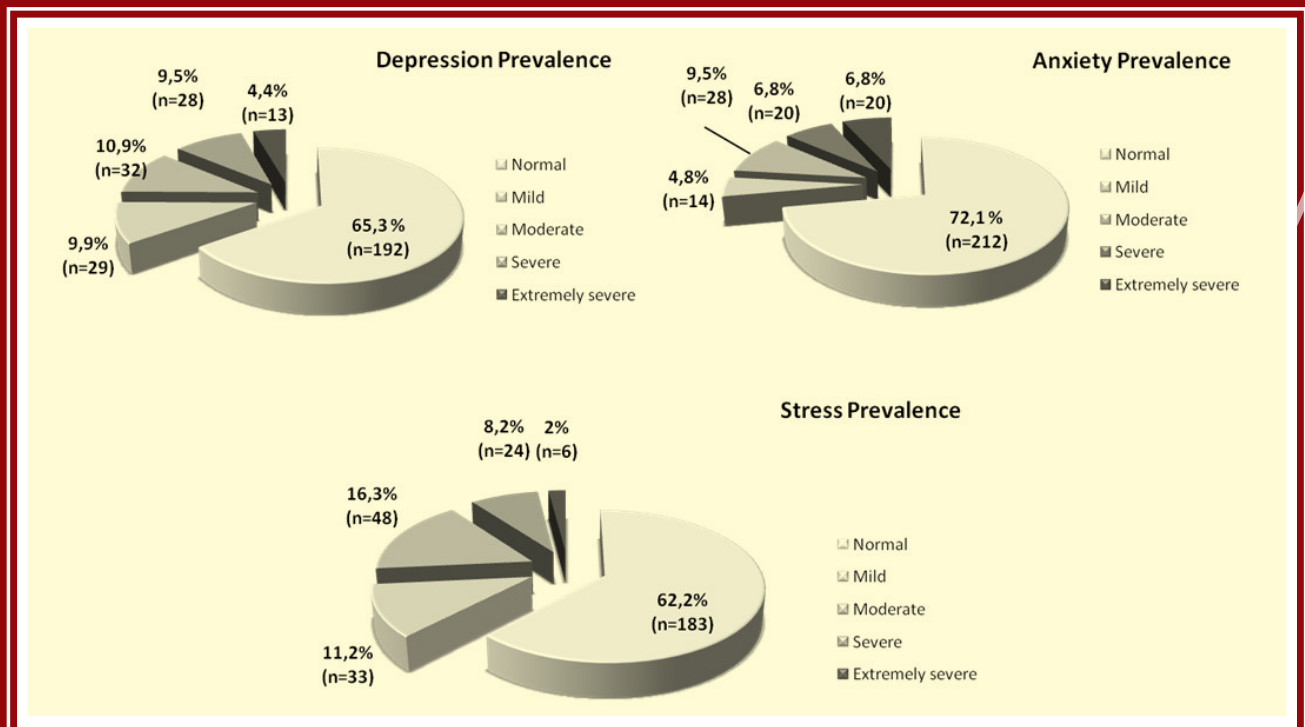




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Prevalence of Depression, Anxiety and Stress in Piraeus residents assessed by DASS-21 (n=294)

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Dear colleagues,

In the current issue, the editorial by Liossis et al. critically discusses the recent data on the severe manifestation of systemic lupus erythematosus, the lupus nephritis, with a special focus on the need to perform a renal biopsy or not. The second editorial, by Zygomalas et al. explores the multifaceted role of artificial intelligence in modern surgery, investigating the theoretical underpinnings and the practical applications across clinical settings. In addition, it discusses future perspectives that hold the promise of revolutionizing surgical practices.

Moreover, this issue includes two original research articles. The original research article by Sakaretsanou et al. assesses the challenges faced by humanitarian aid workers operating in Greece during the COVID-19 pandemic and in parallel discusses feasible solutions to mitigate these challenges. The original research article by Sourgiadaki et al. explores the effect of active musical engagement on the mental health including stress, anxiety, and depression of residents in the region of Piraeus, Greece. Moreover, it correlates and quantifies

the time spent on musical engagement in relation to the reduction or non-reduction of daily anxiety, stress, and depression, according to the participants' subjective opinion.

Lastly, this issue includes two review articles. The first review, by Lykoura et al. highlights the main aspects of the diagnostic approach and treatment of antiphospholipid syndrome in everyday clinical practice of internal medicine physicians. Lastly, the review by Iliopoulos et al. provides the current knowledge concerning the understanding of gout epidemiology, the basic pathophysiology features, as well as the management and follow-up.

Yours sincerely,

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Lupus nephritis: To biopsy or not to biopsy

Stamatis-Nick C. Liossis^{1,2}, Chrysanthi Staveri²

INTRODUCTION

Lupus nephritis (LN) is a severe manifestation of systemic lupus erythematosus (SLE) with significant morbidity and mortality. LN is clinically evident in 50% - 60% of patients with SLE, but histologically evident in the majority of lupus patients. Regular monitoring of kidney function and urinalysis are crucial, because early diagnosis and intervention in LN may improve renal survival.

The traditional approach when a patient with SLE presents with proteinuria, worsening renal function and / or hematuria with or without red blood cell casts, is to perform a kidney biopsy.

To biopsy

Studies have demonstrated that SLE patients with low levels (< 1g) of proteinuria or even without evidence of kidney involvement may indeed have mild or even severe LN [1]. Based on these observations, the European League Against Rheumatism/European Renal Association-European Dialysis and Transplant Association [EULAR/ERA-EDTA] and the American College of Rheumatology (ACR) strongly suggest performing a renal biopsy in patients with SLE who develop at least 500mg/24h proteinuria. However, some authorities have suggested that renal biopsy indications should be expanded to include even lower grades of proteinuria overcoming this selection bias [2].

A patient with SLE that develops kidney disease may not necessarily have LN, and other, more or less common etiologies might be responsible for renal disease. To this end, a kidney biopsy certainly serves a good purpose for the differential diagnosis of kidney involvement in pa-

tients with SLE. Cases of non-immune complex-mediated glomerulonephritis have been reported in patients with SLE [3]. Although focal segmental glomerulosclerosis was the most common finding, other entities such as thin basement membrane disease, amyloidosis, IgM nephropathy and renal thrombotic microangiopathy have also been reported. It is straightforward that patients with SLE and comorbidities, such as diabetes mellitus or arterial hypertension, may also develop lupus-unrelated renal disease.

A renal biopsy may prognosticate the long-term renal function, even though studies have shown that the risk of end stage renal disease (ESRD) is as high as 26% after 15 years in patients with LN, despite successful management. ESRD risk is higher in patients with class IV LN, but lower in patients with class V LN (15-year risk: 44% and 20%, respectively). A study demonstrated a significant association between a chronicity index ≥ 5 and the existence of cellular crescents in $\geq 30\%$ of the glomeruli (in a repeated renal biopsy) with a persistent doubling of serum creatinine level in patients with LN with a median follow-up of 10.5 years [4]. It is generally believed that the chronicity but not the activity index is well-correlated with long-term renal function prognosis.

Kidney biopsy results can also guide treatment decisions. It is only with the use of a kidney biopsy that class switching, a less common occurrence during flares, can be identified. Pathological class transformation during renal flares was found to be more frequent in patients with non-proliferative LN (class II and V) compared to those with proliferative LN (class III and IV) in their initial kidney biopsy [5]. Thus, repeat kidney biopsies during LN flares may result in a modification of the immunosuppressive treatment employed, either by strengthening it in the majority of patients, or less frequently by reducing it.

Key words: *Kidney biopsy; systemic lupus erythematosus; lupus nephritis*

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Not to biopsy

It has been proposed that induction treatment with mycophenolate mofetil (MMF) should not be delayed until the kidney biopsy results are available, because the majority of patients with lupus nephritis respond to this standard therapy [6]. Thus, it could be suggested that a renal biopsy might be performed only in patients that do not respond to the initial standard-of-care treatment.

Sometimes the kidney tissue obtained through a kidney biopsy is inadequate, causing difficulties and delays in the management of patients with kidney disease. An analysis of a total of 123,372 renal biopsies performed by more than 2500 nephrologists in the US illustrated a significantly increased miss rate from 2% in 2005 to 14% in 2020 [7]. The miss rate was reportedly markedly lower for nephrologists compared to radiologists. It is however disappointing that the operator gain of experience does not improve over time.

A renal biopsy is a procedure that is not devoid of risks. An analysis of 5304 kidney biopsies revealed 400 major adverse events in 273 patients (5.1%) [8]. The most frequent was a $\geq 2\text{g/dL}$ reduction of hemoglobin levels. Less frequent events include: macrohematuria, red blood cell transfusion, clinically relevant hematoma, arteriovenous fistula and the need for an invasive post-biopsy procedure. Risk factors associated with a higher bleeding risk included: increased serum creatinine levels, liver disease, a higher number of needles passes and lower levels of proteinuria.

The purpose of histological classification of LN is to treat patients according to the results of a renal biopsy. However, the distinction between focal (e.g., 45% of glomeruli affected) vs. diffuse glomerulonephritis (e.g., 55% of glomeruli affected) should probably not raise major concerns regarding our therapeutic decisions. Furthermore, neither worsening of renal function, or improvement, or even stabilization, seem to be different in patients with segmental vs. those with global proliferative LN [9]. In addition, repeat renal biopsies failed to demonstrate differences between patients with LN receiving azathioprine and those receiving the standard-of-care MMF as a maintenance therapy [10].

Another potential disadvantage of the histologic LN classification is that the currently used classification does not include tubulointerstitial lesions that may exist independently of the glomerular involvement in patients with LN. This is important, because the degree of interstitial inflammation has been reported to be strongly correlated with the rate of worsening of renal

function [11]. Moreover, the risk of ESRD is higher in patients with interstitial fibrosis and tubular atrophy compared to those without [12]. Histological evidence of vascular injury has also been reported to be associated with ESRD risk, even though this association was poor in cases of proliferative LN.

As stated above, the results of a baseline renal biopsy may not be the gold-standard to predict the long-term renal outcome. A novel biopsy index consisting of a Glomerular Activity (GAI), Tubulointerstitial Activity (TIAI), Immunofluorescence (IFI), and Chronic Lesion (CL) indices has been developed, exhibiting better correlations with long-term renal outcome parameters compared to the widely used National Institutes of Health Activity and Chronicity Indices (AI and CI) [13]. According to the results, neither the standard AI and CI, nor the overall biopsy index was found to be predictive for the doubling of serum creatinine 10 years later.

A disappointing discordance between clinical renal responses and histological responses, as seen in renal biopsies performed at six months or even at 40 months after induction treatment, has been demonstrated in several studies [14,15]. It is not unusual that histological activity may persist despite complete clinical renal remission, and conversely, clinical disease activity may persist when there is no evidence of histological activity.

Novel non-interventional approaches

Dealing with the need for a regular assessment and re-assessment of the LN response to treatment, non-invasive approaches of the renal pathology are needed and are currently under investigation. Single and panel biomarkers reflecting underlying renal pathology are summarized in Table 1.

Liquid biopsy is another promising approach employed to overcome the handicaps of a renal biopsy. Liquid biopsy is non-invasive compared to the renal biopsy procedure. Test results of a liquid biopsy could be typically available much earlier than those of renal biopsy histology. The ease in frequency of a liquid biopsy offers an important advantage over the standard kidney biopsy. Furthermore, a liquid biopsy is not associated with adverse events and is usually much less costly than a standard renal biopsy.

Long non-coding RNAs (lncRNAs) regulating the expression of different genes are stable molecules found in human plasma. Transcriptomic analysis of blood samples of patients with LN identified lncRNAs as potential biomarkers of disease activity [18]. Machine-learning

Table 1. Biomarkers reflecting kidney pathology in patients with LN.

