News RHEUM

Volume 2 No 1 - June 2021

BLOOD & BONE

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Contents

Female skeleton glowing in the dark.
Artist: "Fyb" (Dreamstime ID 159810837)

The artwork featured on this NewsRheum edition is a haunting yet romantic depiction of blood and bone. This photograph of bodyart, reminds us of the Mexican tradition celebrating the dead, Día de los Muertos, or Day of the Dead. The eerie form of the skeleton, is softened by a flower crown and colourful bleeding heart. This imagery reinforces the celebration of beauty in that which is often deemed dark or sombre, like death or disease. A further reference to bloodlines can be drawn from the positioning of the skeletons arms - as if in embrace - solidifying the sense of nurturing and family.

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Blood and bone

Editorial

4 **Bone Deep and Bloodlines**
Dr Kavita Makan

Lest we forget

5 **Antiphospholipid syndrome - an enigmatic disorder with a chequered history**
Professor Mohammed Tikly

Rheum Review

7 **Revenge of the bone: Hungry bone syndrome**
Dr Gita Makan

10 **Haematological manifestations in patients with rheumatological conditions**
Dr Marilyn Reddy

Rheum with a view

14 **Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)**
Dr G. Laudin
Dr J. Vaughan

Enter the rheumatology clinic

18 **Cases in osteoporosis management**
Dr Farhanah Paruk

Rheum Lites

23 **Prof Bhettay interview**

25 **Celebrating new rheumatologists who graduated during the peak of COVID-19, 2020**

26 **Arthritis Foundation of South Africa**

26 **CPD Accreditation information**

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Editorial

Bone Deep & Bloodlines

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In this second edition of NewsRheum we consider two extremely challenging aspects of rheumatological disease presentation – Blood and Bone. This theme is vitalised by our provocative cover artwork, which enhances the mystery and haunting beauty of bone disease and haematological conditions in rheumatology.

We burrow bone deep into practical aspects of osteoporosis management, with a clinic-based approach to diagnosis and treatment presented by Dr Farhanah Paruk. We enter the abyss of metabolic bone disease, guided by endocrinologist Dr Gita Makan, with a complete review on a rare but serious complication of parathyroid surgery, the hungry bone syndrome. Primary hyperparathyroidism often manifests with musculoskeletal complaints, and as such often presents to our rheumatology outpatient settings, mimicking more specific rheumatological disease entities such as fibromyalgia or polymyalgia rheumatica. Rheumatologists should be familiar with this disease entity and its complications.

The antiphospholipid syndrome and haemophagocytic lymphohistiocytosis (HLH) or macrophage activation syndromes (MAS) have been a major focus during current times, with both entities shedding light on thrombotic and inflammatory aspects of COVID-19 disease, as well as featured complications of this dreaded viral illness. Professor Mohammed Tikly, in his regular feature highlighting seminal papers in rheumatology, walks us through the history of the antiphospholipid syndrome, including a nod to South African rheumatologist Ron Asherson; whilst our haematology colleagues, Drs Garrick Laudin and Jenny Vaughan, provide a microscopic view of HLH and MAS. Haematological presentations of rheumatic disease is further reinforced in a comprehensive review by Dr Marilyn Reddy.

The blood theme is carried forward in our community news, where we celebrate the contributions of Professor Ebrahim Bhettay, a well-loved paediatric rheumatologist, and father figure in the South African rheumatology community. We also introduce three new rheumatologists, who qualified during the extraordinary times of a pandemic, and share their experiences.

Finally, SARAA would like to thank Lilly, for fully sponsoring this NewsRheum edition. Lilly have recently entered our rheumatology market with their eagerly anticipated JAK-inhibitor, baricitinib, providing a safe and effective treatment option for patients with refractory rheumatoid arthritis.

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Lest we forget

Antiphospholipid syndrome - an enigmatic disorder with a chequered history

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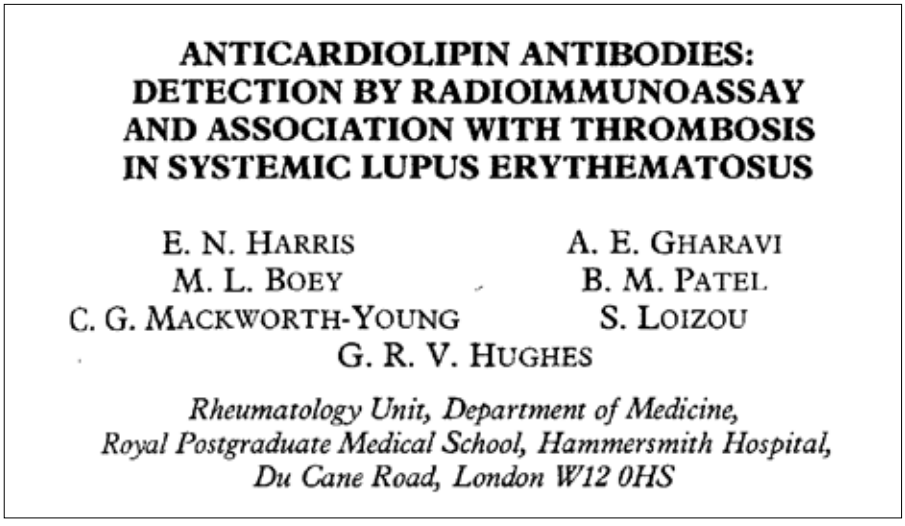
Antiphospholipid syndrome (APS) is an autoimmune thrombophilic disorder in which arterial or venous thrombosis and recurrent foetal loss are associated with circulating antiphospholipid (aPL) antibodies. The disorder was named as such only in the 1980s, but the history of this enigmatic disorder precedes the discovery of antiphospholipid antibodies.[1,2]

The origin of aPL antibodies can be traced back to the early 20th century when Wasserman developed a serological test for syphilis, dubbed the 'Wasserman reaction' (WR). Pangborn, using bovine cardiac tissue, purified the syphilis antigen responsible for the WR and showed it to be a phospholipid and hence coined the term 'cardiolipin'.[3] The concept of a 'biologic false positive serologic test for syphilis (BFP-STS)' was recognised when some patients with other diseases like systemic lupus erythematosus (SLE) and tuberculosis were found to also have a positive WR. Based on a few case reports, Conley and later, Frick and Weimer in the 1950s showed an association of BFP-STS with an inhibitor of blood coagulation.[4,5] The latter was called 'lupus anticoagulant' (LAC) by Feinstein and Rapaport because some SLE patients with LAC had a bleeding diathesis.[6] But In 1964, Bowie and colleagues showed a paradoxical association of LAC with thrombosis rather than bleeding.[7] Further laboratory investigations showed the serum factor inhibiting coagulation to be an immunoglobulin directed against phospholipids. Clinical studies in the 1970s confirmed the association of LAC and BFP-STS with thrombotic events in SLE patients. However, the complexities of performing the functional clotting assay with fresh plasma to detect the LAC impeded further research at the time.

The 1980s was arguably the most exciting period in the evolution of the concept of APS.[2] Boey and colleagues at the Hammersmith Hospital, London, reported a case series of SLE patients who tested positive for LAC and had thrombotic complications, recurrent abortion and/or thrombocytopaenia.[8]

The major laboratory breakthrough came in 1983 when Aziz Gharavi working in the Graham Hughes laboratory at the Hammersmith, postulated, based on three previous hospital observations that antibodies responsible for a positive LAC test would bind to cardiolipin, a negatively charged phospholipid.[2] Firstly, LAC was associated with BFP-STS and that antibodies responsible for the latter were thought to bind cardiolipin. Secondly, that the LAC assay was phospholipid dependent, where *in vitro* clotting times were shown to be inversely related to the amount of phospholipid added to the test mixture. Thirdly, Thiagarajan and colleagues had demonstrated that monoclonal antibodies with LAC activity bound to negatively charged phospholipids. Gharavi, together with his research fellow, Nigel Harris, developed a prototype solid-phase radioimmunoassay to detect anticardiolipin (aCL) antibodies using sera of patients described earlier by Boey and colleagues.

Harris and colleagues shortly thereafter reported their seminal findings in The Lancet that 61% of 65 SLE patients had high levels of aCL antibodies, 90% of



ANTICARDIOLIPIN ANTIBODIES: DETECTION BY RADIOIMMUNOASSAY AND ASSOCIATION WITH THROMBOSIS IN SYSTEMIC LUPUS ERYTHEMATOSUS

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Figure 1. Seminal paper by Harris and colleagues published in The Lancet (1983)

those with a positive LAC test also had raised aCL antibody titres, and lastly that there was a statistical association of aCL antibody positivity with a history of arterial/venous thrombosis and thrombocytopaenia and an equivocal association with pregnancy loss **(Figure 1)**.[9] The solid-phase assay was to be superseded by the technically less complex and standardised ELISA assay and soon several studies reported aCL antibodies in association with other manifestations of SLE such as transverse myelitis, chorea and Libman-Sacks endocarditis.[3]

Following these observations, Hughes proposed an extended spectrum of clinical features of the syndrome to include livedo reticularis and migraine, to the classic features of thrombosis, thrombocytopaenia and pregnancy loss.[2] Moreover, the Hughes team observed that many patients with this constellation of clinical and laboratory features did not meet the classification criteria for SLE and the name 'anticardiolipin syndrome' was proposed, later changed to 'antiphospholipid syndrome' based on their laboratory observations that the antibodies reacted with a range of phospholipids. With increasing global interest, the group organised the first 'International Symposium on Antiphospholipid Antibodies' in 1984. Harris in a 1987 editorial entitled "Syndrome of the Black Swan" published in the British Journal of Rheumatology, suggested criteria for classification of the syndrome (which amazingly largely hold true even today).[9] Patients were classified as having APS if they had at least one of the following clinical features: Venous/arterial thrombosis, recurrent pregnancy loss and/or thrombocytopaenia together with at least one positive laboratory test, either LAC or a medium to high positive aCL antibody test on at least two occasions eight weeks apart. The latter caveat was added to distinguish the syndrome from infectious illnesses which were known to be rarely associated with transient 'false positive' aCL antibodies and LAC.

