Dear Colleague,

It is my pleasure to share this issue of *Rheumatology Connections* with you. The cover features a photomicrograph of granulomatous angiitis pathology because the care of patients with granulomatosis with polyangiitis (GPA) (Wegener’s) is a major focus of both this issue and our Department of Rheumatic and Immunologic Diseases.

Members of our Center for Vasculitis Care and Research share important outcomes studies on the duration of maintenance therapy for GPA (p. 7) and on the frequency of laboratory monitoring for patients with severe GPA receiving cyclophosphamide (p. 12). Additionally, the Director of our Center for Vasculitis Care and Research, Dr. Carol Langford, gives her experienced clinical perspective on the unique challenges of managing GPA in geriatric patients (p. 14).

Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases ranked as one of the top 2 rheumatology programs in the country in *U.S. News & World Report*’s “America’s Best Hospitals” survey for 2012. This ranking is the result of the dedication of the 30 rheumatologists who partner here in patient care, research and education. Other contributions to this issue provide a window into the wealth of activities these rheumatologists are pursuing in our department. Here are just a few examples:

- Dr. Elaine Husni reports on two aspects of her interdisciplinary work surrounding psoriatic arthritis: a major study exploring its links with metabolic syndrome (p. 4) and a multicenter collaboration on a biobank of psoriatic arthritis specimens to steer research and clinical practice (p. 9).
- Dr. Chad Deal describes the burgeoning enrollment in Cleveland Clinic’s Web-based DXA registry system designed to guide research and refine the quality of osteoporosis care (p. 8).
- Drs. Soumya Chatterjee and Ashwini Punjabi share data on the prevalence of pulmonary hypertension in inflammatory myopathies and discuss the potential implications for clinical evaluation (p. 10).

The department’s focus on patient-centered care is reflected in the profile of Dr. Leonard Calabrese’s research on empathy (see opposite page) as he has taken on a leading role in the study of empathy in medicine. The research focuses on the important factors of empathy, interprofessional collaboration and holistic modalities as they affect the outcomes of patients with diverse rheumatic diseases.

It is my honor to share the innovative work of my colleagues here at Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases in this issue. I welcome your feedback as we collaborate to advance rheumatologic care and research.

Respectfully,

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*Best Hospitals* Honor Roll

Cleveland Clinic’s Rheumatology Program is ranked among the top 2 in the nation in *U.S. News & World Report*’s “America’s Best Hospitals” survey

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From the Chair of Rheumatic and Immunologic Diseases

Rheumatology Connections, published by Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases, provides information about leading-edge diagnostic and management techniques as well as current research for physicians.

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*Rheumatology Connections* is written for physicians and should be relied upon for medical education purposes only. It does not provide a complete overview of the topics covered and should not replace the independent judgment of a physician about the appropriateness or risks of a procedure for a given patient.

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Much has been said in the past few years about “treating to target” in the field of rheumatology. Targets for disease activity, biomarkers and X-ray progression are indeed important because they correlate with quality of life and functionality. At the same time, individual patient preferences, needs and values have not figured into the discussion to the same degree. The medical literature is now echoing calls for increased emphasis on goal-oriented measures that favor quality — even over traditional markers such as biomarkers and hard-core measures like survival if personal milestones are not achieved.

To truly engage in patient-centered, goal-oriented care, doctors must establish a rich communication with their patients, and empathy — the ability to stand in another’s shoes — is central to such communication. In recent years, empathy research has begun to demonstrate that empathy can be fortified — even taught — as opposed to merely being lost, as many previously believed.

**Fostering Expertise in Empathy**

Over the past eight years, Cleveland Clinic rheumatologist Leonard Calabrese, DO, R.J. Fasenmyer Chair in Clinical Immunology, has played an active role in the field of empathy research. In 2005 he was asked to consider leading the academic thread known as “Human Values” in the newly organized Cleveland Clinic Lerner College of Medicine.

“I have strong interests in bioethics, communications and empathy,” says Dr. Calabrese, “but at first I was hesitant about assuming this role because I was not trained or engaged in academic research.” However, he has since become an active member of the empathy research community and plans to grow his program even further. He now collaborates with the group at Thomas Jefferson University’s Jefferson Medical College led by Mohammadreza Hojat, PhD, the principal architect of the Jefferson Scale of Empathy. This scale is the benchmark for quantitative research in empathy and has been translated into more than 25 languages.

**Exploring Empathy and Outcomes**

Additionally, Dr. Calabrese, who holds the Theodore F. Classen, DO, Chair in Osteopathic Research and Education, has received a $90,000 grant to examine the relationships among three measures: empathy, interprofessional collaboration and holistic patient care. The project will compare osteopathic medical students on these three measures by gender, year in medical school and specialty interest. It will also compare osteopathic and allopathic medical students on changes in empathy, attitudes toward interprofessional collaboration and attitudes toward holistic care during medical education in cross-sectional and longitudinal studies. Data from this project will be forthcoming by the end of 2012.

