autoinflammatory syndrome 2 (FCAS 2), and it is a rare autosomal dominant disease that is characterized by recurrent fever and musculoskeletal symptoms associated with the mutations in the *NLRP12* gene.

Studies have shown that *NLRP12* is closely related to the inflammasome scaffold, *NLRP3*. While the precise function of *NLRP12* is debatable, it forms inflammasome or regulates inflammasome function. *NLRP12* is reported to regulate inflammation by activation of caspase-1 via inflammasome, leading to the processing and secretion of IL-1β. Meanwhile, caspase-1 induces cell apoptosis and attenuates the negative regulation of NF-κB signaling induced by TNF [16, 17].

Clinical Presentation and Diagnosis

NLRP12-AID can occur in multiple ethnic groups, sporadically in both children and adults. The clinical features of *NLRP12*-AID are similar to *NLRP3*-AID, notably FCAS, including periodic fever, rash (primarily urticaria), myalgia, polyarthralgia/arthritis, abdominal pain/diarrhea, thoracic pain, headache, sensorineural deafness, lymphadenopathy, and splenomegaly. Most patients report cold exposure as a trigger. Elevated acute-phase reactants are common in episodes. The *NLRP12* gene variant, F402, is the most frequent, and some other rare *NLRP12* gene variants have been reported as well. *NLRP12*-AID is diagnosed based on the characteristic clinical phenotype and genotype [16, 18–20].

Treatment

Therapeutically, glucocorticoids and antihistamine drugs are largely effective in the majority of patients with *NLRP12*-AID. IL-1 inhibitors may be beneficial. However, it has been reported that some patients albeit initially responsive eventually developed resistance to anakinra within a few months of treatment. Unlike their definite therapeutic roles in FCAS, IL-1 antagonists may be further evaluated for its potential efficacy in the treatment of the disease [19, 20].

TNF Receptor-Associated Periodic Fever Syndrome

Pathophysiology

TRAPS is caused by mutations in the *TNFRSF1A* gene in chromosome 12p13 which encodes the 55-kD, the TNF receptor 1 (TNFR1) for TNF-α. Most mutations associated with TRAPS (94%) are single-nucleotide missense variants within exons 2, 3, 4, and 6. The pathogenic mechanism of TRAPS is not fully understood. Studies suggest that TRAPS mutations might result from impaired metalloprotease-dependent cleavage of *TNFRSF1A*, producing soluble "shed" receptors. TNFR 1 on the cell surface does not neutralize TNF perhaps due to mutant TNFR1 protein misfolding and endoplasmic reticulum retention. In vitro studies show possible causative links between TRAPS-associated *TNFRSF1A* mutations and impaired TNF-α binding, abnormal apoptosis, and altered NF-kB pathway, as well as defective receptor trafficking to the cell surface [21].

Clinical Presentation

TRAPS often occurs in childhood (age 3) and causes variable and heterogeneous clinical manifestations. The disease is characterized by recurrent fever attacks, typically lasting from 1 to 3 weeks. Febrile attacks recur either spontaneously or after minor triggers (local injury, minor infection, stress, exercise, and hormonal changes) at varying intervals and usually initiate with muscle cramps or myalgia underlying the rash that migrate in a centrifugal pattern. Skin lesions usually start as painful and warm macules and papules, which progressively expand at the periphery, subsequently coalescing into large patches or plaques. Skin biopsies usually show dermal perivascular lymphocytic and monocytic infiltrates. Other less common skin lesions may include erysipelas-like erythema and urticarial rash. Eye involvement can include peculiar periorbital edema, conjunctivitis, and/or uveitis. Arthralgia occurs during febrile attacks in about two-thirds of patients, including mono- or oligo-arthralgia. Arthritis is less common, and joint effusion may occur. Serositis is also common, and amyloidosis can occur as a long-term complication of TRAPS [22, 23].

Diagnosis

TRAPS is diagnosed based on clinical ground and genetic confirmation of specific *TNFRSF1A* mutations. Patients with TRAPS should be regularly screened for proteinuria from renal amyloidosis [21].

Treatment

Patients gain some symptomatic relief from nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids, while colchicine or immunomodulators such as methotrexate, cyclosporine, and thalidomide produce very little benefit. TNF-α blockers, such as etanercept, can be used. IL-1 inhibitor, canakinumab, has been approved by FDA to treat the disease [21].

Mevalonate Kinase Deficiency

Pathophysiology

Mevalonate kinase deficiency (MKD), also known as hyperimmunoglobulin D syndrome (HIDS), is a rare monogenic disorder characterized by recurrent febrile attacks associated with rash, lymphadenopathy, abdominal pain, and elevated serum immunoglobulin D (IgD). HIDS can be divided into classic and variant forms. If the genetic defect is known, it is called the classic form, which accounts for 75% of cases. The variant form has similar clinical symptoms, but there is unclear genetics.

The classic HIDS is an autosomal recessive disorder, caused by loss-of-function mutations in the *MVK* gene which lead to mevalonate kinase (MK) deficiency. The most common mutation found in classic HIDS is the V377I mutation. The MK protein, encoded by the *MVK* gene in the chromosome 12, is an enzyme in the cholesterol synthesis pathway. Mutations in *MVK* that cause a mild to moderate reduction (normal 5–15%) in the enzymatic activity of MK lead to the periodic fever syndrome, HIDS, whereas mutations that cause more severe reduction or loss of MK activity result in a potentially fatal condition with marked developmental delay and mevalonic aciduria. The diminished activity of MK results in accumulation of its substrate mevalonic acid in serum and urine. However, the pathophysiologic mechanism underlying MK deficiency and self-limiting inflammation is still unclear. The cause of the characteristic high concentration of IgD in this syndrome is unclear. It has been suggested that neither elevated level of IgD nor accumulated mevalonic acid is responsible for the pathogenesis in HIDS [24–26].

Clinical Presentation [24–26]

HIDS occurs almost exclusively in childhood, and 90% of patients experienced the first attack within the first year of life, with a median age of 6 months. HIDS affects female and male equally. Most patients reported are of Dutch or French ancestry.

The potential triggers for HIDS attacks include vaccinations, minor trauma, surgery, or stress. Symptom-free intervals between attacks usually last 1–2 months without obvious periodicity. The durations of interval vary greatly and may become longer with increasing age. HIDS attacks are characterized by the rapid onset of moderate to high fever, which typically lasts 3–7 days. The prodrome may include nasal congestion, sore throat, fatigue, backache, and headache. More than 90% of patients have diffuse lymphadenopathy, mostly cervical, during febrile attacks. Palpable splenomegaly is found in 50% of patients. Abdominal pain is reported in 85% of patients, which is often accompanied by vomiting and/or diarrhea; the severity of pain may suggest acute abdomen. Skin rashes are noted in over 80% of patients, and erythematous macular rash is the most common type. Aphthous ulcers may occur in 50% of patients. Polyarthralgia/polyarthritis develops in 80% of patients during febrile episodes. Larger joints are involved more commonly and often in a symmetrical pattern. Secondary amyloidosis is rare.

Laboratory findings during HIDS attacks include leukocytosis with neutrophilia; elevation of acute-phase reactants such as ESR, CRP, SAA, ferritin, and fibrinogen; and increase in urinary mevalonate. The acute-phase reactants commonly return to normal or are only mildly elevated between attacks except for SAA, which may remain elevated in 50% of patients. Elevated serum IgD (>100I U/mL) and IgA levels are seen in over 80% of patients and remain elevated between attacks; elevated serum IgD levels are nonspecific.

Diagnosis

The diagnosis of HIDS should be entertained in patients with early-onset recurrent fever lasting 3–7 days, accompanied by a combination of characteristic clinical findings, such as lymphadenopathy, splenomegaly, arthralgia/arthritis, abdominal pain, and rash. The Eurofever clinical diagnostic/classification criteria may be used [27]. If the diagnostic cutoff score of ≥42 is reached, serum IgD should be measured to confirm the HIDS diagnosis. Clinical suspicion of the diagnosis in normal serum IgD can be corroborated by genetic testing [27].

Treatment

Most patients with HIDS have a normal lifespan and carry a good prognosis. However, if the attacks are frequent and severe, the quality of life will be significantly affected. The goal of treatment is to improve quality of life and to minimize

the risk of drug adverse effects. NSAIDs and/or short courses of oral glucocorticoid may be used; IL-1 inhibitors can be used, and canakinumab is approved by FDA to treat the disease [24–26].

Blau Syndrome [28–30]

Pathophysiology

Blau syndrome (BS) is characterized by an early-onset clinical triad of arthritis, dermatitis, and uveitis, and it is a rare autosomal dominant autoinflammatory granulomatous disorder. It is caused by gain-of-function mutations in the nucleotide-binding domain of the nucleotide-binding oligomerization domain protein 2 (*NOD2*), also called caspase recruitment domain-containing protein 15 (*CARD15*) gene in chromosome 16. In 2018, an international expert committee proposed that a general name, *NOD2*-associated granulomatous disease, should be used to encompass BS, early-onset sarcoidosis, and familial Crohn disease due to the fact that all the disorders are linked to *NOD2* mutations. Similar to NLRP3 protein, NOD2 protein is also a member of the NOD-like receptor family, which plays important roles in innate immune system. Mutations in BS are predominantly located in exon 4 of the *NOD2* gene. The two most common mutations are two missense mutations, R334Q and R334W.

Clinical Presentation

The disease onset of BS typically occurs before the age of 4 years. Three typical sites affected by granulomatous inflammation are joints, eyes, and skin. Joints are affected in over 90% of patients. The chronic granulomatous arthritis is almost always polyarticular, presenting as minimally symptomatic swelling involving the wrists, ankles, and knees. Arthritis of proximal interphalangeal joints of hands can lead to progressive flexion contractures of the fingers (camptodactyly). Symmetric hypertrophic tenosynovitis develops in up to 40% of patients, resulting in the typical periarticular “boggy” appearance, especially about the knees. Granulomatous uveitis is frequent (80%) and usually chronic and persistent. Acute anterior uveitis can be a presenting feature and often extends to panuveitis. Most patients have bilateral ocular involvement, leading to cataracts, glaucoma, and even blindness. Ocular involvement is the most significant morbidity in BS. The BS-associated dermatitis is typified by ichthyosis-like popular-nodular erythematous rash. The typical clinical triad of dermatitis, arthritis, and uveitis is seen in up to 80% of patients, usually in a consecutive fashion. Other manifestations include lymphadenopathy, vasculitis, cranial neuropathies, and granulomatous involvement of visceral organs. Fever and abdominal pain can occur infrequently.

Laboratory findings include leukocytosis, thrombocytosis, and elevation of acute-phase reactants such as ESR and CRP. Biopsies of synovium and skin show noncaseating granulomas in typical cases.

Diagnosis

The diagnosis of BS is based upon characteristic clinical phenotype. Histological findings of granulomas are the most supportive of the disease in the proper clinical setting. Molecular testing for the *NOD2* mutations provides more definitive diagnosis.

Treatment

Optimal therapy for BS has not been well defined. NSAIDs can be used for mild clinical manifestations, and severe symptoms are often treated with systemic glucocorticoids. Immunosuppressants such as methotrexate and cyclosporine are used as glucocorticoid-sparing agents. Biologic agents such as TNF-α blockers (infliximab and adalimumab) can be used. IL-1 and IL-6 inhibitors were anecdotally reported. Uveitis should be managed with both topical and systemic therapies. Early diagnosis and proper management is crucial to avoid long-term ocular complications.

Yao Syndrome

Pathophysiology

Yao syndrome (YAOS, OMIM 617321), formerly called *NOD2*-associated autoinflammatory disease (NAID), is a polygenic AID characterized by periodic fever, dermatitis, arthritis, swelling of the distal extremities, as well as gastrointestinal and sicca-like symptoms. The disorder has a genetic association with certain *NOD2* variants [31].

The pathogenesis of YAOS remains elusive, and it is postulated that the interplay between the NOD2 defect as a risk factor and environmental factors may play a role. It has been recently reported that *NOD2* transcript level was significantly elevated in the peripheral blood mononuclear cells from IVS8^{+158} YAOS patients. Moreover, these patients' cells had elevated basal IL-6 secretion. In contrast, NF-κB activity and TNF-α secretion were uniquely suppressed in haplotype IVS8^{+158}/R702W patients. Specific *NOD2* genotypes may result in distinct NOD2 expression and cytokine profiles. Further study is needed to dissect its pathomechanism [32, 33].

Table 16.2 The diagnostic criteria for Yao syndrome

Clinical criteria	Comments
Major	
1	Periodic occurrence ≥ twice
2	Recurrent fever of dermatitis or both
Minor	
1	Oligo- or polyarthralgia/inflammatory arthritis, or distal extremity swelling
2	Abdominal pain or diarrhea or both
3	Sicca-like symptoms
4	Pericarditis or pleuritis or both
Molecular criterion	*NOD2* IVS8^{+158} or R702W or both, or other rare variants
Exclusion criteria	High-titer antinuclear antibodies, inflammatory bowel disease, Blau syndrome, adult sarcoidosis, primary Sjögren syndrome, and monogenic autoinflammatory diseases

Adapted from Yao et al. [36]

Clinical Presentation and Diagnosis [31, 34, 35]

YAOS is a multisystem inflammatory disease. Recurrent fever occurs in >60% of patients, and typically each febrile episode lasts several days. The fever occurs at varying intervals ranging from several weeks to several months. Intermittent dermatitis is common, manifesting as erythematous patches and plaques on the face, trunk, and limbs. Skin biopsies are usually consistent with spongiotic dermatitis, and other types of dermatitis can be present. Granulomatous changes are extremely rare. Arthritic symptoms are common with oligo- and polyarticular involvement. Some patients (25%) have distal lower extremity swelling involving the ankle and foot with unilateral distribution often. Recurrent or intermittent abdominal pain and/or diarrhea of varying degrees occurs in about two-thirds of patients. Sicca-like symptoms occur in 60% of patients. Other less common manifestations include recurrent chest pain with pleuritis and/or pericarditis, headache, oral ulcers, lymphadenopathy, and sore throat. The diagnosis criteria for YAOS are listed in Table 16.2. YAOS is diagnosed if two major criteria, one or more minor criteria, and the molecular and exclusion criteria are fulfilled.

Treatment

Glucocorticoid therapy is beneficial for reducing the disease frequency and severity. A short course of prednisone (30–40 mg daily for 1–3 days) initiated at the prodromal phase of the disease can shorten the disease flares and severity. A long-term use of prednisone can sustain control of the more frequent flares. Sulfasalazine is also beneficial in 50% of patients. In patients with more frequent disease flares or poor

responses to steroids or sulfasalazine, biologic agents such as IL-1/IL-6 antagonists may offer a long-term benefit for refractory cases. YAOS generally does not respond to colchicine treatment [36].

Summary of the Main Phenotypes and Genotypes of the Above Diseases

The main phenotypes and genotypes of the above diseases are summarized in Table 16.3. The rashes in each of the above diseases are represented in Fig. 16.1 [37].

Table 16.3 Brief summary of the main phenotypes and genotypes of above autoinflammatory diseases

Disease	Gene	Inheritance	Characteristic clinical features	Treatment
FMF	*MEFV*	AR	Fever, polyserositis, arthralgia/arthritis, erysipelas-like eruption on the leg, and amyloidosis	Colchicine, IL-1 inhibitors TNF-α inhibitors
CAPS	*NLRP3*	AD		
FCAS			Fever, cold-induced urticarial rash, conjunctivitis, and arthralgia	
MWS			Fever, urticarial rash, conjunctivitis, episcleritis, arthralgia, neurosensory deafness, and amyloidosis	IL-1 inhibitors
CINCA			Fever, urticarial rash, uveitis, papilledema, deforming arthritis involving large joints, aseptic chronic meningopathy, neurosensory deafness, and amyloidosis	
NLRP12-AID	*NLRP12*	AD	Fever, arthralgia, and cold-induced urticarial rash	Glucocorticoids, antihistamine drugs, and anakinra
TRAPS	*TNFRSF1A*	AD	Fever, myalgia, conjunctivitis, periorbital edema, oligo-arthralgia/oligo-arthritis, serosal involvement, and amyloidosis	Glucocorticoids, etanercept, IL-1 inhibitors
MKD	*MVK*	AR	Fever, polymorphous rash, arthralgia, abdominal pain, diarrhea, lymph node enlargement, and splenomegaly	Anti-inflammatory drugs, glucocorticoids, IL-1 inhibitors
BS	*NOD2*	AD	Granulomatous polyarthritis, dermatitis, panuveitis, occasional fevers, and cranial neuropathies	Glucocorticoids, methotrexate, infliximab
YAOS	*NOD2*	Polygenic	Fever, erythematous patches and plaques, arthritis/arthralgia, distal extremity swelling, gastrointestinal and sicca-like symptoms	Glucocorticoids, sulfasalazine, IL-1 inhibitor, and IL-6 inhibitors

New Monogenic Diseases [38–44]

Some new monogenic diseases has been described in Table 16.4.

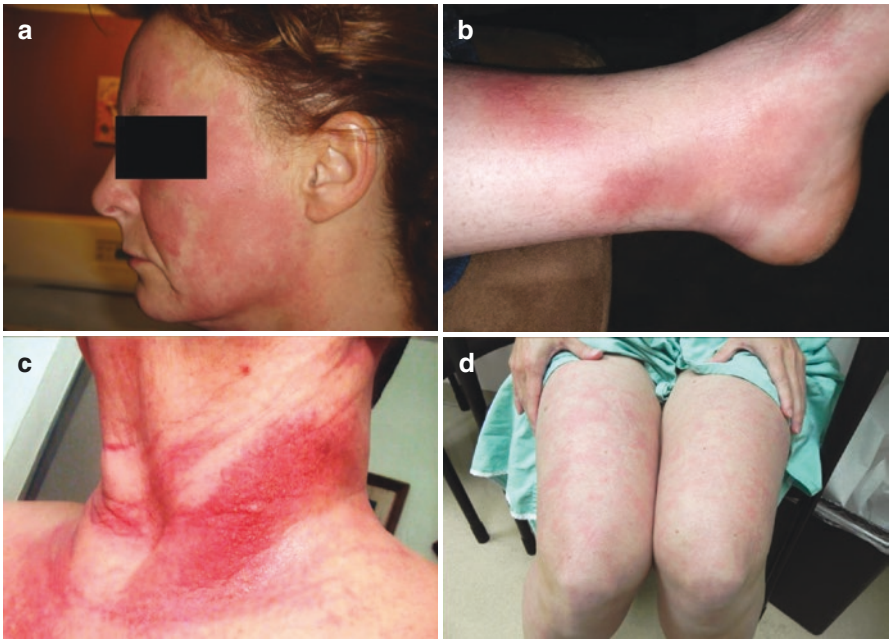

Fig. 16.1 Rashes in autoinflammatory diseases. Erythematous patches on the face in Yao syndrome (NAID) (**a**), erysipelas-like rash on the distal lower extremity in FMF (**b**), plaques on the neck in TRAPS (**c**), and urticaria in CAPS (**d**) (Reprinted with permission from Yao et al. [37])

Table 16.4 New monogenic diseases [38–44]

Acronym	SAVI	DADA2	CANDLE	SIFD	PLAID	DIRA	HA20
Full disease name	STING-associated vasculopathy with onset in infancy	Deficiency of adenosine deaminase 2, also childhood-onset polyarteritis nodosa	Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature syndrome, also known as proteasome-associated autoinflammatory syndrome (PRAAS), or autoinflammation, lipodystrophy, and dermatosis syndrome (ALDD), or joint contractures, muscle atrophy, microcytic anemia, and panniculitis-induced lipodystrophy (JMP) syndrome, or Nakajo-Nishimura syndrome	Congenital sideroblastic anemia with B-cell immunodeficiency, periodic fevers, and developmental delay	PLCG2-associated antibody deficiency and immune dysregulation, also known as familial cold autoinflammatory syndrome 3 (FCAS3)	Deficiency of the interleukin-1 receptor antagonist, also called osteomyelitis, sterile multifocal, with periostitis and pustulosis (OMPP)	A20 haploinsufficiency, also known as familial Behçet-like autoinflammatory syndrome (AISBL)
Gene	TMEM173	CECR1/ADA2	Mostly PSMB8	TRNT1	PLCG2	IL1RN	TNFAIP3
Inheritance	AD	AR	AR	AR	AD	AR	AD
Pathogenesis	Interferonopathy	Small-vessel vasculopathy	Proteasome-associated interferonopathy	Dysregulation in protein clearance pathways and mitochondrial dysfunction	Immune dysregulation	Unopposed interleukin-1 activity	Inappropriate activation of inflammatory cytokines
Age of onset	Infancy, usually before 8 weeks	As early as infancy, most patients have onset of symptoms in the first decade, adult onset has been described	First months of life	Neonatal period or infancy, mostly prior to 3 months of age. Median survival 48 months	Most patients have onset in the first 6 months of life. Most patients note a subjective improvement of the severity of the symptoms after age 30 years	Early infancy	Disease onset before 10 years of age

(continued)