The concept of primary APS was mooted in 1989 by Ron Asherson, a South African rheumatologist, and colleagues, following several reports from both rheumatology and haematology centres that APS often occurred in the absence of underlying SLE.[10] Hence, SLE patients who developed APS were deemed to have secondary APS. Not long thereafter, Asherson and Cervera, as part of the Hughes team, described several cases of what they termed 'catastrophic' APS, where patients presented with acute multi-organ thrombosis akin to disseminated intravascular coagulation, often resulting in death.[2]

Harris in a 1987 editorial entitled "Syndrome of the Black Swan" published in the British Journal of Rheumatology, suggested criteria for classification of the syndrome (which amazingly largely hold true even today).[9]

The next major advance in the understanding of the pathogenesis and diagnosis of APS was in the 1990s when it became evident that aPL antibodies did not bind directly to phospholipids but rather to a complex of a circulating plasma protein co-factor, β2-glycoprotein I (β2GPI), bound to phospholipid.[11] β2GPI belongs to the complement superfamily and functions as a natural 'vacuum cleaner' to remove cellular debris but also inhibits the contact phase of the intrinsic coagulation pathway. These findings subsequently resulted in greater clarity on the multiple mechanisms involved in the characteristic manifestations of APS, including cellular activation, complement activation, and prothrombotic effects. An ELISA assay was developed to detect anti-β2GPI antibodies, which today forms part of the work-up for APS. Moreover, patients who are 'triple autoantibody positive' for aCL, LAC and anti-β2GPI are now known to be at high risk of thrombotic complications.

Prior to the recognition of APS a distinct disorder, thrombotic and pregnancy-related complications were managed mainly with corticosteroids and other immunosuppressive agents, with little or no benefit. The seminal observations that defined APS as principally a thrombophilic disorder resulted in a switch to anticoagulation as the mainstay of therapy, with clear clinical benefits for both thrombotic and obstetric complications.

Many questions remain unanswered with regards to management of the protean and complex manifestations of APS. With growing understanding of the complex interplay of thrombosis, inflammation, and vasculopathy, there is good reason to believe that new therapies will become available in the foreseeable future to better manage the broader spectrum of APS manifestations.

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Revenge of the bone: Hungry bone syndrome

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In 1930 Fuller Albright coined the well known primary hyperparathyroidism pentad - bone pains, renal stones, abdominal groans, psychic moans and fatigue overtones.[1] Through his pioneering study into mineral metabolism he was also the first to identify the cause of primary hyperparathyroidism to be due to parathyroid hyperplasia and adenoma. In 1948 he was the first to describe hungry bone syndrome in a patient post parathyroidectomy for severe primary hyperparathyroidism.[1]

The hungry bone syndrome (HBS) is a rare, but serious complication that can follow parathyroidectomy for both severe primary hyperparathyroidism (PHP) or more commonly secondary hyperparathyroidism (SHPT) in patients with renal failure. This is due to abrupt suppression of bone resorption once PTH levels drop, and greedy uptake of calcium by the demineralised bone.

This article makes particular reference to hungry bone syndrome arising in the setting post surgery for primary hyperparathyroidism.

It is a rare occurrence with an estimated prevalence ranging between 4-13% in this context.[2] Nevertheless, it is important to identify as it can cause significant post operative morbidity and does prolong average hospital stay.

Hypocalcemia in the post parathyroidectomy context is not solely caused by hungry bone syndrome and it is not the commonest cause. The most

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incriminated mechanism is a transient hypoparathyroidism due to a slow recovery of function of the rest of parathyroid, which was inhibited by the hyperfunctional adenoma.[3]

Hungry bone syndrome is considered to be present if serum calcium levels continue to fall below 2.1 mmol after Day 4 post parathyroidectomy. Serum phosphate levels also decline and hypomagnesemia is also frequently encountered. Serum alkaline phosphatase levels (ALP) increase significantly post-operatively and remain elevated sometimes for up to 9 months after surgery.[4]

A review of the literature on HBS suggests the most common and consistent risk factors for hungry bone development in context of PHP:

- High pre op PTH levels
- Elevated alkaline phosphatase
- Higher blood urea nitrogen levels
- Higher BMI
- Larger volume or weight of parathyroid glands removed
- The presence of radiological evidence of bone disease[2]

The aforementioned skeletal manifestations include the classic osteitis fibrous cystica and brown tumours.

Brown tumours are pseudotumours, they are non-neoplastic, areas of focal and intense bone resorption and are histologically characterised by vascular fibroblastic stroma and several osteoclast-like multinucleated giant cells often interspersed with hemorrhagic infiltrates and hemosiderin deposits.[5]

Pathophysiology of HBS

To understand the pathophysiology of HBS it is imperative to remind ourselves of the pathophysiology of PHP.

In the normal state parathyroid hormone (PTH) regulates extracellular calcium by its complex relationship with bone remodelling.

The process of bone resorption, which lasts about 2 weeks is followed by a reversal phase of 2–3 weeks duration, before new bone is formed, which lasts about 3 months. There is therefore a lag between breakdown and building, this results in the so called remodelling space. This space depends on the activation frequency of new remodelling sites, which is considerably increased in PHP. This leads to mineral depletion of bone and the consequent hypercalcaemia of PHP.[2]

Post successful parathyroidectomy there is an abrupt cessation of osteoclastic activity and a decrease in new remodelling sites and thus the remodelling space is closed and bone formation begins.

When this happens there is a resultant extraction of minerals, calcium, phosphate and magnesium from the extracellular pool and thus the aptly named HBS arises.

This HBS can last up to 9 months when bone formation ceases and it has been shown last even longer in cases of parathyroid carcinoma removal.

Radiological changes associated with HBS

Removal of excess circulating PTH leads to rapid and massive accrual of bone with some case reports suggesting an increase of BMD at the greater trochanter as much as 33% at 6 months and of 35-131% at 1 year following surgery. Lumbar spine BMD also increased by about 27-65% at 1 year after parathyroidectomy.[4]

Skeletal scintigraphy also shows an increased radioactive isotope uptake 1 month after parathyroidectomy, known as 'flare phenomenon'- this continues beyond 8 months and normalises about a year following parathyroidectomy. This is similar to what you would see with scintigraphic images of treated bone metastases.

Management of HBS

The first few case reports published on HBS from the 1970s, highlighted the challenges and difficulty in treating hypocalcemia, due in part because this pre-dated the availability of active vitamin D metabolites.[2]

Surprisingly, it still remains a challenge presently with patients often requiring high doses of oral calcium, on average 6-12 grams per day in divided doses to achieve normalalcemia.

Since hypocalcaemia occurs suddenly after surgery, it must be monitored within the first few hours after surgery. Vigilance for lowered phosphate and magnesium levels should also be maintained, especially since lowered magnesium levels could contribute to the persistence of hypocalcemia.[4]

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Initially IV calcium supplementation is needed together with daily active vitamin D metabolites calcitriol) or alfacalcidol (2–4 ug/day).

Oral calcium supplements should be introduced early and the preparations favoured include those with a high amount of elemental calcium.[4]

The preferred choice would be calcium carbonate as it is more freely available than calcium citrate. Both have a high amount of elemental calcium per 1gram. Calcium citrate, however, does not require an acidic environment to be absorbed and is good in patients who are on long term PPI therapy, elderly patients or post gastric bypass.

These oral preparations may need to be continued for a long period after surgery, this should be guided by serum levels of calcium and 25(OH) vitamin D.

Bone turnover markers specifically markers of formation (bone specific ALP, osteocalcin) can also be useful in aiding the onset of resolution of HBS which can last for months but is unlikely to persist for as long as a year following surgery.[4]

Figure 1. Pre-operative x-ray of the left leg (a) and hands (b) showing multiples radiolucent lesions corresponding to brown tumours (↑). X-ray performed 1 month after parathryoidecotmy (c and d) showing ossification of the brown tumours.

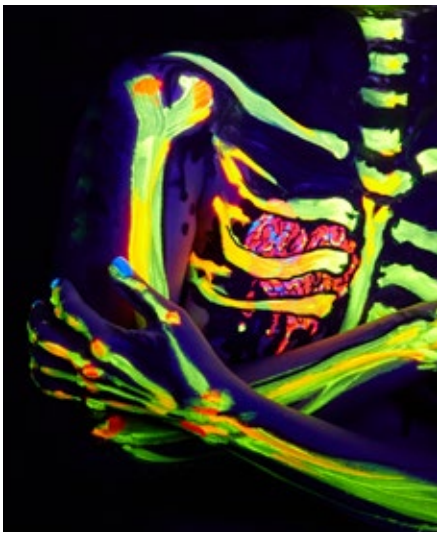
How to mitigate hungry bone syndrome

In the setting of secondary hyperparathyroidism in patients with renal failure, there is benefit in preoperative supplementation of vitamin D.

In the setting of primary hyperparathyroidism about 76% of patients will have co-morbid vitamin D deficiency preoperatively. It has also been postulated that vitamin D deficiency contributes to postoperative hypocalcemia. Preoperative vitamin D supplementation in depleted patients does result in decreased levels of PTH and better suppression of bone turnover (reduction in ALP). However, there are no studies that show that this approach mitigates against hungry bone syndrome.[4]

Although the available data is limited to small case series and retrospective studies, there is a glimmer of hope that prior treatment with bisphosphonates might attenuate or mitigate HBS.

Lee et al showed in a small study that preoperative palmidronate between 1-17 days prior to surgery decreased postoperative hungry bone syndrome. A smaller retrospective study performed by Mayilvaganan et al, evaluating the incidence of hungry bone syndrome in 19 primary hyperparathyroidism patients who received 4 mg of zoledronate 24 to 48 hours preoperatively, demonstrated



Although the available data is limited to small case series and retrospective studies, there is a glimmer of hope that prior treatment with bisphosphonates might attenuate or mitigate HBS.

a shorter duration of hospital stay as well as a nearly statistically significant reduction in the incidence of HBS compared to those who did not receive the bisphosphonate infusion.[3]

In a way the hungry bone syndrome represents a double edged sword, in that the bone remarkably regenerates, however, with this, very frightening to observe and manage complication.

The hungry bone syndrome, however rare, cannot escape recognition.

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RheumQUIZ

For answers to these questions, please see page 24.