			References
Urine biomarkers			
VCAM-1	Associated with AI Increased in class IV LN	P = 0.05 P = 0.02	[21]
CXCL-16	Increased in class IV LN	P = 0.04	[21]
miR-29C	Inversely correlated with CI	P = 0.001	[22]
Angiostatin	Differentiates active from inactive LN	P < 0.0001	[23]
Citrate	Higher concentrations in Class III and IV, lower in Class V LN	P < 0.05	[16]
Taurine	Absent in class III or IV LN, but normal in class V LN	P < 0.01	[16]
Serum biomarkers			
Anti-C1q autoAbs	Associated with necrosis and crescents	Negative predictive value 100% for necrosis and 86% for crescents	[24]
Panels			
sCr + uMCP1	Associated with different levels of interstitial inflammation	Negative predictive value 100%	[17]
uCP + PCR	Associated with different levels of interstitial fibrosis	Negative predictive value 85%	[17]
MCP1 + AAD + CP + PCR	Differentiates an AI <7 from an AI ≥7	AUC = 0.85	[17]
MCP1 + NGAL + GFR	Discriminates a CI < 4 from a CI ≥4	AUC = 0.83	[17]
MCP1 + AAG + GFR + C4	Diagnostic for membranous LN	AUC = 0.75	[17]

Abbreviations: VCAM-1: vascular cell adhesion molecule-1; CXCL16: chemokine (c-x-c motif)ligand 16; sCr: serum creatinine; anti-C1q autoAbs: autoantibodies against complement component C1q; AAG: α (1)-acid glycoprotein; NGAL: neutrophil gelatinase-associated lipocalin; uMCP-1: urine monocyte chemotactic protein 1; uCP: urine ceruloplasmin; GFR: glomerular filtration rate; PCR: protein: creatinine ratio; C4: complement component 4; AI: activity index; CI: chronicity index; LN: lupus nephritis; AUC: area under the curve.

analysis of a large whole blood RNA-sequencing dataset of patients with SLE (employing murine kidney-specific genes as disease predictors) helped to discriminate SLE patients with LN from those without LN [19]. Proteome analysis in urine samples revealed proteins that are specifically increased in patients with SLE compared to healthy individuals. Further attempts aim to illustrate potential associations of such proteins with proteinuria as well as with a prediction of a response to treatment agents employed [20].

CONCLUSION

In conclusion, it has been suggested that the everyday clinical practice strategy of MMF or low-dose intravenous cyclophosphamide administration as the initial treatment of proliferative and membranous LN,

might limit the necessity for the results of a renal biopsy as the leading option among the therapeutic decisions in patients with LN. The results of a renal biopsy are of limited value in assessing a treatment response and may not predict accurately enough the long-term renal survival. Some authors have proposed omitting a baseline biopsy, initiating standard-of-care- treatment and performing a kidney biopsy later on, to assess the response to treatment. Finally, less invasive strategies are under development and evaluation, based on the isolated or the combined use of circulating and/or urinary biomarkers in order to replace the invasive renal biopsies, allowing in addition for a close monitoring of LN activity and disease progression.

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The role of Artificial Intelligence in modern surgery

Apollon Zygomalas^{1,2}, Dimitris Kalles², George Skroubis^{2,3}

INTRODUCTION

Modern medicine is undergoing a profound transformation, with the advent of Artificial Intelligence (AI) ushering in an era of unprecedented possibilities. More than any other domain, this transformation is evident in surgery. Artificial Intelligence, with its capabilities in data analysis, pattern recognition, and machine learning, is rapidly becoming a dynamic partner for surgeons, redefining the boundaries of what is achievable within the operating theater.

Historically, surgery has always demanded a delicate blend of art and science, with the human surgeon at its epicenter. The surgeon's expertise, intuition, and dexterity have been the driving forces behind surgical advancements. However, the limitations of the human eye, hands, and mind have naturally imposed constraints on the precision, efficiency, and outcomes of surgical procedures. This is where AI steps in as a transformative force, augmenting the capabilities of surgeons and pushing the boundaries of what was once deemed impossible.

This editorial explores the multifaceted role of AI in modern surgery, investigating the theoretical underpinnings, the practical applications across clinical settings, and a discussion of the future perspectives that hold the promise of revolutionizing surgical practices for years to come.

Theoretical Foundations

AI refers to the simulation of human-like intelligence in machines and software. It encompasses a wide range of technologies and techniques that enable computers to perform tasks typically requiring human intelligence, such as learning from data, recognizing patterns, making decisions, and solving complex problems [1]. Today, the most successful AI systems are based on artificial neural networks. A neural network is a computational model inspired by the structure and functioning of the human brain. It consists of layers of interconnected nodes, each simulating a neuron. The number of neurons in an AI system can vary widely. In some simple AI models, there may be just a few hundred or thousand neurons, while in more advanced AI systems, intense learning models used in tasks like natural language processing or computer vision can have millions or even billions of neurons [1,2].

The theoretical foundations of AI in surgery are built upon principles of machine learning, computer vision, and data analysis. Machine learning algorithms enable computers to learn from surgical data and medical records, aiding in decision support and predictive modeling. Computer vision allows AI systems to interpret and analyze surgical images and videos, while data analysis helps extract meaningful insights from vast medical datasets, ultimately enhancing surgical precision and patient outcomes.

Clinical Applications

Image Analysis

AI-driven image analysis is crucial in surgery, offering precise insights and decision support tools mainly

Key words: *Artificial intelligence; surgery; image analysis; computer vision; predictive analytics; decision support*

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in the preoperative setting. The primary application of AI is the interpretation of medical images, such as magnetic resonance imaging (MRI), computed tomography (CT) scans, PET scans and X-rays [3,4]. AI algorithms can accurately identify and classify abnormalities like tumors, anatomical variants, or vascular anomalies. This accelerates the diagnosis process and assists surgeons in developing tailored treatment plans, ensuring more effective and personalized patient care.

Regarding intraoperative image analysis, AI can be used for Real-time Monitoring. AI systems can continuously analyze data from intraoperative X-rays, ultrasound devices or other imaging sources like head-mounted cameras, fluoroscopy, etc., enabling real-time feedback [5]. Special algorithms process the images in real time to enhance their quality, making it easier for surgeons to discern fine details and structures. This aids in accurate navigation during surgery. Systems can detect anomalies or unexpected changes like bleeding, tissue damage or the displacement of critical structures in real time, providing immediate alerts to the surgical team. In oncological surgeries, AI can help surgeons identify tumor margins in real time, ensuring that all cancerous tissue is removed while preserving healthy tissue. Augmented reality (AR) systems, backed by AI, can merge radiological images with the surgeon's view, allowing for real-time superimposition of critical information directly onto the surgical field.

An exciting development of AI in image analysis is the field of radiomics. Radiomics involves extracting many quantitative features from radiological images often imperceptible to the human eye. Radiomics relies on advanced image processing techniques and machine learning algorithms [6]. It has the potential to revolutionize how medical imaging data is used to make diagnostic and therapeutic decisions, offering a more detailed and personalized approach to patient care [7].

Computer vision

Computer vision is an application field of AI that enables computers to understand and interpret visual information from images and videos. AI facilitates real-time and post-procedure video analysis in laparoscopic, robotic surgeries and other endoscopic procedures [8]. Computer vision algorithms interpret visual data from endoscopic cameras, providing surgeons with enhanced depth perception and augmented reality overlays [9]. Real-time tracking systems can monitor the position of laparoscopic instruments, effectively minimizing the

risk of unintended injuries. Computer vision can identify various anatomical structures or anomalies during surgery, improving surgical navigation resulting in more accurate minimally invasive procedures.

Surgical videos are a perfect tool for training and skill assessment. AI video analysis provides objective and data-driven evaluation of surgical steps and instrument handling. It can also evaluate factors such as hand-eye coordination, instrument path accuracy, and tissue manipulation, allowing trainees to improve their skills progressively [10]. Computer systems generate detailed metrics and analytics of a surgeon's performance. These metrics can be used to identify areas for improvement and develop personalized training plans.

Predictive Analytics and Decision Support

Decision support systems work in tandem with predictive analytics to assist surgeons in making complex decisions. Machine learning models leverage preoperative and intraoperative data to forecast patient outcomes and potential complications or longer hospital stays [11]. AI algorithms predict and model surgical risk, determining the most effective interventions for high-risk patients. This approach involves the analysis of large volumes of data, enabling the identification of potential risks before symptoms manifest. Utilizing electronic health records, patient history, and real-time patient monitoring enhances the accuracy and reliability of predictive models, ensuring that surgical teams are better prepared and that patients receive timely, personalized care. This predictive capacity is valuable for tailoring treatment plans to individual patient needs, optimizing resource allocation, and enhancing surgical efficiency and safety.

In trauma and emergency surgery, AI-based tools are being used to support complex analysis, aiding surgeons in making informed decisions under time-sensitive conditions [12]. Predictive analytics also plays a crucial role in anticipating and reducing risk based on current patient data. For instance, it can help determine the likelihood of a cancer patient suffering complications from surgery or being readmitted to the intensive care unit (ICU) within 48 hours of discharge. Predictive algorithms can be particularly valuable in ICUs, where timely intervention is critical to patient survival.

Moreover, predictive analytics can assist in managing surgical schedules, reducing patient wait times, optimizing operating room utilization, and improving hospital throughput and cost-effectiveness.

AI supports postoperative care by monitoring patients' progress. AI-powered systems track vital signs, detect early warning signs of complications, and trigger alerts to healthcare providers. This constant vigilance ensures timely interventions and contributes to faster recoveries.

Future Perspectives

AI may significantly improve surgical training by providing personalized, data-driven, immersive experiences. AI-driven simulations and virtual reality environments provide surgeons with realistic training scenarios, allowing them to refine their skills in a risk-free setting [13]. AI analyzes trainees' performances and offers real-time feedback to correct errors. It also enables remote training and collaboration among surgeons, making expertise accessible worldwide. AI-based 3D imaging and augmented reality aid in visualizing complex anatomical structures, hence raising the possibility of a better understanding of surgical field and operation steps. Overall, AI enhances surgical training by ensuring competence, reducing errors, and providing continuous access to the latest surgical advancements.

AI may play a pivotal role in telesurgery. AI could enable rapid patient triage and diagnosis by analyzing medical data and thus facilitating remote consultations and preoperative planning. It enhances decision support through predictive analytics, aiding healthcare providers in making more accurate treatment recommendations. AI could aid surgeons in remote environments by providing real-time guidance and enhancing precision. In the near future, robots driven by AI may execute surgical procedures under remote surgeon supervision, overcoming geographical barriers. AI could make surgical treatments accessible and effective, irrespective of physical location.

Machine learning algorithms can analyze vast datasets to allow robots to make real-time decisions during surgery. These robots can assist or perform complex procedures under the guidance of a surgeon, ensuring steady hands and minimizing the risk of human error. AI can enable predictive modeling to anticipate surgical complications and assist in preoperative planning. Autonomous AI robotic surgery systems can combine advanced technology with human expertise to deliver safer, more precise, and efficient surgical procedures.

Limitations of AI

Apart from those proven or anticipated advantages,

AI-aided surgery also has some limitations. AI systems may struggle to adapt to unforeseen situations during surgery as they rely on pre-trained models. The effectiveness of AI can vary with the surgeon's skill, and inexperienced surgeons may not fully leverage AI [14]. The training of AI systems requires high-quality data, and consequently, inaccurate or incomplete data can lead to errors. Surgeons may become overly reliant on AI, affecting their skills.

As AI becomes more integrated into surgical practice, ethical and regulatory considerations will become increasingly important. Ensuring patient privacy, transparency, and accountability will be crucial. Determining legal responsibility in cases of AI-related surgical errors is complex. Furthermore, compliance with healthcare regulations can be challenging. Implementing AI in surgery can be costly, limiting accessibility for some healthcare facilities.

CONCLUSION

Modern surgery is rapidly evolving with the advancements in technology. While AI offers powerful tools to improve surgical outcomes, the surgeon remains a critical part of the process. It is the surgeon's experience, expertise, and judgment that guide the surgical process, ultimately ensuring the best possible outcomes for patients. This collaborative approach harnesses the strengths of both human skill and artificial Intelligence.