Table 16.4 (continued)

Acronym	SAVI	DADA2	CANDLE	SIFD	PLAID	DIRA	HA20
Disease pattern	Continuous, cold-induced worsening	Intermittent or recurrent	Almost daily, can't be triggered by cold, stress, infections	Recurrent, commonly every 2–4 weeks	Evaporative cooling is the most common trigger	Continuous inflammation	Recurrent
Fever	Recurrent	Recurrent fever	Recurrent fever	Periodic fevers typically last 5–7 days	UK	Recurrent low-grade fevers	Episodic
Cutaneous	Telangiectasia, pustules, and/or blisters, affecting the face, ears, nose, and digits and resulting in ulceration, eschar formation, necrosis, and even amputation. Livedo reticularis, Raynaud phenomenon	Livedo racemosa or reticularis with an inflammatory vasculitis on biopsy, urticarial papules and plaques, purpura	1. Acral, perniotic lesions in newborns and infants 2. Perioral and periocular edema 3. Erythematous or purpuric edematous lesions often with annular shape 4. Progressive lipodystrophy usually well-established before puberty. Histopathology of skin lesions shows an infiltration of immature, myeloid, mononuclear cells, resembling leukemia cutis	Oral ulcers, cellulitis	1. Localized cutaneous urticaria, erythema, and pruritus and sometimes angioedema over unprotected skin after exposure to generalized cold or at the site of exposure to evaporative cooling 2. Onset <5 min after exposure. Resolved within 30 min of rewarming 3. Ulcerative and cutaneous lesions from cold exposure 4. Oropharyngeal swelling after ingestion of cold foods or beverages 5. Cutaneous nodular granulomatous disease	1. Pustular skin rash ranging from discrete crops of pustules to generalized severe pustulosis or ichthyosiform lesions 2. Biopsies of skin lesions show extensive infiltration of epidermis and dermis by neutrophils 3. Nail changes similar to the onychomadesis as in psoriasis 4. Aphthous ulcers	Recurrent painful oral, genital ulcers, rashes, and abscesses

Neurologic	Normal cognition, rarely basal ganglia calcification	Recurrent ischemic stroke affecting the small vessels of the brain, sometimes hemorrhagic stroke. The first stroke often occurs before 5 years of age	Attacks of aseptic meningitis or meningoencephalitis, bilateral basal ganglia calcifications	Delayed psychomotor development mainly manifests as hypotonia and communication problems. Variable neurodegeneration, seizures, ataxia, cerebral atrophy	UK	Cerebral vasculitis or occasional vasculopathy on MRI	Central nervous system vasculitis
Auditory	UK	UK	Otitis, recurrent sinusitis	Sensorineural hearing loss	UK	UK	UK
Ophthalmic	UK	Optic nerve atrophy	Conjunctivitis, keratitis, and nodular episcleritis	Vision impairment, retinitis pigmentosa	UK	Conjunctivitis	Anterior uveitis, retinal vasculitis
Cardiopulmonary	Tachypnea, interstitial lung disease, and lung fibrosis	Coronary aneurysms	Carditis, pneumonitis,	Dilated cardiomyopathy. Cardiac failure was the leading cause of death	Syncope or near syncope usually related to emergence from water	Pulmonary hemosiderosis with progressive interstitial fibrosis in one patient	Pericarditis with effusion, venous thrombi
Abdominal	Failure to thrive	Necrotizing vasculitis of the bowel, abdominal pain, portal hypertension in some patients	Large abdomen and diarrhea during attacks	Poor feeding, vomiting, and diarrhea, enteropathy, failure to thrive, nephrocalcinosis	UK	Poor feeding and failure to thrive are common	Recurrent gastrointestinal ulcers leading to abdominal pain, bloody diarrhea, bowel perforation
Musculoskeletal	Polyarthralgia or polyarthritis, myositis, and joint stiffness	Myalgias	Clubbing of the fingers and/or toes. Arthralgia, disabling joint contractures on the hands and feet usually occur in the long term, muscle wasting, and sometimes myositis. Short stature is common	Dactylitis, arthralgias/arthritis	UK	Sterile multifocal osteomyelitis and periostitis with articular pain. Joint swelling	Polyarthritis

Table 16.4 (continued)

Acronym	SAVI	DADA2	CANDLE	SIFD	PLAID	DIRA	HA20
Reticuloendothelial	Paratracheal or hilar lymphadenopathy, occasionally general lymphadenopathy	Lymphadenopathy, hepatosplenomegaly	Generalized lymphadenopathy, hepatosplenomegaly	Lymphadenopathy, mild hepatosplenomegaly	UK	Splenomegaly	UK
Vasculitis	Skin biopsies showed marked vascular inflammation limited to capillaries, as well as microthrombosis	Renal aneurysms and stenosis, ischemic necrosis of the digits	UK	UK	UK	Histopathologic evidence of vasculitis was observed in the connective and fat tissue adjacent to bone lesions in one patient	Central nervous system vasculitis
Amyloidosis	UK	UK	UK	UK	UK	UK	UK
Lab tests	Elevated ESR, CRP, chronic anemia, thrombocytosis, T-cell lymphopenia with normal B cells, leukopenia, and hypergammaglobulinemia. Normal or low positive ANA, ANCA, antiphospholipid antibodies	Elevated acute-phase proteins, tenfold decrease in serum ADA2 level, abnormal liver enzymes, mild immunodeficiency with hypogammaglobulinemia, pancytopenia, and leukopenia, negative for antiphospholipid antibodies, but lupus anticoagulant can develop over time	Elevation of acute-phase reactants, chronic hypochromic anemia, liver enzymes usually moderately elevated, increased triglyceride, elevated muscle enzymes	1. Elevation of acute-phase reactants during flares 2. Congenital sideroblastic microcytic anemia 3. B-cell deficiency and hypogammaglobulinemia, progressive reduction in T and NK cells 4. Peripheral blood smears typically showed hypochromasia, schistocytosis, and nucleated erythrocytes 5. Hemophagocytic lymphohistiocytosis 6. Aminoaciduria	1. Negative cold stimulation time test with ice-cube and cold-water immersion 2. Antibody deficiency, decreased numbers of B cells, defective B cells, decreased natural killer cells 3. Most had increased IgE 4. Presence of autoantibodies or autoimmune diseases	Markedly elevated inflammatory markers, leukocytosis, thrombocytosis, chronic anemia	Elevated acute-phase reactants during flares. Variable presence of autoantibodies
Year	2014	2014	2010	2013	2012	2009	2016
MIM #	615934	615688	256040	616084	614468	612852	616744

AD autosomal dominant, *AR* autosomal recessive

Board-Style Multiple-Choice Questions with Detailed Explanations

1. A 15-year-old boy of Turkish descent presents with recurrent fever and abdominal pain for 8 years. Ever since the age of 7, he has experienced intermittent episodes of high-grade fevers without consistent triggering events. During the attacks, severe generalized abdominal pain also developed along with the fever, which would confine him to bed for a few days. The patient often suffered from transient unilateral arthritis in his knee or ankle during the febrile attacks. Occasionally, he noted a patch of tender, warm, erythematous skin change on one of his lower legs. During the attacks, laboratory tests showed only leukocytosis and elevated erythrocyte sedimentation rate and C-reactive protein. The symptoms typically lasted for 2–3 days and resolved spontaneously. The intervals between attacks range from weeks to months. He was asymptomatic during intervals, and the abnormal test results returned to normal rapidly. What is the most appropriate management for the patient?

   A. Long-term colchicine on a daily basis
   B. Short course of high-dose colchicine during attacks
   C. Short course of high-dose glucocorticoid during attacks
   D. Anti-IL-1 treatment during attacks

   Correct answer: A
   Explanation: The presence of childhood onset of short (12–72 h), recurrent (≥3) febrile episodes accompanied by severe abdominal pain, monoarticular arthritis, and erysipelas-like skin change without discernible infectious cause in a patient from the Mediterranean region established the clinical diagnosis of familial Mediterranean fever (FMF). Although molecular analysis of the *MEFV* gene provides genetic confirmation of the diagnosis, 10–20% of patients who meet the diagnostic criteria for FMF have no detectable MEFV mutations. The differential diagnosis of FMF includes other periodic fever syndromes. However, the duration of episode and accompanying symptoms in this patient are not typical for other syndromes, such as TRAPS, CAPS, HIDS, and PFAPA. The ultimate goal of treatment in FMF is to prevent acute attacks and minimize subclinical inflammation. The initial treatment choice is a long-term use of colchicine.
   B: Administering colchicine only during attacks or increasing its dose during attacks is usually not quite effective for symptom relief. High-dose colchicine is associated with significant side effects. Intermittent colchicine does not prevent subclinical inflammation during intervals, which may lead to amyloidosis.
   C: Because colchicine prophylaxis is highly effective, high-dose glucocorticoid is neither very effective nor necessary for the self-limiting flares in FMF. Short courses of high-dose glucocorticoid are typically for the treatment of the attacks of TRAPS.

D: Colchicine is the first-line therapy for all FMF patients. Only 10–15% of FMF patients who are resistant or intolerant to colchicine need second-line treatments such as anti-IL-1 agents.

2. A 9-year-old girl presents to your clinic with periodic fever and oral ulcers for 6 years. She experienced periodic fever every 4 weeks. The temperature usually rose abruptly to over 39.5 °C, accompanied with chills and sore throat without cough or coryza. Her parents often noticed small oral ulcers on the inner lips or buccal mucosa and tender cervical adenopathy when fever developed. Physical examinations in other hospitals during attacks found bilateral exudative tonsillitis and no rashes or genital ulcers. The fever always abated suddenly after 4–5 days without antibiotics. Between febrile attacks, this girl appeared healthy and had normal growth and development. Moderate leukocytosis and elevated erythrocyte sedimentation rate and C-reactive protein were present during fever but normalized between attacks. Throat cultures when performed yielded no positive findings. What is your next step in management?

   A. Reassure the patient and family of the benign nature of the diagnosis and that observation without treatment is acceptable.
   B. Glucocorticoids at a dose of 1–2 mg/kg per day should be given orally throughout the whole duration of the attack, usually 4–5 days.
   C. Short course of cimetidine or colchicine at the onset of each attack is the first-line treatment.
   D. Tonsillectomy is ineffective so should be avoided.

   Correct answer: A
   Explanation: Recurrent fevers accompanied by aphthous ulcers, pharyngitis, and cervical adenopathy with clockwork periodicity in a child of less than 5 years old highly suggests the diagnosis of periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome. Cyclic neutropenia and recurrent infections should be excluded, and complete lack of symptoms during intervals and normal growth and development should also be confirmed before the definite diagnosis of PFAPA. It is a relatively benign and self-limiting disease with resolution in most patients by the age of 10 years, so treatment is only optional.
   B: If the patient and family wish to treat, a single dose of 1–2 mg/kg prednisone at fever onset is highly effective to relieve the symptoms.
   C: Prophylactic therapy with cimetidine or colchicine is used in patients with frequent attacks.
   D: Tonsillectomy is an effective option for many patients with PFAPA, even in those who fail medical therapy.

3. A 40-year-old Caucasian female presented with a 2-year history of recurrent rash, fever, and arthritis. The rash commonly manifested as erythematous patches and plaques on her forehead, face, neck, and upper chest, which usually lasted 3–7 days before disappearing. Her recurrent fever typically lasted several days, and the afebrile intervals ranged from weeks to months. She experienced intermittent mono- and oligoarthritis in her lower extremities, accompanied by unilateral pedal swelling. Moreover, she also complained of intermittent abdominal

pain and mild diarrhea. A skin biopsy showed spongiotic dermatitis, and colonoscopy examination showed no evidence of inflammatory bowel disease. Laboratory tests including erythrocyte sedimentation rate, C-reactive protein, and autoantibodies were all normal. Doctors in another hospital who ordered gene sequencing for *MEFV* and *TNFRSF1A I* found no pathogenic mutations. What is this patient's most likely diagnosis?

A. Familial Mediterranean fever (FMF)
B. Tumor necrosis factor receptor-associated periodic fever syndrome (TRAPS)
C. Blau syndrome
D. Yao syndrome (YAOS)

Correct answer: D
Explanation: This patient's presentations are suggestive of Yao syndrome (YAOS), formerly called NOD2-associated autoinflammatory disease (NAID). It occurs predominantly in Caucasian adults. Patients typically have intermittent episodes of fever, dermatitis, mostly spongiotic dermatitis, arthritis, gastrointestinal symptoms, and/or pedal swelling. These patients don't have detestable or high titers of autoantibodies or convincing evidence of inflammatory bowel disease. Acute-phase reactants are elevated in 50% of patients. Genotyping typically shows the *NOD2* gene mutations $IVS8^{+158}$ and/or R702W.
A: Patients with FMF typically experience episodic fever lasting fewer than 3 days, serositis, especially acute abdominal pain, erysipeloid rash on the lower extremities, and arthritis. *MEFV* gene mutations are present in 80% of patients.
B: Blau syndrome is an autosomal dominant disease, caused by mutations in the *NOD2* gene. It is characterized by an early-onset clinical triad of granulomatous dermatitis, uveitis, and arthritis classically leading to finger flexion deformities (camptodactyly). In addition, GI symptoms and fever are infrequent.
C: TRAPS is an autosomal dominant disease, characterized by recurrent fever attacks, typically lasting from 1 to 3 weeks, various forms of rashes with underlying myalgia, and mild mono- or oligo-arthritis. Genetic testing for *TNFRSF1A* is employed to confirm the diagnosis.

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Chapter 17
Pediatric Rheumatology for Adult Rheumatologists

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Juvenile Idiopathic Arthritis (JIA)

Juvenile idiopathic arthritis (JIA) can be classified into one of seven categories based on the International League of Arthritis and Rheumatology (ILAR) classification criteria. It is important to note that children with systemic JIA have clinical features that are distinct from the other categories. There is debate within the rheumatology community as to whether systemic JIA should be included within the ILAR classification criteria and thus will be discussed in a different section.

Diagnosis

The diagnosis of juvenile idiopathic arthritis (JIA) is made clinically and follows ILAR criteria. The subtype of JIA depends on the pattern of arthritis, which presents and evolves 6 months into the disease course.

Juvenile arthritis is characterized by arthritis that persists for over 6 weeks in a child under the age of 16. This cutoff in age was made more so due to practice patterns and less so due to biological variation in disease [1]. In order to confirm onset type, 6 months of disease duration is required for the full phenotypic features to manifest [1].

Arthritis is defined by loss of range of motion along with any evidence of past or current inflammation, which is evidenced by warmth, swelling, tenderness to palpation, or pain with ranging of the joint. The diagnosis of affected joints is made by

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clinical exam and is not made by imaging [1]. Classification of JIA is made based on the number of inflamed joints. Joints of the cervical spine, carpus, and tarsus are each counted as one joint.

JIA can be further subdivided into seven subclasses as per the ILAR criteria (as noted above). These include juvenile ankylosing spondylitis (JAS)/enthesitis-related arthritis (ERA), juvenile psoriatic arthritis (psJIA), oligoarticular JIA (persistent or extended), RF-positive polyarticular JIA, RF-negative polyarticular JIA, undifferentiated JIA (fits no category or fits more than one category), and systemic JIA (sJIA).

Although sJIA is listed in the JIA subclasses, there is question as to whether it should be included within these categories as it is thought that it may be an autoinflammatory disease.

Clinical Features

Children with oligoarticular arthritis tend to present in early childhood and are predominantly female. Anti-nuclear antibodies (ANA) positivity in this population is not uncommon. A positive ANA in children with oligoarticular arthritis places children at an increased risk for uveitis. In this population, frequent ophthalmologic screening is paramount to diagnosing this often asymptomatic disease.

Those with oligoarticular extended disease typically present with four or fewer joints involved, but over time evolve to have more than four joints involved. At 6 months after their diagnosis of JIA, these children typically have a higher joint involvement than they did at presentation.

Enthesitis-related arthritis (ERA), in contrast, occurs typically in males in their second decade of life. ERA is considered to be on the spectrum of juvenile ankylosing spondylitis (JAS). Enthesitis with or without axial arthropathy is commonly seen and may evolve into JAS or adult-onset ankylosing spondylitis. This entity is associated with HLA-B27 positivity. Symptomatic anterior uveitis presenting with a painful and red swollen eye is not uncommonly seen as an extra-articular manifestation of this disease.

Psoriatic arthritis (psJIA) has a variable age distribution and can initially present in younger children with dactylitis. This disease involves both small and large joints. Psoriasis can lag over a decade after the onset of arthritis in the pediatric population, which differs from adult-onset psoriatic arthritis.

Rheumatoid factor (RF)-positive polyarthritis parallels that of adult-onset rheumatoid arthritis and portends a poorer prognosis with a more aggressive and erosive disease than RF-negative polyarthritis. Rheumatoid factor-negative polyarthritis has a more variable presentation and outcome.

Systemic JIA typically presents with fevers, rashes, systemic inflammation, and arthritis. It has no autoantibody association and is likely autoinflammatory in nature.

Constitutional signs such as anorexia, fatigue, weight loss, and growth failure are common in children with JIA. Children may present with nighttime pain which can disrupt their sleep and contribute to fatigue (in the setting of these symptoms,

consideration should also be given to a marrow-based problem). Any signs of weight loss should take into account the possibility of underlying inflammatory bowel disease or celiac disease [1]. Growth failure may also be a consequence of active JIA and may even delay puberty and secondary sexual characteristics [1].

As in adults, joint stiffness occurs especially after prolonged inactivity. This can be described by the parent as the child moving slowly or with a change in gait in the morning or after napping [1]. Stiffness lasting more than 15 min signifies a considerable level of joint inflammation [1]. Tenosynovitis and bursitis can also be seen in children with arthritis.

Osteopenia can occur in young adults who were diagnosed with JIA at a younger age [2]. This places them at an increased risk for fractures in adulthood and for early-onset osteoporosis [3–6]. A determinant of future fracture risk is the peak bone mass achieved by the end of skeletal maturity (typically completed by adolescence) [1].

Muscle atrophy and weakness occurs surrounding affected joints with arthritis resulting in shortened muscles and tendons, which can lead to flexion contractures. Limb length discrepancy may result leading to a pelvic rotation and scoliosis [1]. The involvement of the temporomandibular joint can result in micrognathia or retrognathia.

Uveitis is not uncommonly seen in children with JIA and is characteristically asymptomatic except for those with JAS/ERA where it presents with a painful erythematous eye. Screening guidelines have been implemented for children with JIA as uveitis is commonly silent and can have deleterious effects if left untreated.

Some laboratory evidence of JIA include leukocytosis, thrombocytosis, elevated erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Many children have normal laboratory evaluations including serologies. IgM RF positivity is unusual in a child under the age of 7 [1]. It can be seen in diseases other than JIA and is thus of little utility (although it is included in the ILAR criteria and may indicate a poorer prognosis) [1]. RF positivity is typically seen in older children with polyarticular disease, subcutaneous rheumatoid nodules, and articular erosions [1]. These children typically have a poorer functional class [1]. ANA frequency is the highest in girls with JIA at a younger age of onset with articular disease. There is a 65–85% prevalence among young girls who have oligoarticular arthritis and uveitis [7, 8].

Pathology and Pathogenesis

The etiology of JIA is unknown and is likely multifactorial. Autoantibodies are common in oligoarticular arthritis (anti-nuclear antibody) and RF-positive polyarthritis (IgM rheumatoid factor). ERA/JAS, RF-negative polyarthritis, and psoriatic arthritis are less commonly associated with autoantibodies. ERA/JAS is associated with the genetic marker HLA-B27.

Chronic inflammation in the joints is pathologically mediated by both the innate and adaptive immune system. In all categories of JIA, synovitis is mediated by activated T cells and macrophages, which are pathologically involved.

Treatment

Treatment for JIA has changed by use of intra-articular glucocorticoid therapy, low-dose methotrexate, and biologic therapies (anti-TNF-α, anti-IL-1, anti-IL-6, costimulation-inhibiting biologics). Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used in combination with the aforementioned treatments. Response to treatment is based on the child's clinical course, their objective improvement on physical exam, laboratory evidence of inflammatory markers normalizing, global responses, and charting of the articular severity index [1].

Physical and occupation therapy help to prevent deformity and disability in these children. Orthopedic surgical procedures are not commonly utilized in younger children. Typically, surgical interventions would include treatment for joint contractures, dislocations, and joint replacements, which are seen in older children.

In a study of 44 adults who had a follow-up of 24.7 years after the diagnosis of JIA, those with JIA had greater disability, bodily pains, overall fatigue, lower levels of exercise, poorer health perception, decreased physical function, and lower rates of employment when compared to a healthy control group [8].