Questions

1. For which infections is the Wasserman reaction (WR) a serological test?
2. What is the commonest cause of hypocalcemia post parathyroidectomy?
3. Which combination of triple positive tests confers the highest risk of secondary anti-phospholipid syndrome in patients with systemic lupus erythematosus?
4. Which of the following is not a lab feature of automimmune haemolytic anemia? a. Unconjugated hyperbilirubinemia b. Urine hemosiderin, c. Polychromasia, d. Raised Haematocrit or e.Raised LDH

Haematological manifestations in patients with rheumatological conditions

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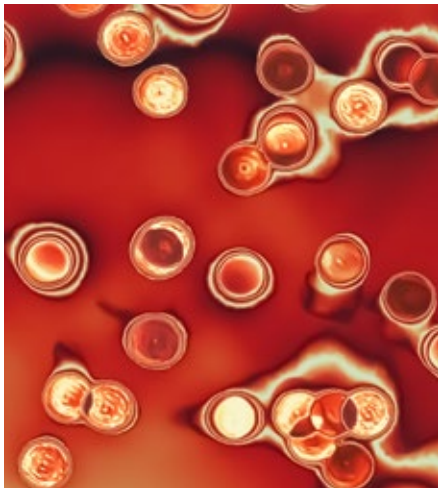
The many cellular and molecular networks that accompany rheumatic conditions, drive a complex reaction involving the haemopoetic tissue and peripheral blood cells.[4] This results in one or more cellular lineages being affected. Various treatment approaches exist for these haematological abnormalities in patients with rheumatic conditions, some requiring significant immunosuppression.[5] Moreover, conventional disease-modifying anti-rheumatic drugs and biological agents may also cause haematological manifestations.[1]

Leukopenia

Leukopenia is defined as a total white cell count of < 4000/mm^3.[1,2] In patients with autoimmune rheumatic conditions, it can be due to disease activity, immunosuppressive treatment or non-autoimmune related causes like infection or malignancy. Many haematological abnormalities occur with a particularly high frequency in patients with systemic lupus erythematosus (SLE) and these are considered in the systemic Lupus International Collaborating Clinics (SLICC) SLE classification criteria.[3] These include leukopenia, lymphopenia, autoimmune haemolytic anaemia (AIHA) and thrombocytopenia.[1] Leukopenia can also occur in patients with rheumatoid arthritis (RA) and primary Sjögrens syndrome.[1]

The pathogenesis of lymphopenia in patients with rheumatological conditions may be variable. It may involve autoimmunity by anti-lymphocyte antibodies, circulating lympho-toxic antibodies, anti-Ro/SS-A antibodies, and accelerated lymphocyte apoptosis.[1] Lymphopenia is one of the most common hematologic manifestation of SLE and is listed as a criterion.[3,4] It is shown to correlate with higher disease activity and damage accrual in SLE patients.[4] Lymphopenia can be seen in primary Sjögrens and dermatomyositis patients, involving mainly CD4+ T cell lineage and CD8+ respectively.[4] Prophylaxis against opportunistic infections may be required in patients with severe lymphopenia.[2]



Many haematological abnormalities occur with a particularly high frequency in patients with systemic lupus erythematosus (SLE) and these are considered in the systemic Lupus International Collaborating Clinics (SLICC) SLE classification criteria.[3] These include leukopenia, lymphopenia, autoimmune haemolytic anaemia (AIHA) and thrombocytopenia.[1]

The mechanisms responsible for neutropenia are not completely clear. It is thought to be related to marrow suppression by T lymphocytes, peripheral destruction by anti-neutrophil antibodies, and complement activating anti-neutrophil autoantibodies.[1] Neutropenia is a common haematological manifestation seen in the lupus population and its basis is likely immune mediated secondary to anti-neutrophil antibodies.[4] Neutropenia in SLE patients can be associated with lymphopenia, thrombocytopenia, low complement, and or positive Coombs results.[1]

Additionally, anti-Ro/SS-A antibodies may be associated.[1] Severe neutropenia can result in significant morbidity and mortality in lupus patients.[1] Similarly, neutropenia can also occur in patients with primary Sjögrens and antiphospholipid syndrome (APS). Seeing that the bone marrow can be a target organ in these autoimmune conditions, a bone marrow test should be considered if there is pancytopenia or any suspicion of marrow failure or infiltration. Granulocyte colony stimulating factor can be of benefit in these patients.[1,2]

Felty's syndrome is a condition that develops in seropositive rheumatoid arthritis (RA).[2] It is characterised by a triad of splenomegaly and neutropenia in a patient with longstanding RA. Persistent neutropenia with absolute neutrophil count of less than 1,500/mm^3 remains an important diagnostic criterion.[1] There are several mechanisms postulated in the aetio-pathogenesis of the neutropenia in Felty's syndrome. A complex interplay of immune mechanisms results in defects of neutrophil production (impaired bone marrow granulopoiesis; inhibition of

G-CSF-induced maturation), increased peripheral destruction and splenic sequestration.[1,4] Extra-articular manifestations of rheumatoid nodules, lymphadenopathy, hepatomegaly, anemia, and thrombocytopenia frequently accompany the neutropenia in these patients.[1] Patients are consequently exposed to infections involving the skin, oral cavity and chest especially with absolute neutrophil counts less than 1000/mm^3.[1] Recurrent infections specifically bacterial infections, is a frequent cause of morbidity and mortality in patients with Felty's syndrome.[4] They are usually treated with methotrexate and G-CSF.[1]

Eosinophilia

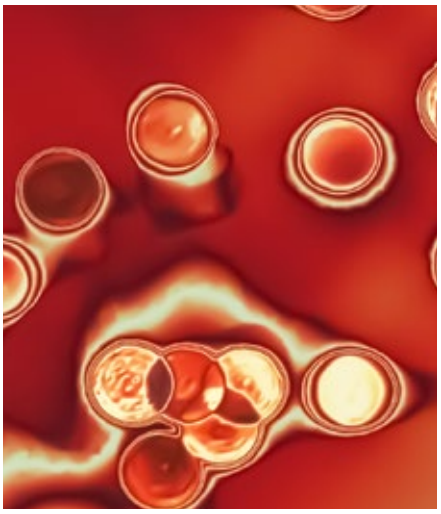
Eosinophilia (eosinophil count >500/mm^3) may occur in eosinophilic granulomatosis with polyangiitis (E-GPA), *Eosinophilic fasciitis* or eosinophilic myopathies.[4]

Thrombocytopenia

Thrombocytopenia is a well-established manifestation of SLE, APS and Felty's syndrome.[1] It may also result from immunosuppressive medication used in the treatment of rheumatic conditions.

Isolated thrombocytopenia can sometimes precede the diagnosis of SLE by several months to years.[1,2] About 10% of SLE patients present with severe thrombocytopenia. Due to thrombocytopenia being associated with more aggressive disease,[4] it is a poor prognostic factor in lupus patients and generally portends a greater morbidity and mortality.[1,4] There may be associated SLE disease activity and in particular renal disease and haemolytic anaemia.[1,4]

Thrombocytopenia is mainly immune mediated in these patients, in the form of anti-platelet antibodies.[1] Anti-platelet antibodies result in peripheral platelet aggregation or destruction and this may be coupled with impaired compensatory megakariopoiesis.[4] Moreover, thrombocytopenia in SLE patients can also be associated with anti-phospholipid antibodies.[1] Thrombocytopenia is a frequent haematological manifestation of primary APS. However, it is generally mild with only a small number of patients manifesting with severe thrombocytopenia.[4]



The mechanisms responsible for neutropenia are not completely clear. It is thought to be related to marrow suppression by T lymphocytes, peripheral destruction by anti-neutrophil antibodies, and complement activating anti-neutrophil autoantibodies

Glucocorticoids are used as initial therapy in these patients. Hydroxychloroquine can be added. Steroid-sparing immunosuppressive agents that can be considered include azathioprine, cyclosporine, mycophenolate mofetil, cyclophosphamide and vincristine.[1] Intravenous immunoglobulin (IVIG), rituximab and thrombopoietin (TPO) mimetics can be considered in refractory cases. The use of the latter, however, is controversial (not recommended) in patients with APS due to a higher risk of thrombotic events.[1] Splenectomy may provide long-term response in refractory thrombocytopenia.[4]

Thrombocytosis

Thrombocytosis is frequently observed in RA and is seen as a marker of disease activity.[4] Additionally, thrombocytosis may indicate myelofibrosis or malignancies in patients.

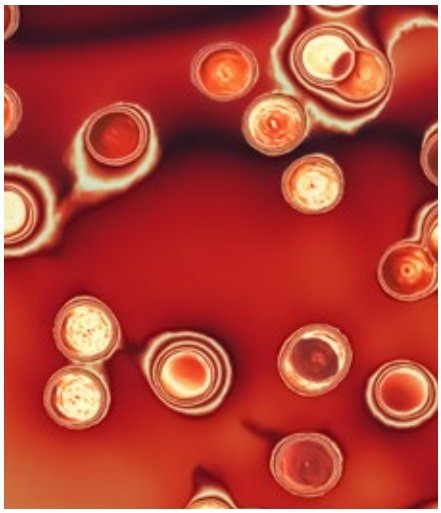
Anaemia

One of the most common hematological abnormality observed in rheumatic patients is an anaemia.[4] The pathogenesis of anaemia can be of autoimmune or of non-autoimmune origin.[4] Persistent immune activation in rheumatic patients is the most plausible cause for anaemia of chronic disease (ACD) seen in these patients.[4] Anaemia is identified as a predictor of an unfavorable prognosis in patients with rheumatic conditions.[4] It is the most common extra-articular manifestation in RA.[4] Patients with RA can develop ACD or iron deficiency anaemia.[4] Patients with Sjögrens and systemic sclerosis can also present with an anaemia with relative frequency. Anaemia has emerged as a common morbidity in patients with lupus; having a strong association with disease activity/flare and being a predictor of mortality as well.[4]