Dr. Calabrese also served as co-investigator in a recently published study that examined the effects of reflective writing among a group of senior faculty who met regularly over a one-year period at Cleveland Clinic. The study revealed the power of reflection and narrative writing to bolster empathy, concluding that its findings should encourage medical educators to design strategies for enhancing reflection and empathic behavior in medical students and practicing physicians alike.

**Reference**


**Dr. Calabrese is Director of the R.J. Fasenmyer Center for Clinical Immunology in the Department of Rheumatic and Immunologic Diseases. He is also Professor of Medicine in the Cleveland Clinic Lerner College of Medicine and holds a joint appointment in the Center for Ethics, Humanities and Spiritual Care. He is currently designing studies examining empathy among rheumatology trainees and attending physicians. He can be reached at 216.444.5258 or calabrl@ccf.org.**
Is Metabolic Syndrome the ‘Silent Killer’ in Patients with Psoriatic Arthritis?

By M. Elaine Husni, MD, MPH

A recently published study (Arthritis Care Res. 2011;63:195-202) demonstrated that metabolic syndrome is more common in patients with psoriatic arthritis (PsA) than in those with rheumatoid arthritis. In general, PsA patients are more prone to obesity and dyslipidemia, so it is understandable that these patients’ odds of having metabolic syndrome are high. However, the mechanism underlying this risk remains unclear. Because PsA is characterized by inflammation of both skin and joints, we may be underestimating the cardiovascular (CV) risk in this population compared with the risk faced by patients with other forms of inflammatory arthritis.

Metabolic syndrome is a combination of factors that multiply a person’s risk for heart disease, diabetes and stroke. Having three or more of the following factors satisfies the criteria for metabolic syndrome:

- Large waist circumference (≥ 40 inches for men; ≥ 35 inches for women)
- Triglyceride level ≥ 150 mg/dL
- Low HDL cholesterol level (< 40 mg/dL for men; < 50 mg/dL for women)
- Blood pressure ≥ 130/85 mm Hg
- Fasting glucose ≥ 100 mg/dL

Many studies have found that up to 50 percent of psoriatic disease (both PsA and psoriasis) patients with atherosclerosis do not have the traditional CV risk factors such as advanced age, male gender, smoking and a history of diabetes. Thus, additional factors, such as disease-specific or treatment-related variables, need greater study in this population. Moreover, an incremental increase in inflammatory pathways in PsA (including both skin and joint involvement) may contribute to an even higher risk for CV disease and metabolic syndrome compared with psoriasis alone.

COMPASS Sheds Light on Metabolic Syndrome Risk

Further investigation of the risk of subclinical atherosclerosis in PsA is being conducted at Cleveland Clinic in a study known as COMPASS (Cardiometabolic Outcome Measures in Psoriatic Arthritis Study) among more than 250 patients with psoriatic disease. One goal of COMPASS is to establish whether the presence of inflammatory joint disease in patients with psoriasis is a risk factor for metabolic syndrome. We investigated the hypothesis that the incremental inflammatory pathways in PsA, involving both skin and joints, will confer greater atherosclerotic burden than is seen in psoriasis alone.

The study’s early results showed demographics to be comparable between the 145 patients with psoriasis alone (58 percent) and the 107 patients with PsA (42 percent), including no significant differences in gender distribution, prior CV events or family history of CV risk. However, compared with psoriasis alone, PsA was associated with significantly higher prevalences of hypertension, obesity, hypertriglyceridemia and metabolic syndrome (Figure 1).
In addition, COMPASS showed that PsA patients who are not on active DMARD therapy have a significantly higher prevalence of metabolic syndrome \((P < .001)\) and increased Framingham risk scores \((P < .005)\) compared with their counterparts who have psoriasis alone. However, the significance of these differences was lost when patients who were on DMARD treatment were analyzed. Psoriasis with inflammatory joint disease was found to be a risk factor for metabolic syndrome \((\text{unadjusted OR} = 2.658; 95\% \text{ CI, 1.518-4.653})\). Notably, after adjustment for age, family history of CV risk, C-reactive protein level and treatment with DMARDs, inflammatory arthritis remained a significant risk factor for metabolic syndrome \((\text{OR} = 3.423; 95\% \text{ CI, 1.431-8.189})\).

**Drawing Conclusions:**

**Tailor Treatment to Comorbidities Linked to PsA**

Our results suggest that the presence of inflammatory joint disease in patients with psoriasis is a significant risk factor for metabolic syndrome. PsA patients also have significantly higher prevalences of conventional CV risk factors and higher Framingham risk scores compared with their counterparts who have psoriasis alone. However, there is no significant difference once patients are on active DMARD therapy for psoriatic diseases. These results suggest that treatment regimens for PsA patients must be tailored to comorbidities associated with PsA, including metabolic abnormalities.

Additional prospective controlled studies in patients with PsA and metabolic syndrome are needed to better understand the pathophysiology, especially as it relates to circulating and cellular biomarkers of inflammation and the risk of both diabetes and arteriosclerotic CV disease. This is the focus of an ongoing study within COMPASS.