Questions

1. A 30-year-old man presents to your clinic with complaints of back pain. He notes that he wakes up every morning with stiffness in his lower back, which is alleviated after 20 min of movement. He had seen a pediatrician as a teenager for these symptoms and was thought to have some muscular strains due his rigorous physical training while being on the football team. His Schober test increases by 2 cm on forward flexion along with tenderness to palpation over his sacroiliac joints. As a teenager this young man likely had:

   A. Asymptomatic uveitis
   B. Anti-nuclear antibody positivity
   C. Enthesitis
   D. Recurrent fevers
   E. A swollen knee

   Children with enthesitis-related arthritis (ERA) may have some complaints of back pain and stiffness and or enthesitis. It is not uncommon for these symptoms to progress over time and for the diagnosis to be made later as the disease progresses. Imaging modalities (including both X-rays and MRIs) are somewhat helpful in diagnosis, but since children are actively growing, it is difficult for radiologists to determine whether children have sacroiliitis versus them having

radiographic findings suggestive of normal physiologic growth on imaging. Enthesitis with or without back pain or stiffness in a male in his second decade of life is the classic way that this disease presents. This JIA subtype is more likely to have a symptomatic uveitis presenting with a red swollen painful eye as opposed to their other JIA counterparts who present with asymptomatic uveitis. ANA positivity may be seen in this subtype but is more common in oligoarticular JIA. Recurrent fevers in a child with arthritis is more characteristic of systemic JIA. Swollen knees are not uncommonly seen in children with JIA, but the ERS/JAS subtype has a higher proportion of axial involvement.

2. What test is likely to be positive in this disease?

   A. Anti-nuclear antibody
   B. HLA-B27
   C. Rheumatoid factor
   D. Anti-cyclic citrullinated peptide
   E. Double-stranded DNA

   HLA-B27 is a genetic marker that is seen in a higher proportion of children with ERA/JAS and with adult onset ankylosing spondylitis. A positive anti-nuclear antibody, rheumatoid factor, cyclic citrullinated peptide, and double-stranded DNA are not normally seen in those with ERS/JAS or ankylosing spondylitis.

3. A 25-year-old Caucasian female presents to you for transition from her pediatric rheumatologist. She notes that she had arthritis starting at the age of 2 which has been well controlled on methotrexate. She also mentions to you that she had uveitis around that time. What class of juvenile idiopathic arthritis (JIA) did she belong to?

   A. Systemic JIA
   B. Oligoarticular JIA
   C. Psoriatic JIA
   D. Polyarticular RF-positive JIA
   E. Polyarticular RF-negative JIA

   This patient is a Caucasian female that was diagnosed at an early age with JIA and had been diagnosed with uveitis. She mostly had oligoarticular JIA which is commonly the way that these young Caucasian females present. The other JIA subtypes present in children with different demographics.

4. What autoantibody was most likely positive in this disease?

   A. Rheumatoid factor
   B. Anti-cyclic citrullinated peptide
   C. Anti-nuclear antibody
   D. Anti-Ro (SSA)
   E. Anti-La (SSB)

   Young Caucasian females with oligoarticular JIA commonly have a positive anti-nuclear antibody. Rheumatoid factor, anti-cyclic citrullinated peptide, and anti-Ro antibodies are not commonly seen in this demographic with oligoarticular JIA. RF and anti-CCP antibodies are seen in a subset of JIA which parallels

the disease of RF-positive arthritis in adults. Anti-La antibodies are not associated with arthritis.

5. She tells you that recently due to her leg length discrepancy, she tripped over the sidewalk and landed on her wrist where she was complaining of pain on her distal ulna. A radiograph was completed showing osteopenia and a non-displaced fracture. When should her bone mass have been checked in order to have assessed her risk of future fracture risk?

   A. At adolescence when peak bone mass is completed
   B. When she was diagnosed and every 5 years thereafter
   C. Prior to puberty along with vitamin D studies annually
   D. Prior to transition to the adult rheumatologist
   E. At 21 years of age

   The best time to check the bone mass for children with JIA is in adolescence when their peak bone mass has been completed. This could help identify those patients who may have a risk of future fracture risk.

6. Compared with their adult counterparts, adults diagnosed with JIA as children suffer from all of these except:

   A. Greater disability
   B. Bodily pains
   C. Overall fatigue
   D. Lower levels of exercise
   E. Lower bone fracture risks

   Adults diagnosed with JIA suffer from a higher bone fracture risk, greater disability, bodily pains, overall fatigue, and lower levels of exercise.

Systemic Juvenile Idiopathic Arthritis (sJIA)

Diagnosis

The diagnosis of sJIA is a clinical one. The International League of Associations for Rheumatology (ILAR) diagnostic criteria for sJIA is based on the presence of arthritis in addition to 2 weeks of a quotidian fever (lasting at least 3 days) and one or more of the following: serositis, hepatomegaly or splenomegaly, generalized lymphadenopathy, and an evanescent rash [9, 10]. It is important to exclude patients who are found to have a positive rheumatoid factor (RF) IgM on at least two occasions (at least 3 months apart) as well as patients with or with a history of psoriasis or psoriasis in a first-degree relative [9, 10]. Males with arthritis who are older than 6 years of age and found to have HLA-B27 positivity, enthesitis and arthritis, uveitis, or inflammatory bowel disease or a history of one of these disorders in a first-degree relative should also be excluded from this diagnosis [9, 10].

Clinical Features

Children with new-onset sJIA are typically very ill, febrile, and fatigued. They can present with myalgias, arthralgias, and chest and abdominal pain [9]. The other systemic features may predominate, and so the arthritis associated with this disease may initially be overlooked. Many children do not fulfill the ILAR criteria at the onset of disease. The arthritis in sJIA may appear 10 years after systemic symptoms [9]. This contrasts with the Yamaguchi criteria for adult-onset Still's disease which does not require the presence of arthritis to satisfy criteria. Adult-onset Still's disease (AOSD) has similar hallmarks to that of sJIA but occurs after the age of 16, and a sore throat is more commonly a symptom of AOSD [11].

Laboratory findings of systemic inflammation are typically seen in those with sJIA including leukocytosis, thrombocytosis, and anemia. There is typically an accompanied elevated erythroid sedimentation rate (ESR) and C-reactive protein (CRP). It is common to see an elevated ferritin, fibrinogen, and D-dimer along with these high inflammatory indicators.

Macrophage activation syndrome (MAS) has a high degree of morbidity and mortality in sJIA associated with 8% of those with sJIA and occurs in at least 7% of those during their disease course [12, 13].

Pathology and Pathogenesis

sJIA is likely related to the dysregulation of the innate immune response evidenced by the dramatic efficacy of treatments with IL-1 and IL-6 inhibitors [9]. The absence of both autoantibodies and autoreactive T cells in this disease point toward sJIA being an autoinflammatory disease [9].

Treatment

Children with sJIA are typically acutely ill and require hospitalization for both the diagnosis and management of their disease. Treatment is often initiated with nonsteroidal anti-inflammatory drugs (NSAIDs) for both treatment of fever and arthritis (oftentimes stronger agents for arthritis are necessary). Glucocorticoids are used with the route of administration and dose based on the severity of the disease onset. Biologic agents such as IL-1 or IL-6 with or without glucocorticoid treatment are often used. Methotrexate is not as efficacious for the arthritis in children with sJIA as it is with the other JIA subtypes.

Questions

1. A 24-year-old man is seen in clinic complaining of some pain in his wrists. He was diagnosed with arthritis as a young child and was told he had many episodes of fevers and rashes when he was diagnosed at the age of 2. What autoantibody is likely present in patients with this disease?

   A. Anti-nuclear antibody.
   B. IgM rheumatoid factor.
   C. Anti-cyclic citrullinated peptide.
   D. This disease is not associated with autoantibody production.

   The symptoms described in this question stem are classic of systemic juvenile idiopathic arthritis (sJIA) which is not associated with any specific autoantibody production.
2. In contrast to systemic JIA, which of these is part of the minor criteria for the diagnosis of adult-onset Still's disease?

   A. Sore throat
   B. Uveitis
   C. Anorexia
   D. Myalgias
   E. Injected conjunctiva

   Sore throat is a part of the minor criteria for the diagnosis of adult-onset Still's disease which is classically not seen in children and which is not present in the diagnostic criteria for systemic JIA.

Pediatric Systemic Lupus Erythematosus (SLE)

Pediatric-onset systemic lupus erythematosus (SLE) commonly occurs in the teenage years, and approximately 15–20% of the lupus population presents prior to adulthood. The time to diagnosis (as for adults) is variable and typically can take up to 5 years [14].

Diagnosis

Similar to adult-onset SLE, the diagnosis is made using the Systemic Lupus International Collaborating Clinics (SLICC) criteria including 11 clinical and 6 immunologic categories. Similar to adult-onset SLE, four items must be present for the diagnosis of SLE with a minimum of one clinical and one immunologic fulfilled category (if not meeting biopsy-proven nephritis compatible with SLE in the presence of an anti-nuclear antibody (ANA) or an anti-double-stranded antibody (anti-dsDNA)).

Clinical Features

Those diagnosed with childhood onset of SLE typically have a more severe disease activity, organ involvement, and laboratory abnormalities than their adult counterparts [15, 16]. Most children with SLE present with vague constitutional symptoms along with clinical signs of immune activation such as generalized lymphadenopathy and hepatosplenomegaly [14]. Renal involvement is common and children may present with acute nephrosis and nephritis.

Pathology and Pathogenesis

SLE is a disease of immune dysregulation, which involves both the innate and adaptive immune system. The current hypothesis is that there is a loss of tolerance of the host.

Complement deficiencies are more commonly seen in childhood onset of SLE. Oftentimes, those with homozygous deficiencies of certain complements (specifically C1, C2, or C4) have a high incidence of lupus nephritis due to impaired clearance of apoptotic cells and immune complexes. Anti-C1q antibodies can also result in an anti-C1q deficiency [17]. In those with a C1q deficiency, 90% have been found to have SLE [18]. Thirty-three percent of those with a homozygous C2 deficiency develop SLE, while those with C4 allelic deficiencies have an increased risk of SLE [19, 20].

Treatment

Treatment of pediatric SLE is similar to that of adult-onset SLE and depends on disease activity and specific organ involvement. Hydroxychloroquine is commonly used in this population, as the benefits of its use are abundant. Glucocorticoid therapy is often used to treat both systemic and organ-specific involvement in various doses and forms dependent on a multitude of factors including severity of disease and organ involvement. Cyclophosphamide is reserved for severe manifestations of SLE organ involvement. Azathioprine and mycophenolate mofetil have been used as steroid-sparing agents and have been used particularly in treating lupus nephritis. Belimumab has been recently approved for the treatment of childhood SLE. Many other treatments have been trialed with some efficacy in treatment of specific SLE manifestations but with limited or conflicting data.

Questions

1. A 32-year-old Caucasian female is seeing you for follow-up. She appears to be in remission from her proliferative nephritis since she was 10 years old. Her labs are unremarkable except for a persistently low C4. The likely contributing factor to her childhood-onset lupus includes:

   A. A likely homozygous complement deficiency.
   B. Exposure to preservatives in the measles, mumps, and rubella vaccine.
   C. Maternal exposure to influenza during her 1st trimester with the patient.
   D. Her ethnicity places her at an increased risk for childhood lupus.

   Those with C4 homozygous complement deficiencies have a higher incidence of childhood onset of SLE. Vaccine preservative exposures, exposures to viruses in utero, and a Caucasian ethnicity are not known risk factors contributing to a child developing SLE.

Juvenile Dermatomyositis

Juvenile dermatomyositis (JDMS) is an idiopathic inflammatory myopathy (IMM) of presumed autoimmune dysfunction resulting in proximal muscle weakness and characteristic rash.

Diagnosis

Diagnosis generally can be made from physical exam, lab work, and diagnostic studies. Other myopathies must be excluded. Often MRI is used to confirm the diagnosis as there can be a hyperintense signal throughout the affected muscles on T2-weighted imaging.

The five findings used for the diagnostic criteria of JDMS include a proximal symmetric muscular weakness, elevated muscle enzymes, characteristic cutaneous manifestations (erythematous papular rash over the extensor surfaces of joints, heliotrope rash with periorbital edema), characteristic muscle biopsy findings consistent with JDMS, and characteristic electromyography findings with suggestive of inflammatory myopathy and denervation [24]. The diagnostic criteria for dermatomyositis and polymyositis include three out of five findings for a probable diagnosis and four out of five criteria for a definite diagnosis [24].

Clinical Features

Juvenile dermatomyositis (JDMS) can be monophasic or polyphasic illness with the majoring of children remitting in 2–3 years (if monophasic). It typically presents with an insidious progression of constitutional symptoms including proximal muscle weakness, fevers, and characteristic rash (heliotrope rash, malar rash, and Gottron papules). The muscle weakness of JDMS is typically proximal and includes anterior neck flexors, back, abdominal muscles, pharyngeal, hypopharyngeal, and palatal muscles. Deep tendon reflexes are usually preserved.

Abnormal nailfold capillaries can generally be seen in these children. One third of children have an acute onset in symptoms. Regression of gross motor milestones is not uncommonly seen in some of these children. Calcinosis and visceral vasculopathy are more extreme manifestations of the disease and are a considerable source of morbidity and mortality but are not as frequently seen in children. Lipodystrophy and metabolic abnormalities are some additional findings that manifest during the disease course. Those that are found to have myositis-specific and myositis-associated antibodies present with a phenotypically distinct disease [21, 22].

Adults previously diagnosed with JDMS have an increased carotid intimal medial thickness and brightness in young adulthood, and those with calcinosis and a higher disease activity may be at a higher risk for atherosclerosis [23].

Pathology and Pathogenesis

JDMS is thought to occur as a result of an environmental trigger in a genetically susceptible individual which leads to immune dysregulation causing tissue pathology. Both the humoral and adaptive immune system contribute to the development of this disease. The immune system attack on muscle capillary endothelium with resultant plasmacytoid dendritic cell infiltration and a type 1 interferon signature response leading to MHC class I expression on myofibril surfaces is seen in JDMS [24]. A perivascular and perimysial infiltrate of plasmacytoid dendritic cells occurs along with other cellular infiltrates such as TH17 cells and B cells. These infiltrating cells produce pro-inflammatory chemokines and cytokines, which ultimately lead to tissue damage [25–29].

Treatment

Glucocorticoid treatment is always included in the treatment of JDMS. There are varied opinions as to dose and route of administration but steroids clearly remain the mainstay of treatment and are often noted to be the single most important factor in improving the prognosis of these children [24]. Hydroxychloroquine is effective in

treating the dermatitis of JDMS and is recommended as a steroid-sparing medication [30]. Methotrexate with or without IVIG can be used in those with moderate to severe disease activity [31]. Physical and occupational therapy is also very important and should be started at diagnosis to prevent decreased range of motion. These therapies are thought to improve functional activity overall.

Questions

1. A 28-year-old male with a history of JDMS who is now stable for 20 years is seeing you for the first time since transition from pediatric rheumatology. He continues on Plaquenil but is on no other medications. You know that he may be at risk for early atherosclerosis. What risk factor may increase this risk?

   A. Male gender places him at a greater risk for early atherosclerosis.
   B. Noncompliance with Plaquenil during active disease increases his risk for atherosclerosis.
   C. His calcinosis notable on exam places him at a greater risk for early atherosclerosis.
   D. Lack of cutaneous involvement during the beginning of his diagnosis portends a poorer prognosis and therefore a higher risk for early atherosclerosis.

   Adults with diagnosis with JDMS may have an increased risk of atherosclerosis if they have calcinosis. These individuals have an increased carotid intimal medial thickness and brightness which may place them at a higher risk for atherosclerosis.
2. This young man is at an increased risk for:

   A. Lung cancer within the next 10 years.
   B. A higher rate of colon cancer and should be screened starting at the age of 30.
   C. There is no increased risk for cancer as he was diagnosed with JDMS which is not associated with malignancy.
   D. He is at an increased risk for cutaneous malignancy and should have skin checks yearly.
   E. He should be screened yearly for liquid tumors.

   In the adult population, DM is associated with malignancy. This is not true of adults who were diagnosed with juvenile DM, and so there is no increased risk of malignancy in this population and no particular screening guidelines are in place.
3. Twenty years ago, this patient was very ill. The major source of morbidity and mortality in JDMS includes:

   A. Gastrointestinal involvement with perforation
   B. Recurrent calcinosis with superimposed staphylococcal infection
   C. Steroid-induced myopathy and osteopenia

D. Liquid tumors within the first year of diagnosis
E. Myocardial infarction with treatment of IVIG

Of those with JDMS, gastrointestinal involvement with perforation is a major source of morbidity and mortality. Recurrent calcinosis with superimposed staphylococcal infection and steroid-induced myopathy and osteopenia do place the patient at risk for a considerable amount of morbidity and possible mortality, although it is not as high as those with gastrointestinal involvement and perforation.

Kawasaki Disease

Kawasaki disease (KD) is also known as mucocutaneous lymph node syndrome. It is one of the most common systemic inflammatory disorders in childhood, which is accompanied by vasculitis.

Diagnosis

KD is diagnosed clinically with a requirement of a fever lasting 5 or more days (not explained by any other infectious cause or disease entity). Additionally, four of the five following criteria should be met: a bilateral non-exudative conjunctival injection, oropharyngeal mucous membranes changes (with injected pharynx, erythematous lips, and/or strawberry tongue), acute-phase palm and/or sole erythema and/or edema (or periungual desquamation – seen in the convalescent phase), cervical lymphadenopathy measuring over 1.5 cm, and a truncal polymorphous rash [32].

The diagnosis of KD is often accompanied by certain laboratory findings including leukocytosis ≥15,000, CRP ≥ 3.0 mg/dL, ESR ≥ 40 mm/h, albumin ≤ 3.0 g/dL, anemia for age, elevated ALT, platelets ≥450,000 after 7 days, and sterile pyuria with ≥10 WBCs/ hpf [32].

Clinical Features

Typical features of KD include more than 5 days of spiking fevers, non-exudative conjunctivitis, cervical lymphadenopathy, strawberry appearance of the tongue, erythematous changes of the lips and oral cavity, dryness and cracking of the lips, swelling and erythema of the palms and soles, and a polymorphous rash (which typically involves the trunk). Coronary artery aneurysms commonly develop in the acute and subacute phases of the disease [32]. Left without treatment, the disease course resolves within 1 month but may recur.

There are three phases to the disease. This acute febrile phase is oftentimes preceded by an upper respiratory or gastrointestinal illness and is accompanied by the aforementioned symptoms listed above [31]. In the subacute phase, desquamation of the skin along with periungual desquamation of the digits may be the major findings. During the convalescent phase, acute-phase reactants normalize and horizontal ridging of the nails can be seen [32].

Cardiac involvement and long-term sequelae is the most concerning feature of this disease and can include myocarditis, pericarditis, aneurysmal dilatation and thrombosis of the coronary arteries, and myocardial infarction. KD is the leading cause of acquired heart disease of children in the United States [32]. In one series, about 60% of the children under the age of 1 year with KD developed coronary aneurysms [33]. Catastrophic cardiac events occur in about 5% of children, but many have some cardiac involvement [32].

Pathology and Pathogenesis

The cause of KD remains unknown although an infectious trigger has been long sought. The cause for the propensity toward damage of the cardiac vasculature is unknown. Coronary aneurysms are most likely to occur in younger children [32]. Cardiac complications result from a severe panvasculitis, which leads to a narrowing of the coronary lumina. This occurs when the myointimal cells migrate from the vascular media to the elastic lamina [32].

Treatment

IVIG is the mainstay of therapy for the prevention of coronary aneurysms. Aspirin is used in high doses for anti-inflammatory activity during the febrile phase and is typically decreased to low dose for antiplatelet activity thereafter. Infliximab and corticosteroids for refractory KD have been shown to be efficacious in small studies. Serial echocardiograms are used to help determine coronary involvement and response to therapy. Typically ESR, CRP, and platelet count guide response to treatment.

Questions

1. A 24-year-old Asian male had a cardiac arrest and wound up dying in the streets very suddenly. His family requested an autopsy as a result of this unfortunate and unexpected event. The medical examiner noted multiple coronary artery lesions on the LAD. Upon discussion with the family, the medical

examiner was told that he had had a prolonged febrile illness when he was younger which resolved spontaneously. What medication could have possibly prevented these lesions?

A. Low-dose aspirin therapy
B. High-dose aspirin therapy
C. Plaquenil
D. Intravenous immunoglobulin therapy
E. Rituximab

Intravenous immunoglobulin therapy has been proven to help prevent coronary aneurysm progression in children with Kawasaki disease. High-dose aspirin is used for anti-inflammatory properties but is not the main therapy indicated for the prevention of coronary aneurysms in this population. Low-dose aspirin has an antiplatelet effect. Rituximab and Plaquenil are not the mainstays of therapy for this disease.

2. Which of these symptoms is not part of the diagnostic criteria of Kawasaki disease?

A. Arthritis of one or more peripheral joint
B. Fever over 38 °C for over 5 days
C. Cervical lymphadenopathy
D. Swelling and erythema of the palms and soles
E. Polymorphous rash

Arthritis is not uncommonly seen in children diagnosed with Kawasaki disease but is not listed as part of the diagnostic criteria. The other choices are listed as part of the diagnostic criteria.