Autoimmune haemolytic anaemia (AIHA) is one of the clinical criteria for SLE.[3] It can precede the diagnosis of lupus, occur during disease presentation, or during a lupus flare.[1,5] Anti-erythrocyte antibodies are usually of warm-type IgG in SLE.[1] IgG-antibody coated red blood cells undergo changes in their membrane whilst transiting through the spleen. Consequently, the resultant spherocytes are removed by phagocytosis.[1] AIHA in lupus patients is frequently associated with renal disease and mortality risk.[4] Antiphospholipid antibodies may also be present in these patients.[4] Glucocorticoids offer a good response rate.[1] Myelofibrosis, aplastic anaemia and pure red cell aplasia can also occur in patients with rheumatic conditions.[5]

Bicytopenia/Pancytopenia Evans Syndrome

The presence of AIHA and autoimmune thrombocytopenia can occur with or



TMA can occur in rheumatological conditions like SLE, catastrophic anti-phospholipid syndrome (CAPS) and scleroderma with renal crisis (SRC). Around 5 -10% of patients with systemic sclerosis can present with SRC.

without leukopenia, also known as Evans syndrome.[1,5] Evans syndrome can occur in SLE and APS.[4]

Thrombotic microangiopathy (TMA)

Thrombotic microangiopathy (TMA) is a life-threatening complication that can arise in patients with autoimmune connective tissue diseases.[1] It presents as a medical emergency with multi-system involvement. It is characterised by microangiopathic hemolytic anaemia (MAHA)-characteristic erythrocyte fragmentation on peripheral morphology **(Figure 1)**; thrombocytopenia and microvascular occlusion by platelet thrombi.[4] This results in end organ ischemia involving mainly the lung, kidney and or central nervous system. TMA can occur in rheumatological conditions like SLE, catastrophic anti-phospholipid syndrome (CAPS) and scleroderma with renal crisis (SRC).[1] Around 5 -10% of patients with systemic sclerosis can present with SRC.[1] It manifests with sudden increase in blood pressure, renal failure, MAHA and target organ dysfunction. The thrombocytopenia is usually above 50 000/mm^3 and settles as blood pressure normalises. Angiotensin converting enzyme (ACE) inhibitors improve outcome and survival in these patients.[1] CAPS is a life-threatening complication of APS that presents with multi-organ thrombosis. Options for therapy includes glucocorticoids, anticoagulation, plasma exchange, IVIG and cyclophosphamide.[1]

TMA can occur in SLE patients where it may be initially undetected. Profound thrombocytopenia, anaemia, deteriorating renal function and fever or confusion can arise as part of the TMA presentation.[1] Patients with renal TMA have considerably higher lupus disease activity.[1] There is a correlation with lower C3 levels and anti-Ro seropositivity. An association of autoantibodies to ADAMTS13 and complement activation has been reported.[1] Early recognition and prompt treatment is critical as treatment can be quite complex in these patients. Main therapeutic pillars are plasma exchange and immunosuppressive therapy.[1]

Haemophagocytic syndrome/macrophage activation syndrome (MAS)

Haemophagocytic syndrome is a life-threatening condition associated with high mortality rates. It can be seen in SLE, systemic juvenile idiopathic arthritis (S-JIA), adult onset stills disease and certain vasculitides.[6] Less commonly, it can occur in patients with Sjögrens, RA and systemic sclerosis.[4]

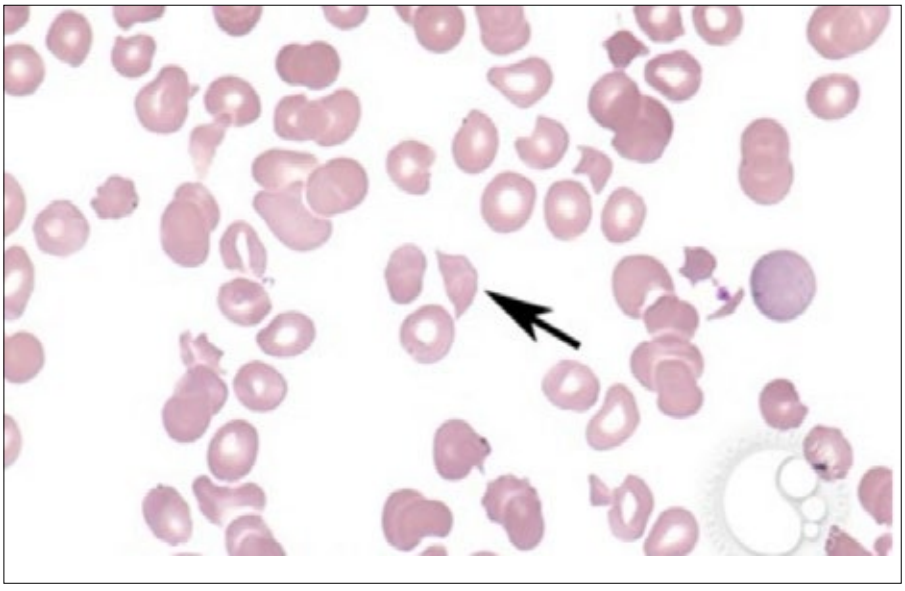


Figure 1. Peripheral blood morphology slide illustrating red cell fragments in a patient with microangiopathic haemolytic anaemia (ASH Image Bank, American Society of Haematology)

It is characterised by peripheral cytopenia's and bone marrow infiltration of histiocytes/macrophages that undergo haemophagocytosis **(Figure 2)**.[4,5,6]

There is increasing evidence that haemophagocytic macrophages can also infiltrate organs like liver, lymph nodes, skin and lungs.[6] Patients with MAS often manifest with massive systemic inflammatory response and coagulopathy causing multi-organ dysfunction.[6] There is pancytopenia with associated hyper-ferritinaemia (above 10 000ng/ml),[6] low complement, low fibrinogen and raised triglycerides.[5,6] Immunosuppressive therapy including high dose glucocorticoids and cyclosporine A, etoposide, IVIG and biological agents are considered as therapy in patients with MAS.[5,6]

Thrombosis

There is a higher risk of hypercoagulability and thrombosis in patients with rheumatic conditions due to the chronic inflammation associated with these conditions.[1] Conditions like SLE, APS, vasculitis, Behcets syndrome, RA and Sjögrens syndrome are a few conditions to name that harbour a higher risk of thrombosis.[1] Patients with SLE have a heightened risk of thrombosis even in the absence of APL antibodies.[5]

Malignancy

An increased frequency of haematological malignancies has been observed in patients with rheumatic conditions.[4] Lymphoproliferative disorders have been reported in patients with Sjögrens syndrome, SLE, RA, polymyositis and dermatomyositis.[4] The link likely exists between the chronic immune dysregulation in these patients and the associated proliferative risk and malignant transformation.[4] Immunosuppressive treatment may also enhance oncogenic risk.[4]

Conclusion

Haematologic abnormalities are common and quite diverse among patients with rheumatic conditions. It is important to distinguish the haematological abnormalities as either part of the disease manifestation, consequence of immunosuppressive therapy or part of another blood dyscrasia.[2] The clinical picture can vary from mild to life-threatening presentations.[5] These abnormalities also represent important prognostic factors in rheumatic patients as well.[4] In most patient's immunosuppressive therapy has an important role in the management of these conditions. Biological agents have facilitated a broader option of therapeutic regimens specifically in severe and refractory patients with haematological manifestations. However, further clinical trials are required.[5]

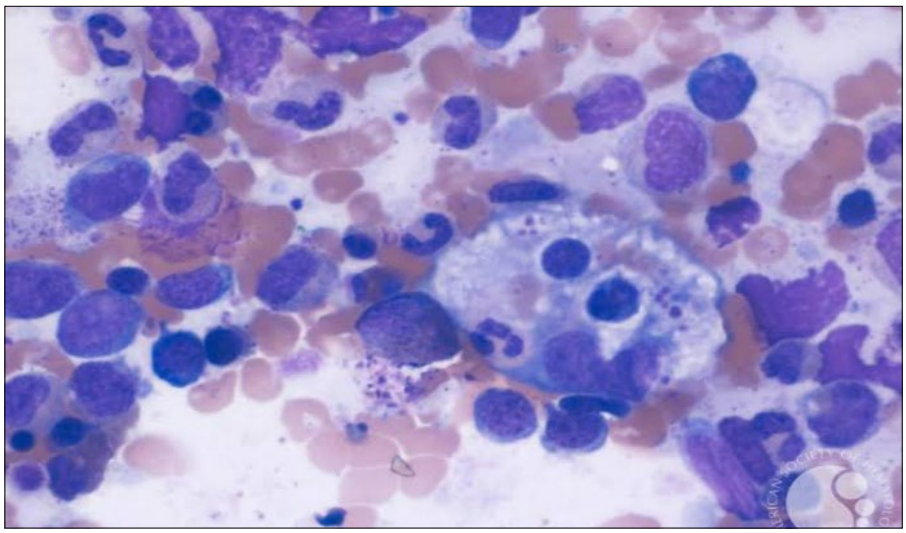


Figure 2. Haemophagocytosis – Activated macrophages phagocytose haematopoeitic elements (ASH Image Bank, American Society of Haematology)

There is a higher risk of hypercoagulability and thrombosis in patients with rheumatic conditions due to the chronic inflammation associated with these conditions. Conditions like SLE, APS, vasculitis, Behcet's syndrome, RA and Sjögrens syndrome are a few conditions to name that harbour a higher risk of thrombosis.

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Haemophagocytic lymphohistiocytosis (HLH) and macrophage activation syndrome (MAS)

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Haemophagocytic lymphohistiocytosis (HLH) occurs due to hyperintense activation of the immune system with significant elaboration of both macrophage and cytotoxic T-cell function.[1] It represents a rare clinical entity which carries significant mortality if unrecognised and if prompt therapy is not initiated timeously.[1,2]

Haemophagocytic lymphohistiocytosis can be subclassified into primary (inherited) and secondary (acquired) subtypes. The inherited form is termed familial HLH (fHLH), and typically occurs in infancy due to mutations in genes involved in the downregulation of the immune response following exposure to an immune trigger. Secondary forms of HLH (sHLH) generally represent immune hyperactivation due to infection, neoplastic disease processes[1,2,3] (particularly non-Hodgkin and Hodgkin lymphoma) or autoimmune conditions. Autoimmune sHLH is conventionally labelled as macrophage activation syndrome (MAS), with juvenile idiopathic arthritis (JIA) as the prototypical condition associated with this entity. MAS is also prevalent in adulthood in patients with adult-onset Still's disease, and may also occur with other rheumatologic diseases (including dermatomyositis, systemic sclerosis, mixed connective tissue disease, antiphospholipid syndrome, Sjogren's syndrome, ankylosing spondylitis as well as the vasculitides).[3] MAS can occur throughout the course of a rheumatologic disease and a high index of suspicion should be maintained when characteristic features typical of the syndrome develop. It is also not uncommon for MAS to develop during the treatment of a rheumatological disease.