**Confirmation from Studies on Atherosclerotic Burden**

In the final phase of COMPASS we are comparing carotid intima-media thickness (cIMT) between patients with psoriasis alone and those with PsA. cIMT is defined as the distance between the leading edge of the luminal echo and the leading edge of the media/adventitia echo. It is a marker for early atherosclerosis and vascular remodeling and is an independent predictor of coronary disease.

As shown in Figure 2, patients with PsA had a significantly greater cIMT, using both mean \((P = .048)\) and maximum \((P = .01)\) measurements, compared with psoriasis patients.

**Directions for Future Studies**

COMPASS demonstrates that there is an incremental deleterious effect in patients with PsA beyond that seen in patients with psoriasis, which affects the skin alone. This study on psoriasis and PsA can serve as a model to further explore the role of inflammation and atherosclerosis. Specifically, identification and characterization of the CV biomarkers that exist in this population may allow earlier detection of patients at risk. Better evaluation of risk for premature CV disease in PsA patients may provide opportunities for prevention and lead to insights about CV risk in other patients with chronic inflammatory illnesses.

*Dr. Husni is leading the COMPASS trial at Cleveland Clinic. She is Department Vice Chair for the Arthritis and Musculoskeletal Center and Director of Clinical Outcomes Research for the Department of Rheumatic and Immunologic Diseases. She can be contacted at 216.445.1853 or husnie@ccf.org.*
Case Study: How Musculoskeletal Ultrasonography Clarified a Confusing Case of Elbow Pain and Swelling

By Matthew P. Bunyard, MD, FACR

Presentation
A 60-year-old man presented to Cleveland Clinic’s Rheumatology Clinic with a four-day history of right elbow pain and swelling. His long-term history included episodes of gout every one or two years dating back to 1995. He had a long-standing history of hypertension and had developed chronic kidney disease as a result. He also had been diagnosed with nephrolithiasis.

The patient described his gout attacks as episodes of pain, swelling and redness in the first metatarsophalangeal joint of either foot. These attacks would resolve with indomethacin or prednisone therapy. Over the previous nine months, however, his attacks had become more frequent, and he also began to experience pain, swelling and redness in his knees, hands and elbows. He had been off and on prednisone during these most recent flare-ups, and allopurinol had been added to his regimen approximately three months prior to presentation. He did not believe he had ever undergone arthrocentesis to confirm the presence of crystals.

Evaluation
Examination of the right elbow revealed swelling, warmth and tenderness of the olecranon bursa. The pain had limited his elbow extension by 5 degrees. The rest of the elbow area did not appear swollen.

Aspiration of the olecranon bursa yielded 6 mL of serosanguineous fluid. No crystals were seen, and a Gram stain and culture were negative for bacteria. Serology showed that his WBC count was 7,300 cells/mm³ with 60 percent segmented neutrophils.

The patient was given a presumptive diagnosis of gout and prescribed a tapering regimen of oral prednisone starting at 40 mg/day.

Follow-up
At a return visit three days later, the patient reported only minimal improvement. Findings on physical examination were unchanged except that a new area of swelling, warmth and tenderness appeared on the right posterior arm just proximal to the swelling of the olecranon bursa. His pain on full extension of the right elbow appeared to have increased, and comfortable extension was now limited by 20 degrees.

Evaluation with Musculoskeletal Ultrasound
At this point, musculoskeletal ultrasonography (MSUS) of the posterior right elbow was performed (Figures 1-3), which clearly defined the fluid in the olecranon bursa. No synovial fluid was seen in the true elbow at the olecranon fossa on orthogonal views. However, significant tendonitis was noted at the triceps insertion onto the olecranon process. This was demonstrated by disruption of the distal tendon fibers.
and an increased color power Doppler signal. Intratendinous multilobulated material with mixed echogenicity consistent with gouty tophaceous changes was noted. A repeat aspiration of the olecranon bursa yielded monosodium urate crystals.

At this point, the oral prednisone was continued, and an intrabursal injection of triamcinolone was administered. The elbow was temporarily splinted.

Comment
This case demonstrates the usefulness of MSUS in clarifying a confusing clinical scenario. In this case, MSUS was critical in defining the tendonitis and intratendinous gouty tophaceous material, which had contributed to the patient’s pain and limited the elbow’s motion. Moreover, MSUS also detected the lack of synovial fluid in the olecranon fossa.

Duration of Maintenance Therapy for GPA (Wegener’s): Longer Appears to Be Better
By Jason Springer, MD, and Alexandra Villa-Forte, MD, MPH

A major goal of the management of patients with granulomatosis with polyangiitis (GPA) (Wegener’s) is the prevention of relapses, which have the potential to threaten organ function and even lead to death. This has resulted in the practice of using immunosuppressive medications for the maintenance of GPA remission following induction therapy. Patients frequently ask about the duration of maintenance therapy because of concerns about these medications’ potential long-term side effects. However, there is limited published evidence on how long maintenance therapy should continue.