3. A 21-year-old male is being transitioned to your clinic for the first time. As part of his medical history, he tells you that he had a prolonged febrile illness as a child requiring hospitalization and IVIG. His records indicate that he had Kawasaki disease as a young child. What long-term sequelae should you be concerned about in this individual?

A. He likely will have a much higher rate of atherosclerosis in adulthood.
B. An echocardiogram should have been completed to check for coronary aneurysms.
C. He has an increased risk for granulomatosis with polyangiitis in the future and should be tested for ANCA positivity.
D. Kawasaki disease resolves spontaneously with no long-term sequelae.

For children with KD, an echocardiogram should have been serially completed to check for the development or persistence of coronary aneurysms. This is the one known long-term consequence which may develop if no intervention undertaken during the acute phase of the disease. These is no known increased risk of atherosclerosis or granulomatosis with polyangiitis (or other form of vasculitis, other than recurrence of the disease) in children with KD.

Periodic Fever with Aphthous Stomatitis Pharyngitis and Cervical Adenopathy (PFAPA)

Periodic fever with aphthous stomatitis, pharyngitis, and adenitis (PFAPA) is a common condition seen in the field of pediatric rheumatology. PFAPA is a benign disease with a good prognosis. The typical onset of PFAPA occurs prior to 5 years of age.

Diagnosis

The diagnosis of PFAPA is one of exclusion. A workup excluding sources of chronic infectious, underlying immunodeficiency or autoimmune disease and malignancy must be undertaken prior to the diagnosis. During PFAPA episodes, an elevated white blood cell count and C-reactive protein (CRP) can be seen. Neutropenia is not a characteristic finding and often is accompanied by an elevation of immunoglobulins including IgD. Exclusion of cyclic neutropenia by completing serial neutrophil counts before, during, and after symptomatic episodes should be completed [34]. Gene expression profiling may aid in differentiating this fever syndrome from other fever syndromes with a known genetic underlying mutation.

The diagnostic criteria of PFAPA includes an onset of illness occurring prior to the age of 5 with normal growth and no other clinical manifestations other than the following: recurrent episodes of fever lasting approximately 5 days with elevated acute-phase reactants (i.e., ESR or leukocytosis) and pharyngitis or aphthous ulcers with or without cervical lymphadenopathy [34]. The exclusion of this diagnosis includes a known respiratory tract infection, interval-free periods lasting more than 10 weeks, cyclic neutropenia, other periodic fever syndromes, immunodeficiency, autoimmunity, and chronic infection [34].

Clinical Features

In an American series, fevers associated with this disease occurred every 28 days and lasted for an average of 5 days [35]. Children with PFAPA are typically well between episodes and have no issues with growth. Typically, children present with constitutional symptoms such as generalized fatigue, chills, and malaise. Additionally, the presence of aphthous stomatitis and/or pharyngitis with or without cervical lymphadenopathy, along with a self-resolving fever reaching 40°–41 °C, is seen. Generalized lymphadenopathy and hepatosplenomegaly are not characteristic findings of this syndrome. Arthralgias, mild abdominal complaints, and headaches are not uncommon during the febrile episodes. Acute-phase reactants including

leukocytosis or elevated erythrocyte sedimentation rate are commonly found during the workup.

The prognosis is overall excellent for children with PFAPA as it is generally outgrown with no sequelae into adolescence. Episodes over time typically shorten in duration and reduce in frequency.

Pathology and Pathogenesis

There is no known genetic mutation associated with PFAPA. Most cases occur sporadically. An elevation of IFN-gamma, TNF, IL-1B, and IL-6 has been observed in children with this disease [35].

Treatment

Prednisone is known to cause rapid resolution of fevers if taken on the first 1–2 days of the episode. Rapid response to prednisone has been suggested as diagnostic criteria. This does not prevent episode recurrence and may actually decrease the interval between episodes [35–37].

Tonsillectomy or adenoidectomy may induce remission [38, 39]. Cimetidine and anecdotally colchicine may be effective in preventing recurrences [40–42]. Anakinra has been used for this condition and has demonstrated a prompt clinical and laboratory response [43].

Questions

1. While obtaining a history and physical for a new patient, they mention to you that they had a tonsillectomy in early childhood. When you further ask for additional clarification as to why, the patient notes that she had monthly fevers and sore throats with aphthous ulcers as a child with requiring monthly corticosteroid doses during her illnesses. She mentions that this procedure helped eradicate the episodes of fevers and sore throats. She is looking to become pregnant and is wondering what she can do to prevent her progeny from inheriting the illness. What do you offer this patient?

   A. Once pregnant you can send chorionic blood for gene expression sequencing for periodic fevers.
   B. This is inherited in an autosomal dominant fashion and the child should be closely monitored throughout life by a general pediatrician with a referral to pediatric rheumatology if symptomatic.

C. Test the child for neutropenia once born and then at monthly intervals for cyclic neutropenia.
D. This fever syndrome is not hereditary with only a few sporadic cases noted in familial clusters. There is low likelihood that her child will have the fever syndrome, and no testing or surveillance is necessary.
E. Prophylactic antibiotics is helpful in this condition, and the child should be placed on antibiotic prophylaxis if symptomatic.

This vignette is pointing to an underlying diagnosis of PFAPA, which is not a hereditary disease. There are few sporadic cases noted in familial clusters, and so there is a very low likelihood that her child will have a fever syndrome. Thus, no testing or surveillance is necessary for this child.

2. A 37-year-old male tells you that he had PFAPA as a child. He noted that his symptoms resolved prior to the end of his adolescence. What medication is known to reduce the fever episode but decrease the fever interval?

A. Tonsillectomy or adenoidectomy
B. Cimetidine
C. Anakinra
D. Prednisolone
E. Colchicine

Prednisolone is known to reduce the fever episode but tends to decrease the fever interval. Tonsillectomy or adenoidectomy can induce remission in severe cases. Cimetidine, anakinra, and colchicine have also been used in patients with PFAPA with some success.

3. The same patient above is concerned about the likelihood of him developing an autoimmune disease at a later time. You tell him that he should be screened:

A. Every 5 years for the presence of auto-antibodies for lupus as this condition is closely linked with this autoimmune disease.
B. He should be screened for serum amyloidosis at regular intervals due to the chronic inflammatory markers associated with PFAPA in childhood.
C. He may develop adult-onset Still's disease at a later date and should only be evaluated if symptoms such as fevers and rashes emerge.
D. No screening is necessary, PFAPA is a condition which self-resolves in adolescent years with no specific development of other autoimmune diseases.

PFAPA is a condition which resolves typically in adolescent years. There is no association for the development of an additional autoimmune disease. No screening would be necessary for this patient.

IgA Vasculitis (Formerly Henoch-Schönlein Purpura)

IgA vasculitis is a small vessel vasculitis (affecting predominantly capillaries, arterioles, and venules). It is commonly seen in children, but with a few cases reported in adults. The typical presentation occurs in children between 3 and 15 years of age and is more common in boys [44, 45]. There is some genetic association with this disease as familial clusters have been recognized.

Adults often have a lower frequency of abdominal pain and fever but an increased likelihood of both joint involvement and renal involvement, which tends to be more severe [46].

Diagnosis

As per the Pediatric Rheumatology European Society in 2010, new classification criteria included palpable purpura in gravity-dependent regions plus at least one of the following: diffuse abdominal pain, leukocytoclastic vasculitis on skin biopsy or IgA deposition with proliferative glomerulonephritis, arthralgias or arthritis, or renal involvement as evidenced by increased urinary sediment and/or proteinuria [47]. The glomerulonephritis of this disease is indistinguishable from IgA nephropathy.

Clinical Features

The cutaneous involvement of this disease includes a classic palpable purpura, which is most commonly seen in gravity-dependent regions mainly affecting the lower extremities and buttocks. Petechiae, purpura, and even hemorrhagic bullae can be seen with an initial erythematous color, which gradually progresses to brown. In young children, subcutaneous edema of the hands and feet may be evident.

Abdominal pain is seen surrounding the onset of the characteristic rash and is caused by vasculitis of the bowel wall. Intussusception is an emergency that should be suspected if a child with IgA vasculitis presents with severe abdominal pain.

Renal disease typically occurs after the cutaneous involvement of IgA vasculitis. Serious renal disease in these children occurs within 4–6 weeks of the inciting illness and can present in many different ways (hypertension, microscopic hematuria, microscopic or gross proteinuria, acute nephritis, and even renal failure). Some factors associated with an increased risk of nephritis include an age over 7 years at

diagnosis of IgA vasculitis, persistent cutaneous involvement, and gastrointestinal involvement (which are typically described as severe) [48–50]. Renal disease can occur much later on and even after multiple recurrences of cutaneous lesions. The recommendation is to follow children with IgA vasculitis for a minimum of 6 months to monitor for renal involvement.

Arthritis and arthralgias are found in a majority of children with this disease with large joints most commonly being affected. The joint disease is typically fleeting and resolves without any residual abnormality.

Pathology and Pathogenesis

There is debate over whether IgA vasculitis has an association with infectious etiologies or allergy to either drug or food. The vascular deposition of IgA implicates an immune dysregulation, but no known mechanism for pathogenesis has been confirmed.

Treatment

Supportive care is typically all that is required for those afflicted by HSP. If kidney involvement occurs, it is important to monitor electrolytes and hypertension and monitor for proteinuria and hematuria. Acetaminophen can be used for analgesia. Glucocorticoids can be used for severe disease including gastrointestinal disease or hemorrhage. Glucocorticoids do not help prevent nephritis in this population. Less than 5% of those with renal involvement progress to end-stage disease [46].

Questions

1. A 37-year-old Asian female with stage 2 chronic kidney disease presents to you for the first time. As you obtain her past medical history, she notes that she had an illness at the age of 15 where she had a raised palpable rash, abdominal pain, and arthritis for 10 days and was hospitalized for 3 days. She was found to have some protein in her urine and after a full workup was placed on 7.5 mg of enalapril which she has taken ever since. Which of these factors portended a poorer prognosis for her disease?

   A. Her age at disease onset
   B. Asian descent
   C. Arthritis at the time of presentation
   D. Lack of hypertension at the onset of disease
   E. The need for continued treatment with enalapril

The poor prognostic features for IgA vasculitis include an age of over 7 years at diagnosis, persistent cutaneous lesions, and severe gastrointestinal involvement. Demographics, arthritis, lack of hypertension, and continued use of enalapril do not factor into the prognosis of IgA vasculitis.

Growing Pains

Growing pains occur in 3–37% of school-aged children and typically occur in children between the ages of 3 and 12 years (not during the peak growth of adolescence) [51–55]. There is no associated disease with growing pains, but the symptoms of the child may lead to a negative familial impact.

Diagnosis

There are no diagnostic or laboratory tests that are available for the diagnosis of growing pains. Physical exam is typically normal and motor milestones are met on time. This is a diagnosis of exclusion, and investigations should be considered for those with non-classic symptoms and systemic involvement or with an abnormal physical exam.

Clinical Features

Children tend to have abdominal pain and migraine headaches associates with their pain. The typical pain associated with growing pains includes a nocturnal episodic nonarticular leg pain, which can occur in any portion of the lower extremity. This pain is typically bilateral and is responsive to massage and analgesics. The pain is typically not present during the day and does not inhibit normal activity. These children may suffer from fatigue and pain, which may lead to school or work absences and chronic use of analgesics.

Pathology and Pathogenesis

There is likely some familial genetic association for growing pain, but there is no current known pathology or disease pathogenesis implicated.

Treatment

Education and reassurance are important to the families understanding of growing pains. Treatment typically is comprised of over-the-counter analgesics, which may be useful in addition to passive stretching along with orthotics (if needed) [56].

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Chapter 18
Musculoskeletal Manifestations of Systemic Diseases

Michael Malekan and Apostolos Kontzias

Endocrine Disorders

Cushing syndrome is caused by exogenous or endogenous excess of corticosteroids due to corticosteroid use, a primary adrenal adenoma, a hypersecreting pituitary adenoma, or a paraneoplastic process. Universally, there is increased risk for decreased bone mineral density (BMD) and fractures, avascular necrosis, and corticosteroid myopathy. Decreased BMD may be seen with doses as little as 7.5 mg prednisone or equivalent. Prevention and potential treatments include calcium, vitamin D, bisphosphonates, denosumab, or teriparatide. Avascular necrosis while typically associated with prolonged corticosteroid use has been described with short high-dose courses as well (Fig. 18.1). Corticosteroid myopathy may be sudden or gradual. Muscle biopsy will show type 2 muscle fiber atrophy. Nerve conduction studies and muscle enzymes are normal, and electromyogram shows decreased motor unit action potentials [1]. Symptoms should improve with discontinuation of steroids.

Acromegaly is characterized by hypersecretion of growth hormone (GH) and insulin growth factor-1 (IGF-1), usually the result of a hyperfunctioning pituitary adenoma. Hypothalamic tumors and ectopic production are possible but rare. The disease affects middle-aged men and women. Increased somatomedins secreted by hepatocytes under the influence of GH stimulate bone and cartilage leading to chondrocyte replication, increased proteoglycans, collagen, osteoblastic proliferation, and increased bone collagen leading to increased bone mass, large joint arthralgias, and proximal muscle weakness. Fibrous synovial thickening and bony overgrowth of PIPs and DIPs may be seen on physical examination. Muscle enzymes will be

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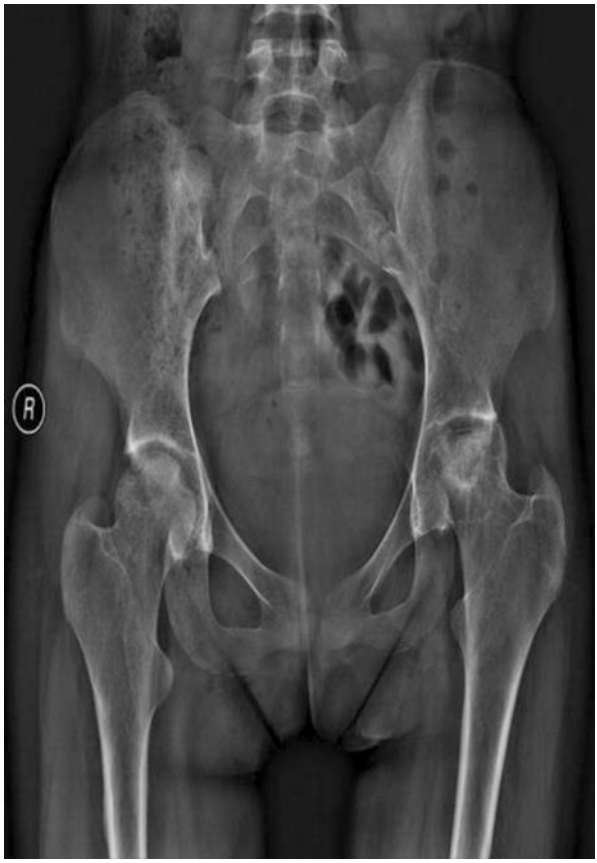

Fig. 18.1 Avascular necrosis of the left hip in a patient with sickle cell disease (Reprinted with permission from Springer [2])

normal, and muscle biopsy will show variation in fiber size without active inflammation. Musculoskeletal imaging may identify an enlarged sella turcica, increased thickness of enlarged frontal sinuses, an elongated mandible, soft tissue thickening, broad metacarpals and phalanges, prominent distal tufts, widened joint spaces due to cartilage hypertrophy, increased thickness of the heel pad, broadening of the sternal ends of ribs, kyphosis, and enlarged vertebral bodies (Fig. 18.2). Arthralgia is one of the most commonly reported symptoms, and axial involvement may resemble diffuse idiopathic skeletal hyperostosis syndrome (DISH). Morning stiffness and joint swelling are not characteristic. Bilateral carpal tunnel syndrome may be seen in over half of patients. Surgical resection of the adenoma is used to treat acromegaly, but musculoskeletal symptoms often persist. BMD is often normal or elevated; however, patients remain at increased risk of vertebral fracture [1].

Diabetes mellitus type 2 (*DM2*) leads to altered connective tissue, increased fibrosis, and tendinopathies, and neuropathy can lead to severe osteoarthropathy. In the shoulder, there is increased risk of adhesive capsulitis. Calcific tendinitis

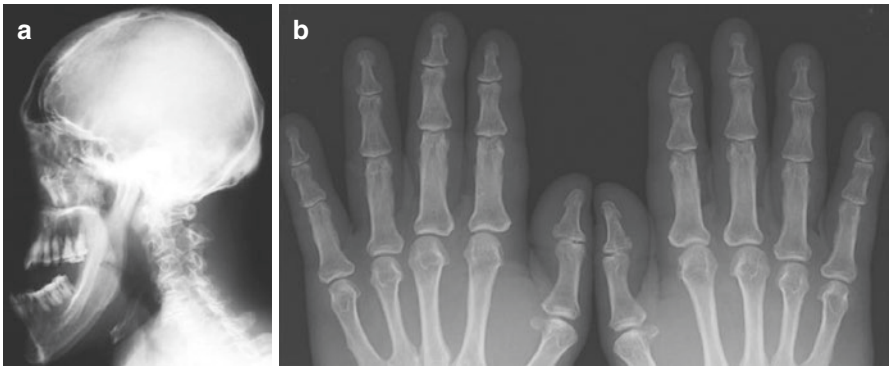

Fig. 18.2 Elongated mandible (**a**) and broad metacarpals and phalanges (**b**) characteristic of acromegaly (Reprinted with permission from Springer [3])

often develops due to deposition of calcium hydroxyapatite within rotator cuff tendons. Common hand pathology includes flexor tenosynovitis and trigger finger, Dupuytren's contracture, carpal tunnel syndrome, and diabetic cheiroarthropathy (limited joint mobility related to thickened skin in longstanding diabetics). In the feet patients may suffer from diabetic osteoarthropathy or Charcot's arthropathy as a result of neurovascular disease. In Charcot's, increased blood flow to subchondral bone is associated with increased osteoclastic activity and bone resorption. Resulting osteopenia leads to osteolysis of bone, fragmentation, and sclerosis (Fig. 18.3). MRI or bone scintigraphy is used to evaluate extent of disease. Sudden muscle infarction is also described in uncontrolled patients with DM2. Ossification of the anterior longitudinal ligament of the spine often with osteophyte formation, a condition known as DISH, is associated with DM2; the condition characteristically spares the intervertebral disc spaces and sacroiliac (SI) joints allowing clinicians to differentiate DISH from axial spondyloarthritis [1].

Hyperthyroidism and hypothyroidism can both present with musculoskeletal symptoms. In hypothyroid states, patients manifest with symmetric arthropathy involving stiffness of the hands and knees with "gelling" phenomenon. Synovial fluid is non-inflammatory and viscous with increased hyaluronic acid. CPPD crystals may be present. Myopathy will present with cramps, myalgia, stiffness, proximal muscle weakness, fatigue, and elevated CK, and muscle biopsy will show type 2 fiber atrophy with increased type 1 fibers. Carpal tunnel syndrome has been described as a result of excess glycosaminoglycan deposition. Hoffman syndrome describes a rare condition of hypothyroidism manifesting as increased muscle mass (pseudohypertrophy). Kocher-Debre-Semelaigne syndrome describes infants with muscle pseudohypertrophy in iodine-deficient mothers [1].

In Graves' disease (autoimmune hyperthyroid state), patients can develop several musculoskeletal manifestations. Proximal muscle weakness, adhesive capsulitis of

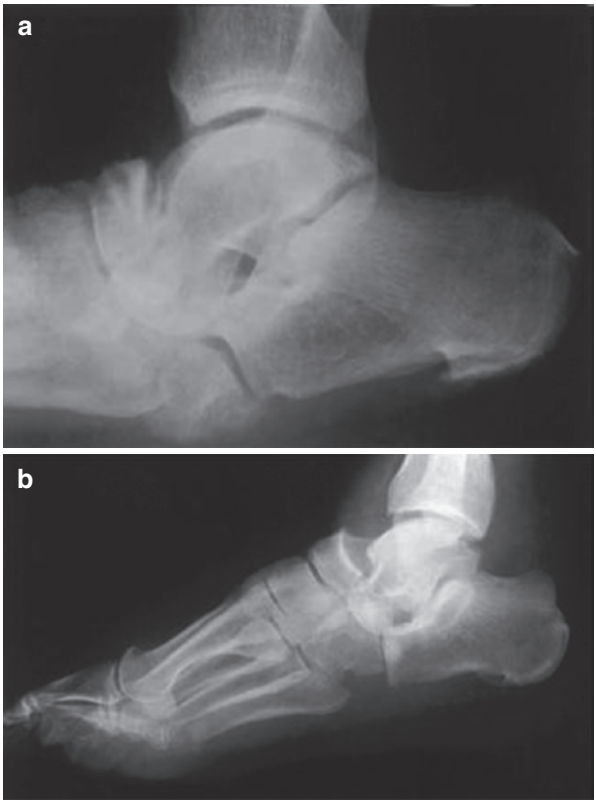

Fig. 18.3 Example of Charcot's arthropathy (Reprinted from Springer with permission [4]), (**a**) Hypertrophic form of neuroarthropathy on radiography. Lateral image of the foot shows the hypertrophic form of neuroarthropathy, characterized by sclerosis, osteophytosis, and radiographic appearance of extreme degenerative change. (**b**) Midfoot deformity related to neuroarthropathy on radiography. Lateral radiograph demonstrates dorsal dislocation of the tarsometatarsal joints

the shoulder, loss of muscle mass, and weight loss are all expected to improve after treatment. Onycholysis, clubbing, and thyroid acropachy related to periostitis surrounding MCPs may not resolve. Associated osteopenia and osteoporosis are most commonly associated with hyperthyroidism [1].