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Challenges faced by humanitarian workers in Greece during the COVID-19 pandemic and suggestions to address them

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Abstract

Background and Aim: The COVID-19 pandemic has been an unprecedented global experience, with multiple consequences affecting various aspects of modern life. This study focuses on exploring the challenges faced by humanitarian aid workers operating in Greece during the pandemic and, subsequently, offering feasible solutions to mitigate these challenges.

Methods: We conducted a cross-sectional study in August and September 2022 to explore this topic. Data were collected through a comprehensive electronic questionnaire distributed via email to humanitarian organizations in Greece and disseminated through various social media platforms, such as Facebook and closed groups for humanitarian workers. The questionnaire included 73 questions, three of which were open-ended. The open-ended questions were evaluated using thematic analysis.

Results: A total of 153 participants took part in the study, 115 (75.2%) of whom were women. The thematic analysis revealed five main categories of challenges: i) communication, ii) accessibility, iii) funding, iv) education, and v) mental health. To address these challenges, participants suggested various actions, including continuing education, seeking support from various organizations, increasing resources and donations, establishing additional structures for psychological empowerment structures, and encouraging collaborations with researchers who can influence government policy through the dissemination of research findings. Most participants reported emotional exhaustion, a condition that was exacerbated during the pandemic.

Conclusions: Our study has shed light on the considerable emotional exhaustion experienced by a significant number of humanitarian workers, exacerbated by the far-reaching impacts of the coronavirus. These challenges include

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economic hardships, communication barriers, and strained interpersonal relationships. To gain a deeper understanding of this complex issue, further research using qualitative methods, such as in-depth interviews, is warranted.

Key words: *Greece; humanitarian aid workers; Covid-19; difficulties; suggestions; thematic analysis*

INTRODUCTION

Humanitarian Aid Organizations provide assistance and support to people affected by human-made disasters, wars, natural disasters, or other crises. The services they provide include food, water, medical care, shelter, psychological support, education, and access to basic infrastructure. They aim to help people overcome difficulties and regain their dignity after crises and disasters. During COVID-19, these humanitarian organizations focused on providing medical supplies, and healthcare services, and disseminating information to help contain the spread of the virus.

Greece, like many other countries, faced unique challenges in coping with the COVID-19 pandemic and the lockdown policy which had a psychological impact on the population [1,2]. Migrants and refugees living in Greece, as in other countries, are particularly vulnerable to COVID-19 infection, with both clinical and socioeconomic consequences [3,4].

The vital importance of integrating refugees into pandemic readiness strategies is emphasized, considering their crowded living environments that can promote virus transmission. To address the challenges faced by refugees, conducting "site-specific epidemiological risk assessments" is proposed to gauge the potential for outbreaks within vulnerable communities [5,6]. Migrant workers also encounter significant difficulties, as many live near other migrants. The suspension or cessation of manual labor and informal jobs due to COVID-19 poses serious economic concerns for them. Furthermore, decisions regarding their legal status in host countries are currently pending [5,6].

Lockdown measures in countries with large migrant and refugee populations have significantly impacted volunteer community services. For instance, the lack of linguistically accessible information about COVID-19 has led to confusion among migrants and refugees, hindering their understanding of the virus and appropriate safety measures. Refugees often face discrimination and may hesitate to seek medical assistance or disclose information, posing increased risks not only to themselves

and other migrants but also to host communities [5,6].

Numerous humanitarian workers have sacrificed their lives to assist and safeguard the communities they serve, which include millions of the world's most vulnerable women, children, and adolescents. The challenges confronting humanitarian workers are compounded by the unequal distribution of COVID-19 vaccines and the inherent difficulties in delivering health services in humanitarian contexts [7].

The following research questions guided our investigation: 1. Which difficulties did workers in humanitarian aid organizations encounter in Greece during the COVID-19 pandemic? 2. In their perspective, how can these challenges be effectively addressed? 3. In what manner can researchers contribute to alleviating these challenges? By delving into these inquiries, our study endeavors to contribute valuable insights that can inform strategies to enhance the resilience and efficacy of humanitarian aid efforts during public health crises. Thus, our study aimed to identify the difficulties faced by employees in humanitarian aid organizations in Greece during the COVID-19 pandemic. Employing a qualitative approach, we sought to identify these challenges and explore proposed solutions.

MATERIAL AND METHODS

Participants

A total of 153 individuals, comprising 115 (75.2%) women and 38 (24.8%) men employed in humanitarian aid organizations in Greece, answered an online survey between August to September 2022. The mean age was 39.3 years old (SD=10.6), 43.8 % (n=67) had one-five years' experience in the humanitarian sector, 49.6% (n=76) had more than six years of experience, and 87.6% (n=134) had direct contact with the beneficiaries.

Participants were recruited from International Federation of Red Cross (IFRC) societies and various International and National non-Governmental Organizations (NGOs) in Greece, such as Solidarity Now, Greek Council for Refugees, AMURTEL (Amanda Marga Universal Relief Team Ladies) Greece, Lesbos Solidarity, KAST (Khora

Asylum Support Team), INTERSOS Hellas, Médecins Sans Frontières and other.

We used both convenience and snowball sampling methods. All participants provided informed consent at the beginning of the questionnaire, with explicit emphasis on anonymity and secure data handling, and the research conformed to the ethical guidelines of the Helsinki Declaration.

Data Collection

Data collection was carried out by means of a comprehensive electronic questionnaire that was distributed by email to humanitarian organizations in Greece. Additionally, the survey was advertised via various social media platforms aimed exclusively at humanitarian aid workers. The questionnaire included 73 questions, three of which were open-ended. The answers to the open-ended questions were analyzed thematically.

Data Analysis

Following the collection of data, the necessary preparations for the analysis were initiated. Specifically, the researcher transferred the files from Google Forms and assigned a unique number from 1 (for the first participant) to 153 (for the last participant) to each recording. The researcher then highlighted the most important elements, followed by systematic grouping to allow a comprehensive analysis and interpretation of participant responses. The process of data analysis consisted of three phases: data analysis, data display, and conclusion drawing, which allowed for a robust examination of patterns and themes that emerged from the participants' contributions.

RESULTS

Difficulties faced by humanitarian workers

The responses of humanitarian aid workers revealed several salient themes that provided a nuanced understanding of the challenges faced during the COVID-19 pandemic. These themes encompass a range of difficulties in different dimensions and mainly relate to communication, accessibility, funding, education, and mental health (Table 1).

In particular, cultural differences, perceptions and language barriers proved to be significant barriers to effective communication, which can lead to disputes and social inequalities. One participant recounted his experience: *"When carrying out different activities, I often*

had difficulties communicating with beneficiaries due to cultural differences and different perceptions" (P.3/male/age 36).

The switch to remote working during the pandemic brought logistical and interpersonal challenges. Some employees commented on the difficulties arising from the lack of face-to-face contact with beneficiaries and colleagues: *"I could not have any interpersonal contact with my beneficiaries and colleagues"* (P.83/female/age 30), *"Because we were working remotely, we had a lot of difficulties because the families in care did not have the necessary technical equipment and the internet"* (P.129/female/age 35) or *"Working remotely cannot meet people's needs"* (P.137/female/age 30). Additionally, remote working hindered support efforts and made accessing services a complex task as it was not possible to physically visit beneficiaries.

In terms of funding, the respondents highlighted a shortage of materials, infrastructure, donations and staff, as well as minimal government support: *"...Lack of funding from the state, fear of anything different, sloppiness and lack of planning in dealing with humanitarian issues"* (P.22/male/age 69) or *"The uncertainty about the continuation of the programs due to a lack of stable funding"* (P.23/male/age 42).

The lack of knowledge and training, unclear responsibilities and lack of supervision were also prevalent, as one participant said: *"...There is a terrible ignorance of public health issues and health protocols..."* (P.97/female/age 39).

Mental health issues were a dominant theme among respondents, as feelings of insecurity, frustration and uncertainty seem to be prevalent in their working environment: *"Facing the fear of others, but also your own fear of the coronavirus"* (P.12/male/age 70), *"To what extent can I give my beneficiaries the feeling of safety and security they need when I don't feel that way myself"* (P.55/female/age 22) or *"Burnout from colleagues, trauma and existential needs that cannot be met"* (P.93/female/age 35). Others also stated that there was *"a lot of pressure, little reward, a lot of uncertainty"* (P.119/female/age 29), or *"...emotional exhaustion"* (P.124/female/age 38), and *"... the feeling of futility, that you cannot change the situation for the better"* (P.144/female/age 26).

Notably, some respondents reported no difficulties at all in their work, while one person even expressed optimism: *"So far everything is manageable"* (P.109/female/age 41).

These identified themes underscore the multifaceted

Table 1. Themes Emerging from Humanitarian Aid Workers' Quotations.

Themes	
Communication	<ul style="list-style-type: none"> • Cultural differences and perceptions. • Different languages lead to misunderstandings. • Disagreements and conflicts arise from different points of view. • Effects of teleworking on interpersonal relationships. • The lack of personal contact promotes social inequalities. • Cases of racism and the loss of human ties. • Challenges arising from the spread of misinformation.
Accessibility	<ul style="list-style-type: none"> • Inability to provide effective support due to teleworking. • Complications in accessibility of services due to pandemic-related measures.
Financing and resources	<ul style="list-style-type: none"> • Limited services and insufficient financial support. • Lack of essential materials, infrastructure, and resources. • Shortages of agencies, donations, staff, and contractual agreements.
Education and training	<ul style="list-style-type: none"> • Insufficient knowledge and training opportunities. • Lack of clear job descriptions and supervision.
Mental health and well-being	<ul style="list-style-type: none"> • Emotional exhaustion, emotional strain, and fatigue. • High pressure and stressful situations leading to burnout. • Lack of adequate psychological support. • Feelings of insecurity and uncertainty about the future. • Diminished sense of creativity. • Feelings of alienation and lack of respect in the workplace. • Perceived selfishness among colleagues. • The emotional impact of confinement and fear.

nature of challenges faced by humanitarian aid workers during the pandemic, shedding light on the complexities inherent in their work environment.

Proposals of employees

In response to the challenges identified, humanitarian workers have made concrete proposals to address the complex problems they face. These suggestions include a range of strategies, such as continuing education and skills development, training strategies, psychological support, collaboration with local institutions, organizations and governmental agencies, and more donations, resources, materials and funds (Table 2).

In particular, many workers emphasized the need for continuous training and development under supervision and with a clear mandate. Furthermore, seminars, conferences, and organized programs would improve communication and technical skills: "*continuing education*" (P.5/male/age 41), and "*development of communication and technical skills (wherever/whoever needed)*"

(P.48/female/age 32).

Suggestions also included establishing more psychological seeding, as psychological support plays an important role in providing help, resilience building and decompression/relaxation after challenging incidents: "*support, resilience building*" (P.12/male/age 70), "*... Decompression/relaxation measures ...*" (P.23/male/age 42) or "*... believe more in ourselves and our abilities*" (P.118/female/age 28). One participant state more specifically that: "*... it would be good if the service provided a psychologist at least twice a month to get rid of the pressure and negative thoughts and doubts after a difficult incident*" (P.49/female/age 32).

Collaboration and support were also highlighted, with staff suggesting collaboration with local agencies and organizations, and asking for support from state agencies. They also acknowledged the interdependence of these suggestions with the need for adequate funding through more donations, resources, materials and money

Finally, one participant brought up a holistic perspective that encompasses everything mentioned by most: *“Approaches need to be holistic, mind, spirit and body... Services need to be people-centered... In this way, the outcome for professionals will be affirming and rewarding. The information and the conferences where it was held are now much more important than how we can apply this knowledge in practice”* (P.64/female/age 56).