Infections initiating HLH due to aberrant immune hyperactivation include the herpes group of viruses (particularly Epstein-Barr virus (EBV)), influenza virus as well as the human immunodeficiency virus (HIV).[1,4] *Mycobacterium tuberculosis* is also an important trigger of HLH in the South African setting given the high incidence of tuberculosis in South Africa (567 cases per 100 000 in 2017).[5] It is of interest to note that infectious agents like varicella-zoster and EBV are often the trigger for MAS/HLH in patients with systemic (1/3rd of cases)[2] and fHLH respectively.

Whilst the herpes virus family of infections and HIV have long been recognised as triggers in the pathogenesis of HLH, the novel coronavirus (SARS-CoV-2) has recently also emerged as an important aetiopathogen.

Whilst the herpes virus family of infections and HIV have long been recognised as triggers in the pathogenesis of HLH, the novel coronavirus (SARS-CoV-2) has recently also emerged as an important aetiopathogen.[6] COVID-19 disease induces aberrant activation of the immune system through direct SARS-CoV-2 interaction with the angiotensin converting enzyme receptors (ACE-2) on macrophages and monocytes.[6] Subsequent immune activation eventually triggers the so called "cytokine storm" with marked hypercytokinemia. The hypersecretion of inflammatory cytokines including gamma interferon, tumour necrosis factor alpha and interleukin six (IL-6) results in upregulation of macrophage receptors and an expansion in inflammatory monocytes. The end result of histiocyte expansion is diffuse tissue inflammation with eventual tissue necrosis and ensuing organ failure. Diseases with similar pathophysiology which form part of the "cytokine storm" syndromes include sHLH, MAS, macrophage activation-like syndrome of sepsis and cytokine release syndromes.[6]

Diagnosis of HLH

Clinically, patients with HLH are acutely ill with multiorgan dysfunction. The signs and symptoms are a product of hypercytokinemia (persistent fever and organ dysfunction (hepatitis, respiratory distress, renal dysfunction)) and the accumulation of activated macrophages (hepatosplenomegaly, skin rashes, neurological dysfunction). As the clinical presentation is non-specific, a high index of suspicion is required for the recognition of HLH. In particular, a markedly elevated ferritin level (especially if >10 000 ng/mL in adults) should serve as a red flag for this entity.[7]

A revision of the Histiocyte Society's original HLH-94 criteria is the basis for the new HLH-2004 diagnostic criteria for the primary form of the disease.[2] In the absence of a known HLA-associated genetic aberration, this requires the presence of 5 of the following 8 criteria:

1. Fever >38.7
2. Splenomegaly
3. Cytopenias (2 of 3): Haemoglobin <9 g/dL, Platelets <100 x109/L, Neutrophils <1 x109/L)

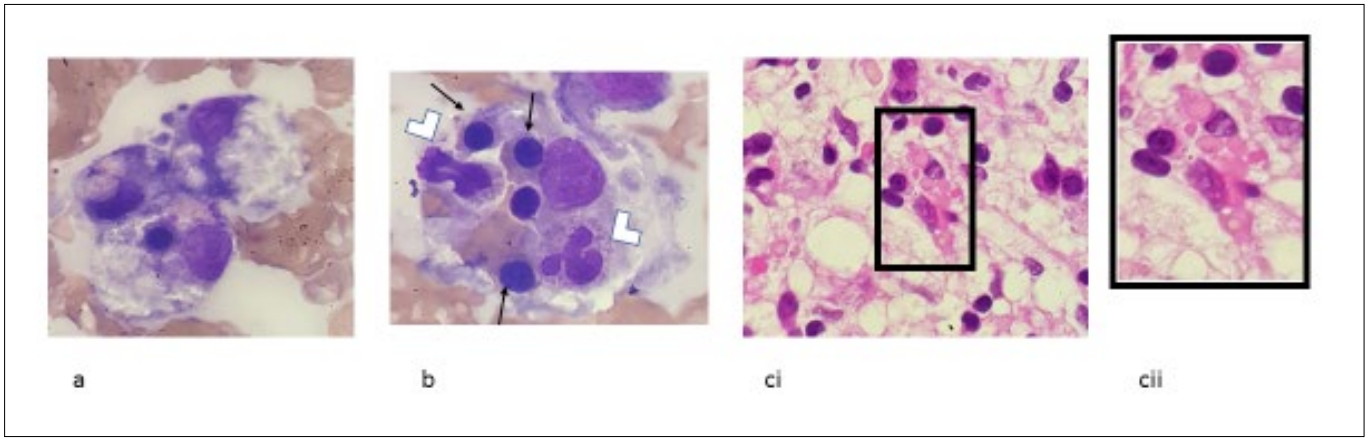

Figure 1. Images from the bone marrow aspirate (1a and 1b) and trephine biopsy (1c) in patients with HLH. Early in the disease course, macrophage activity may be increased with only occasional haemophagocytosis (Figure 1a). Figure1b depicts a macrophage which has phagocytosed multiple erythroid precursors (black arrows) and granulocytes (white arrow heads). Haemophagocytosis is appreciated with more difficulty in tissue sections. Figure 1ci demonstrates increased background macrophage activity in the trephine biopsy from a patient with HLH, with haemophagocytosis identified occasionally (enlarged in Figure 1cii).

Bone marrow aspirate stained with May-Grünwald Giemsa, 500x and 1000× magnification in Figure 1a and 1b respectively. Bone marrow trephine stained with hematoxylin and Eosin, 400× magnification.

4. Hypertriglyceridemia (>265mg/dL) or hypofibrinogenaemia (<150mg/dL)
5. Haemophagocytosis in the bone marrow **(Figure 1)**, spleen or lymph nodes
6. Reduced or absent NK cell activity
7. Ferritin >500ng/mL
8. Increased soluble CD25 (IL-2a) (testing not currently available in South Africa). Diagnosing sHLH and MAS makes use of scoring calculators like the HLH probability calculator (HScore) for adults as well as the PRINTO criteria in children.[2,8]

The original Hscore divides HLH diagnostic criteria into nine clinical features and laboratory indices **(Table 1)**.[2] In the setting of MAS, some patients do not completely fulfil diagnostic criteria for HLH, but treatment should not be withheld if there is a strong clinical suspicion in the setting of a known predisposing condition (particularly JIA), as MAS has high morbidity and mortality rates.[9] A bone marrow aspirate and trephine biopsy are indicated when HLA/MAS is suspected, but it should be noted that haemophagocytosis is not seen in up to 25% of cases.[7] Furthermore, the presence of haemophagocytosis is not invariably indicative of HLH, as it may occur non-specifically as a result of severe illness and in the setting of other immune-mediated conditions (such as autoimmune haemolytic anaemia or incompatible blood transfusion).

Table 1: The Reactive Haemophagocytic Syndrome diagnostic Score[10] (HScore)

Clinical	
Fever (°C)	<38.4 (0), 38.4 - 39.4 (33) and >39.4 (49)
Organomegaly: Hepatomegaly and splenomegaly	Neither (0), either hepatomegaly OR splenomegaly (23), both (38)
Immunosuppression	No (0), yes (18)
Laboratory	
Cytopenia(s)	One lineage (0), two lineages (24), three lineages (34)
Hypertriglyceridemia (mmol/L)	<1.5 (0), 1.5–4 (44), >4 (64)
Hypofibrinogenaemia (g/l)	>2.5 (0), <2.5 (30)
Liver function test (IU/L)	AST <30 (0), >30 (19)
Haemophagocytosis (bone marrow biopsy)	No (0), yes (35)
Score interpretation: scores >169 are 93% sensitive and 86% specific for sHLH	

Lancet Rheumatology defines its own criteria for the COVID-19 associated hyperinflammatory syndrome (cHIS) with criteria similar to the HScore but with other additional contribution from laboratory parameters like degree of D-dimer elevation and lymphocyte to neutrophil ratio.[6]

Treatment options

The heterogenous number of inciting disease processes in sHLH often warrants a patient-specific treatment programme with therapies directed at the underlying inciting event.[1]

The cornerstone of MAS treatment is the introduction of glucocorticosteroids (GCS) as first-line therapy with pulses of high dose methylprednisolone (1g/d) for three to five consecutive days. If the initial response to steroids is deemed insufficient, add on therapies include second line therapy with calcineurin inhibitors as well as IL-1 blocking agents like anakinra.[2] Concurrent antibiotic treatment aimed at treating identifiable infections is also instituted.[2]

Patients with severe disease or CNS involvement may require treatment with weekly reduced dose etoposide.[2]

Overall, the management of patients with suspected or confirmed HLH/MAS is an apt representation of the theme of this volume of NewsRheum entitled "Blood and Bone" as its management requires contributions from varied specialised disciplines of haematology, haematopathlogy, oncology as well as rheumatology.

Summary

- Haemophagocytic lymphohistiocytosis (HLH) is termed macrophage activation syndrome (MAS) when associated with rheumatic disease
- HLH occurs due to hyperintense activation of the immune system and secondary forms of the disease may be due to infection, autoimmune conditions or malignancies.
- Fever, organ dysfunction, cytopenias as well as hyperferritinemia in the context of a systemic illness should always prompt the clinician to consider the diagnosis of HLH/MAS.

The cornerstone of MAS treatment is the introduction of glucocorticosteroids (GCS) as first-line therapy with pulses of high dose methylprednisolone (1g/d) for three to five consecutive days.