Hypoparathyroidism results in altered calcium homeostasis leading to altered bone structure and turnover. This can result in enthesopathy and paravertebral and subcutaneous calcifications [1].

Renal osteodystrophy is seen in patients with chronic kidney disease and is characterized by abnormal bone remodeling with or without abnormalities in bone mineralization in the setting of untreated secondary hyperparathyroidism. Chronic renal insufficiency and hemodialysis contribute to biochemical disturbances in calcium and phosphate metabolism leading to a wide spectrum of bone and soft tissue abnormalities. Patients present with osteomalacia, osteitis fibrosa cystica, osteosclerosis, and osteoporosis. Occasionally axial symptoms mimic ankylosing spondylitis or DISH with characteristic morning stiffness and gait posture. Serum testing for PTH, vitamin D, serum calcium or phosphorus, and bone imaging may help to characterize

the underlying disease, and bone biopsy remains the gold standard as bone turnover may be increased or decreased in these patients. Arthralgia in these patients will not respond to NSAIDs but may respond to calcitriol. CKD leading to hyperphosphatemia and secondary hyperparathyroidism may also increase the risk of crystal deposition diseases. Long-term dialysis may also be complicated by beta-2 microglobulin amyloid deposition, destructive spondyloarthropathy, osteonecrosis, and musculoskeletal infections [7].

Hyperparathyroidism presents with arthralgia, osteitis fibrosa cystica (OFC), and subperiosteal resorption along radial side of phalanges. OFC is a skeletal disorder resulting in loss of bone mass due to replacement of calcified structures with fibrous tissue and formation of cyst-like brown tumors in and around the bone (Fig. 18.4). Brown tumors are lytic lesions in the skeleton resulting from localized areas of fibrous tissue as a result of increased osteoclastic activity, giant cells, and decomposing blood. Arthritis involves small joints of hands and typically spares the PIPs. While symptoms may mimic rheumatoid arthritis, subperiosteal resorption is distinctive and acute-phase reactants RF and CCP will not be elevated. Radiocarpal, inferior radioulnar, and MCP joints are most commonly involved. Patients with hyperparathyroidism are also at increased risk of CPPD, gout, or both. Hyperparathyroidism can also lead to proximal muscle weakness with normal muscle enzymes; EMG and muscle biopsy will show denervation [1].

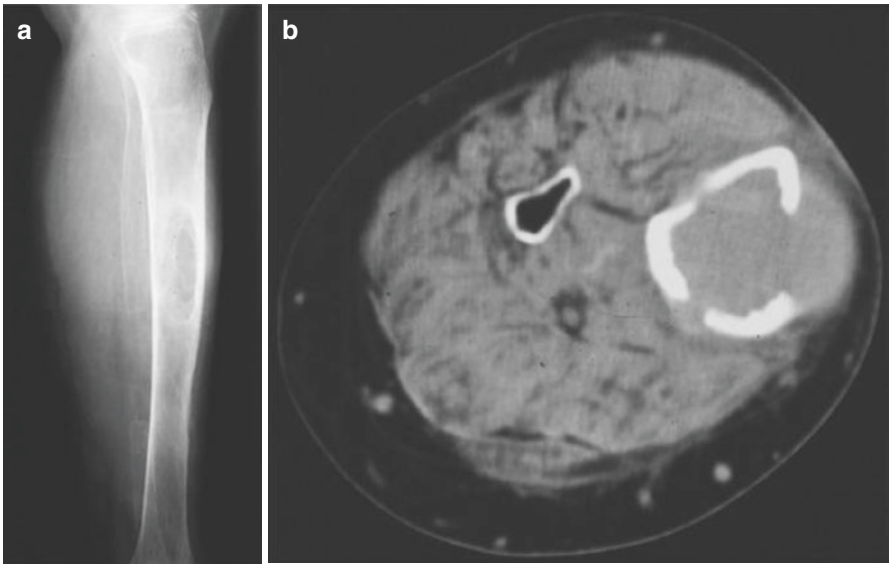

Fig. 18.4 Example of brown tumor associated with hyperparathyroidism (Reprinted with permission from Springer [5]) (**a**) Osteolytic lesion on X-ray examination of tibia, (**b**) Osteolytic lesion on transverse section of tibia on CT scan

Metabolic Disorders

Wilson's disease (*WD*) is a rare autosomal recessive genetic disorder defined by excess copper deposition in tissues, particularly the liver and nervous system. Mutations in ATP7B lead to abnormal copper transport, and symptoms usually present between 6 and 20 years of age. In addition to the characteristic hepatic and neurologic manifestations, a significant proportion of patients may first present with musculoskeletal symptoms. Early osteoarthritis, chondrocalcinosis, and spinal osteochondritis have been described. Otherwise unexplained arthralgia or effusion or early radiographic features of osteoarthritis warrant copper survey. Diagnosis is based on clinical, biological, radiographic, and sometimes histologic findings including the characteristic blue-green or red-brown peripheral deposit surrounding the cornea known as the Kayser-Fleischer ring. Of note, D-penicillamine, a chelating agent commonly used in the treatment of WD, has been associated with drug-induced lupus [6].

Alkaptonuria is a rare autosomal recessive disorder caused by abnormal tyrosine and phenylalanine metabolism. Deficiency in the enzyme homogentisate 1,2-dioxygenase (HGD) leads to excess circulating homogentisic acid (HGA) which accumulates as pigment in connective tissues including cartilage, heart valves, and sclera of the eyes. Clinical symptoms begin in early adult life and become prominent in the fourth and fifth decade and may include blue-black pigmentation of the ear cartilage and sclera of the eyes, cardiac valvular disease, and osteoarthropathy. The clinical syndrome associated with pigment-related diseases is known as ochronosis.

Osteoarthropathy in ochronosis leads to premature joint and spinal disease in the peak of adulthood. Patients often require multiple joint replacements and suffer from degenerative disc disease and progressive kyphoscoliosis. Tendon and ligament ruptures, osteopenia, and fractures have also been described. Osteoarthropathy is thought to be the result of pigmented deposits in the hyaline cartilage disrupting normal load distribution with subsequent damage to the subchondral plate. Therapeutic options remain limited [7].

Hemochromatosis (*HHC*) is a disorder defined by excess iron deposition in body tissues as a result of increased iron absorption. Hereditary hemochromatosis is inherited in an autoimmune recessive fashion. In addition to skin pigmentation iron deposition leads to endocrine dysfunction as well as liver failure with alternate terminology including "bronze diabetes" or "pigmented cirrhosis." Phenotype is highly variable, and several extra-articular manifestations including hepatic and cardiac abnormalities, hyperpigmented skin, diabetes mellitus, erectile dysfunction, and increased susceptibility to certain infections have been defined. Risk of liver carcinoma is significantly increased as well. Phlebotomy in early disease may prevent or postpone complications. Arthralgia and arthritis have been described in the majority of patients and are often a late manifestation but rarely can be the presenting symptom in undiagnosed cases. Often the 2nd and 3rd MCP are involved, but arthritis may also be seen in the PIPs, wrists, shoulder, hip, knee, and ankle. Patients

develop pain and stiffness but not synovitis. Studies have shown an increased risk of prosthesis loosening after hip arthroplasty. Patients are seronegative, and radiographs show characteristic joint space narrowing of 2nd and 3rd MCP, hook-like osteophytes, and chondrocalcinosis of the triangular fibrocartilage adjacent to the ulnar styloid. Unlike many of the extra-articular manifestations of hemochromatosis, arthritis usually does not respond to phlebotomy. NSAIDs, colchicine, and intra-articular steroids can be effective [8].

Hematologic Disorders

Hemophilia and other bleeding disorders may lead to hemarthrosis. Intra-articular bleeding can cause a range of musculoskeletal symptoms as highlighted below, including hemophilic arthrosis which presents with features resembling rheumatoid arthritis or osteoarthritis.

Acute hemarthrosis usually involves the large joints. Early symptoms include tingling and tightness of the joint with subsequent rapidly progressive swelling, reduced range of motion, pain, and warmth. Flexion is often the most comfortable position, and symptoms should respond with administration of clotting factor. Arthrocentesis is not recommended in the setting of acute hemarthrosis unless symptoms do not respond to conservative treatment and should only be performed after clotting factor replacement. Embolization remains an option in severe or recurrent cases.

Synovitis results from incomplete clearance of blood products after recurrent hemarthrosis. Subsequent angiogenesis further increases the risk of repeat bleeding leading to a vicious cycle. Painless swelling may be visible but will not be tense (in contrast to acute hemarthrosis), and symptoms will not respond to acute administration of clotting factor in the acute setting. Long-term factor replacement can prevent recurrent hemarthrosis and improve symptoms. Treatment of acute synovitis includes COX-2 inhibitors but other NSAIDs should be avoided as they may increase the risk of bleeding. Synovectomy may be indicated in severe cases.

Hemophilic arthropathy in the setting of recurrent hemarthrosis is the result of progressive degeneration of cartilage, synovial inflammation, and bone changes. Symptoms include chronic pain, joint stiffness, and severe limitations in range of motion. Deformity, subluxation, laxity, malalignment, and spontaneous arthrodesis can develop (Fig. 18.5). Treatment options include those available in other degenerative arthritis.

Extra-articular manifestations in patients prone to bleeding can be subtle or at times dramatic. Intramuscular hemorrhage presents with painful swelling, worse with active contraction or stretching, and may result in spasm and flexed position. Palpable tender hematoma can be present on examination but deeper bleeds can be difficult to identify and carry a risk of potentially life-threatening compartment syndrome. Muscular hemorrhage can also lead to the formation of a pseudotumor

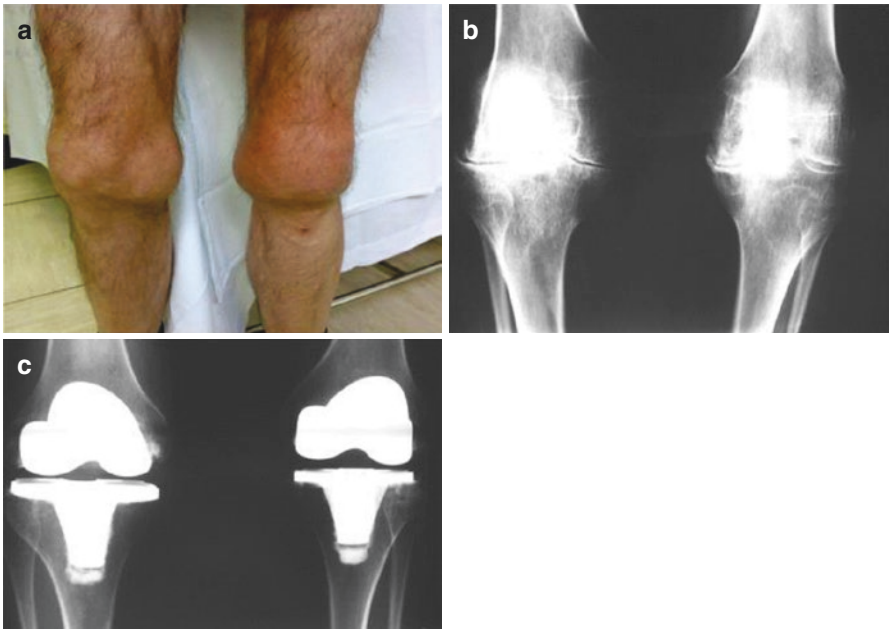

Fig. 18.5 Example of hemophilic arthropathy before and after joint replacement (Reprinted with permission from Springer [9]) (**a**) Knees kept in mild flexion which is the position of minimum discomfort; chronic synovitis evident on exam, (**b**) Destruction of articular cartilage with severe narrowing of the joint space, (**c**) Knee XRs status post total bilateral knee arthropasty

which can erode into adjacent bone, compress neurovascular structures, rupture, lead to fistula, and contribute to pathologic fracture requiring surgical excision [10].

Hemoglobinopathies are inherited diseases caused by mutations in globin genes. They include thalassemias and sickle cell anemia, both of which afflict the musculoskeletal system. They are common in the Mediterranean basin and tropical regions of Asia and Africa.

Thalassemia refers to inherited defects in globin chain biosynthesis. Abnormal globin chains lead to reduced function of hemoglobin tetramers which display as anemia, hypochromia, and microcytosis on complete blood count. Osteoporosis is commonly observed as a result of bone marrow hyperplasia, resorption of bone cortex, decreased cancellous bone, and coarsened trabeculae. In the spine reduced BMD and cortical thinning are associated vertebral compression fractures and subsequent scoliosis and kyphosis. MRI shows predominance of red marrow in vertebrae and early degeneration of intervertebral discs in the lower thoracic and lumbar spine. Abnormal intravertebral iron deposition may be seen. Extramedullary hematopoiesis is radiographically evident in the paravertebral and presacral spaces as a symmetric extra-osseous spread of marrow. Spinal cord compression has been described as a rare complication of marrow expansion. Marrow changes in the skull will cause a characteristic “hair-on-end” appearance (Fig. 18.6). Frequent blood transfusions in these patients may lead to iron overload and contribute to mild arthralgias or arthritis. Symptoms are often self-limited or responsive to NSAIDs [11].

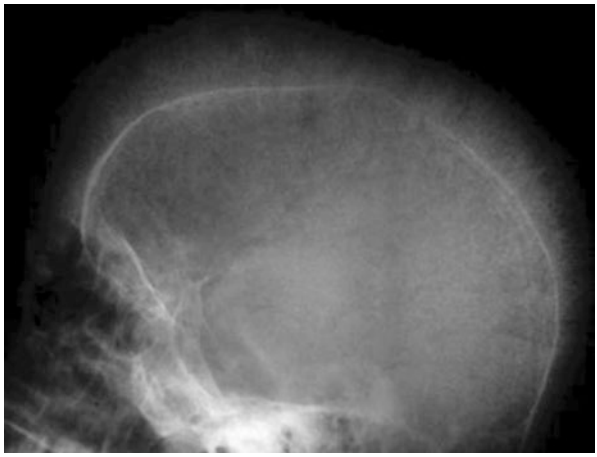

Fig. 18.6 "Hair-on-end" appearance of skull on radiography in beta-thalassemia major (Reprinted with permission from Springer [12])

Sickle cell disease (SCD) is a single gene disorder caused by homozygous inheritance for sickle hemoglobin (Hb S). Affected Hb units polymerize to form rigid rods distorting normal morphology of red blood cells. Disease flares are precipitated by dehydration or hypoxia and are accompanied by hemolytic anemia and acute vaso-occlusive episodes defined by bouts of pain and progressive organ damage.

Vaso-occlusive crisis of the bone is a common complication of SCD and a frequent cause of hospitalization in children with SCD. Painful episodes often involve the chest, lower back, or extremities and may be accompanied by leukocytosis, fever, or abdominal pain. Acute painful crises are the result of microvascular occlusion in low flow vascular areas including bone marrow leading to bone thrombosis. Vertebral body infarction may lead to collapse with typical fish mouth deformity on plain radiography. Infarcts have a predilection for the long bones and may be identified with MRI. Dactylitis can be seen in children under 7 years old and has been termed "hand foot syndrome" defined by painful swelling of one or more digits. Subperiosteal new bone formation leads to a characteristic moth-eaten pattern on radiography. Epiphyseal involvement can lead to premature fusion and shortened digits [11].

Osteomyelitis is more common in SCD than the general population as these patients are predisposed to infection with encapsulated organisms. Infection of the bone can be difficult to differentiate from bone infarcts, particularly as bony infarcts commonly involve the epiphysis and can clinically resemble synovitis, and appearance on MRI may be indistinguishable. Synovial analysis and bone biopsy may be required to confirm the diagnosis.

Arthritis resembling RA has been described in sickle cell patients with polyarticular symmetric synovitis affecting the knees and ankles. Symptoms are self-limited and radiography may show periarticular osteopenia, bony erosions, and joint space narrowing.

SCD in children causes growth disturbances including delayed puberty by 12–24 months and delayed skeletal age.

Osteonecrosis is common in SCD patients often presenting as avascular necrosis of the femoral head. Concurrent hemoglobinopathy (alpha thalassemia) or frequent vaso-occlusive crises are risk factors for avascular necrosis. Multiple joints can be affected, and clinical clues include chronic joint pain and progressive decreased range of motion to the joints.

Iron overload due to repeat transfusions results in a symmetric polyarticular arthropathy with bony enlargement and minimal inflammation affecting the MCPs, PIPs, wrists, elbows, shoulders, and hips mimicking hemochromatosis. Compared to the latter, patients have less severe iron-induced cardiac and endocrine dysfunction.

Crystal arthritis as a consequence of hyperuricemia due to increased red blood cell turnover is common in SCD.

Primary Immunodeficiencies (PIDs)

Several primary immunodeficiencies (*PIDs*) have been associated with rheumatologic disorders. Thought to be a consequence of immune dysregulation, rheumatologic manifestations may even precede characteristic infectious complications of PID. Incidence of primary PID may be as high as 22% in the rheumatology clinic population, and it is confounded prospectively by concomitant immunosuppressive medications predisposing patients to infections. Red flags for PIDs include personal or family history of recurrent infections, family history of PID, as well as with concomitant rheumatologic diseases.

Systemic lupus erythematosus has been associated with C1q, C1r/C1s, C4, C3, and C2 deficiencies, chronic granulomatous disease (CGD), selective IgA deficiency (SIgAD), and common variable immune deficiency (CVID). Early complement deficiencies are more strongly associated with development of autoimmune disease, as well as risk of infection with encapsulated organisms (late complement more associated with Neisseria infection). Autoimmune lymphoproliferative syndrome (ALPS) is associated with serologic evidence of lupus but not with clinical disease.

Arthritis pattern in PID is highly variable and can be mono-, oligo-, or polyarticular with or without rheumatoid nodules. Any monoarticular arthritis especially in this population is considered septic until proven otherwise. Arthritis is more strongly associated with hypogammaglobulinemia or agammaglobulinemia. The large joints of the lower extremities are more commonly affected in X-linked agammaglobulinemia (XLA), whereas SIgAD and CVID are associated with RA and juvenile inflammatory arthritis (JIA). DiGeorge syndrome (DS) is linked to a chronic early-onset polyarticular arthritis. Other PIDs afflicted by arthritis include Wiskott-Aldrich syndrome (WAS), hyper-IgM syndrome, ALPS, and CGD. Treatment of the underlying disease usually leads to symptomatic benefit; corticosteroids and steroid-sparing immunosuppressants are rarely required posing challenges.

Vasculitis has been described with WAS, C4 deficiency, autoimmune polyendocrinopathy candidiasis ectodermal dysplasia (APECED), ALPS, CVID, and SIgA and is thought to be mediated by impaired clearance of immune complexes. Treatment is the same for PID and PID-unrelated vasculitis.

Sarcoidosis must be differentiated from the typical caseating inflammatory lesions seen in CGD. Granulomatous lesions have also been described in CVID. GLILD or granulomatous and lymphocytic interstitial lung disease is characterized by non-necrotizing pulmonary granuloma with radiographic findings that mimic sarcoidosis. In the syndrome of immunodysregulation, polyendocrinopathy, and enteropathy, X-linked (IPEX) sarcoid-like granulomas responsive to immunosuppression have been described.

Dermatomyositis-like syndromes have been described in association with XLA, WAS, and CVID, and *Sjögren's syndrome* has been associated with APECED, as well as CVID and C4 deficiency. Several organ-specific manifestations may mimic rheumatologic conditions and should be considered in the differential of autoimmune manifestations. For example, patients with hyper-IgM syndrome and WAS have been reported to have uveitis and optic neuritis [13].

Rheumatic Diseases and Malignancy

Musculoskeletal symptoms may be first manifestation of underlying malignancy. At times cause and effect is difficult to define, as some cancers present more frequently in patients with underlying autoimmune disease, while some autoimmune diseases are associated with underlying malignancy. To further complicate the matter, various medications used to treat autoimmune diseases have been associated with an increased risk of malignancy. Finally, musculoskeletal symptoms may be the result of a paraneoplastic process.

Common musculoskeletal manifestations of solid tumors include carcinomatous polyarthritis, reflex sympathetic dystrophy, digital necrosis, palmar fasciitis, multicentric reticulohistiocytosis (Fig. 18.7), osteogenic osteomalacia, and sarcoidosis. Vasculitis, mixed cryoglobulinemia, lymphomatoid granulomatosis, and erythromelalgia are more commonly associated with underlying lymphoproliferative disorders. Panniculitis, polymyalgia rheumatica, remitting seronegative symmetric synovitis with pitting edema (RS3PE), lupus-like syndromes, and antiphospholipid production have been attributed to a variety of underlying malignancies.