These proposals underscore once more the multifaceted nature of the challenges faced by humanitarian aid workers. Their proposals provide a comprehensive framework for addressing and overcoming the difficulties. Emphasis should be given on skill development, collaboration, resource enhancement, and well-being, in order to reflect a holistic approach in creating a more supportive and effective working environment for those engaged in humanitarian aid efforts.

Proposals of employees for researchers

The third open-ended question related to employees' views on how researchers can contribute to overcoming the identified challenges. In their response to this question, humanitarian aid workers expressed different perspectives on the potential role of researchers in mitigating the problems identified. They emphasized the crucial role of researchers in conducting meaningful studies and disseminating their findings, but also their role in providing practical advice through seminars, training programs and the development of crisis management handbooks (Table 3).

The publication of survey results was seen as an effective tool for communicating the challenges to the relevant authorities, as they can help to: *“...put pressure on the state apparatuses to make improvements”* (P.23/male/age 42), *“... Highlight the problems faced by employees”*

Table 2. *Proposals of Employees to deal with the challenges.*

Themes	
Communication	<ul style="list-style-type: none"> • Training in communication skills. • Collaboration with psychologists who have undergone appropriate training. • Joint actions between organizations and collaboration with local institutions.
Accessibility	<ul style="list-style-type: none"> • Infrastructure improvement. • Better living conditions for refugees. • Help and guidance from the state to address living conditions and infrastructure challenges.
Financing and resources	<ul style="list-style-type: none"> • More and better resources, donations, and basic materials. • More funds to support humanitarian efforts. • Improvement of infrastructure and living conditions. • Proposing a salary increase and advocating for more transparency at work.
Education and training	<ul style="list-style-type: none"> • Seminars, organizational programs, and ongoing training. • Need for supervision and clear lines of responsibility. • Training programs for translators.
Mental Health and well-being	<ul style="list-style-type: none"> • Importance of stress management. • Participation in social events. • Improved physical and mental safety measures. • Additional days off to facilitate stress reduction. • The importance of serenity and believing in one's own abilities. • Experiential workshops and self-care. • Initiatives to strengthen self-determination. • Strategies to strengthen resilience. • Psychotherapy as a means of support. • Decompression and relaxation measures. • Incorporating therapeutic activities such as dance, theater, or art to enhance well-being.

(P.25/male/age 30) or "... raise awareness in society and put pressure on the state" (P.98/female/age 59).

Researchers were also seen as valuable contributors in the workplace providing practical advice through seminars, training programs and the development of a crisis management manual/guide. Therefore, collaboration between researchers and staff was seen as essential to encourage open discussions, identify deficiencies, and implement solutions through counseling programs. One participant stated: "...it would be useful if some of your colleagues had experience in humanitarian organizations" (P.12/male/age 70).

Mental health issues continue to be a recurring problem as mentioned by most participants, who even suggested the introduction of a mental health officer.

Table 3. Suggestions for Researchers.

Themes	
Communication	<ul style="list-style-type: none"> • Publication of results and proposals. • Consultative identification of problems. • Media and public perceptions. • Mitigating public panic. • Dissemination of information. • Collaboration between researchers and workers.
Accessibility	<ul style="list-style-type: none"> • Forwarding identified problems to the relevant authorities. • Raising social awareness. • Exerting pressure on state institutions and political figures.
Funding and resources	<ul style="list-style-type: none"> • Voluntary monitoring and psychological support structures. • Establishment of voluntary supervision. • Free benefits and mental health services accessible to all. • Free weekly sessions.
Education and training	<ul style="list-style-type: none"> • Provision of seminars, training programs and special sessions. • Practical advice. • Development of a manual/guide for crises.
Mental Health and wellbeing	<ul style="list-style-type: none"> • Stress management strategies, risk reduction. • Appointment of an emotional distress manager.

This person could offer support in the form of experiential seminars and help staff manage stress and other related risks: "... knowing the attitude and psychological state of colleagues through research data certainly offers us the opportunity to observe and perhaps offer more for ourselves..." (P.55/female/age 22).

However, two participants acknowledged certain limitations, recognizing that some challenges may be beyond the direct control of researchers and attributing them to the responsibility of the state: "...this is purely a state issue" (P.18/male/age 40) and "... I don't think anything can be done ..." (P.31/male/age 44).

These various perspectives highlight the multi-faceted ways in which researchers can contribute to addressing the challenges faced by humanitarian aid workers. However, the employees recognize the inherent complexities and limitations in certain aspects of these challenges.

DISCUSSION

Our study aimed to explore the challenges faced by humanitarian aid workers in Greece during the COVID-19 pandemic and to propose solutions to address these issues. The data for the present study came from 153 humanitarian aid workers in Greece. The results showed a high prevalence of emotional exhaustion linked to the communication, accessibility, funding, education and mental health challenges amplified by the coronavirus.

Similar findings have been identified in a pre-pandemic study, which highlighted the influence of socio-cultural factors, language barriers and problems related to access and funding [8]. Above all, the state itself plays an important role, failing to invest in workforce, resources, and the accurate dissemination of information. A prevailing sense of uncertainty and skepticism among Greeks regarding the effectiveness of existing political institutions further complicates the process of restructuring [9].

It is emphasized that the improvement of living conditions in these facilities is an immediate priority and that free, comprehensive and universal access to care without any discrimination must be guaranteed [3]. Addressing these fundamental aspects is crucial to mitigate the challenges faced by humanitarian workers and promote a more resilient support system. To delve deeper into these complexities, future studies could utilize more comprehensive research methods, such as questionnaires or interviews. This would allow for a more comprehensive analysis of the complicated

dynamics surrounding the experiences of humanitarian aid workers in the context of the pandemic.

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Active musical engagement and subjective levels of stress, anxiety and depression in the area of Piraeus

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Abstract

Background and Aim: Numerous studies have been conducted on the relationship between music and mental health, demonstrating its positive correlation with the promotion of well-being and prosperity. However, there is a lack of research on the impact of active musical engagement on the mental health of the population. The aim of this study was to investigate the effect of active musical engagement on the mental health of residents in Piraeus.

Methods: A cross-sectional study was conducted on a convenience sample of adults, using questionnaires distributed through social networks. The questionnaires included demographic and socio-economic questions, as well as inquiries about musical engagement and the Greek version of the DASS-21 questionnaire.

Results: A total of 377 individuals participated, of which 78% were Piraeus residents, and 61.6% of them were female. Absence of depression was reported by 65.3% of Piraeus residents, while the corresponding percentages for absence of anxiety and stress were 72.1% and 62.2%, respectively. Women exhibited higher mean scores for depression, anxiety, and stress compared to men. Individuals engaging in musical activities, either in professional or amateur capacity, lower levels of depression, anxiety, and stress compared to people who did not engage in music actively.

Conclusion: The study highlights the positive impact of active musical engagement, particularly on anxiety levels. Factors influencing depression, anxiety, and stress include gender, family status, and living arrangements.

Key words: *Active musical engagement; stress; anxiety; depression; DASS21; Greece*

INTRODUCTION

According to the World Health Organization (WHO), mental health is recognized as a critical component of overall well-being. It is considered one of the four domains that constitute quality of life [1], a multidimen-

sional concept encompassing an individual's physical health, social relationships, environmental factors and the individual's ability to perform activities and participate in meaningful activities.

Mental health problems increased globally by 13% during the period 2007-2017, affecting 1 in 5 years lived with disability [2]. On a global scale, approximately 5% of adults suffer from depression, with serious consequences such as suicide [3,4]. Particularly in Greece, 3.8% of the population in 2019 reported experiencing depression, with women being more affected. The positive result is that a percentage of around 4.1% visited a psychiatrist or psychologist for the mental health issues they were facing [5].

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Anxiety is the normal response of the human organism to stress, as a mechanism of mental defense, and is a natural part of the human experience. However, its excessive and long-standing expression can lead to generalized anxiety disorder [6,7]. The term “stress” is used to describe the effects of physical or mental pressure on the organism, with chronic stress being linked to autoimmune diseases, depression, and worsening of other psychopathological conditions [7]. Depression, as a mood disorder, is often associated with anxiety and stress and can lead to serious consequences such as suicide [7–9].

The management of the above mentioned mental disorders typically involves the use of psychotropic medication and/or psychological treatment [3,4]. However, according to modern perspectives, new, complementary approaches are also being explored, primarily through artistic engagement [10,11], recognizing it as an effective tool for regulating emotions and promoting well-being. Engagement in artistic activities, whether receptive involvement (e.g., listening to music, attending theater, visiting museums, etc.) or active participation (e.g., playing a musical instrument, composing songs or music, singing, etc.) [12,13] has been shown to be associated with the reduction of depression and anxiety, emerging as an approach related to positive outcomes for mental health [11].

Music has been recognized as an effective tool for regulating emotions and promoting well-being [10,11]. Active musical engagement has been recognized as an accessible and effective tool for improving mental health, addressing concerns, and reducing social isolation [9–12,14–23]. It is associated with positive outcomes for individual health and well-being, as well as social functioning [24]. To our knowledge, in only two studies [14,25] the professional musician status was correlated with increased incidents of mental health disorders, as well as high rates of depression and suicides. Despite efforts to explore the correlation between music and mental well-being in the Greek context, no results have as yet been reported.

The purpose of the current study was to investigate whether adults residing in Piraeus who actively engage in music perceive themselves to have lower levels of stress, anxiety, and depression in their daily lives compared to those who are not actively involved. As a secondary objective, the study aimed to correlate and quantify the time spent on musical engagement in relation to the reduction or non-reduction of daily

anxiety, stress, and depression, according to the participants’ subjective opinion.

MATERIALS AND METHODS

A cross-sectional quantitative study was conducted using anonymous electronic surveys through Google Forms. The sample consisted of adults aged 18 and above, healthy men and women, residents of Piraeus. Responses were collected from individuals actively involved in music and those not actively involved, allowing for a comparison of results. The number of participants was determined using the Raosoft sample size calculator, resulting in a sample size of 377 individuals. After the approval by the Ethics Committee of the University of Patras (10.07.2023/15484), and the necessary permissions were granted for using the DASS-21 questionnaire, the surveys were distributed on social media platforms and were completed between April 3, 2023, and May 5, 2023. The collected data were statistically analyzed using IBM SPSS (Superior Performance Software System) 26 for Microsoft Windows, using T-test (2 tailed), one way ANOVA test and multiple regression F-test for correlation of depression, anxiety, and stress.

The questionnaires comprised two parts. The introductory section included a paragraph informing participants about the purpose of the study and the anonymity and confidentiality of their responses. The first part of the questionnaire included 6 demographic questions and 5 questions regarding active musical engagement.

The second and final part included 21 questions related to perceived anxiety, stress, and depression using the Greek standardized DASS-21 questionnaire. This is a brief form of the DASS42 by Lovibond, S.H. & Lovibond, P.F. (1995), measuring the severity of a range of symptoms common to anxiety, stress, and depression. The Greek validated translation [26], was used after obtaining necessary permission from the authors, following the questionnaire’s usage manual [7].

During the completion of the DASS-21, the individual had to indicate the presence of a symptom during the previous week. Each item is scored from 0 (did not apply to me at all in the last week) to 3 (applied to me very much or most of the time last week). The scale has three subscales, each one consisting of 7 items designed to measure depression, anxiety, and stress.

The Depression scale assesses dysphoria, hopelessness, life devaluation, self-deprecation, lack of interest/participation, anhedonia, and inertia. The Anxiety scale

evaluates autonomic nervous system arousal, skeletal muscle effects, situational anxiety, and the subjective experience of anxious feelings. The Stress scale is sensitive to levels of chronic non-specific arousal. It assesses difficulty relaxing, nervous arousal, being easily upset/disturbed, being irritable/over-reactive, and impatience [7].

Depression is considered absent when its DASS score is between 0-9, mild when 10-13, moderate when 14-20, severe when 21-27 and extremely severe when it exceeds 28+. Anxiety is considered absent when its DASS score is between 0-7, mild when 8-9, moderate when 10-14, severe when 15-19 and extremely severe when exceeds 20+, respectably. Similarly, stress is considered absent when its DASS score ranges between 0-14, mild between 15-18, moderate between 19-25, severe between 26-33 and extremely severe when exceeds 34+.