Abbreviations	
ACE-2	angiotensin converting enzyme-2
COVID-19	novel corona virus disease
cHIS	COVID-19 associated hyperinflammatory syndrome
HLH	hemophagocytic lymphohistiocytosis
EBV	Epstein Barr Virus
fHLH	familial hemophagocytic lymphohistiocytosis
IL	interleukin
JIA	juvenile idiopathic arthritis
MAS	macrophage activation syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2/novel coronavirus
sJIA	systemic onset juvenile idiopathic arthritis

GL & JV contributed equally to the write up of this document. Images courtesy of JV and remain property of the National Health Laboratory Service (NHLS). No patient identifiers were utilised in this document.

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Abbreviations
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Cases in osteoporosis management

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Osteoporosis and its consequent fragility fractures pose a major health problem. Traditionally osteoporosis has been considered a rare disease in Africa. As life expectancy improves, the demographics of the world populations are set to change with more elderly living in developing countries and the number of osteoporotic fractures are set to increase exponentially in Africa.

Fragility fractures usually occur following minimal trauma. While the commonest site for a fracture is the spine, hip fractures (HF) have the direst impact in terms of morbidity, mortality and health care costs.[2,3] The pathogenesis of osteoporosis is complex. Apart from age and hormonal factors there are multiple causes for low bone mass; including nutritional disorders and auto-immune diseases.[4] Glucocorticoids (GC) often a mainstay of treatment for auto-immune diseases are recognised as one of the commonest causes of secondary osteoporosis.[5] Observational studies suggest that osteoporotic fractures are seen in up to 40% of patients who use long-term GC therapy.[6]

How is osteoporosis and fracture risk assessed and diagnosed?

Osteoporosis can be diagnosed either on the basis of prior fragility fracture or by the measurement of bone mineral density (BMD). The WHO recommends dual-energy x-ray absorptiometry (DXA) scan as the gold standard for diagnosing osteoporosis **(Table 1)**.[7]

However, measurement of BMD via DXA is not feasible in many developing countries due to either lack of access to DXA or failure of medical aids to reimburse the test.[8] BMD alone, without clinical risk factors (CRFs), is also a poor predictor for fragility fractures as it fails to include the non-skeletal determinants of fracture risk, and >50 % of fractures occur in persons with osteopaenia or a normal BMD **(Figure 1)**.[9]

In order to address BMD limitations, the WHO developed the Fracture Risk Assessment (FRAX®) tool;[10] which is available at www.shef.ac.uk/FRAX. The FRAX tool measures the 10-year probability of having a major osteoporotic fracture (MOF) or HF based on the local epidemiology of fracture and the risk of death of each country. The fracture probability is based on age, body mass index and CRFs (prior fragility fracture, parental history of HF, current tobacco smoking, overuse of long-term oral GC, rheumatoid arthritis (RA), other causes of secondary osteoporosis and alcohol consumption) with or without a BMD score. The use of CRFs in combination with BMD and age improves the sensitivity of fracture prediction. Additionally while BMD enhances the FRAX score, FRAX without BMD still has a predictive value for fractures that is comparable to the use of BMD alone. The FRAX tool, however, has several limitations in that it is only

Table 1. WHO classification criteria for osteoporosis based on DXA[7]

Definition	Criteria
Normal	BMD or BMC value (measured with DXA at either the spine, total hip or femur neck) within 1 SD of the young adult reference mean (T - score at or above -1.0)
Low Bone Mass	BMD or BMC value more than 1 SD, but less than 2.5 SD below the young adult mean (T - score between -1.0 and -2.5)
Osteoporosis	BMD or BMC value is 2.5 SD or more below the young adult mean

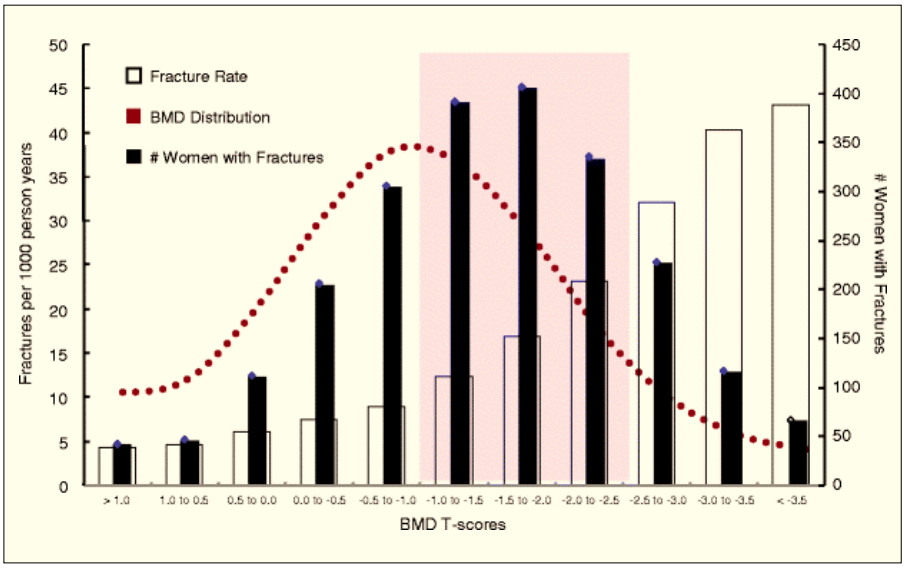

Figure 1. Relationship of bone mineral density and fracture rates in women from the NORA study. Adapted from Sris ES,. Arch Intern Med.

Table 2. Adjustment of 10 year probabilities of a hip fracture or major osteoporotic fracture by age and glucocorticoid dose[11]

Dose	Prednisone equivalent (mg/day)	Age (years)						
		40	50	60	70	80	90	All ages
Hip fracture (percentage (%) adjustment depending on dose)								
Low	< 2.5	-40	-40	-40	-40	-30	-30	-35
Medium[a]	2.5 - 7.5							
High	≥ 7.5	+25	+25	+25	+20	+10	+10	+20
Major osteoporotic fracture (percentage (%) adjustment depending)								
Low	< 2.5	-20	-20	-15	-20	-20	-20	-20
Medium[a]	2.5 - 7.5							
High	≥ 7.5	+20	+20	+15	+15	+10	+10	+15
[a]No adjustment required for medium doses								

applicable to untreated patients and was designed for use in post-menopausal women. The tool also requires country specific incidence rates and health economic data. Recently, modifications to the tool to adjust for exposure to GC **(Table 2)**, include concurrent data on lumbar spine BMD, information on trabecular bone score (TBS), hip axis length and falls history have been proposed.[11]

The intervention thresholds to decide on treatment also vary since they depend on local factors such as reimbursement and health costs. The FRAX model for South Africa (SA) was recently published,[12] however, intervention thresholds for SA are yet to be determined. As an example a 63 year old White South African woman with a prior fracture will have 7.8% risk for MOF and 2.1% for HF but if the ethnicity only is changed to Black African the risk will be reduced to 4.5% and 1.5% respectively.

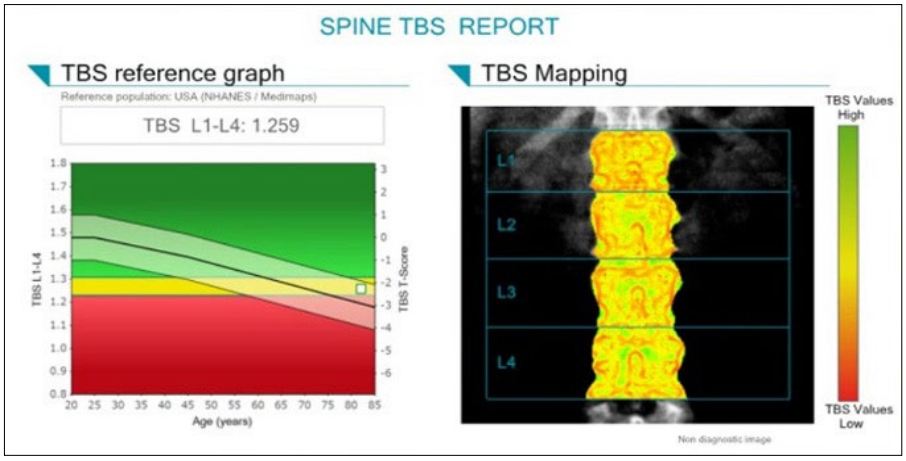

Figure 2. Example of a trabecular bone score

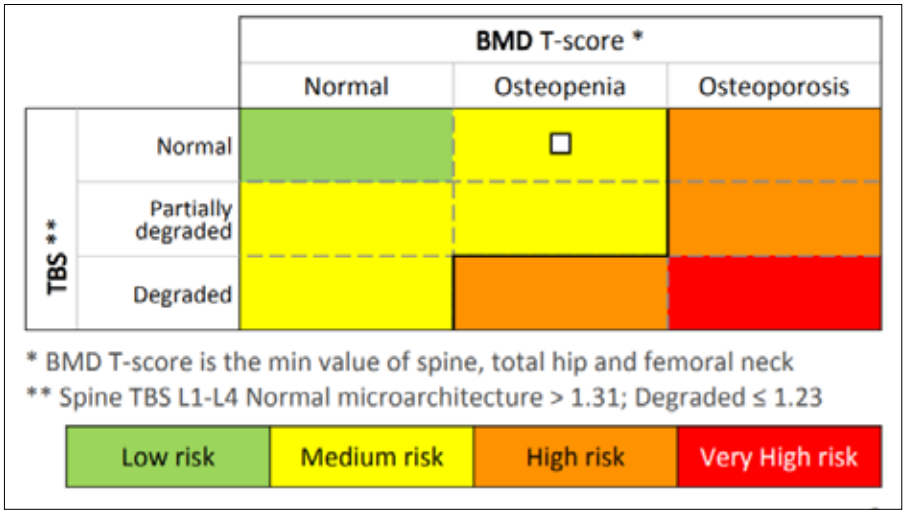

Figure 3. Colour coded bone health categories of fracture risk using trabecular bone score and bone mineral density score.

Apart from the FRAX score there are several other fracture risk calculators available including the Garvan and Q-Fracture®. The Q-Fracture includes a greater number of CRFs and includes RA and systemic lupus erythematosus.[13]

The TBS, a surrogate marker of bone microarchitecture is extracted from spine DXA and is available on some densitometers **(Figure 2)**.[14]

The TBS score can predict fragility fractures independently of BMD, CRF, and the FRAX, and when used together, it enhances their accuracy **(Figure 3)**.