Increased suspicion for an underlying *paraneoplastic process* is appropriate any time the clinical scenario diverges from that which is expected. This includes late onset of arthritis, asymmetric involvement, abrupt and severe onset of symptoms, treatment refractory disease, seronegative disease, an absence of family history, and nonspecific findings on histopathology. Concurrent fever or weight loss should also raise suspicion. Symptoms often resolve after treatment of the underlying malignancy.

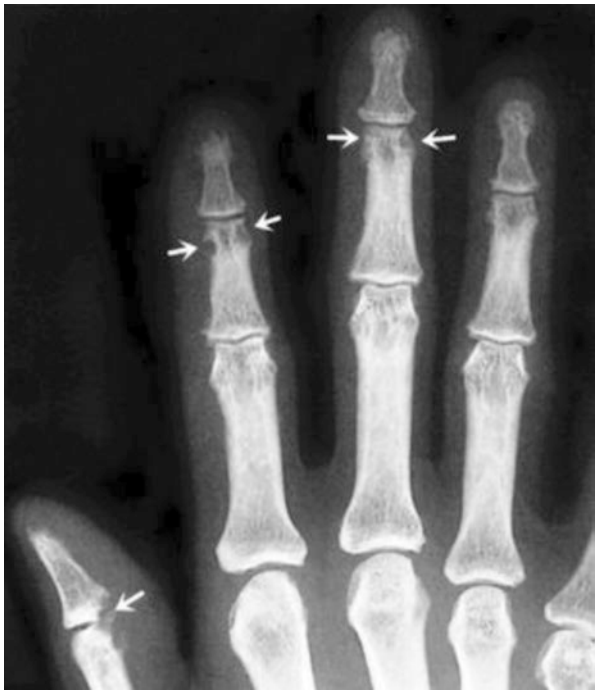

Fig. 18.7 Example of multicentric reticulohistiocytosis (Reprinted with permission from Springer [14])

Inflammatory myopathies have been linked to ovarian, lung, and gastric cancer in the European population and nasopharyngeal in the Asian population. Solid tumors have the strongest association. It is thought that damaged or regenerating muscle fibers expose myositis-specific antigens that may trigger an autoimmune response leading to clinical inflammatory myositis. Malignancy is most strongly associated with dermatomyositis, with a frequency approximately twice that of polymyositis. Overall the incidence of carcinoma in patients with inflammatory myositis ranges from five to seven times that of the general population. Malignancy associated with inflammatory myopathies usually presents within 1 year but has been described to develop years after initial diagnosis. Diagnostic evaluation to rule out underlying malignancy is recommended in these patients and should be tailored to the patients' age and symptoms. Age greater than 45, male sex, dysphagia, cutaneous necrosis, cutaneous vasculitis, rapid onset over less than 4 weeks, presence of shawl sign, elevated acute-phase reactants, as well as treatment refractory disease should all prompt consideration for underlying malignancy. Conversely, associated ILD, arthritis, Raynaud's phenomenon, Jo-1 antibody, positive anti-ENA, or other myositis-specific antibodies may be protective for malignancy.

Rheumatic manifestations are frequently reported in the background of *cancer treatments* to include chemotherapy, aromatase inhibitors, and immunotherapy. Non-inflammatory self-limited migratory arthropathy presenting weeks to months

after completion of chemotherapies including cyclophosphamide and 5-fluorouracil is reported. Up to half of patients on aromatase inhibitors such as tamoxifen for breast cancer experience arthralgias, myalgia, stiffness, and arthritis involving small joints of hands, ankles, and knees. While symptoms may resemble rheumatoid arthritis, patients will not have synovial thickening, radiographic, or serologic evidence to suggest RA. Symptoms usually resolve within 1 year [15]. Immune checkpoint inhibitors such as cytotoxic T-lymphocyte-associated protein 4 (CTLA-4), programmed death 1 (PD-1), and PDL1 inhibitors are designed by default to activate T cells against tumor antigen presenting cells, and the spectrum of indications is exponentially expanding. The most common rheumatic immune-related adverse events are arthralgia/arthritis, myalgia/myositis, polymyalgia rheumatica, lupus, rheumatoid arthritis, and Sjögren's syndrome. Of note, these drugs can also cause an exacerbation of established rheumatologic disease. High index of suspicion and multidisciplinary care of these patients is warranted. Many patients require immunosuppression, and a minority require discontinuation of their immunotherapy [16].

Finally, graft-versus-host disease (GVHD) is a complication of bone marrow transplant which may lead to both acute (<3 months) or chronic (>3 months) musculoskeletal symptoms. Symptoms vary but may mimic characteristic findings seen in systemic sclerosis and Sjögren's syndrome including arthralgia, arthritis, myositis, Raynaud's phenomenon, and serositis [17].

Amyloidosis

Amyloidosis refers to a group of diseases defined by extracellular deposition of insoluble fibrillar proteins in tissues and organs. Over time accumulation of these proteins may lead to organ failure and even death. Subtypes are classified by their biochemical makeup as well as clinical presentation. Protein deposition in systemic amyloidosis may occur anywhere in the body and can resemble autoimmune rheumatologic disorders when involving the synovial tissue. The major subtypes of systemic amyloidosis include the most common *AL amyloid* (Ig light chain, or primary amyloidosis), the *AA amyloid* (reactive, or secondary amyloidosis), the *AB2M amyloid* (B2-microglobulin, or dialysis associated), and the most common of the inherited amyloidosis *ATTR amyloid* (transthyretin amyloidosis). Amyloid proteins are identified with Congo red dye creating a unique green birefringence with polarized light microscopy. Deposits can also be visualized with hematoxylin-eosin sections, and immunohistochemical staining differentiates types of amyloid deposits. Classic manifestations of amyloidosis include renal insufficiency, proteinuria, chronic heart failure associated with low voltage ECG, MI, concentric thickened ventricles with normal/mildly reduced EF, peripheral neuropathy autonomic dysfunction, hepatomegaly, cutaneous ecchymoses nail dystrophy, alopecia, and arthropathy. Macroglossia is pathognomonic but only seen in approximately 10% of patients with AL amyloidosis.

Amyloid arthropathy includes thickening of the synovial membranes, joint pain, subcutaneous tissue deposits, muscle pseudohypertrophy, adenopathy, and carpal tunnel syndrome. Submandibular glands may be enlarged mimicking other rheumatologic conditions. In dialysis-associated amyloidosis, large joints are primarily affected with presence of non-inflammatory effusions. Spondyloarthropathy has also been described with destructive changes in intervertebral discs and paravertebral erosions. Limited therapeutic options exist, although symptomatic improvement is reported after renal transplant.

Diagnosis requires tissue biopsy with visualization of amyloid fibrils. Abdominal fat pad biopsy is the preferred sampling method, but false-negative biopsy results remain a possibility. If clinical suspicion remains high, biopsy of a clinically involved organ is recommended. Immunohistochemical staining for AA protein must be done to confirm the diagnosis [18].

Sarcoidosis

Sarcoidosis is a heterogeneous multisystem inflammatory disease of unknown etiology characterized by noncaseating granulomas commonly affecting the lungs, although any organ system can be involved. Up to 1/4 of patients have joint involvement. Direct involvement of the bone, or osseous sarcoidosis, has been described in a subset of patients and often affects the axial skeleton and sacroiliac joints. Muscle involvement, termed sarcoid myopathy, is frequently observed but is often asymptomatic [19].

Arthritis in sarcoidosis can be acute or chronic. In acute sarcoid arthritis, patients can be febrile and present with symmetric polyarthritis affecting ankles, knees, wrists, and elbows. Contemporaneous bilateral hilar adenopathy and erythema nodosum constitute Lofgren syndrome. Symptoms last weeks to months but often do not recur once resolved. ESR may be elevated. In contrast, chronic sarcoid arthropathy is less common affecting multiple organs and is seen mostly in African Americans. Patients present with oligoarthritis or polyarthritis and variable features including joint destruction or Jaccoud's arthropathy. Phalangeal cysts or a trabecular pattern may be seen on X-ray. Damage may occur early or late in the course. Concurrent lupus pernio or chronic uveitis may coexist. Symptoms can mimic rheumatoid arthritis, reactive arthritis, or rheumatic fever, and tissue biopsy from an affected organ is necessary to confirm the diagnosis. Due to variable and nonspecific presentation and a multitude of other conditions associated with granulomas, sarcoidosis remains a diagnosis of exclusion (Hodgkin's lymphoma, TB). Heerfordt syndrome, also known as uveoparotid fever, or Waldenstrom's uveoparotitis is a rare manifestation of sarcoidosis characterized by uveitis, parotid swelling, chronic fever, and facial nerve palsy.

Workup includes chest radiography to evaluate for hilar lymphadenopathy, pulmonary infiltrates, and/or fibrosis. Biomarkers such as serum ACE have been suggested, but they are not sensitive nor specific for diagnostic or monitoring purposes. Hand X-rays can show phalangeal cystic changes which are relatively specific for sarcoidosis, but trabecular changes, osteolysis, cyst formation, and punched out lesions have also been described. MRI is useful to identify cardiac or CNS involvement. FDG-PET can help to identify extrapulmonary involvement including cardiac disease. First-line treatment of sarcoidosis includes corticosteroids. Second-line agents include disease-modifying or steroid-sparing agents. TNF inhibitors including infliximab and adalimumab have been used successfully. Patients with sarcoidosis produce excess 1,25(OH)D and are at risk for vitamin D toxicity [20].

Key Points Table

- Longstanding DM is associated with flexor tenosynovitis and trigger fingers, Dupuytren's contracture, carpal tunnel syndrome, diabetic cheiroarthropathy, and Charcot foot.
- Arthritis in hemochromatosis is a late manifestation frequently affecting the 2nd and 3rd MCP, and typical XR findings include joint space narrowing of 2nd and 3rd MCP, hook-like osteophytes, and chondrocalcinosis of the triangular fibrocartilage.
- Sickle cell disease is associated with dactylitis especially in children, osteomyelitis, and avascular necrosis.
- Any monoarticular arthritis in a patient with immunodeficiency is considered septic until proven otherwise. Arthritis is more strongly associated with hypogammaglobulinemia or agammaglobulinemia.
- Paraneoplastic arthritis should be suspected in late onset of arthritis, asymmetric involvement, abrupt and severe onset of symptoms, treatment refractory disease, seronegative disease, absence of family history, and presence of constitutional symptoms such as fever and weight loss.
- Malignancy is most strongly associated with dermatomyositis and usually presents within 1 year but has been described to develop up to 5 years after initial diagnosis.
- Early osteoporosis and osteoarthritis should raise suspicion for systemic conditions.
- Amyloid arthropathy causes synovial thickening, arthralgia, subcutaneous tissue deposits, muscle pseudohypertrophy, adenopathy, and carpal tunnel syndrome.
- Sarcoid arthropathy can be acute or chronic and axial or peripheral and present as poly- or oligoarthritis with variable features including joint destruction or Jaccoud's arthropathy.

Questions

1. A 28-year-old male with hemophilia presents to the ER with acute-onset knee pain and swelling. Exam shows tense large effusion. CT of the knee is highly suggestive of acute hemarthrosis. Which is the next best therapeutic strategy?

   A. Arthrocentesis
   B. Ibuprofen
   C. Pain control
   D. Clotting factor

   Correct answer: D
   Explanation: Administration of clotting factor should promptly improve acute hemarthroses in patients with hemophilia. Arthrocentesis is not recommended, as instrumentation may exacerbate bleeding. NSAIDs should be avoided in these patients for similar reasons, but COX-2 selective agents may have a role in chronic synovitis related to hemophilia. While controlling this patient's symptoms remains a priority, addressing the underlying issue is a better therapeutic strategy.
2. A 32-year-old African American male presents to the ER with non-remitting pain in the mid-back. He has a history of dactylitis as a child. Screening X-rays show characteristic fish-mouth deformity to the thoracic vertebrae and vertebral fracture of T12.
   What is the most likely underlying disorder?

   A. Acromegaly
   B. Osteoporosis
   C. Sickle cell disease
   D. Sarcoidosis

   Correct answer: C
   Explanation: Fish-mouth deformity of the spine XRs is the result of a collapsed vertebrae due to microvascular occlusion in low-flow vascular areas including bone marrow leading to bone thrombosis in sickle cell disease. Dactylitis and ethnic background are clues for the possibility of sickle cell disease in this patient.
3. Which of the following is correct regarding AB2M?

   A. Strongly associated with underlying plasma cell disorder
   B. A result of chronic inflammation related to underlying autoimmune disease
   C. Associated with longstanding hemodialysis
   D. Inherited in an autosomal dominant pattern

   Correct answer: C
   Explanation: *AB2M amyloid* represents the B2-microglobulin, or dialysis-associated amyloid. In dialysis-associated amyloidosis, large joints are primarily affected with presence of non-inflammatory effusions.

4. A 48-year-old male patient with a significant medical history of longstanding ESRD on hemodialysis secondary to hypertensive nephropathy is referred to your office with symmetric polyarthralgia involving the bilateral hands, wrists, shoulders, hips, and low back. Additional history reveals pathologic fractures, and existing lab work shows an undetectable level of hydroxyvitamin D. Clinical examination shows no evidence of synovitis. In addition to serum testing to rule out underlying inflammatory arthritis, which of the following would most accurately confirm the diagnosis?

   A. Serum testing for PTH, vitamin D, calcium, and phosphorus
   B. Bone mineral density/DEXA scan
   C. Musculoskeletal ultrasound of the bilateral hands and wrists
   D. Bone biopsy with tetracycline labeling

   Correct answer: D
   Explanation: The transiliac bone biopsy remains the gold standard for diagnosis (and characterization) of renal osteodystrophy. Serum PTH levels are commonly used to assess bone turnover in dialyzed patients. However, it is found that serum PTH levels between 65 and 450 pg/ml seen in the majority of dialysis patients are not predictive of the underlying bone disease. The use of newer vitamin D analogs such as paricalcitol may result in improved patient outcomes compared to therapy with the native hormone, calcitriol, yet such studies need to be confirmed.
5. Patient presents with unexplained fevers. Biopsy of associated lymphadenopathy shows granuloma. Which of the following is not part of the differential for granulomatous inflammation?

   A. Sarcoidosis
   B. Tuberculosis
   C. Hodgkin's lymphoma
   D. Crohn's disease
   E. Lyme disease

   Correct answer: E
   Explanation: Due to variable and nonspecific presentation and a multitude of other conditions associated with granulomas, sarcoidosis remains a diagnosis of exclusion (Hodgkin's lymphoma, TB).
6. A 53-year-old obese male with history of diabetes mellitus presents with a chief complaint of bilateral hand pain and stiffness. He has also had abnormal liver function tests attributed to nonalcoholic steatohepatitis. Exam shows fullness over the MCPs bilaterally. XR image is shown below. Which of the following is the most likely explanation for this patient's chronic polyarthralgia?

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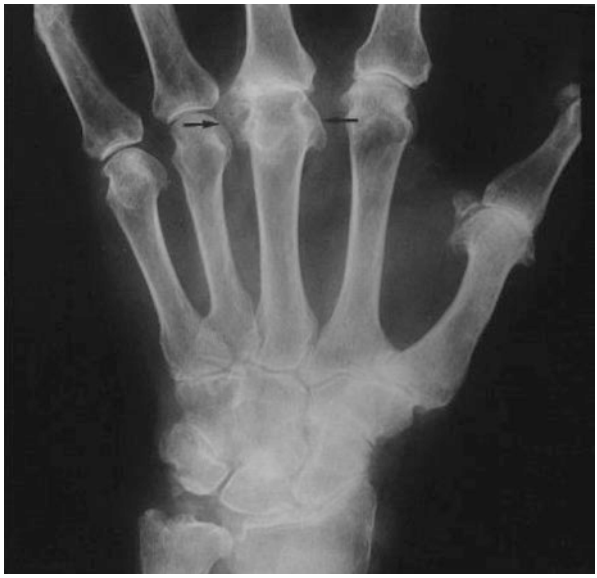

A. Hemochromatosis
B. Acromegaly
C. Chondrocalcinosis
D. Rheumatoid arthritis

Correct answer: A
Explanation: XRs are typical for hemochromatosis with hook-like osteophytes. Other historical clues include history of diabetes and liver function abnormalities which may complicate the disease. Chondrocalcinosis can also be an associated finding of hemochromatosis classically in the triangular ligament.

7. A 28-year-old male with hemophilia and a history of recurrent hemarthrosis presents with severe knee pain and swelling. As part of the workup, an ultrasound is performed showing synovitis without acute hemarthrosis or effusion. What is the next best therapeutic option?

A. Administration of clotting factor
B. Celecoxib
C. Arthrocentesis
D. Synovectomy

Correct answer: B
Explanation: While acute hemarthrosis will respond to administration of clotting factor, synovitis related to prior recurrent hemarthrosis will not respond to acute administration of clotting factor. Instead therapeutic options include those used for other inflammatory arthritis. NSAIDs, apart from COX-2 selective

agents, should be avoided given the increased risk of bleeding. Chronic administration of clotting factor may reduce the severity and frequency of synovitis in these patients over time. Synovectomy is reserved for severe refractory cases. Arthrocentesis is of limited value given the absence of effusion on ultrasound and remains a high-risk procedure in a patient with an underlying bleeding disorder.

8. A 54-year-old male presents for initial outpatient rheumatology consult for evaluation of bilateral hand pain and stiffness, worst in the morning for 2 months. She has a significant history of bladder cancer treated with nivolumab thought to be in remission, a recent diagnosis of type 1 diabetes, and earlier this year she completed a course of prednisone for presumed autoimmune hepatitis. Examination is consistent with bilateral symmetric active synovitis affecting the MCPs and decreased grip strength. Serologies are negative for ANA, CCP, and rheumatoid factor. ESR is raised. X-rays show only mild DJD. Ultrasound confirms active synovitis with no erosions.

   What is the most appropriate next step?

   A. Trial with conventional disease-modifying anti-rheumatic drugs.
   B. Trial with biologic disease-modifying anti-rheumatic drugs.
   C. Hold nivolumab.
   D. Parvovirus B19 serologies.
   E. Prednisone taper.

   Correct answer: E
   Explanation: Patient exhibits several immune-related adverse effects (irAEs) due to nivolumab which is an immune checkpoint inhibitor specifically that is a fully human monoclonal immunoglobulin G4 antibody to programmed death PD-1. Immune checkpoint inhibitors block the inhibitory signals of T cells, therefore resulting in T cell activation mediating their effect in cancer cells but also several immune-mediated phenomena. These include type 1 diabetes, autoimmune hepatitis, and inflammatory arthritis. The median time from checkpoint inhibitor to musculoskeletal irAE in GU malignancies is 5 months, and patients are treated initially usually with prednisone with a median initial dose of 40 mg/day for up to a year. A subset of patients may require disease-modifying medications, and a minority may have to hold the immunotherapeutic agent. Usually MSK manifestations of parvovirus infection resolve within 4–6 weeks.

9. A 70-year-old man with longstanding history of type 2 diabetes mellitus for 10 years is referred for evaluation of hand symptoms the past 6 months. Symptoms include paresthesia, pain, and numbness over the first through third digits of both hands especially at night. She denies joint stiffness or swelling. Her medical history is notable for recent-onset kidney disease, proteinuria, and peripheral neuropathy, all of which have been attributed to diabetes. Her only medications are metformin 500 mg orally twice daily and an aspirin daily.

While giving her history, the patient displays some difficulty with her speech, and lateral tongue indentations are noted on physical examination.

Which is the next best step?

A. Electrophoresis with immunofixation
B. Electromyogram
C. Abdominal fat biopsy
D. Kidney biopsy

Correct answer: A

Explanation: Patient exhibits features of a systemic process. DM is associated with carpal tunnel syndrome, kidney disease, and proteinuria. Macroglossia is not a common finding in amyloidosis, but this is classically seen in AL amyloidosis and not seen in DM. Microscopic examination will reveal amyloid deposits upon staining with Congo red. Biopsy of involved tissue in conjunction with serum and urine electrophoresis with immunofixation and serum-free light chain analysis are the most appropriate studies in the investigation for AL amyloidosis.

10. A 20-year-old male with 6-month history of polyarthralgias comes for evaluation. Symptoms started after a trip to the Caribbean islands during summer time including stiffness and intermittent swelling in her hands especially after rest and in the morning. He feels more tired and having to take a nap during the day. Patchy hair loss is also noted. He endorses having frequent sinus infections since childhood and had one hospitalization for pneumonia in the past. He takes ibuprofen 400 mg twice daily which alleviates symptoms. His basic workup revealed hemolytic anemia and mild lymphopenia with mild liver function test abnormalities and normal kidney function.

What is the next best test to identify the underlying diagnosis?