RESULTS

A total of 377 individuals aged 18 and above participated in the study, with the largest percentage (36.3%) belonging to the age group of 36-45 years. Among these participants, 78% identified themselves as residents of Piraeus (Table 1). The results of the DASS-21 for Piraeus residents indicated that 9.9% have mild depression, 10.9% moderate depression, 9.5% severe depression, and 4.4% extremely severe depression. In the anxiety subscale, 4.8% reported mild anxiety, 9.5% moderate anxiety, 6.8% severe anxiety, and 6.8% extremely severe anxiety. Regarding stress, 11.2% reported mild stress, 16.3% moderate stress, 8.2% severe stress, and 2% extremely severe stress (Fig.1). Of the Piraeus residents 61.6% were women. Women showed higher mean scores for depression, anxiety, and stress compared to men (10.42 vs 7.77, $p_d=0.019$; 8.14 vs 4.55, $p_a=0.003$; 14.53 vs 11.17, $p_s=0.00$, respectively) (Table 2).

The T-test and one-way ANOVA statistical analyses revealed statistically significant differences in the occurrence of depression and stress between residents of Piraeus and those living outside Piraeus (Table 3). Additionally, they showed that widowed individuals exhibit higher scores in depression, anxiety, and stress, while married individuals have lower scores (24.40 vs 7.06; 25.20 vs 5.55; 26.80 vs 11.57, respectively; $p=0.00$) (Table 4). Furthermore, people living with parents or other relatives exhibited higher depression scores compared to other living arrangements (Table 5). People actively engaging in music had significantly lower anxiety levels compared to those not actively involved in music (4.11

and 5.72 vs. 7.74, respectively, with $p=0.04$), while no difference was observed in depression and stress levels between amateur and professional musicians (Table 6).

Regarding age, educational level, and family monthly income, no statistically significant difference was observed in the mean scores of depression, anxiety, and stress. The type of active musical engagement (singing, composing music or songs, choir, or musical group), the type of instrument (wind, percussion, or string), or the time spent on engagement per week did not play a role in any of the levels of mood disorders. According to the F-test in a multiple regression ANOVA table, it is indicated that depression, anxiety, and stress are positively correlated with each other.

DISCUSSION

The overall results of the study both agree and disagree with various studies from the existing literature. Our study showed that women report higher levels of symptoms of anxiety, stress and depression than men. This statistically positive correlation between gender and mood disorders is in agreement with data previously reported [27], especially when discussing gender and stress [25]. Furthermore, in line with prior research [28], it is suggested that women tend to participate more in creative activities (including active musical engagement) to regulate their emotions, while men are inclined to use music for cognitive purposes [29]. This could also possibly account for the elevated levels of depression, stress, and anxiety observed in women in our current study.

Additionally, the higher scores in women are consistent with the existing literature [27], which indicates that female professional musicians commonly experience more frequent mental health issues, possibly due to challenges such as gender discrimination, lower compensation compared to male counterparts, and the juggling of family responsibilities. Our study indicates this also.

Furthermore, there is agreement between the study results and other research [29], which suggests that certain mental health disorders, such as anxiety disorders, depression, bipolar disorder, etc., are likely explained by common genetic or environmental factors. In the current study, a possible connection might exist between living arrangements and the levels of depression, stress, and anxiety, especially for individuals still living with parents or relatives, who exhibit higher rates. This could be attributed to the sense of responsibility for caring for these relatives or the perceived inability to achieve independence.

Table 1. Demographic characteristics of Piraeus' residents (n=294, 78%).

Characteristics	n	%	Characteristics	n	%
Gender			Do you think music is beneficial for one's mental health?		
Male	113	38.4	Yes	289	98.3
Female	181	61.6	No	3	1.0
			I don't know	2	0.7
Age Group			Do you play a musical instrument?		
18-25	31	10.5	String	70	23.8
26-35	34	11.6	Wind	10	3.4
36-45	119	40.5	Percussion	8	2.7
46-55	86	29.3	I don't play an instrument	206	70.1
56+	24	8.2			
Educational Level			Do you sing in a formation/choir?		
Primary school	4	1.4	Musical formation	24	8.2
			Choir	19	6.5
High School	56	19.0	I don't sing	243	82.7
Post-secondary education	52	17.7	Other (Alone at home, because I feel like it, etc))	8	2.7
University	103	35.0			
MSc	75	25.5			
PhD	4	1.4			
Marital Status			Do you compose music or songs?		
Single	111	37.8	Music	22	7.5
Married	155	52.7	Songs	13	4.4
Widower	5	1.7	I don't compose	259	88.1
Other	23	7.8			
Living Condition			If you do any of the above, how many hours a week do spend doing it?		
With partner	60	20.4	1-3 h/week	50	17.0
With partner and children	126	42.9	4-8 h/week	26	8.8
With parents or other relatives	46	15.6	9-15 h/week	13	4.4
With roommate	5	1.7	15+ h/week	8	2.7
Alone	57	19.4	I don't do any of the above	197	67.0
Monthly family income			Do you consider your active musical engagement to be:		
0-1000 €/month	82	27.9	Amateur	108	36.7
1001-2000 €/ month	100	34.0	Professional	19	6.5
2001+ €/ month	62	21.1	No active engagement	167	56.8
I prefer not to answer	50	17.0			

The results of the current research are consistent with studies indicating that family status plays a role in self-reported symptoms of depression, stress, and

anxiety, particularly for individuals who are widowed [11,23]. Both literature and our study suggest that active musical engagement benefits an individual's mental

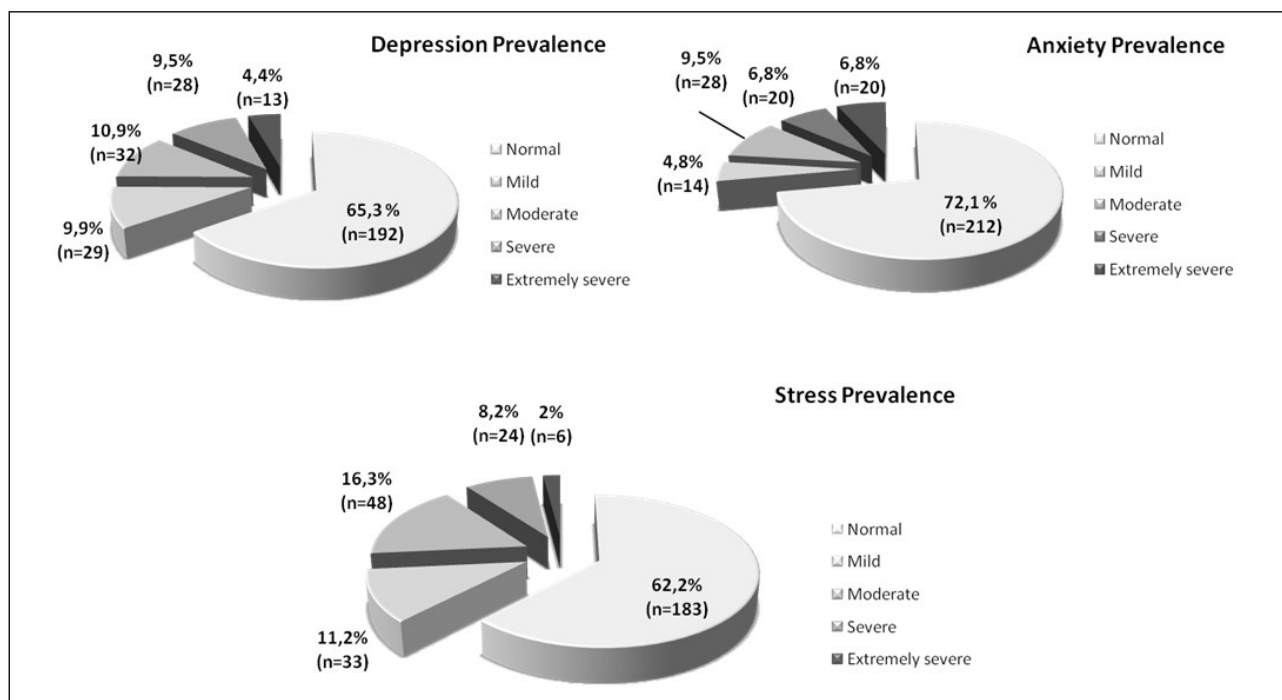


Figure 1. Prevalence of Depression, Anxiety and Stress in Piraeus residents assessed by DASS-21 (n=294).

Table 2. Mean scores assessing depression, anxiety, and stress in residents of Piraeus by gender (n=294): 2- tailed t-test.

	Males (n=113)	Females (n=181)	t values	p-value
Depression score mean \pm SD	7.77 \pm 9.168	10.42 \pm 9.456	-2.365	0.019
Stress score mean \pm SD	11.17 \pm 9.011	14.53 \pm 9.806	-2.949	0.003
Anxiety score mean \pm SD	4.55 \pm 6.377	8.14 \pm 8.577	-3.841	<0.001

Table 3. Mean scores assessing depression, anxiety, and stress by residence (n=377): 2- tailed t-test.

	Piraeus Residents (n=294)	Residents outside Piraeus (n=83)	t values	p-value
Depression score mean \pm SD	9.40 \pm 9.42	9.77 \pm 9.599	-2.168	0.031
Stress score mean \pm SD	13.24 \pm 9.633	13.94 \pm 9.837	-2.634	0.009
Anxiety score mean \pm SD	6.76 \pm 7.987	7.08 \pm 8.133	-1.441	0.15

Table 4. Mean scores assessing depression, anxiety and stress considering in residents of Piraeus by marital status: one way – ANOVA test.

	Single (n=113)	Married (n=155)	Other (n=28)	F value	p-value
Depression score mean \pm SD	11.64 \pm 10.12	7.06 \pm 7.975	13.50 \pm 10.648	11.326	<0.001
Stress score mean \pm SD	14.67 \pm 9.65	11.57 \pm 9.608	16.79 \pm 7.988	5.602	0.004
Anxiety score mean \pm SD	7.35 \pm 7.494	5.55 \pm 7.516	11.14 \pm 10.561	6.541	0.002

health, providing protection against stress and depression. Simultaneously, it fosters a sense of purpose in life, boosts self-confidence, enhances positive overall

life emotions, and provides post-bereavement support, while significantly reducing anxiety symptoms.

Education in performing artistic activities and regular

Table 5. Mean scores assessing depression, anxiety and stress considering in residents of Piraeus by living conditions: **one way – ANOVA test.**

	With partner (n=60)	With partner and children (n=126)	With parents or other (n=51)	Alone (n=57)	F value	p-value
Depression score mean ± SD	8.03 ± 9.319	7.67 ± 8.473	13.49 ± 10.739	11.02 ± 9.104	5.889	0.001
Stress score mean ± SD	11.10 ± 8.352	12.54 ± 9.948	15.76 ± 10.382	14.77 ± 8.982	2.913	0.035
Anxiety score mean ± SD	5.83 ± 7.19	6.17 ± 8.279	9.10 ± 7.852	6.95 ± 8.037	1.982	0.117

Table 6. Mean scores assessing depression, anxiety and stress in residents of Piraeus by active musical engagement (n=294): **one way- ANOVA test.**

	Amateur (n=108)	Professional (n=19)	No active engagement (n=167)	F value	p-value
Depression score mean ± SD	8.37 ± 8.652	8.26 ± 8.875	10.31 ± 9.888	1.928	0.147
Stress score mean ± SD	12.83 ± 8.772	10.21 ± 7.627	13.84 ± 10.313	1.368	0.256
Anxiety score mean ± SD	5.72 ± 7.712	4.11 ± 5.753	7.74 ± 8.259	3.258	0.04

engagement in them are associated with an individual's ability to use artistic activities for emotion regulation and mental health management [27,30]. Musical engagement, including active music creation (playing an instrument, singing), influences social and emotional development throughout an individual's life [31], improving mood symptoms and cognitive functions [32]. The current study's results are consistent with the finding that professionals and amateur musicians have lower levels of the studied emotional disorders, as they are the ones regularly engaged in music, although the time of engagement does not play a role in the rates among musicians.