We recently conducted a retrospective study to assess patient outcomes according to the length of maintenance therapy to sustain GPA remission. We share our results here and discuss their implications for the duration and dosing of maintenance therapy for GPA.

From a Life-Threatening to a Chronic Disease
The prognosis for GPA has changed dramatically over the last 50 years. With current induction strategies using cyclophosphamide (CYC), rituximab (RTX) or methotrexate (MTX), more than 90 percent of patients are able to achieve remission. Once remission is achieved, typically after three to six months of therapy, patients are transitioned to maintenance medications. Both MTX and azathioprine (AZA) have been shown to be effective maintenance agents in prospective studies. With these current treatment strategies, mortality and morbidity have improved and GPA has increasingly become a chronic disease. Yet because these medications can be associated with adverse effects, particularly infections, these effects must be weighed against the medications’ potential benefits.

With this kind of demonstrated potential, MSUS may be the imaging modality of choice for tendon pathology. Its utility is now well supported by published data on ultrasound characteristics of gouty tophaceous changes in articular or periarticular areas.

Dr. Bunyard is Director of Clinical Operations for the Department of Rheumatic and Immunologic Diseases and a rheumatologist in Cleveland Clinic’s Arthritis and Musculoskeletal Center. He can be contacted at 216.445.3460.
Web-Based DXA Registry System Enables Broad Data Capture to Guide Quality Metrics and Clinical Trials

By Chad Deal, MD

Cleveland Clinic is a rich resource for bone density data. In 2009 we started a DXA registry system — a Web-based clinical/research registry into which data are entered for each patient who has a bone density measurement (dual-energy X-ray absorptiometry [DXA] scan). The registry system is automated and incorporated into the DXA workflow; patient demographics appear on the screen for the DXA technician based on schedules in the Epic electronic medical record (EMR) system. The technician completes a short series of questions that include all the risk factors from the World Health Organization’s FRAX® absolute fracture risk model as well as data about the patient's current and past osteoporosis therapies. Completion of the registry questionnaire takes only one to two minutes. Because the data do not exist as discrete elements in the EMR, the registry allows for rapid retrieval of bone density data that would otherwise be difficult to access.

More than 27,000 cases are currently in the registry (Figure). Between 96 and 97 percent of all scheduled patients are successfully registered. We have used the registry system to evaluate treatment status in patients who have a T-score of less than -2.5 and who report taking no osteoporosis medication. When duration of treatment was considered as a continuous variable, longer courses showed an inverse relationship with the risk of relapse (HR = 0.70 [95% CI, 0.58-0.84], P < .001), which remained significant even after adjustment for prednisone dose (HR = 0.59 [95% CI, 0.42-0.83], P = .003).

Among patients who continued AZA or MTX for longer than 18 months, 90 percent of the relapses occurred after they stopped maintenance therapy. This is consistent with a prior study demonstrating a high relapse rate after discontinuation of maintenance therapy.1 Of patients taking MTX or AZA at relapse, 52 percent were taking less than 15 mg/week of MTX, and 67 percent were taking less than or equal to 50 mg/day of AZA. There were no differences between the groups in overall adverse events or GPA-related morbidity.

Lessons for Clinical Practice

Physicians and patients frequently discuss the possibility of stopping maintenance medications following long periods of sustained remission, especially if patients have never had a relapse. However, GPA characteristically has a relapsing course, and results from our study support continuation of maintenance medications for at least 36 months. When possible, clinicians should strive to use maintenance medications at doses used in clinical trials (at least 15 mg/week for MTX and approximately 2 mg/kg for AZA). Lower doses are associated with a higher risk of relapse, as demonstrated by our data.

Reference


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Recent work by Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases is demonstrating that the practice of biobanking research specimens holds promise for driving rich discoveries. Our Psoriatic Disease Biobank was born in part as a result of a recent translational research grant from the National Psoriasis Foundation. As a large-scale effort to standardize collections and annotations of research samples, it requires both proper funding and a dedicated multidisciplinary team of clinicians, research coordinators, research administrators, statisticians, bioinformaticians and tissue resource managers.

**The Biobank at a Glance**
A biobank, also known as a biorepository, stores biological samples such as blood, urine and tissue (skin, etc.) collected from patients for future scientific and medical research. The Psoriatic Disease Biobank is both a biorepository for blood and urine specimens and a database of clinical information that includes family history, comorbidities, medications, disease activity and quality-of-life measures. Since November 2010, more than 150 patients have consented to participate in the biorepository and have provided rich clinical data along with samples of blood and urine. Our goal is to recruit 300 subjects who will each provide blood and urine samples on an annual basis for five years, for a total of approximately 3,000 samples of blood and urine.

**Why Biobanking Makes Sense in Psoriatic Disease**
Psoriatic diseases comprise a spectrum of chronic immune-mediated disorders that can affect the skin alone (psoriasis) or the skin and joints (psoriatic arthritis). They are extremely heterogeneous disorders, with extra-articular and dermatologic manifestations such as dactylitis, enthesitis, nail changes, and (more uncommonly) spondylitis and arthritis mutilans.