The white dot on the graph represents the patient's risk of fracture based on minimum BMD T-score and TBS: Osteopaenic or osteoporotic patients with degraded TBS are at high risk (orange) or very high risk (red) of fracture. Normal or osteopaenic patients with partially degraded or normal microarchitecture are at medium (yellow) or low (green) risk of fracture.[14, 15]

Other methods for diagnosing osteoporosis include quantitative ultrasound and quantitative computed tomography. However, the National Osteoporosis Foundation of South Africa (NOFSA) currently does not recommend these methods. These methods may however assist in diagnosis in resource limited settings after proper validatation.[16]

How to appropriately evaluate osteoporosis?

All patients should have a thorough history and examination to exclude secondary causes of osteoporosis. Apart from routine tests, bone turnover markers (BTM) may be useful in the initial evaluation and follow-up of osteoporosis patients. Although elevated levels can predict higher rates of bone loss and fracture risk, inconsistencies in technical factors and biological variations complicate interpretations. BTMs are not routinely recommended.[16] BMD testing is indicated in the following persons **(Table 3)**.[16]

Who should be commenced on pharmacologic therapy?

Despite medical therapy decreasing the risk of fragility fractures in high quality randomised controlled trials,[17] only a minority of patients receives treatment even after sustaining a fragility fracture. Treatment after a first fracture can significantly decrease the risk of a second fracture.

All patients should receive life-style monitoring and adequate doses of calcium 1g/day and vitamin D 800 IU/day prior to commencing anti-osteoporotic drugs **(Table 4)**.[16]

What medication should be used to treat osteoporosis?

There are several different drugs classes available which work on different pathways of the bone remodelling cycle **(Figure 4).**

Treatment strategies and monitoring are dependent on fracture risk assessment and are summarised in **Table 5**. Follow-up of patients should ideally be conducted in the same facility with the same DXA system.

Table 3. Indications for BMD measurements

1. Women aged 65 years and older and men aged 70 years and older
2. Known secondary osteoporosis
• Early menopauses (< 45 years), other causes of hypogonadism or prolonged oligo-amenorrhoea > 1 year
• Systemic disease that affects bone (include RA and SLE)
• Bone-toxic drugs
3. Radiographic evidence of vertebral fractures
4. Fragility fractures after 40 years of age
5. Clinical risk factors for fractures
6. Assist in initiation or discontinuation of drug treatment

Table 4. Non-pharmacological treatment for osteoporosis

1. Lifestyle modification • Stop alcohol • Stop smoking • Decrease bone toxic drugs to lowest doses
2. Prevention of fall
3. Visual assessment

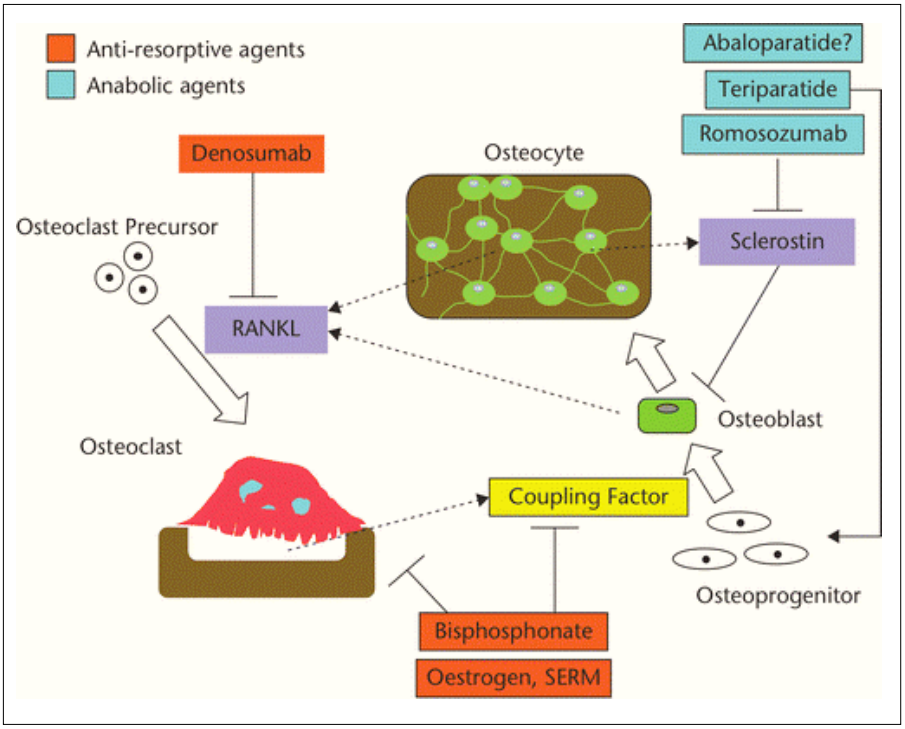

Figure 4. Mechanism of actions of anti-osteoporosis drugs. Adapted from EFORT Open Rev 2019;4:158-164. DOI: 10.1302/2058-5241.4.180018

In peri-menopausal women who have a low fracture risk, HRT may be instituted during the window of opportunity, i.e. in the 10 years after menopause and before the age of 60 years. HRT should not be used in patients with an increased risk of venous thromboembolism.[17]

Bisphosphonates are first line therapy for patients at moderate to high fracture risk. They include alendronate, zoledronate and ibandronate. Zoledronate is increasingly being used as it is a yearly infusion and well tolerated. Current dosage recommendation is 3 annual infusions followed by three-year drug holiday.[18] Zoledronate within

90 days after repair of a low-trauma HF decreases the rate of new clinical fractures (RR 35%) and improves survival. Denosumab, a RANKL inhibitor, has recently been registered in SA and inhibits osteoclast activity. According current guidelines it may be used as a first line drug. It has excellent efficacy at all fracture sites [68% reduction for vertebral fractures, 39% for HF, and 19% for non-vertebral fractures]. The risk of osteonecrosis of the jaw and atypical femur fractures seems to be less than with bisphosphonates. Denosumab is not secreted by the kidneys and can be used in patients with eGFRs of 35 mL/min/1.73 m^2. However, it should be administered with caution as the drug lowers bone turnover rapidly and blocks calcium mobilisation from bone in defence of hypocalcemia.[19,20]

Anabolic therapy is recommended as second line treatment when bone-specific treatment has failed, either because of a new fracture or because of unacceptable rates of bone loss following appropriate and compliant antiresorptive therapy. Anabolic therapy is also recommended as first line in patients with high fracture risk[21,22] **(Table 4).**

Teriparatide is the only anabolic agent available in SA, and significantly reduces both vertebral and non-vertebral fractures risk. Previous bisphosphonate therapy does not prevent the use of teriparatide but concomitant use is not advocated. The main limitation to teriparatide use is the exorbitant cost. Abaloparatide is a novel analogue of human PTH-related protein, and has superior increases in BMD compared to teriparatide.[22]

What is the ideal duration of osteoporosis treatment?

Patients on teriparatide should be treated for 2 years and then continued on a bisphosphonate or denosumab. Patients on oral bisphosphonates, may have a drug holiday after 5 years of treatment if fracture risk is no longer high (T score >-2.5, or if there were no fractures), otherwise continue treatment for an additional 5 years. Similarly patients on zoledronate, may have a drug holiday after 3 years or continue for up to 6 years in very high risk patients. Drug holidays are not recommended for non-bisphosphonates antiresorptive drugs and treatment with such agents should be continued for as long as required. [22,23]

Table 5. Fracture risk categorisation, treatment and monitoring strategies

	High risk	Moderate risk	Low risk
Criteria	• Fracture in the last 12 months • Multiple fractures • Fractures on treatment • Fracture while on GC • T score < -3.0 • FRAX >30% of MOF or >4.5% HF	• Age: post-menopausal • Prior fracture • T score of < -2.5 • T score of -1.0 to -2.5 with FRAX > 20% MOF or >3% HF	• Age: post-menopausal • No prior fracture • T score of > -1.0 with FRAX < 20% MOF or <3% HF
Treatment	• PTH/Teriparatide • Denosumab • Bisphosphonates	• Bisphosphonates • Denosumab	• HRT • Raloxifene
Monitoring duration	• BMD every 1-2 years or • After a fracture	• BMD every 1-3 years or • After a fracture	• BMD every 2-4 years or • After a fracture

GC: glucocorticoids, MOF: major osteoporotic fracture, HF: hip fracture, HRT: hormone replacement treatment

Special considerations

1. Glucocorticoid-induced osteoporosis (GIOP)

The American College of Rheumatology (ACR) treatment recommendation for GIOP are stratified according to the GC dose and fracture risk assessment based on FRAX calculations. Low- and medium-risk patients (FRAX <10 and 10–20 % probability of a MOF, respectively) should be treated if their GC dose is greater than or equal to 7.5 mg/day. High-risk patients (FRAX >20% MOF) should be treated if they receive GC at any dose for >1 month or if they are on ≥5 mg/day prednisolone equivalent even for <1 month.[23]

2. Treatment in pre-menopausal women (PMW)

Unlike post-menopausal women, the studies and efficacy of all bone-specific drugs to prevent fractures in PMW, is less clear. Treatment in PMW should be reserved for patients with major fragility fractures, or those with a DXA-confirmed low BMD (according to the Z-score) with ongoing significant bone loss or with a secondary cause that are inadequately controlled.[22] Both the ISCD and NOF reserve the diagnosis of osteoporosis in PMW for those with a low BMD and evidence or history of a fragility fractures. BMD testing in this group also helps to differentiate patients who failed to attain peak bone mass from those who have active ongoing bone loss. Similarly BTMs may be useful, especially if there is only one DXA reading available to make treatment decisions. The role of TBS is less well defined in PMW and a recent study failed to show that a TBS added to fracture risk prediction in PMW.[24] The long half-life and skeletal accumulation of bisphosphonates raise concern about their safety in pregnancy in PMW and they should be avoided for at latest a year before falling pregnant.[25] Teriparatide is indicated in PMW with GIOP but is also contraindicated in pregnancy. Denosumab may potentially be an alternative agent in PMW as it has a shorter half-life, absence of skeletal accumulation and safer pharmacokinetic profile relative to bisphosphonates.