Another study has suggested that individuals, especially women, with lower socio-economic status use artistic creative activities to regulate their emotions [33], which does not seem to be the case in the present study. In contrast, in this research, symptoms of depression, anxiety, and stress do not appear to be associated with economic and educational demographic factors. Moreover, musical studies and knowledge in Greece is costly to the family budget and therefore tends to be directed towards higher social classes.

Other studies [10–12] have demonstrated that individuals who actively engage in music report lower anxiety levels, which is in complete agreement with the results of the present study, as statistically significant differences in anxiety levels were observed between people actively engage in music, compared to people who do not. Although there was no statistically significant difference in depression and stress levels, a trend

of lower percentages in professionals and amateur musicians was noted.

The results of our study seem to be at odds with a study [14] which suggests that individuals who actively play a musical instrument (but not necessarily professionally) may have a somewhat increased risk of mental health problems. There seems to be some inconsistency in the beneficial effects of music on daily life and mental health between professional musicians and the high rates of depression and suicides among them, possibly due to the highly competitive and stressful professional environment, something that has not been observed in our research. Moreover, our results contradict with the results of a previous study [25], which indicated that musical education did not reduce the relationship between mood regulation related to music and psychopathology.

According to all the above, marital status plays a role in all disorders, as well as gender, with women having higher levels as opposed to men. Being Piraeus' citizens possibly leads to lower levels of depression and stress and living with parents or other relatives may lead to higher levels of depression, probably because of lack of independence. Age, educational level and monthly family income did not correlate with the levels of mood disorders.

To conclude, musical engagement seems to play a role in decreasing anxiety and could be protective against symptoms of depression and stress. Active music engagement seems to be a promising way to enhance

an individual's mental health and well-being, resulting in their total everyday function.

LIMITATION

Given that the study sample is not random but convenience-based, inherent bias in the study implies that the sample is unlikely to be representative of the population. As a result, generalizations from the sample to the studied population should be made with caution. The questionnaires were distributed and answered electronically, so only individuals with access to electronic devices and social media accounts could participate. A future prospective, longitudinal randomized controlled trial study could answer reliably whether musical engagement could be beneficial on mood disorders. Additional emphasis on objective measures, such as blood pressure and heart rate, during interactions with music is necessary to ascertain its beneficial effects in daily life and its potential as a complementary method of mood regulation.

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Antiphospholipid Syndrome: Highlights for internal medicine physicians

Chrysa Lykoura

Abstract

This narrative review is an attempt to summarize the pathogenesis, diagnostic approach and latest guidelines for the treatment of antiphospholipid syndrome (APS) in adults. APS is a chronic autoimmune disease that is associated with the presence of antiphospholipid antibodies and is usually presented with thrombotic events or obstetric complications but can have other manifestations. Differential diagnosis can be challenging. Treatment options focus on antithrombotic medications and aim to prevent recurrent thrombotic events but also include immunosuppressants. Catastrophic antiphospholipid syndrome (CAPS) has a high mortality rate and is challenging to diagnose and treat. Laboratory tests for antiphospholipid antibodies should always be interpreted carefully according to clinical presentation. Finally, patients should be thoroughly informed and guided to lifestyle changes as well as compliance with necessary long term pharmacological therapy.

Key words: *Antiphospholipid syndrome; highlights; internal medicine*

INTRODUCTION

Antiphospholipid syndrome is a relatively rare disease. The overall estimated prevalence ranges between 40 and 50 cases per 100,000 worldwide [1]. It is a chronic autoimmune disease that is usually presented with thrombotic events or specific obstetric complications but can have other manifestations, as will be discussed later. It can be primary or secondary, mostly associated with systemic lupus erythematosus (SLE). Upon appropriate clinical suspicion, the diagnosis is confirmed by laboratory tests that detect the presence of antiphospholipid antibodies. Usually, lifelong treatment is necessary after initial rescue therapy.

MATERIALS AND METHODS

The aim of this literature review is to highlight the

main aspects of the diagnostic approach and treatment of APS in everyday clinical practice of internal medicine physicians. The existing literature on the subject has been reviewed, including original research articles, reviews, books, as well as the latest EULAR/ACR (European Alliance of Associations for Rheumatology/American College of Rheumatology) guidelines.

Pathogenesis of APS

Pathogenesis of APS is not perfectly clear; however, it is believed that antiphospholipid antibodies play a key role. Antiphospholipid antibodies are a family of autoantibodies that recognize phospholipids or phospholipid-binding proteins. It is believed that the main target of antiphospholipid antibodies is $\beta 2$ glycoprotein one ($\beta 2$ GPI), a normal plasma protein that binds avidly to phospholipid membranes. This connection is even stronger when $\beta 2$ -GPI is dimerized by binding to its antibody (anti- $\beta 2$ -GPI). This connection on a membrane surface is believed to cause activation of endothelial and inflammatory cells and finally lead to thrombosis. Some

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of the assumed mechanisms include increased expression of prothrombotic molecules, such as E-selectin and tissue factor (TF), as well as complement pathway activation and reduced activation of protein C [2,3]. Monocytes, neutrophils, and platelets are some of the involved cells. The result is thrombosis, which causes most of the clinical presentations of APS. Thrombotic events in trophoblast, decidua, or placenta can cause specific obstetric complications.

DIAGNOSTIC APPROACH

Antiphospholipid antibodies

In the appropriate clinical context, the diagnosis of APS is based on the detection of antiphospholipid antibodies in the patient's plasma. The three types of detectable antiphospholipid antibodies in everyday clinical practice are lupus anticoagulant (LA), anti- β 2GPI and anti-cardiolipin (antiCL) antibodies. Their presence is not always clinically significant. They can be transiently present in almost 10% of the healthy population, according to some surveys [2]. Antiphospholipid antibodies can also be transiently detectable during infections such as syphilis [4]. Therefore, tests for antiphospholipid antibodies should be requested only when there is clinical suspicion of APS or as part of expert follow-up or investigation of patients with SLE as guidelines suggest. The interpretation is not always simple and should be discussed with a rheumatologist.

Among the three (LA, anti- β 2GPI and antiCL), the LA is the most clinically significant in that it has the greatest statistical and seemingly pathogenetic correlation with thrombotic and other events of the disease. Unfortunately, the LA test can be unreliable (mostly false positive) when the patient is on anticoagulant medication, which can often lead to diagnostic problems. LA is an "anticoagulant" in vitro in that it prolongs aPTT (activated Partial Thromboplastin Time). A specific three-stage test should be performed in experienced laboratories to detect Lupus Anticoagulant, but prolonged aPTT measured before anticoagulant treatment could be useful to suspect LA presence in the appropriate clinical context. Anti- β 2GPI and antiCL antibodies are usually detected using the ELISA (Enzyme-linked Immunosorbent Assay) method, which is not influenced by the possible administration of anticoagulant treatment. Now, what antiphospholipid profile is considered high-risk? Is of high risk in the presence (in at least two measurements at least 12 weeks apart) of LA or triple positivity or double positivity (any combination of LA, anti- β 2GPI,

antiCL) or persistent high titres of antiphospholipid antibodies. On the contrary, low-to-moderate titres of isolated anti- β 2GPI or antiCL are considered low-risk, especially if they are transient [5]. IgG antibodies are more clinically significant than IgM, while IgA have unknown clinical significance.

Clinical presentation

Typical clinical presentations include thromboses (arterial or venous) and specific obstetric complications (included in Sapporo Classification Criteria for APS) [6]. Therefore, APS is usually categorized as thrombotic or obstetric. A history of obstetric APS is supposed to present a lower risk for thrombotic events and is mostly associated with the risk of complications in future pregnancies. Thromboses can be arterial or venous, possibly affecting blood vessels of any size, including microthrombotic lesions that require a biopsy of the affected tissue to be confirmed. The most common affected blood vessels are the same as in the general population, causing strokes, deep venous thromboses or pulmonary embolism. As far as obstetric complications are concerned, according to the revised Sapporo classification criteria and latest guidelines, only specific presentations should raise clinical suspicion. An unexplained spontaneous abortion or fetal death after the 10th week of gestation requires exclusion of APS, while one spontaneous abortion before the 10th week of gestation is not uncommon and is usually caused by chromosomal abnormalities of the fetus. Three or more consecutive spontaneous abortions before the 10th week of gestation though, do require investigation. Maternal causes such as anatomical or hormonal disorders should always be excluded by the gynecologist. Another criterion is premature birth (before the 34th week of gestation) caused by placental insufficiency, eclampsia, or severe pre-eclampsia. For a definite diagnosis, according to the revised Sapporo classification criteria, at least one confirmed thrombosis or one obstetric criterion must be positive in combination with at least one type of antiphospholipid antibodies (LA, anti- β 2GPI or antiCL) detected at least two times at least 12 weeks apart.

However, there are other possible clinical manifestations of APS that are not included in the Sapporo Classification Criteria. These include hematologic disorders such as thrombocytopenia, usually mild ($>50,000$ platelets per mm^3) with or without thrombotic microangiopathy, as well as hemolytic anemia, either due to thrombotic microangiopathy or immune mediation.

Hemorrhage is uncommon. Renal manifestations are also caused by thrombotic microangiopathy and can be acute or chronic. The heart can also be affected; Libman–Sacks endocarditis usually affects the mitral or the aortic valve. Skin is sometimes affected as well, with livedo reticularis or racemosa being the most common presentation. Neurologic manifestations of the central nervous system (in the absence of stroke) are less common but possibly severe and challenging to diagnose. The 2023 ACR/EULAR classification criteria for APS [7] are generally more inclusive than Sapporo criteria, but stricter as far as obstetric complications are concerned, with placental insufficiency or severe pre-eclampsia being necessary to meet criteria.

Considering all the possible presentations listed above, when should a physician suspect APS? Mostly as part of the investigation of recurrent thrombosis or thrombosis in an uncommon vessel or unprovoked thrombosis at a young age. The obstetric complications that require investigation for APS are listed above. Moreover, mild thrombocytopenia or prolonged aPTT can cause further clinical suspicion. Clinical history and physical examination can also suggest underlying SLE or other rheumatic diseases (Table 1). The involvement of multiple organs or systems should be investigated. Livedo-like skin lesions, even though not specific, are quite typical and should raise suspicion for APS. On the contrary, in the absence of organ involvement or any of the clinical presentations described above, laboratory testing for antiphospholipid antibodies is not recommended as part of screening, except for SLE patients.

Catastrophic APS (CAPS) is characterized by rapid development of clinical presentations, typically within seven days, and multi-organ involvement ($>=3$), typically including histopathologically confirmed thrombotic microangiopathy and SIRS (Systemic Inflammatory

Response Syndrome). The laboratory criterion for APS (persistent antiphospholipid antibodies) must be met. Manifestations may include acute renal failure, ARDS (Acute Respiratory Distress Syndrome), diffuse alveolar hemorrhage, encephalopathy and adrenal hemorrhage. Mild thrombocytopenia is common [10]. CAPS has a high mortality rate (20–45%) [8,9]. Therefore, an aggressive treatment approach is needed. Hemorrhagic complications can cause challenges in treatment decisions, considering the cost-benefit balance of administering anticoagulant medication. These are rare ($<1\%$ of APS cases) and relapses are uncommon. It is possibly triggered by treatment discontinuation, malignancy, infections, pregnancy, exogenous estrogens, trauma, surgery or SLE flare. In the differential diagnosis of CAPS, other forms of thrombotic microangiopathies must be considered e.g. hemolytic-uremic syndrome, thrombotic thrombocytopenic purpura, heparin-induced thrombocytopenia or diffuse intravascular coagulation [10], which may also be associated with underlying infections or malignancies. When CAPS is the first clinical presentation of APS, differential diagnosis is even more challenging.