The National Institutes of Health estimate that as many as 7.5 million Americans are living with psoriasis; psoriatic arthritis affects one-third of these patients. Because there is no known cure, undertreatment of psoriatic disease is a huge burden to society in terms of healthcare costs and loss of economic productivity as well as the significant impact on patients’ quality of life. There is thus a great need to advance scientific investigation of the complex cellular and genetic relationships involved in psoriatic disorders, as new discoveries may directly impact how we diagnose and treat psoriatic arthritis and its associated illnesses.

Psoriatic diseases may be associated with comorbid disorders such as obesity and cardiovascular disease. Given that psoriatic arthritis and cardiovascular disease are both linked to inflammatory processes, we hypothesize that patients who suffer from psoriatic arthritis have greater inflammatory burden than those who suffer from psoriasis alone.

The ability to integrate bioinformatics on both clinical data and biospecimens holds the promise of advancing our knowledge of the development of psoriatic disease and its comorbidities, which may translate into better prevention and treatment strategies.

**Collaboration Is Critical**
Biobanking gives researchers access to large numbers of individual samples. Current research practice makes it desirable for collaborating institutions to share and exchange samples, enabling them to progress from being single-center research groups to integral parts of a next-generation multicenter quantitative research infrastructure.

Cleveland Clinic’s Department of Rheumatic and Immunologic Diseases is excited to be collaborating with multiple partners to expand our biorepository. These partners include our colleagues in Cleveland Clinic’s Preventive Cardiology Program as well as the Department of Dermatology at Case Western Reserve University and Brigham and Women’s Hospital at Harvard Medical School. The goal of this collaboration is to develop a research infrastructure that will accelerate collection of biosamples and clinical data for discoveries. At the same time, such collaboration can bring logistical and financial challenges. Reducing barriers to expansion is key to promoting collaboration in the research community. We recognize that consolidating tasks and reducing duplication will lower manual labor costs and can accelerate the timeline to data analysis and new discoveries.

Sharing samples leads to sharing ideas. This, in turn, leads to the expansion of knowledge and the opportunity to prove theories and perhaps change the way we deliver healing to our patients. Cleveland Clinic researchers are committed to building bridges to facilitate the establishment of best practices and standardization for biobanking.

**Dr. Husni directs the Psoriatic Disease Biobank. She is Department Vice Chair for the Arthritis and Musculoskeletal Center and Director of Clinical Outcomes Research for the Department of Rheumatic and Immunologic Diseases. She can be contacted at 216.445.1853 or husnie@ccf.org.**

A few members of the Psoriatic Disease Biobank’s multidisciplinary team.
Patients with inflammatory myopathies (polymyositis and dermatomyositis) can suffer significant morbidity and even death from pulmonary complications. In these patients, the etiology of dyspnea is multifactorial, as it could result from interstitial lung disease (ILD), hypoventilation and recurrent aspiration pneumonias. Hypoventilation arises from diaphragmatic and intercostal muscle weakness. Involvement of the striated muscles of the upper esophagus, cricopharyngeus and hypopharynx makes these patients susceptible to aspiration pneumonias. The increasing recognition of pulmonary involvement in inflammatory myopathies (IM) may be partly attributed to improvement in screening modalities and increased physician vigilance as manifested by screening of all patients newly diagnosed with myositis.

Although pulmonary hypertension (PH) has been associated with other autoimmune rheumatic diseases such as scleroderma, lupus, mixed connective tissue disease and Sjögren syndrome, it has not been a well-recognized cause of morbidity and mortality in patients with IM. For this reason, routine screening of IM patients for PH (at diagnosis and periodically thereafter) has not been considered the standard of care. To assess the potential utility of such screening, we conducted a retrospective chart review of patients with IM from our clinical database at Cleveland Clinic to determine the prevalence of PH in this population.

**Our Study Design**

Our retrospective review included approximately 450 patients with a confirmed IM diagnosis seen at Cleveland Clinic between January 2003 and December 2010. PH was “suspected” in this cohort based on transthoracic echocardiography (TTE) (Figure 1) and was “confirmed” by right heart catheterization (RHC) criteria in a subset of these patients. Because the diagnosis of PH should never be established without an RHC, our primary interest was in the subset of patients whose diagnosis was confirmed by RHC. A diagnosis of ILD in these patients was based on a high-resolution thoracic CT scan, but not on spirometry, because a reduction of forced vital capacity could also result from respiratory muscle weakness. The prevalence of PH in this cohort was compared with the population prevalence of idiopathic PH and with the prevalence of scleroderma-associated PH. The primary outcome was mortality. Clinical and demographic factors were analyzed separately based on the presence or absence of concomitant ILD.