Conclusion

Osteoporosis with the correct measures can be prevented, diagnosed, and treat-

ed before fractures occur. Decisions regarding the choice of therapies must take into account the country-specific availability of various drugs, local guidelines, patient preferences and costs.[26]

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Interview: Dr Ebrahim Bhettay

NewsRheum and SARAA takes pleasure in presenting an interview with Dr Ebrahim Bhettay as we pay tribute to his dedication and contribution to the field of rheumatology for over 60 years.

My early career

I matriculated in 1949 and planned to enter university, but because I refused to attend an apartheid institution in South Africa, I went to India to study Philosophy. After graduating, I changed course to study medicine because my passion was to work with and for children. My five-year experience of freedom in India led me to refuse attending an apartheid institution in South Africa, and so I graduated in Ireland in 1961. After an internship in South Africa, I trained to be a paediatrician in the UK (1963-67) in the London and Oxford region. I was also fortunate to work at Taplow under Professor Eric Bywaters and Dr Barbara Ansell, the doyens of paediatric rheumatology. After obtaining Edinburgh & Glasgow Memberships (and Fellowshipss) I returned to South Africa in 1967.

I accepted a post at Livingstone Hospital (LH) on condition that the appointment was under the same conditions as the white staff - a promise they made, but did not keep. It was a cultural shock to re-enter the coalface of apartheid society. Here, we formed a clinical society with an academic programme that attracted local and international experts. I was then lured to Cape Town, where I joined the University of Cape Town Department of Paediatrics, starting at Somerset Hospital (NSH) in September 1970.

A move into the pain field

Joining the nutrition research team culminated in my first publication titled ' lymphocyte transformation in malnourished children' in the Archives Diseases of Childhood. Shortly thereafter, a child with Stills Disease was presented at the Red Cross War Memorial Children's Hospital (RCWMCH), and I seized the opportunity to redirect my focus, thinking that a challenge to cope with chronic pain, suffering, deformity and disability would prove more rewarding. The result was the establishment in 1971 of the first Juvenile Arthritis clinic in Africa.

In 1974, I joined Prof OL Meyers in establishing the arthritis clinic at the Princess Alice Orthopaedic Hospital. There, we developed and established a multi-disciplinary team, working alongside orthopaedic surgeons and other specialists. Because this clinic served all races, a white doctor was appointed to attend to white patients. Here, we pioneered the creation of a TMJ prosthesis for children.

As a consultant and senior lecturer, I adopted a strong advocacy role for trainees who were 'of colour', to enable them to benefit from the experience and exposure that their white colleagues encountered. I repeatedly pleaded for the NSH registrars, restricted to NSH to limit their interaction with white patients - to be allowed to join their white peers in rotations between the other academic hospitals e.g. Groote Schuur Hospital (GSH), Mowbray Maternity Hospital, and RCWMCH. This was repeatedly denied. Later however, white registrars rotated through NSH, to broaden their experience and exposure in clinical neurology and rheumatology. I was able to attend meetings and hold an outpatient clinic at the RCWMCH, where I was eventually allowed access to the tea room.

From 1971 to 1991 I served on the editorial board of the EULAR Bulletin, and the Paediatric Rheumatology Standing Committee (PRSC). This Committee developed the original nomenclature and classification criteria for Juvenile Chronic Arthritis in Oslo in March 1977. These criteria were further developed by the ILAR PRSC in Santiago, Chile, where I was the only African representative. In 1995 I brought the ILAR PRSC to Durban, where the new modified criteria were introduced.

In 1991 a meeting was held in Cairo to launch the formation of AFLAR. I arranged to meet interested members with a view to forming a paediatric committee. Considerable interest was expressed, and contact details were exchanged. Several attempts were made to develop this further, but I soon realised that Africa was not only a 'dark' but also a silent continent. Sadly, attempts to revive this at the second AFLAR Congress in Tunis also failed.

Another exciting development was the public sponsorship towards the regular weekend camps. These camps helped relieve the boredom and depression of

prolonged hospitalisation. Hospitalised children engaged with other children, with and without arthritis, to socialise, have fun and games, and enjoy open-air freedom. They displayed remarkable agility in the pool, and relished non-hospital meals.

The rheumatology academic meetings which I started in the 1980s evolved into high-quality sponsored events which continued for 40 years, until sadly becoming another casualty of the COVID-19 pandemic.

Our treatment development

Our restricted pharmacology was simple: Aspirin and corticosteroids. The advent of a host of NSAIDs improved matters, but too often we stood by helplessly watching the disease progress. Our arsenal grew over the years to the troublesome and disappointing gold injections and penicillamine. Thankfully, research and innovation forged ahead, culminating in the introduction of the biologic agents. This hitherto exciting development, along with joint replacement and other orthopaedic procedures, gave us greater control over a relentless disease, and promised a return to normal life. But new technology provides increasingly expensive solutions, and clinicians discovered a battlefield of medical politics and economics in which they are forced to fight for access to remedies on behalf of a disadvantaged patient demography.

Growth of the profession

Our early rheumatologists were orthopaedic surgeons, who founded SARAA. Then physician-rheumatologists appeared. I was a paediatrician who learnt my trade by rubbing shoulders with people who knew the way. We now have a growing band of rheumatologists and more recently, paediatric rheumatologists, ably led by Professor Christiaan Scott. While I may have given birth to childhood arthritis in South Africa, it has matured into adolescence under the likeable Scott.

I have lost track of recent developments in rheumatology, but I feel strongly that future success lies in the exciting field of pharmaco-genetics, which may provide answers and shed light on more directed and appropriate individualised therapies. Of concern is the progressive disappearance of orthopaedic surgeons from our meetings.

I introduced an academic programme at the LH, lectured students, conducted research, presented at local and international meetings, published in peer-reviewed journals, and mentored and trained specialists. I sincerely hope these newly-qualified "Young Turks" do not become so pre-occupied with information overload and engrossed in research so as to forget that the patient always remains the centre of the universe.

I have derived such great enjoyment from my career of more than 60 years, that I am proud to be able to claim that "I never worked a day in my life".

RheumQUIZ

Answers to quiz questions on page 9

1. Syphilis
2. Transient hypoparathyroidism - transient suppression of the remaining glands with removal of the hyper-functional adenoma.
3. Anti-beta2glycoprotein1 antibodies, lupus anticoagulant and anticardipin antibodies
4. Raised Haematocrit

Celebrating new rheumatologists who graduated during the peak of COVID-19, 2020

Dr Namhla Mvambo-Madubela

Apart from the obvious stress and challenges around exam preparations, writing exams during the pandemic was not only scary but I had a so much anxiety. It was difficult to focus on studying alone without focusing on the pandemic crisis. Things at work and at home changed as the country was responding to the crisis. Studying while trying to stay safe and still provide services at work was a huge challenge, especially facing an unknown virus by us all. Not knowing how the exam will be structured and having exams also postponed brought a whole lot more anxiety.

This whole experience taught me that hard times do build determination and inner strength.

For those who will be writing during this pandemic, it will be challenging and tough. But, remember the end goal, keep your head up, ask for help when you need it and you will get through. “The best view comes after the hardest climb”.

Good luck with your exams!

Dr Sanvir Sirriram

Specialist Physician & Rheumatologist

“Live as if you were to die tomorrow, learn as if you were to live forever”, Mahatma Gandhi

In summary, this was my experience of writing my rheumatology final exam during the first wave of the Covid-19 pandemic. The Covid catastrophe was playing out simultaneously while I was trying to prepare for my exam. Covid ensured we had limited clinical training because of the risk of contracting the virus. Complete lack of social support because of the rigid lockdown regulations, the uncertainty of whether I would contract Covid and not be able to write the exam. The uncertainty was overbearing and suffocating. Studying and staying focused was extremely difficult during the pandemic. I would like to thank the Rheumatology Department at CHBAH and my mentor Dr Nimmisha Govind for their invaluable support during my “darkest days”. I wish all the current exam candidates good luck with their exams. They should find courage in our triumph. If I could do it, so can you. At the end of the day, we all have to adapt to our new Covid reality.

Nadia Duvenhage

I stand thankful towards the mentors who put in numerous hours to prepare me for the reality of patient care by way of a virtual exam, which was made a success by these same giants in rheumatology, in whose footsteps I hope to follow in the future.

PharmaNEWS

2021 saw the introduction of two JAK-inhibitors, tofacitinib (Xeljanz) and baricitinib (Unamity) into the South African market. These targeted synthetic DMARDs (tsDMARDs) are registered for the treatment of moderate to severe rheumatoid arthritis (RA), with tofacitinib also approved for use in psoriatic arthritis.

The good safety and efficacy profile, the oral formulation, rapid onset of action, as well as possible use as monotherapy, have cemented the importance of these agents in the treatment of refractory RA. The EULAR 2019 guidelines have positioned tsDMARDs at level pegging with biologic DMARDs, following failure of csDMARD therapy (alone or in combination). This strategy is supported by SARAA.

Notable safety concerns include a higher risk of herpes zoster infection and venous thromboembolic disease. Despite these concerns, the JAK-inhibitors will have an important place in RA management in SA; with a low TB risk profile, and an easy oral mode of administration, especially in resource constrained settings where injectable medications can be challenging. However, this will ultimately depend on the cost of these therapies to the patients in need.

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Our philosophy? Listen and understand. Our commitment? Create innovative medicines and practical solutions. Our passion? Help people live longer, healthier and more active lives.

Rheumatic diseases are uncompromisingly complex. They can have a devastating impact on people's lives. That's why we are determined to fight them. Our heritage and expertise fuels that fight.

PP-BA-ZA-0068, Expiry Date 31 Jan 2022
S4 UNAMITY® 2 mg film coated tablets. REG No.: 52/3.1/0231.229. Each film coated tablet contains 2 mg of baricitinib.
S4 UNAMITY® 4 mg film coated tablets. REG No.: 52/3.1/0232.230.Each film coated tablet contains 4 mg of baricitinib.
For full prescribing information refer to the Professional Information approved by the medicines regulatory authority.
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