MANAGEMENT

Management includes antithrombotic treatment of acute clinical presentations, long-term treatment to prevent relapses, with specific guidelines for obstetric APS and a more aggressive approach, including immunosuppressants, for manifestations that are not included in the Sapporo classification criteria, such as renal involvement, hematologic disorders, and CAPS.

It must be emphasized that management includes much more than pharmacological therapy. Patients diagnosed with APS should be thoroughly informed and guided to make lifestyle changes and, in collaboration with their attending physicians, attempt to eliminate modifiable risk factors for thrombotic events, such as smoking, hypertension and hypercholesterolemia. Moreover, exogenous estrogens (e.g., oral contraceptives or hormone replacement therapy) should be avoided and aggressive prophylactic perioperative anticoagulant treatment should be administered. Recommended vaccination schedules should also be followed. These methods of prevention also apply to asymptomatic people with a high-risk antiphospholipid antibody profile. If APS is secondary, the underlying rheumatic disease should also be treated and closely monitored [2].

Table 1. Common “red flags” raising suspicion for APS.

Recurrent or multiple thromboses
Thrombosis of uncommon blood vessel
Unprovoked thrombosis at a young age
Placental insufficiency or severe pre-eclampsia or eclampsia
Livedo reticularis or racemosa
SLE diagnosis
Prolonged aPTT
Mild thrombocytopenia

Thrombotic APS

According to the 2019 EULAR guidelines [5], even asymptomatic people with a high-risk antiphospholipid antibody profile should be prescribed with a low dose of aspirin (75-100mg daily), indefinitely (primary prevention).

In case of thrombotic APS with a history of venous thrombosis, after initial anticoagulant treatment (usually LMWH (low-molecular-weight heparin), vitamin K antagonists (such as warfarin) should be administered long-term, with target INR (International Normalized Ratio of Prothrombin Time) 2-3. If the thrombotic event was provoked, e.g. after surgery, there is less data to support indefinite anticoagulant therapy. At this point, it should be emphasized that DOACs (Direct-acting Oral Anticoagulants) are not part of the treatment options for APS, as data is insufficient. The existing trials are negative; rivaroxaban failed, specifically for triple-positive APS patients [11].

When the diagnosis of APS is based on arterial thrombosis, the main treatment approach is the same, except for the option to target INR 3-4 or to co-administer aspirin with vitamin K antagonists, especially if the patient is considered high-risk. In high-bleeding-risk, frail, elderly patients with unclear diagnosis (low-risk antiphospholipid antibody profile) after a stroke, monotherapy with aspirin could be considered. Relapse, as far as thromboses are concerned, is defined as a recurrent thrombotic event that is diagnosed while the patient is on proper anticoagulant treatment and reaching the target INR. If the patient had previously discontinued the anticoagulant treatment or INR is below target for any reason, then a new thrombotic event should not necessarily lead to treatment reevaluation and escalation. In case of true relapse besides treatment, therapeutic options include adding aspirin to warfarin (double antithrombotic therapy), increasing the target INR from 2-3 to 3-4 and switching to parenteral heparin.

Obstetric APS

As far as obstetric APS is concerned, treatment is necessary during future pregnancies. Moreover, for women with a history of obstetric APS, indefinite prophylaxis with low-dose aspirin is generally recommended. A prophylactic dose of LMWH is also recommended for the puerperium period (at least six weeks postpartum). During pregnancy, double antithrombotic therapy is recommended; with the co-administration of aspirin with LMWH (in prophylactic dose for women with a

history of obstetric APS, especially with fetal death, or in therapeutic dose for women with a history of thrombotic APS). Vitamin K antagonists are of course contraindicated during pregnancy because of their teratogenicity. There is less evidence to support obstetric guidelines for asymptomatic women with high-risk antiphospholipid antibody profile, but aspirin should be considered during pregnancy [5].

Treatment beyond antithrombotic medication

Some manifestations of APS, most of which have an underlying pathogenetic mechanism of thrombotic microangiopathy, require immunosuppressive treatment.

Hematologic complications, specifically hemolytic anemia and severe thrombocytopenia (<20,000 platelets per mm³), can be treated with high-dose glucocorticoids, IVIG (intravenous immunoglobulin) or rituximab (an anti-CD20 monoclonal antibody). Other options include cyclophosphamide, azathioprine and MMF (mycophenolate mofetil). Splenectomy is generally avoided, because surgery in patients with APS is a potential trigger for further thromboses or even CAPS.

Antiphospholipid-antibody-related nephropathy is less studied. It can be chronic or acute. In case of acute renal failure, plasmapheresis is recommended. Treatment options also include rituximab, eculizumab (anti-C5 monoclonal antibody) or conventional immunosuppressants such as MMF or azathioprine.

Livedo reticularis or racemosa or livedoid vasculopathy, with skin ulcers, is difficult to treat. Glucocorticoids are generally ineffective. Some therapeutic options are antiplatelet treatment (aspirin, clopidogrel, dipyridamole), sildenafil, thrombolysis e.g. with alteplase, and hyperbaric oxygen therapy.

Catastrophic antiphospholipid syndrome, because of its severity, is aggressively treated with intravenous pulses of glucocorticoids (followed by high-dose continuous treatment), parenteral anticoagulants (classic heparin intravenously) and plasmapheresis or IVIG. Refractory CAPS can be treated with rituximab or eculizumab. Underlying infections should also be treated. Therapeutic decisions can be challenging in case of severe infections or active bleeding [2].

CONCLUSIONS

APS may be challenging to diagnose, partly because of possible non-thrombotic or microangiopathic manifestations that may require histopathological confirmation. Moreover, laboratory findings, specifically

antiphospholipid antibody tests, can be difficult to interpret, especially if they are transiently positive. Reevaluation and exclusion of other underlying conditions, such as infections or malignancies, is usually necessary. Underlying rheumatic diseases such as SLE should also be investigated. CAPS is a rare presentation of the disease but should be considered in the differential diagnosis because it requires urgent aggressive treatment, considering its high mortality.

Treatment is based on antithrombotic agents, but many manifestations require immunosuppressive therapy. Regulating the modifiable traditional risk factors for cardiovascular disease as well as necessary vaccinations are part of the disease management approach. Finally, patients with APS, as most patients with chronic disease, should be informed about the importance of lifestyle changes along with complying with long term pharmacological treatment and medical follow-up.

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Understanding and treating gout: A narrative review

Georgios Iliopoulos

Abstract

Gout is a chronic form of inflammatory arthritis characterized by monosodium urate (MSU) crystal deposition in mostly articular but also periarticular structures, such as tendons and bursae. Typically, gout is presented as acute monoarthritis, with self-limiting flares lasting from a few days up to two weeks. Although gout is treatable, 15% of patients can progress to advanced disease, if left untreated. Hyperuricemia, defined as serum uric acid (UA) higher than 6.8mg/dl, is considered the main driver of gout in most cases. Hyperuricemia and therefore MSU crystal formation stems from two broad categories being purine overproduction and decreased UA excretion. Hyperuricemia is usually asymptomatic in the early stage, but frequent gout flares may lead to chronic disease characterized by the presence of tophi, also known as tophaceous gout. Diagnosis can be clinical mostly in cases of podagra, but the gold standard is synovial fluid aspiration from involved joints where applicable. MSU crystal discovery on polarized microscopy yields 100% specificity in gout diagnosis. Gout treatment revolves around two main axons, acute flare management and chronic urate lowering therapy (ULT). Acute flares can be controlled with non-steroidal anti-inflammatory drugs (NSAIDs), colchicine or corticosteroids. The ULT drug of choice is allopurinol, a xanthine oxidase (XO) inhibitor. When ULT is prescribed, concomitant colchicine is administered as gout flare prophylaxis. Therapeutic measures regarding gout patients ought to be individualized, based on gout flare risk and comorbidity burden. In this narrative review we aimed to summarize and enhance the understanding of gout epidemiology, basic pathophysiology features, as well as management and follow-up.

Key words: *Gout; hyperuricemia; tophi*

INTRODUCTION

Gout is a chronic form of inflammatory arthritis characterized by monosodium urate (MSU) crystal deposition in mostly articular but also periarticular structures, such as tendons and bursae [1]. Typically, gout is presented as acute monoarthritis, with self-limiting flares lasting from a few days up to two weeks, while peak intensity of pain arises in the first 12 hours. Although gout is treatable, preventable and certainly not life-threatening, 15% of patients can progress to advanced disease (tophi and

erosive arthritis), if left untreated [2]. In this narrative review, we aimed to summarize and enhance the understanding of gout epidemiology, basic pathophysiology features, as well as management and follow-up.

MATERIALS AND METHODS

We conducted an electronic data search on Medline and Scopus from inception until November 2023. We used the keyword “gout” in combination with “hyperuricemia, clinical presentation, treatment” and assessed all articles. The inclusion criteria were that articles should derive from clinical trials, reviews or meta-analyses and should be written in English. Exclusion criteria were sporadic case reports with peculiar or atypical forms of gout. All in all, we chose the most representative and

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high-impact articles that served the purpose of this narrative review.

EPIDEMIOLOGY AND RISK FACTORS

Hyperuricemia is considered the main driver of gout in most cases. According to the definition of hyperuricemia, blood serum uric acid (UA) exceeds 6.8 mg/dl, which surpasses the point of MSU solubility threshold and subsequently MSU crystallization occurs [3]. Hyperuricemia is very common with a prevalence of 20% approximately [4]. However, according to recent data, less than 50% of those with UA over 10mg/dl will develop a gout attack throughout a 10–15-year period [5]. Consequently, although hyperuricemia is necessary for gout development, people with asymptomatic hyperuricemia may never develop gout. While gout epidemiology varies among different ethnic groups, 4-6% of the population suffer from this disease [6], whereas incidence revolves around 1-3 per thousand person-years [7]. Gout is most common in older males and the most prevalent risk factor is a purine-rich diet, especially excess alcohol consumption with a great emphasis on beer [8]. High purine diets include shellfish and red meat amongst others. Gout was known in the past as the “disease of kings” because if anyone could afford to eat a steak and accompany it with an alcoholic beverage, then he must have been a king [9]. Other renowned risk factors include men over the age of 40 and post-menopausal women, smoking, family history (heritability of hyperuricemia up to 60%) [10] and comorbidities like chronic kidney disease (CKD), metabolic syndrome, thyroid dysfunction, diabetes and certain medication, such as diuretics, beta-blockers and aspirin (mainly low dose) [11]. However, a recent mendelian study failed to prove a clear association between alcohol consumption and gout development [12]. Taken together, these data question the role of environmental risk factors in gout incidence.

ETIOLOGY AND PATHOPHYSIOLOGY

Purine overproduction and decreased UA excretion are the 2 main mechanisms leading to hyperuricemia and subsequent MSU crystal formation [5]. MSU crystals are formed because the solubility threshold of monosodium urate (6.8 mg/dl) is exceeded. Hematologic malignancies, metabolic syndrome, psoriasis, cytotoxic drugs and substances, especially alcohol can lead to purine overproduction. On the other hand, decreased UA excretion can be noted in several situations as in

metabolic acidosis, CKD and volume depletion conditions. It is established that transmembrane transporters in the proximal renal tubule dictate UA excretion [13]. Many transporters have been described, the most common being ATP binding cassette G2 (ABCG2), Glucose transporter 9 (GLUT9), urate transporter 1 (URAT1) and organic anion transporters (OAT). Latest research revealed the role of gut in UA excretion [14]. Increase of harmful bacteria, namely *Prevotella* and *Bacteroides* species and the decrease of protective ones, such as *Enterobacteriaceae* and *Faecalibacterium* species, leads to increase UA production and decreased kidney and intestine UA excretion, resulting in hyperuricemia and possibly facilitating gout flares. Enterocytes have been proven to express similar transporters that facilitate UA transfer. ABCG2 is a shared transporter of both gut and renal tubules. Mutations and polymorphisms in those transporters have been associated with hyperuricemia and can lead to impaired UA handling by the kidney [15]. Although gout pathophysiology is not entirely clear, innate immunity is considered the main driver of associated inflammatory responses [16]. Macrophages express Toll-Like Receptors (TLRs) on their surface, which recognize MSU crystals in the form of danger-associated molecular patterns. Then, MSU crystals are phagocytosed leading to upregulation of proinflammatory pathways such as nuclear factor kappa B (NF- κ B) pathway and NOD-Like Receptor 3 (NLRP3) inflammasome is constructed leading to caspase 1 production. Then, caspase cleaves pro-IL1b to its active form, IL-1b. This cytokine in turn orchestrates the inflammatory response through endothelium activation and neutrophil recruitment with neutrophils being the main offenders of gout flare [17]. As stated above, gout flares are self-limited and usually resolve within a few days. This is possible because even though neutrophils drive gout inflammation, they are also capable of stopping it. They excrete their DNA content, known as neutrophil extracellular traps (NETs), which bind MSU crystals and along with concomitant production anti-inflammatory cytokines, mostly IL-10 and TGF- β lead to flare resolution [18].