**Our Findings: PH Prevalence Is Elevated in Patients with IM**

Among all patients with IM who were evaluated, 16 percent were suspected of having PH based on TTE, and the diagnosis was confirmed by RHC in 7 percent of patients (Figure 2). Of the latter group, 22 percent had isolated PH confirmed by RHC (Dana Point 2008 classification: group 1 [pulmonary arterial hypertension associated with connective tissue diseases]) (Figure 2). The prevalence of isolated PH confirmed by RHC was significantly higher than the population prevalence of idiopathic PH.
Prevalence of Pulmonary Hypertension in Inflammatory Myopathy: Comparison with Prevalence in Other Settings and Implications for Screening

By Ashwini Mhatre Punjabi, MD, MS, and Soumya Chatterjee, MD, MS, FRCP, FACP, FACR

PH (P < .001). The remaining 78 percent of patients with RHC-confirmed PH had concomitant ILD (Dana Point 2008 classification: group 3 [PH associated with ILD]). None of the patients in either group had exercise-induced PH. At the time of our analysis, 70 percent of patients were alive. Survival was independent of the presence of ILD and the use of immunosuppressive and vasoactive therapies.

Perspectives and Limitations
This study was an earnest attempt to systematically estimate the prevalence of PH in IM for the first time. It should be noted, however, that there was uncertainty about the estimates due to the study’s retrospective nature and the lack of a standardized, accepted approach for comprehensively evaluating IM patients for PH. Nevertheless, there is merit in the available information.

Curiously, none of the patients in our cohort had significant left heart disease (left ventricular systolic or diastolic dysfunction on TTE). Therefore, there was no evidence of group 2 disease (PH owing to left heart disease, Dana Point 2008 classification1) in our cohort.

Certain additional aspects of our analysis could limit the generalizability of its results. Because this study was conducted at Cleveland Clinic, a tertiary care referral center, a selection bias is possible. The true prevalence of PH in IM patients in the community might be different. Since this was a retrospective study, not all IM patients had a routine screening TTE, which may have caused us to miss subjects who might have had PH but did not undergo any workup for its evaluation. So the prevalence of PH in our study was likely underestimated. Moreover, not all patients with suspected PH on TTE underwent RHC, which is the gold standard for confirming a PH diagnosis. Still, the prevalence of PH in our cohort (confirmed by RHC) was significantly higher than the population prevalence of idiopathic PH and thus not attributable to chance alone.

Conclusions
This study, the first to systematically evaluate the association of PH with IM, indicates that PH can develop in the setting of IM (with or without concomitant ILD) similar to the way that it does in other autoimmune rheumatic diseases where the association is well recognized. In our cohort, PH seemed to be an independent contributor to the pulmonary manifestations of IM and an important determinant of prognosis and survival in these patients. Our observation that isolated PH can occur in patients with IM was particularly interesting and not previously well recognized.

If early diagnosis and early initiation of vasoactive therapies are found to alter the natural history of IM-associated PH (which is not proven at this time), then our results suggest that routine screening of IM patients for PH at diagnosis and periodically thereafter may be worthwhile. Further research is warranted to evaluate the outcome of early intervention with novel vasoactive medications in these patients.

Reference

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Treatment with high-dose glucocorticoids and cyclophosphamide (CYC) is an effective therapy for patients with severe granulomatosis with polyangiitis (GPA) (Wegener’s). However, CYC use is associated with several adverse effects, including infection, malignancy and hematologic or bladder toxicities. Leukopenia is one of the most common adverse effects of CYC and typically occurs 10 to 14 days after the oral CYC dose. Patients may be more predisposed to leukopenia from CYC use if they have been subjected to multiple previous courses of CYC therapy or have been exposed to CYC for prolonged periods in the past. Concomitant glucocorticoids can confound the quantitative as well as immunologic assessments of WBCs in patients with GPA.

Severe infection is the most dreaded consequence of leukopenia (especially neutropenia). Notably, a recent meta-analysis of the trials conducted by the European Vasculitis Group showed that 50 percent of the reported first-year mortality in patients with GPA was attributable to infection vs. only 14 percent attributable to active vasculitis.¹ Half of these infections occurred in the first two months, which is when patients are most likely to be on induction therapy with a combination of CYC and high-dose glucocorticoids.

**How Often to Monitor for Leukopenia?**

Serious adverse outcomes of leukopenia, including sepsis and potentially death, can very likely be prevented with appropriate monitoring. However, there are no standardized recommendations for WBC monitoring while patients are on CYC therapy. In addition to the serious medical implications of suboptimal WBC monitoring, there are serious potential cost implications of missing the opportunity to intervene for leukopenia. These cost implications range from development of non-life-threatening infection requiring treatment with antibiotics to life-threatening sepsis requiring intensive care and with a serious impact on quality of life. At Cleveland Clinic’s Center for Vasculitis Care and Research, we check the CBC weekly for the entire time that patients are on CYC. To assess the potential merits and drawbacks of this approach, we undertook a study to compare the cost-effectiveness of two CBC monitoring strategies — weekly vs. monthly — for surveillance of leukopenia and its consequences in patients treated with CYC for severe GPA.