A. Antinuclear antibody
B. Coombs test
C. Immunoglobulin levels
D. Rheumatoid factor

Correct answer: C

Explanation: This patient's most likely underlying diagnosis is common variable immunodeficiency. Clues include sinopulmonary infections at an early age and associated autoimmune phenomena. CVID is associated with both systemic lupus erythematosus and rheumatoid arthritis. Coombs test, rheumatoid factor, and antinuclear antibody may be part of the workup but would not pin down the underlying association with CVID which is important.

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Chapter 19
Clinical Genetics in Rheumatology

Ruth Fernandez-Ruiz and Petros Efthimiou

Introduction

The dramatic advances in human genome research and the number of available genetic tests call for improved genetic knowledge among healthcare providers, including rheumatologists. Genetic testing is most clinically applicable in monogenic conditions, where a mutation in a single gene is directly responsible of the disease. In this setting, genetic testing may confirm or refute the diagnosis and can guide therapeutic interventions. Nonetheless, genetics is a fundamental component of complex multifactorial disorders, where multiple susceptibility genes, along with environmental influences, play a role in the etiopathogenesis of several rheumatologic conditions such as rheumatoid arthritis, systemic lupus erythematosus, and osteoarthritis, among others [1–4].

Overview of General Concepts in Clinical Genetics

A mutation is any change in the primary nucleotide sequence of DNA. Mutations can have a variety of functional consequences ranging from silent (without phenotypical significance) to loss- or gain-of-function mutations. Usually, mutations need to affect the exons (i.e., the encoding regions of the genome) in order to cause a disease. Germline mutations lead to potential transmissibility of genetic diseases.

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The patterns of transmission in monogenic or single-gene disorders is typically autosomal (affecting one of the 22 nonsex chromosomes) dominant (AD) or autosomal recessive (AR). A disease is said to be transmitted on an AD pattern if one mutated copy of the gene in each cell is enough for a person to be affected by such disorder, while for AR diseases to manifest, there needs to be two copies of an abnormal gene (one paternal and one maternal). Other conditions are transmitted in the sex chromosomes (X or Y chromosomes) and therefore affect males or females differently. For instance, X-linked disorders will be expressed fully in men as they only possess one X chromosome, while the same disease may be less severe or not expressed at all in females. Notably, X-linked conditions are only transmitted from the maternal side, which is important to consider while evaluating a patient's family history [4–6].

AD conditions can have variable penetrance, which refers to the proportion of people with a genetic change who will exhibit signs and symptoms of the particular genetic disorder. In this sense, a typical Mendelian inheritance pattern may not be seen if there is incomplete penetrance of an AD disorder. Another possibility for unaffected parents in the cases of AD diseases is a new germline mutation, such as it has been reported in Marfan syndrome. However, in most cases, AD disorders are present in one of the parents, and the probability of transmission to the offspring is 50% for each child, with the same risks for males and females. Variable expressivity is another relevant concept in clinical genetics, which refers to the degree to which a specific genotype is expressed in the phenotype, and can affect the severity, type of organ involvement, or age of onset of the disease. A phenomenon called heterogeneity also increases the complexity of identifying genetic disorders, as mutations in different genes can sometimes translate into a very similar clinical phenotype, which is sometimes seen in conditions affecting the inflammasome pathways or the extracellular matrix, causing autoinflammatory syndromes or heritable connective tissue disorders, respectively [4–6].

Mosaicism and mitochondrial disorders are also exceptions to simple Mendelian inheritance patterns. In mosaicism, there are two or more genetically distinct cell lines in the tissues due to mutations occurring during or after embryonic development. Inherited mitochondrial disorders occur due to mutations in genes encoded by DNA in the mitochondria and are transmitted in a matrilineal fashion (i.e., all children from an affected mother will inherit the mutations, but there will be sparing of all the progeny from affected males) [4–6].

AR disorders are less common than AD diseases and usually relate to consanguinity or when mutations are very common due to selective evolutionary advantage (such as protection against deadly infections). The mutated genes cause a partial or complete loss of function, leading to alterations in receptors, enzymes, or adaptor proteins in intracellular signaling or metabolic pathways. X-linked and Y-linked (sex chromosomes) transmitted disorders are less commonly seen in rheumatology [1, 2, 4–6].

Genetic Testing in Rheumatology

Hereditary diseases often present early in childhood, but adult-onset genetic disorders are also seen in rheumatology practice. The first challenge is to identify based on history when a clinical scenario may be due to a genetic disease. As with any ancillary testing, before initiating genetic evaluation, it is crucial to obtain a thorough history, including detailed family history, which may help with recognition of clinical patterns associated with specific genetic diseases. Physical exam findings, as well as laboratory (such as inflammatory markers), biochemical, and imaging tests are often useful in establishing a differential diagnosis. In rheumatology, genetic testing for autoinflammatory disorders and hereditable connective tissue disorders has become an essential tool in the last decade, as an accurate diagnosis can lead to appropriate and timely therapeutic interventions and/or monitoring for specific organ affectation [1, 2, 7–9].

Before performing genetic testing, it is imperative to discuss with patients the benefits and expectations and to obtain an informed consent. It is also important to consider the sensitivity and specificity of the test, as some mutations are not identified in standard testing, particularly in cases of mosaicism or new undiscovered variants [1–4, 10–12]. For instance, cases of somatic mosaicism of the nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 3 (NLRP3) have been reported in patients with chronic infantile neurological cutaneous and articular (CINCA) syndrome or neonatal-onset multisystem inflammatory disease (NOMID) [13].

The involvement of a genetic counselor is strongly recommended in all cases to address the emotional burden of genetic testing, and to help communicating the results, as well as the nature, and recurrence risk of the disease [3, 11].

Genetic testing for diagnostic purposes is not to be confused with direct-to-consumer testing, where the test is offered as a service from a private company directly to the consumer, without a clinician or expert geneticist to interpret the results. These types of genetic tests are not typically comprehensive enough to identify specific single-gene disorders [14].

Clinically Available Methodologic Approaches to Genetic Testing

In general, genetic testing involves the use of specific assays to study the genes in an individual's genome, who is suspected to be at an increased risk for a specific inherited condition based on clinical findings and family history. All types of genetic testing involve the analysis of specimens (commonly leukocytes, buccal cells, fibroblasts, o other tissues). There are different methods for genetic testing with variable sensitivity, specificity, expensiveness, and requirement for expertise

and time. Gene panels assess alterations in multiple genes that have been implicated in specific genetic conditions. For instance, many commercial laboratories have panels to evaluate for heritable connective tissue disorders and autoinflammatory or periodic fever syndromes that include a few to dozens of probable genes, depending on the laboratory. This is particularly relevant as multiple rheumatologic conditions have very similar clinical presentations but may be caused by mutations in different genes (a phenomenon called heterogeneity, as previously mentioned). Single-gene testing is also commercially available for most heritable connective tissue disorders and autoinflammatory monogenic diseases [4, 15, 16].

Since the use of next-generation sequencing (NGS) technologies has dramatically expanded, it is now widely used in commercial laboratories. The use of targeted deletion/duplication analysis has now also become a standard test when no pathogenic aberrations are detected by NGS. With this test, it is possible to identify partial or whole gene deletions and duplications in the associated genes. The required specimens for single-gene testing or gene panels are usually whole blood in an EDTA tube (purple or lavender top tube) and/or buccal swabs/saliva, and the turnaround time is generally 10–21 days for most commercial laboratories [4, 15].

Prior to NGS, the traditional Sanger sequencing test was widely used for DNA sequencing. Sanger sequencing is based on the selective incorporation of chain-terminating nucleotides in vitro, which were radioactively or fluorescently tagged for detection in automated equipment. This method has good accuracy, but it only allows to identify mutations in a specific gene and cannot be used to provide information about larger portions of the genome. Sanger sequencing is currently mainly used in commercial laboratories as a confirmation step once the pathogenic variants have been identified [4, 15, 17].

In individuals with unexplained syndromes that are suspected to be inherited or genetic disorders, whole-genome sequencing (WGS) is available. Genome sequencing can include only coding regions (whole-exome sequencing) or the entire genome (regulatory and noncoding regions included). Besides increased cost and being more time-consuming, WGS also increases the likelihood of identifying unexpected genetic alterations that may be completely unrelated to the test indication or of unclear clinical relevance [4].

Genetic testing regulations are similar to other specialized laboratory tests. The Clinical Laboratory Improvement Amendments (CLIA), a Centers for Medicare and Medicaid Services (CMS) program, are the federal regulatory standards that ensure quality laboratory testing in the United States, including in the field of genetics [18]. As of April 2018, the Food and Drug Administration (FDA) issued new guidelines to ensure the analytical and clinical validity of NGS-based testing results [19].

Genetic Testing in Monogenic Autoinflammatory Syndromes

Autoinflammatory syndromes are a group of diseases characterized by recurrent and spontaneous episodes of fever, arthritis, serositis, elevated inflammatory markers, skin rashes, and long-term serious complications such as AA

amyloidosis as the result of chronic inflammation. In contrast to autoimmune diseases where there are autoantibodies or reactive T cells, autoinflammatory diseases are mediated by the innate immune system. Specifically, they are caused by anomalous activation of the inflammasome, a multiprotein scaffold complex that leads to generation of interleukin-1 (IL-1) and consequent uncontrolled inflammation. Many of the monogenic autoinflammatory syndromes (MAIS) present during early childhood, but adult-onset forms are also often seen, particularly familial Mediterranean fever (FMF) and tumor necrosis factor receptor-associated periodic syndrome (TRAPS) [1, 7, 8].

Genetic testing has become essential to accurately diagnose MAIS. Most commercial genetic laboratories in the United States use NGS technology followed by targeted deletion/duplication analysis if no pathogenic aberrations are detected by NGS (see "Clinically Available Methodologic Approaches to Genetic Testing" for more details). A summary of the clinical presentation, pattern of inheritance, and affected gene/protein for most common MAIS is shown in Table 19.1.

Familial Mediterranean fever (*FMF*) is the most common monogenic periodic fever syndrome. FMF is an AR disorder caused by mutations at the MEFV gene which codes for the protein pyrin. Although FMF typically presents during childhood, adult-onset forms can be occasionally seen. The clinical diagnosis is made based on the Tel Hashomer criteria (two major criteria or one major and two minor criteria are needed to make the diagnosis): major criteria, (1) recurrent febrile episodes with serositis (peritonitis, synovitis, or pleuritis), (2) AA amyloidosis without a predisposing disease, and (3) favorable response to regular colchicine treatment; and minor criteria – (1) recurrent febrile episodes, (2) erysipelas-like erythema, and (3) FMF in first-degree relative [1, 8, 20, 21].

TRAPS is a monogenic periodic syndrome with an AD pattern of inheritance, caused by mutations in the TNF receptor superfamily member 1A (TNFRSF1A) gene. TRAPS is characterized by recurrent inflammatory attacks lasting 1–3 weeks, with fever, arthralgia or arthritis, rash, serositis, cramps, myalgia, lymphadenopathy, headache, and fatigue. Secondary AA amyloidosis is common in untreated patients [8, 20, 21].

Mevalonate kinase deficiency (*MKD*), formerly known as hyper-immunoglobulin D syndrome, is an AR disorder caused by a mutation in the mevalonate kinase (MVK) gene. Clinically, the inflammatory attacks are characterized by fever, gastrointestinal compromise, skin rash, lymphadenopathy, arthralgia or arthritis, and fatigue. The attacks usually last for 3–7 days and they resolve spontaneously [8, 20, 21].

The *cryopyrin-associated periodic syndromes* (*CAPS*) comprise a group of AD disorders that include the *familial cold autoinflammatory syndrome* (*FCAS*), *Muckle-Wells syndrome* (*MWS*), and *chronic infantile neurological cutaneous and articular* (*CINCA*) *syndrome*, caused by mutations in the NLRP3/CIAS1 gene that codes for cryopyrin. *Nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 12* (*NLRP12*)*-associated autoinflammatory disorder* (*NLRP12AD*) is caused by NLRP12 mutation (monarch-1). The CAPS most commonly present in the first 6 months of life, but there have been rare cases reported in adulthood. CAPS commonly present with fever, urticaria-like rash, conjunctivitis, and arthritis, but more specific clinical features depend on the time of onset, with the

Table 19.1 Monogenic autoinflammatory diseases [1, 8, 20, 21]

Classification	Clinical features	Gene/ chromosome/ OMIM	Protein	Inheritance
Monogenic periodic fevers				
Familial Mediterranean fever (FMF)	Recurrent febrile episodes with serositis and arthritis. Long-term development of AA amyloidosis in untreated patients. Good clinical response to colchicine	*MEFV* (*chromosome 16p13.13*). OMIM #249100. More than 70 mutations have been reported	Pyrin (marenostrin)	AR
Tumor necrosis factor receptor-associated periodic syndrome (TRAPS)	Recurrent inflammatory attacks lasting 1–3 weeks, with fever, skin rash, arthritis/ arthralgia, fatigue, GI involvement. Secondary AA amyloidosis is common in untreated patients	*TNFRSF1A* (*chromosome 12p13.31*). OMIM #142680. More than 60 mutations have been reported	TNF receptor 1	AD with incomplete penetrance
Mevalonate kinase deficiency (MKD) or hyper-IgD syndrome (HIDS)	Recurrent inflammatory attacks lasting 3–7 days, with fever, skin rash, arthritis/arthralgia, fatigue, GI involvement	*MVK* (*chromosome 12q24.11*). OMIM #260920; #610377. At least 80 mutations have been described	Mevalonate kinase	AR
Cryopyrin-associated periodic syndromes				
Familial cold autoinflammatory syndrome (FCAS) 1 Muckle-Wells syndrome (MWS) Chronic infantile neurological cutaneous and articular (CINCA) syndrome or neonatal-onset multisystem inflammatory disease (NOMID)	Episodes of fever, urticaria-like rash, conjunctivitis, and arthritis. The perinatal-onset form (NOMID) is the most severe presentation, with uveitis, optic nerve atrophy, chronic aseptic meningitis, sensorineural hearing loss. FCAS is the mildest form, while MWS is intermediate in severity	*NLRP3/CIAS1* (*chromosome 1q44*). OMIM #120100; #191900; #607115. Almost all mutations have been described in exon 3	Cryopyrin	AD
NLRP-12-associated autoinflammatory disorder (NLRP12AD) or famlial cold autoinflammtory syndrome 2 (FCAS2)		*NLRP12* (*chromosome 19q13.42*). OMIM # 611762	Monarch-1	AD with incomplete penetrance

Table 19.1 (continued)

Classification	Clinical features	Gene/ chromosome/ OMIM	Protein	Inheritance
Autoinflammatory granulomatous disorders				
Blau syndrome (BS) and early-onset sarcoidosis (EOS) or sporadic form of BS	Clinical presentation is characterized by a triad of arthritis (usually polyarticular), dermatitis, and uveitis. Histologic feature is noncaseating granulomatous inflammation	*NOD2/CARD15* (*chromosome 16q12.1*). OMIM #186580. At least 22 mutations have been found in association with BS	NOD2	AD/ sporadic
Autoinflammatory pyogenic disorders				
Pyogenic arthritis, pyoderma gangrenosum and cystic acne (PAPA) syndrome	Recurrent and self-limited episodes of pyogenic arthritis, pyoderma gangrenosum, and nodulocystic acne	*PSTPIP1/ CD2BP1* (*chromosome 15q24.3*). OMIM #604416	CD2-binding protein	AD
Majeed syndrome (MS) or chronic recurrent multifocal osteomyelitis (CRMO)	Chronic recurrent multifocal aseptic osteomyelitis (CRMO), congenital dyserythropoietic anemia, and neutrophilic dermatoses (such as Sweet syndrome)	*LPIN2* (*chromosome 18p11.31*). OMIM # 609628. At least three mutations have been reported in Middle Eastern families	Lipin 2	AR/ sporadic
Deficiency of the interleukin-1 receptor antagonist (DIRA)	Periostitis, pustulosis, nail involvement, CRMO	*IL1RN* (*chromosome 2q14.1*). OMIM #612852	IL-1 RA	AR

AD autosomal dominant; *AR* autosomal recessive; *BS* Blau syndrome; *CARD15* caspase recruitment domain-containing protein 15; *CD2BP1* cluster of differentiation 2 binding protein 1; *CIAS1* cold-induced autoinflammatory syndrome 1; *CINCA* chronic infantile neurological cutaneous and articular syndrome; *CRMO* chronic recurrent multifocal osteomyelitis; *DIRA* deficiency of the interleukin-1 receptor antagonist; *EOS* early-onset sarcoidosis; *FCAS* familial cold autoinflammatory syndrome; *FMF* familial Mediterranean fever; *HIDS* hyper-immunoglobulin D syndrome; *IL-1 RA* interleukin-1 receptor antagonist; *MKD* mevalonate kinase deficiency; *MS* Majeed syndrome; *MVK* mevalonate kinase; *MWS* Muckle-Wells syndrome; *NLRP3* nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 3; *NLRP12* nucleotide-binding domain, leucine-rich repeat, and pyrin domain-containing protein 12; *NLRP2AD* NLRP12-associated autoinflammatory disorder; *NOD2* nucleotide-binding oligomerization domain-containing protein 2; *NOMID* neonatal-onset multisystem inflammatory disease; *OMIM®* Online Mendelian Inheritance in Man®; *PAPA* pyogenic arthritis, pyoderma gangrenosum and cystic acne syndrome; *PSTPIP1* proline-serine-threonine phosphatase-interacting protein 1; *TNF* tumor necrosis factor; *TNFRSF1A* tumor necrosis factor receptor superfamily member 1A; *TRAPS* tumor necrosis factor receptor-associated periodic syndrome

perinatal form being the most severe presentation (uveitis, optic nerve atrophy, chronic aseptic meningitis, sensorineural hearing loss) [8, 20, 21].

Blau syndrome (*BS*) and *early-onset sarcoidosis* (*EOS*) are autoinflammatory granulomatous disorders caused by mutations in the nucleotide-binding oligomerization domain-containing protein 2/caspase recruitment domain-containing protein 15 (NOD2/CARD15). BS and EOS present during childhood and have the characteristic histologic findings of noncaseating granulomatous inflammation in affected tissues. BS is transmitted on an AD pattern and presents with a triad of granulomatous arthritis, dermatitis, and uveitis, while EOS is the sporadic form and patients present with polyarthritis with lymphadenopathy and skin and ocular involvement [8, 20, 21].

Pyogenic arthritis, pyoderma gangrenosum and cystic acne (*PAPA*) *syndrome*, *Majeed syndrome* (*MS*), and *deficiency of the interleukin-1 receptor antagonist* (*DIRA*) are autoinflammatory pyogenic disorders that typically present in early childhood. PAPA syndrome is an AD disorder caused by mutations in the proline-serine-threonine phosphatase-interacting protein 1/cluster of differentiation 2 binding protein 1 (PSTPIP1/CD2BP1) gene. MS is predominantly an AR disorder (although sporadic forms have been described), caused by mutations in the LPIN2 gene coding for lipin-2. DIRA is an AR disorder due to mutations in the IL1RN gene that codes for the interleukin-1 receptor antagonist protein [8, 20, 21].

Genetic Testing in Heritable Disorders of Connective Tissue

The heritable disorders of connective tissue (HDCT) are a heterogeneous group of diseases characterized by defects in several extracellular matrix elements including elastin, collagen, mucopolysaccharides, and many others, producing clinically obvious changes in the skeleton, skin, ligaments, tendons, and other soft tissues [22, 23].

As with the MAIS, genetic testing has allowed a reliable pathway to confirm the diagnosis of many HDCT. Among the clinical features that should lead to a high index of suspicion for HDCT and subsequent genetic testing include joint hypermobility or frequent dislocations, abnormal skin findings (cutis laxa, abnormal scarring, spontaneous bruising, velvety, highly elastic or translucent skin), tissue fragility (multiple hernias or rectal prolapse in early childhood), early-onset hearing loss, ocular findings (ectopia lentis, retinal detachment, scleral fragility, vitreous abnormalities), spontaneous or recurrent pneumo- or hemothoraces, classic cardiovascular abnormalities (early-onset aneurysms, dissections, arterial tortuosity, or family history of any of these disorders), musculoskeletal findings such as pectus excavatum or carinatum, arachnodactyly, brachydactyly, osteoarthritis before age 40, congenital clubfoot or Marfanoid appearance, and craniofacial abnormalities (including cleft palate and hypertelorism), among others [9, 22, 23]. For a summary of clinical findings, affected genes, and the pattern of inheritance of most common HDCT, see Table 19.2.