**Cost-Effectiveness Methodology**

For the weekly CBC monitoring arm, we used Cleveland Clinic’s GPA database, which includes patients with GPA referred to and managed at Cleveland Clinic between 1992 and 2004. For the monthly arm, we used published studies from the literature involving patients with GPA who received oral CYC or both oral and intravenous CYC. For studies with patients on both oral and intravenous CYC, only data regarding the oral CYC group were used for analysis.

The two CBC monitoring approaches were compared using a decision analysis model (TreeAge Pro™ software) (Figure 1) and a societal perspective. The willingness-to-pay threshold was set at $50,000. The selected studies were carefully screened for the following: strategy for monitoring CBC, incidence of leukopenia (severe and nonsevere), incidence of infectious complications (severe and nonsevere) and mortality attributable to infection. For our analysis, leukopenia was defined as a WBC count less than 4,000/mm³ and severe leukopenia as a WBC count less than 2,000/mm³. The prevalences of leukopenia, infections and outcomes were obtained from an existing registry and published reports. Costs were in 2010 dollars, and effectiveness was defined as quality-adjusted life-years (QALYs) gained, which is a measure of disease burden reflecting both the quantity and quality of life lived.

After the probabilities, costs and estimates of QALYs were entered into the decision tree, an initial rollback analysis was performed, followed by a cost-effectiveness analysis and then by a one-way deterministic sensitivity analysis for each variable in the decision tree. Finally, a probabilistic sensitivity analysis (Monte Carlo simulation) was performed.

**Results: Weekly Dominates Monthly**

Demographic data were available for 131 patients — 62 females (47 percent) and 69 males (53 percent) — from Cleveland Clinic’s GPA database (weekly CBC arm). The frequencies for variables in the monthly CBC arm were derived from a literature review. The frequency of severe infection given severe leukopenia was 3 percent in the weekly CBC arm compared with 10 percent in the monthly CBC arm. Our results showed that the expected utility of weekly CBC monitoring for leukopenia in these patients was 18.74 QALYs, as compared with 18.52 QALYs for monthly CBC monitoring (Figure 2).
Weekly CBC monitoring yielded an expected gain of 0.22 QALYs and incurred $489 less in cost per patient compared with monthly monitoring. We therefore concluded that weekly CBC monitoring is cost-effective for prevention of severe leukopenia and severe infections in patients on daily CYC for severe GPA.

Although measuring WBC counts allows us to assess only one facet of the effects of CYC on leukocytes, it is a practical and economically feasible testing strategy. It is important to remember that glucocorticoid use also should be factored into the analysis, since glucocorticoids have qualitative and quantitative effects on leukocytes and patients are also on high doses of glucocorticoids during the induction phase of treatment for GPA. Likewise, it is important to remember that there are indirect consequences of severe infections beyond hospitalization, such as the morbidity that can occur after such events, and that these can have significant impact on patients’ quality of life.

Reference

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Case Presentation
You are asked to see a hospitalized 79-year-old male who was just diagnosed with granulomatosis with polyangiitis (Wegener’s) (GPA). His disease features include pulmonary infiltrates, glomerulonephritis with a creatinine level of 2.5 mg/dL, episcleritis, positivity for proteinase 3-cANCA and a renal biopsy demonstrating a pauci-immune crescentic glomerulonephritis. His past medical history is notable for hypertension, chronic obstructive pulmonary disease and prostatic enlargement with large post-void residuals.

This patient’s case raises the following questions:

• How does age affect disease presentation and outcome in GPA?
• What impact does age have on treatment decisions and monitoring?

GPA: Disease-Related Ramifications in Older Patients
Although giant cell arteritis remains the vasculitic disease most commonly seen in geriatric patients, it is not uncommon for many forms of vasculitis to present after age 65. As illustrated by this case, GPA can occur in the later years of life, with series from the United Kingdom demonstrating onset peaking among individuals aged 65 to 74 years.

Establishing the diagnosis of GPA can be complex in older patients, in whom the potential for infection and neoplasm plays an even larger role in the differential diagnosis of many features. The presence of comorbid diseases frequently affects the symptoms and signs with which older patients may present. These comorbidities can also influence the recovery potential of organs as well as treatment decisions.

Age and degree of renal impairment have been associated with unfavorable outcomes. While this should not be interpreted to mean that older patients with GPA uniformly fare poorly, it highlights the need to employ strategies to minimize adverse events, many of which are related to treatment.

How Does Older Age Impact Treatment Decisions and Monitoring?
There are no differences in the medications used to treat GPA in older vs. younger adults. However, complete care of the patient with GPA must take into account how factors common to advanced age may affect treatment and outcome. This includes the risk of infection seen with all immunosuppressive therapies as well as medication-specific issues.