Table 19.2 Heritable disorders of connective tissue [20–23]

Classification	Clinical features	Gene/chromosome/OMIM	Protein	Inheritance
Ehlers-Danlos syndrome (EDS)				
EDS I and II (classic) and EDS V (X-linked)	Joint hypermobility, skin fragility and hyperextensibility, and atrophic scarring. EDS I is the severe classic form and EDS II is the mild type	*COL5A1* (*chromosome 9q34.3*) *and COL5A2* (*chromosome 2q32.2*). OMIM #130000; #130010	Collagen pro-α1 and pro-α2 (V) chains	AD and X-linked
EDS III (hypermobile)	Predominantly joint hypermobility without skeletal deformities, with less severity of skin involvement compared to classic EDS	*Unknown*. OMIM #130020	Unknown	AD
EDS IV (vascular)	Extensive vascular and intestinal involvement manifested by life-threatening spontaneous rupture of blood vessels and internal organs (intestines or uterus). Translucent skin but only mildly hyperextensible. Mild joint hypermobility (predominantly confined to the fingers)	*COL3A1* (*chromosome 2q32.2*). OMIM #130050	Collagen pro-α1 (III) chain	AD
EDS VI (kyphoscoliotic type 1 and type 2)	Severe muscle hypotonia at birth, generalized joint laxity, scoliosis, Marfanoid habitus, osteopenia, and scleral fragility	*PLOD1* (*chromosome 1p36.22*) *and FKBP14* (*chromosome 7p14.3*). OMIM #225400 and #614557, respectively	Lysyl hydroxylase and FKBP prolyl isomerase 14	AR
EDS VII A and VII B (arthrochalasia type 1 and type 2)	Congenital hip dislocation, extreme joint laxity, recurrent joint subluxations, and minimal skin involvement	*COL1A1* (*chromosome 17q21.33*) *and COL1A2* (*chromosome 7q21.3*). OMIM #130060 and #617821, respectively	Collagen pro-α1 and pro-α2 (I) chains	AD
EDS VIIC (dermatosparaxis)	Dysmorphic features, severe joint hyperextensibility, redundant and fragile skin, short stature, prominent hernias	*ADAMTS2* (*chromosome 5q35.3*). OMIM #225410	Procollagen peptidase	AR

(continued)

Table 19.2 (continued)

Classification	Clinical features	Gene/chromosome/OMIM	Protein	Inheritance
EDS VIII (periodontal type 1 and type 2)	Severe periodontal inflammation, premature teeth loss, skin fragility, easy bruising, generalized joint hypermobility	*C1R and C1S* (*chromosome 12p13.31*). OMIM #130080 and #617174, respectively	Complement C1r and C1s	AD
Classic-like EDS	Mild joint hypermobility and skin hyperextensibility (similar to EDS II)	*TNXB* (*chromosome 6p21.33-p21.32*). OMIM #606408	Tenascin X	AR
EDS spondylodysplastic type 1 and type 2	Short stature, developmental anomalies of the extremities, joint laxity, skin hyperextensibility, and poor wound healing	*B4GALT7* (*chromosome 5q35*) and *B3GALT6* (*chromosome 1p36.33*). OMIM #130070 and #615349, respectively	β-1,4-Galactosyltransferase 7 and β-1,3-galactosyltransferase 6	AR
EDS musculocontractural type 1 and type 2	Dysmorphic features, congenital contractures of thumbs and fingers, clubfeet, kyphoscoliosis, hypotonia, hyperextensible and fragile skin, joint hypermobility, ocular, cardiac, respiratory, and gastrointestinal involvement	*CHST14* (*chromosome 15q15.1*) and *DSE* (*chromosome 6q22.1*). OMIM #601776 and #615539, respectively	Carbohydrate sulfotransferase 14 and dermatan sulfate epimerase	AR
EDS cardiac valvular	Joint hypermobility, skin hyperextensibility, severe cardiac valvular and aortic involvement	*COL1A2* (*chromosome 7q21.3*). OMIM #225320	Collagen pro-α2 (I) chain	AR
EDS myopathic type (Bethlem myopathy 2)	Hypotonia, skin changes, and proximal joint contractures (elbows and ankles)	*COL12A1* (*chromosome 6q13-q14*). OMIM #616471	Collagen type XII α1 chain	AD
Brittle cornea syndrome 1 and 2 (formerly EDS type IVB)	Blue sclerae, corneal abnormalities and rupture after minor trauma, joint hypermobility, and skin hyperextensibility	*ZNF469* (*chromosome 16q24.2*) and *PRDM5* (*chromosome 4q27*). OMIM #229200 and #614170, respectively	Zinc finger protein 469 and PR/SET domain 5	AR

Marfan syndrome and related disorders				
Marfan syndrome	Long and thin extremities, tall stature, scoliosis, chest deformities, aortic aneurysms and dilated aortic root, mitral valve prolapse, ectopia lentis, retinal detachments, spontaneous pneumothorax and hernias	*FBN1* (*chromosome 15q21.1*). OMIM #154700	Fibrillin 1	AD with variable expression
Congenital contractural arachnodactyly (arthrogryposis type 9)	Joint contractures, arachnodactyly, scoliosis, osteopenia, abnormally shaped (crumpled) ears	*FBN2* (*chromosome 5q23.3*). OMIM #121050	Fibrillin 2	AD
Loeys-Dietz syndrome 1 and 2	Arterial tortuosity and aneurysms, dysmorphic features (bifid uvula, cleft palate, craniosynostosis, hypertelorism)	*TGFBR1* (*chromosome 9q22.33*) and *TGFBR2* (*chromosome 3p24.1*). OMIM #609192 and #610168	TGF-β receptors 1 and 2	AD
Osteogenesis imperfecta				
Osteogenesis imperfecta type I	Bone fragility (fractures with minimal trauma), blue sclerae, hearing loss, thin and fragile skin, joint hypermobility, kyphoscoliosis, mitral valve prolapse, and normal dentition and stature. Most common form	*COL1A1* (*chromosome 17q21.33*). OMIM #166200	Collagen pro-α1 (I) chain	AD/sporadic
Osteogenesis imperfecta type II (perinatal form)	Bone fragility, with many perinatal fractures, severe bowing of long bones, and perinatal death. Most severe form	*COL1A2* (*chromosome 7q21.3*) and *COL1A1* (*chromosome 17q21.33*). OMIM # 166210	Collagen pro-α2 and pro-α1 (I) chains	AD/AR/ sporadic/ mosaicism
Osteogenesis imperfecta type III (progressively deforming with normal sclerae)	Scleral color (may be blue at birth) normalizes with age, profoundly abnormal dentinogenesis, dysmorphic facial features, progressive deformities of the chest and extremities, severe scoliosis	*COL1A2* (*chromosome 7q21.3*) and *COL1A1* (*chromosome 17q21.33*). OMIM #259420	Collagen pro-α2 and pro-α1 (I) chains	AD/AR/ sporadic

(continued)

Table 19.2 (continued)

Classification	Clinical features	Gene/chromosome/OMIM	Protein	Inheritance
Osteogenesis imperfecta type IV (with normal sclerae)	Bone fragility of variable severity, occasional bowing of long bones, abnormal dentinogenesis may be present, scleral color lightens to white with age	*COL1A2* (*chromosome 7q21.3*) and *COL1A1* (*chromosome 17q21.33*). OMIM #166220	Collagen pro-α2 and pro-α1 (I) chains	AD/AR/ sporadic
Osteogenesis imperfecta type V (with normal sclerae)	Hyperplastic callus formation, calcification of interosseous membranes, moderate to severe bone fragility of long bones and vertebral bodies, deformities, without abnormal dentinogenesis or blue sclerae	*IFITM5* (*chromosome 11p15.5*). OMIM #610967	Interferon-induced transmembrane protein 5	AD

AD autosomal dominant, *ADAMTS2* a disintegrin and metalloproteinase with thrombospondin motifs 2, *AR* autosomal recessive, *B3GALT6* β-1,3-galactosyltransferase 6, *B4GALT7* β-1,4-galactosyltransferase 7, *CHST14* carbohydrate sulfotransferase 14, *COL1A1* collagen type I alpha 1, *COL1A2* collagen type I alpha 2, *COL12A1* collagen type XII alpha 1, *COL3A1* collagen type III alpha 1, *COL5A1* collagen type V alpha 1, *DSE* dermatan sulfate epimerase, *EDS* Ehlers-Danlos syndrome, *FKBP14* FKBP prolyl isomerase 14, *IFITM5* interferon-induced transmembrane protein 5, *OMIM®* Online Mendelian Inheritance in Man®, *PLOD1* procollagen-lysine,2-oxoglutarate 5-dioxygenase 1, *PRDM5* PR/SET domain 5, *TGF-β* transforming growth factor-β, *TGFBR1* TGF-β receptor 1, *TGFBR2* TGF-β receptor 1, *TNXB* tenascin XB, *ZNF469* zinc finger protein 469

While some of the HDCT have a known genetic background with specific mutations that serve for diagnostic purposes, others are still not well understood. For instance, the joint hypermobility syndrome/Ehlers-Danlos syndrome hypermobility type (JHS/EDS-HT) is the most common HDCT described so far. JHS/EDS-HT is an AD disorder considered a clinical diagnosis but without a defined molecular basis in most cases (although mutations in the TNXB gene causing heterozygous tenascin X defects has been described in some of these patients), in contrast to the other *Ehlers-Danlos syndrome* (*EDS*) variants where mutations in different types of collagen are typically found. EDS is characterized by joint hypermobility and hyperextensible skin. There are several types of EDS (some of them categorized as EDS I to EDS VIII), based on the tissues involved and the molecular and biochemical abnormalities involved. EDS I and II are the classic forms, with predominant joint hypermobility, skin fragility, and hyperextensibility, related to mutations in COL5A1/COL5A2 causing defects in collagen V. EDS IV is the vascular form, which predisposes to spontaneous intestinal and vascular ruptures, with life-threatening consequences. EDS IV is an AD disorder due to mutations in COL3A1 (collagen III gene) [9, 20–23].

Many other forms of EDS have been described, with variable joint, skin, dental, and ocular manifestations, secondary to enzymatic or protein defects involving extracellular matrix-related genes such as ADAMTS2 (procollagen I N-terminal proteinase), PLOD1 (procollagen-lysine 5 dioxygenase), B4GALT7 (galactosyltransferase 7), and COL1A1/COL1A2 (procollagen). In contrast, mutations in the elastin gene (ELN) can be associated with similar clinical features in non-EDS conditions, including the AD form of *cutis laxa*, manifested by loose and redundant folds of skin due to lack of elasticity. Other forms of cutis laxa include X-linked form or occipital horn syndrome, caused by mutations in the ATP7A gene (which codes for a transmembrane copper-transporting protein) [20–23].

Marfan syndrome (*MFS*) is another common HDCT that primarily affects the musculoskeletal (long and thin extremities, tall stature, scoliosis, chest deformities), cardiovascular (predominantly aortic aneurysms and dilated aortic root, mitral valve prolapse), and ocular (ectopia lentis with upward displacement, retinal detachments) systems, as well as increased frequency of spontaneous pneumothorax and hernias. MFS is typically associated with mutations in the FB1 gene which codes for fibrillin 1. Similarly, *congenital contractural arachnodactyly* (an MFS-like disorder) has been linked to mutations in the FB2 gene. In contrast, some patients with an MFS phenotype have mutations in TGFBR2 (transforming growth factor-β or TGF-β receptor 2). *Loeys-Dietz syndrome* (*LDS*), an MFS-related disorder, is also associated with mutations affecting TGF-β signaling, specifically the TGFBR1 and TGFBR2 genes, likely illustrating the important role of this molecule in the pathogenesis of these disorders. LDS is usually manifested by craniofacial abnormalities (mainly hypertelorism and cleft palate) [20–23].

Osteogenesis imperfecta (*OI*) is an AD disorder caused mainly by mutations affecting type I collagen, the most abundant protein in skin, bones, and tendons. Specifically, more than 90% of mutations in OI involve the genes coding for the pro-α1 or pro-α2 chain of type I procollagen (COL1A1 or COL1A2, respectively).

Main clinical features include blue sclerae, multiple fractures, abnormal dentinogenesis, progressive early-onset hearing loss, and a positive family history (although sporadic new mutations and germline mosaicism have also been described). However, less classic clinical manifestations are also seen, including joint laxity, kyphoscoliosis, excessive cutaneous scarring, cardiac valvular disease, and fragility of large blood vessels [20–23].

Summary

- Genetics is a fundamental component of complex multifactorial disorders, but genetic testing is most clinically applicable nowadays in the diagnosis of monogenic disorders in rheumatology.
- Most genetic conditions are transmitted in an autosomal dominant, autosomal recessive, or X-linked pattern.
- A typical Mendelian inheritance pattern may not be seen in cases of incomplete penetrance, variable expressivity, and mosaicism.
- A thorough history, physical exam, and laboratory testing are usually necessary to establish a differential diagnosis focused on genetic conditions.
- Obtaining an informed consent and discussing the potential benefits and risks are essential prior to performing genetic testing.
- Most commercial laboratories have genetic panels available to evaluate for monogenic autoinflammatory syndromes and heritable disorders of connective tissue based on next-generation sequencing technologies.
- Genetic panels evaluate multiple probable genes, in contrast to single-gene testing where each gene is tested individually.
- Autoinflammatory syndromes are a group of diseases characterized by recurrent and spontaneous episodes of systemic inflammation and long-term development of secondary AA amyloidosis, as a result of anomalous activation of the inflammasome and generation of interleukin-1.
- The heritable disorders of connective tissue are a heterogeneous group of diseases characterized by defects in several extracellular matrix elements, producing clinically obvious changes in the skeleton, skin, ligaments, tendons, and other soft tissues.
- Genetic testing has allowed a reliable pathway to confirm the diagnosis in monogenic autoinflammatory syndromes and many heritable disorders of connective tissue.

Questions and Answers

1. A 29-year-old man presents for evaluation of severe scoliosis, tall stature, history of retinal detachments, and recurrent spontaneous pneumothoraces. A diagnosis of Marfan syndrome is suspected. On further evaluation, patient reveals his

father also has tall stature and ectopia lentis, but no history of cardiopulmonary disease. The patient's paternal grandfather died at the age of 28 due to a ruptured aneurysm. The different clinical presentations in this patient's family members are most likely due to:

A. The mutated genes are different in each family member.
B. Incomplete penetrance.
C. Mosaicism.
D. Variable expression.
E. The patient does not have a genetic disorder.

Correct answer: D
The question illustrates a case with multiple features of Marfan syndrome (MFS), including tall stature, scoliosis, classic ocular manifestations, and recurrent pneumothoraces in a young man. Moreover, his father and paternal grandfather also show features of MFS. Variable expression (or expressivity) refers to the degree to which a specific genotype is expressed in the phenotype and can affect the severity, type of organ involvement, or age of onset of the disease. MFS commonly shows variable expression. Incomplete penetrance refers to a proportion of people with a genetic change who will not exhibit signs and symptoms of the particular genetic disorder but are able to transmit the mutations to their offspring. As all the generations have some degree of organ involvement from MFS, option B is incorrect. Mosaicism occurs when there are two or more genetically distinct cell lines in the tissues due to mutations occurring during or after embryonic development. Mosaicism would not explain the different clinical presentations in this patient's family members (option C). It would be very unlikely that every family member had a different mutation that would explain their similar pattern of symptoms suggestive of MFS or that the patient did not have a genetic disease (options A and E).

2. An 18-year-old woman presents to rheumatology clinic for evaluation of recurrent episodes of fever, skin rash, and joint and abdominal pain. The episodes started approximately 18 months ago, and she has had multiple admission to the emergency department due to this. During her last ED visit 4 weeks ago, she was diagnosed with appendicitis, but she decided to leave against medical advice as she has noticed her symptoms resolve after a few days with rest and ibuprofen. She is otherwise healthy and does not take any prescription medications. The patient is adopted and is unable to provide a family history. Today she feels well and denies any of her typical symptoms. Regarding this patient's clinical presentation:

A. The patient has features of a monogenic autoinflammatory syndrome, but no additional intervention is necessary as her symptoms resolve spontaneously.
B. The age of onset in this case rules out a monogenic autoinflammatory syndrome.
C. The patient has appendicitis and requires antibiotics and a referral to surgery.

D. The patient likely has monogenic autoinflammatory syndrome, but due to lack of family history, she should be sent for whole-exome sequencing.
E. The patient's clinical presentation is suggestive of an autoinflammatory syndrome, and the risks and benefits of genetic testing should be thoroughly discussed with the patient.

Correct answer: E
A young woman with recurrent episodes of inflammation with fever, arthralgias, skin involvement, and likely peritonitis (abdominal pain and previous misdiagnosed appendicitis) is strongly suggestive of an autoinflammatory syndrome. The lack of family history in this case can make the diagnosis more challenging, but sending the patient directly for whole-genome sequencing would be premature (option D). Option E is the most appropriate option as this patient would benefit from genetic testing, preceded by obtaining an informed consent and a thorough discussion, including rationale and implications, risks versus benefits of genetic testing, and alternatives. Many of the monogenic autoinflammatory syndromes (MAIS) are associated with secondary AA amyloidosis if left untreated; therefore, option A is incorrect. Even though some of the MAIS present during early childhood, adult-onset forms are common and must be considered (option B). Serositis, particularly peritonitis, is frequently associated with the recurrent inflammatory episodes in MAIS which are sometimes misdiagnosed with acute abdomen in the emergency department. Her previous history of recurrent symptoms with spontaneous resolution without antibiotics makes a diagnosis of acute appendicitis much less likely (option D).

3. An 18-year-old woman presents for follow-up. During early childhood, she developed recurrent episodes of fever, conjunctivitis, polyarthritis, and generalized hives lasting for 24–48 h. After clinical evaluation and genetic testing, she was diagnosed with familial cold autoinflammatory syndrome and has been appropriately treated since then. She feels well and has not noticed any significant flares. This patient's autoinflammatory syndrome is due to abnormalities in which of the following proteins:

A. Mevalonate kinase (MVK gene)
B. Pyrin (MEFV gene)
C. Cryopyrin (NLRP3 gene)
D. IL-1 receptor antagonist (IL1RN gene)
E. TNF receptor 1 (TNFRSF1A)

Correct answer: C
This patient has been diagnosed with familial cold autoinflammatory syndrome (FCAS), which is a cryopyrin-associated periodic syndrome (CAPS). CAPS are caused by mutations in the NLRP3/CIAS1 or NLRP12 genes, which code for the proteins cryopyrin or monarch-1, respectively. Mevalonate kinase is the affected protein in mevalonate kinase deficiency, formerly known as hyper-IgD syndrome (option A). Familial Mediterranean fever is caused by mutations in the MEFV gene, which codes for pyrin (option B). Deficiency of the IL-1 receptor antago-

nist and mutations affecting the TNF receptor 1 are also causes of monogenic inflammatory syndromes but are not specifically associated with the familial cold autoinflammatory syndrome (options D and E).

4. Which of the following is a true statement about genetic testing?

   A. Genetic testing is strictly regulated and under similar federal regulatory standards as other specialized laboratory tests.
   B. Direct-to-consumer testing is an adequate initial approach for patients with a suspected genetic disease.
   C. Single-gene testing is most helpful when the clinical presentation is vague and there are multiple candidate genes as potential causes for the disease.
   D. Next-generation sequencing has become obsolete since the Sanger sequencing technique became commercially available.
   E. Genetic testing is safe; therefore, obtaining an informed consent is not recommended.

   Correct answer: A
   Genetic testing regulations are similar to other specialized laboratory tests to ensure the analytical and clinical validity, under the Clinical Laboratory Improvement Amendments (CLIA), a Centers for Medicare and Medicaid Services (CMS) program. Direct-to-consumer genetic testing is not currently recommended as a diagnostic tool for genetic diseases (option B). In contrast to genetic panels where multiple genes are evaluated, single-gene testing is a much narrower strategy and would only be useful if there is only one or very few candidate genes (option C). Next-generation sequencing (NGS) technologies are widely used in commercial laboratories, while the Sanger technique is mostly used for confirmatory purposes (option D). Even though genetic testing is considered safe, the emotional impact and the possibility of identifying unexpected and unrelated genetic alterations, among other implications of genetic testing, need to be discussed with patients, and an informed consent should be obtained (option E).

5. A 22-year-old woman presents to rheumatology clinic for evaluation of effort-related arthralgias. She reports that since childhood she has been more flexible than her peers. She can bend her thumbs backward to her wrists but cannot touch the floor with her palms when bending forward with her knees extended. She also states that her skin bruises very easily and is thin. Her mother died in her 20s while pregnant due to uterine rupture, and her father died in his 30s due to a spontaneous bowel perforation. A diagnosis of vascular Ehlers-Danlos syndrome (EDS) is considered. What is the most likely affected gene in this type of EDS?

   A. FBN1
   B. ADAMTS2
   C. COL3A1
   D. PLOD1
   E. TNXB

   Correct answer: C

Vascular or type IV EDS is an AD disorder caused by a mutated COL3A1 gene, which codes for a collagen III pro-α1 chain. Vascular EDS is a life-threatening disease due to spontaneous rupture of blood vessels and internal organs (intestines or uterus). FBN1 codes for fibrillin 1, the protein affected in Marfan syndrome (option A). ADAMTS2 is a procollagen peptidase associated with EDS VIIC or dermatosparaxis type, an AR characterized by prominent redundant and extremely fragile skin, hernias, and short stature (option B). PLOD1 codes for a lysyl hydroxylase and is associated with EDS type VI or kyphoscoliotic EDS type 1 (option D). TNXB mutations (option E) are associated with classic-like EDS (AR disorder) and in less than 10% of patients with hypermobile EDS (AD inheritance).

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