Infection and immunization. Infection is the primary cause of death in older patients with GPA. Discussion of infection symptoms with patients and their families is important, as it increases the likelihood of rapid reporting and intervention should infection occur. Bacterial infections most commonly include pneumonia, sepsis and urinary tract infections. Pneumocystis jiroveci is an important opportunistic pathogen associated with a high mortality rate. All patients with GPA receiving an induction regimen should receive prophylaxis against P jiroveci, which ideally consists of trimethoprim/sulfamethoxazole in patients without sulfa allergies.

In older patients, maintaining up-to-date immunizations is important, particularly against pneumococcal infections and influenza. Because the herpes zoster vaccine, zoster vaccine live (Zostavax®), is a live attenuated vaccine, it is contraindicated in immunosuppressed patients with GPA. It is important to recognize that patients with GPA receiving immunosuppressive therapies have an increased risk of developing zoster. Should zoster develop, antiviral therapy should be initiated immediately (with dosage adjustment as needed) to minimize the likelihood of dissemination or complications.

Additional risks from glucocorticoids. Falls are an important cause of morbidity and mortality in older patients. Prednisone can contribute to an increased risk of falls through cataract formation, which affects visual acuity, and proximal myopathy, which can compromise mobility. Patients should undergo a regular assessment of muscle strength at clinic visits, which should also include a review of strategies to prevent falls, in some instances supplemented by an in-home assessment.
Prednisone-induced bone loss can intensify the risk of both fall-related and insufficiency fractures. Because older patients may already have bone loss before starting prednisone, densitometry should be obtained early in treatment and every one to two years thereafter. Proactive measures to protect bone health are essential and include assessment of calcium intake, measurement of vitamin D levels, a patient-appropriate exercise program and pharmacologic therapy to correct or prevent bone loss.

Prednisone can induce diabetes or complicate glucose management in existing diabetes and can also increase blood pressure. Older patients may be particularly sensitive to the neurocognitive effects of prednisone, which can include mood swings, memory impairment and even psychosis — all of which can compromise patient safety.

**Induction treatment.** Whether to use cyclophosphamide or rituximab for remission induction in newly diagnosed severe GPA is an important decision in patients of all ages. Although cyclophosphamide should continue to be viewed as a valid and appropriate treatment option for older patients, several considerations should be factored into how to most safely use this medication in these individuals.

With both daily and intermittent cyclophosphamide, bone marrow sensitivity — with the attendant risk of cytopenias — plays a role in toxicity for the older patient. In many instances, a lower starting dose of cyclophosphamide may be appropriate to assess the effects on blood counts. The recommendation that all patients treated with cyclophosphamide undergo blood count monitoring every one to two weeks has particular importance in geriatric patients. In addition to concerns regarding white blood cell and platelet counts, the red blood cell count may have greater significance in older adults, especially those with heart or lung disease, who may tolerate anemia poorly.

For patients receiving daily cyclophosphamide, effective urinary elimination of toxic metabolites is critical in order to minimize urothelial injury. Patients with urinary retention are at higher risk of hemorrhagic cystitis with cyclophosphamide, so this may be a setting in which rituximab is favored.

Older patients may also have received past treatment for solid or hematologic neoplasms. For such patients, cyclophosphamide poses concerns in terms of potential bone marrow effects and reduction of host surveillance. Recent guidelines for rheumatoid arthritis have favored rituximab as a choice for patients with past neoplasms who require biologic therapy, although any extrapolation of this recommendation to GPA must be considered with caution.

Methotrexate may be another option for remission induction in GPA patients who do not have severe disease and are able to take this agent despite the precautions discussed below.

**Maintenance therapy.** Azathioprine, methotrexate and mycophenolate mofetil are the primary agents used for remission maintenance in GPA. With all three medications, laboratory monitoring should be performed every one to two weeks for the first month of therapy and monthly thereafter. Methotrexate is contraindicated in patients with renal insufficiency, and it must be prescribed only after careful assessment of the patient's reliability in taking medications, as life-threatening toxicity can occur if this agent is taken more than once a week.

The optimal duration of maintenance therapy is unclear. Because the desire to avoid relapse and the associated requirement for high-dose prednisone may be particularly important in older individuals, continuation of maintenance therapy for longer durations should be considered in the absence of side effects.

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**Case Continued**

After careful discussion, our case patient elected to receive rituximab because of his significant urinary retention. His course was complicated by a urinary tract infection that was successfully treated and a rise in blood pressure requiring adjustment of his medications. He experienced some proximal weakness with prednisone but was able to remain ambulatory with physical therapy and appropriate assistive devices. With treatment, his renal function improved to his prior baseline of 1.8 mg/dL and his pulmonary infiltrates cleared. Although he has had to cut back on some activities, he and his family are very pleased with his level of functioning, and he maintains a good quality of life.

**Summary**

As this case illustrates, GPA is a treatable disease, and excellent outcomes can be achieved in people of all ages. In older patients, outcome is influenced by comorbid illnesses and an enhanced risk for medication toxicities. Recognition of these issues, proactive monitoring and patient education all play an important role in optimizing the potential for recovery in geriatric patients with GPA and all forms of vasculitis.

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