CLINICAL CHARACTERISTICS

A typical gout attack usually involves the 1st metatarsophalangeal joint (MTP) and in this case it is called podagra [19]. Monoarthritis is the most frequent presentation, but oligoarthritis (2-4 joints) is not uncommon, whereas polyarthritis is rare. Other commonly involved joints include the knees, ankles, wrists and other MTP

and finger joints [20]. The attacks are self-remitting within a few days and the peak pain intensity occurs in the first hours. Clinical presentation encompasses all the textbook signs of inflammation such as redness, swelling, warmth and great sensitivity to touch [21]. Lab tests can reveal elevated inflammatory markers, leukocytosis and sometimes the patient may complain of fever and malaise. Recurrent gout flares can lead to chronic disease called tophaceous gout identified by tophi formation [22]. Tophi are subcutaneous nodules made of MSU crystals. The most frequent sites of tophi deposition are the ears [23], elbows, small joints of the hands and feet. Except for the aesthetic aspect, tophi can be dangerous if left untreated without proper urate lowering therapy (ULT) and monitoring. They can cause bone erosions, structural joint damage and can become infected [24].

EVALUATION AND DIFFERENTIAL DIAGNOSIS

When evaluating an acute monoarthritis, one must contemplate that although gout necessitates hyperuricemia, serum UA is of extremely low specificity in gout for 2 reasons [25]. Firstly, during a gout flare and inflammation in general, serum UA might be falsely normal or even decreased [26]. Secondly, individuals with hyperuricemia may never suffer a gout attack. Diagnosis can be clinical mostly in cases of podagra, but the gold standard is synovial fluid aspiration from involved joints where applicable [27]. This is especially true for large joints, the most prominent being the knees and elbows. MSU crystal discovery on polarized microscopy yields 100% specificity in gout diagnosis. Negative birefringence is characteristic of gout, where needle-shaped crystals appear yellow when parallel to polarized light axis [28]. They should not be confused with Calcium Pyrophosphate Dihydrate Deposition Disease (CPPD) crystals, which have a rhomboid appearance and have positive birefringence, appearing blue when parallel to the polarized light axis. That being said, perhaps the greatest utility of joint aspiration is the exclusion of septic arthritis, a potent gout mimic with high mortality [29]. Septic arthritis occurs when a pathogen, usually bacteria, invades and assaults the joint microenvironment. Most common pathogens in fluid culture include *Staphylococcus Aureus*, *Neisseria gonorrhoeae* and streptococcal species. Fluid analysis typically reveals a white blood cell (WBC) count of over 50,000 cells with a Polymorphonuclear Neutrophil (PMN) predominance of over 75%. Treatment approach

in septic arthritis is a far cry from gout [30]. Measures encompass joint immobilization, percutaneous fluid drainage and empirical administration of wide spectrum antibiotics until culture results are available [31]. Rarely, septic arthritis can coexist with gout, as described in several case reports [32]. The most involved joint is the knee. Synovial fluid aspiration is important in such cases because the presence of high cell count (>50000 cells) along with concomitant fever and remarkably high inflammatory markers, may alert physicians towards septic arthritis coexistence. Other gout mimics include CPPD arthropathy, also known as pseudogout, meaning “false” gout, indicating similarities in both entities. Both are characterized by monoarthritis (for the most part) due to crystal deposition [33]. However, CPPD arthropathy is regularly associated with hyperparathyroidism, hypomagnesemia, CKD and hypothyroidism and predominantly affects elderly patients. Other systemic rheumatic diseases (RMDs), for instance rheumatoid arthritis (RA) or psoriatic arthritis (PsA), can showcase similar clinical presentation to gout [34]. The key differential diagnostic feature in this case is the acuteness of onset. Gout presents with an acute and sudden onset, whereas RMDs unravel joint-related symptoms gradually. Notably, psoriasis and PsA patients have a higher risk of developing gout compared to the general population [35]. Gout differential diagnosis is summarized concisely in Table 1.

Radiologic tests, although not mandatory for diagnosis, have their utility in patients with mono- or oligoarthritis [36]. Plain X-rays are often performed mainly for differential diagnostic purposes and not for gout diagnosis per se. For example, when history of trauma is present, X-rays may reveal a fracture or when CPPD is suspected, chondrocalcinosis of the involved joint may be observed. Furthermore, X-rays can confirm tophi, which are radio-opaque due to calcification [37]. Erosions can also be noted, especially in chronic tophaceous gout, giving the appearance of “overhanging edges”, a sign resulting from disruption of the outer bone cortex. Wherever available, ultrasound (U/S) of the involved area may reveal the double contour sign resulting from MSU crystal deposition on hyaline cartilage, which is unique to gout [38]. Dual-energy computed tomography (CT) can provide useful information in patients with chronic gout, as MSU crystals can deposit in periarticular tissues [39], even in peculiar places like the spine [40]. It is a specific CT sequence, where MSU crystals appear in green color most of the time [41]. Cases of low-back pain have

Table 1. Gout Differential Diagnosis.

GOUT MIMIC	FEATURES
Septic arthritis	Acute monoarthritis. High grade fever, prosthetic joint or bacterial infection history. Joint fluid aspiration and synovial culture are necessary.
Osteomyelitis	Subacute onset, extra-articular involvement, bone oedema in MRI and positive bone culture.
Cellulitis	Extra-articular localization. Skin and soft tissue involvement.
CPPD arthropathy	Very similar to gout. Rhomboid crystals on polarized light microscopy. Association with endocrinopathies. Usually elderly over the age of 65 years. Chondrocalcinosis is a common finding in X-rays.
Osteoarthritis (OA)	Chronic onset, absence of inflammation in blood or synovium. Joint pain worsens during daily activities and recedes with rest. OA evident in plain radiographs.
Rheumatoid Arthritis	Subacute onset, frequently symmetrical polyarthritis and longer symptom duration. Rheumatoid nodules can be mistaken for tophi.
Psoriatic Arthritis	Often coexists with gout. Higher incidence of gout. Skin disease and more gradual onset of arthritis can pinpoint PsA exacerbation.

been attributed to gout after performing dual-energy CT, which uncovered MSU crystals accumulating in the spine. However, higher cost dictates that dual-energy CT should be used sparingly [42].

TREATMENT AND FOLLOW-UP

Gout treatment revolves around three main axons, non-steroidal anti-inflammatory drugs (NSAIDs), corticosteroids (CS) and colchicine [43]. One therapeutic measure is not necessarily better than the other and physicians should follow an individualized approach [44]. NSAIDs, albeit a valid option for younger relatively healthy individuals, should be avoided in patients with many comorbidities, most notably cardiovascular disease (CVD) or CKD [45,46]. If NSAIDs are chosen as the drug of choice though, their full anti-inflammatory dose should be prescribed for one week approximately and not just symptomatic treatment [47]. CS, at a dose of 0.5mg/kg of bodyweight, can be effective for treating gout flare. Parenteral CS can possibly lead to faster flare resolution and constitute a more practical approach as they can be administered intramuscularly (IM) in the form of betamethasone or triamcinolone once or twice throughout the gout attack [48]. Nonetheless, patients with uncontrolled or poorly monitored diabetes should avoid CS [49]. Colchicine remains the cornerstone of gout flare treatment and prophylaxis [50]. When choosing to use colchicine, a tablet of 1 mg must be administered at the time of gout flare diagnosis and 0.5mg 1 hour after the first pill. Then, 0.5mg can be given once or twice daily for a week or longer if prophylactic therapy is needed. In

that case, colchicine should be prescribed as prophylaxis along ULT until the target of serum UA below 6mg/dl is reached and the patient is without flare for at least 1 month [51]. Recently, we have proven that IM tetracosactide, an ACTH analogue, showed favorable therapeutic outcomes in hospitalized patients with gout [52]. That should come as no surprise, since ACTH as a drug is approved by the Food and Drug Administration (FDA) in gout [53]. Except for cortisol production mobilization, the mechanism of action of tetracosactide pertains to a potent anti-inflammatory effect stemming from melanocortin receptor (MCR) binding, especially MC3R. The cortisol produced, along with the anti-inflammatory action of tetracosactide, makes this agent a plausible alternative to GCs. Anakinra, an IL-1 receptor antagonist, administered subcutaneously (SC) at a dose of 100mg daily, can be reserved for severe gout flares in patients with heavy comorbidity burden, which does not allow for the usual therapeutic agents [54]. Albeit effective for gout flares, anakinra should be used sparingly due to high cost-to-benefit ratio. Canakinumab, a selective IL-1 β blocker, constitutes another potent therapeutic option in severe gout [55]. Nevertheless, canakinumab is directed towards special cases due to high cost.

Once gout flare is resolved, decisions regarding hyperuricemia must be made. All patients with even one gout attack in their lifetime should be assessed for comorbidities creating a hyperuricemic environment, especially cardiometabolic disease. Nevertheless, patients with very sporadic gout attacks may not need ULT [56]. However, more than two flares per year and

the presence of tophi or erosions necessitates ULT. The ULT drug of choice is allopurinol, a xanthine oxidase (XO) inhibitor [57]. An initial dose of 100mg is administered and serum UA must be measured every three to six weeks until target serum UA is reached. According to consensus and recommendations, the target is 6mg/dl and allopurinol dosage can be escalated up to 800mg daily to achieve this goal [58]. In the case of tophaceous arthritis, the target UA threshold is lowered to 5mg/dl [47]. Also, due to the destructive nature of tophi and their erosive potential, ULT tends to require closer monitoring. When ULT is prescribed, concomitant colchicine is administered as gout flare prophylaxis until target serum UA is reached and the patient is free of flares for at least 1 month [59]. The rationale behind colchicine prophylaxis revolves around the hypothesis of MSU crystal mobilization from periarticular structures following ULT that can trigger local immune responses inflicting a gout flare. Colchicine as prophylaxis is usually administered at the dose of 0.5mg daily or bidaily. Second line ULT agents encompass febuxostat [60], another XO inhibitor, which is prescribed in cases of allopurinol allergic

reaction or intolerance. Another ULT class, uricosurics, especially probenecid can be useful in treating gout in patients who cannot tolerate a XO inhibitor, but extra attention should be warranted towards the patient having adequate liquid daily intake due to high risk of renal stone formation [61]. That being said, uricosurics have been combined with XO inhibitors with success regarding serum UA lowering compared to monotherapy [62]. In extreme case of gout and tophaceous arthritis where all therapeutic approaches have failed, pegloticase, a recombinant uricase, can be administered with biweekly intravenous (IV) infusions, but physicians must be aware of two possible hazards [63]. The first is the development of antidrug autoantibodies and the second is the high risk of infusion reaction. To avoid both situations, concomitant immunosuppressive therapy is recommended from the start and the agents of choice are methotrexate and mycophenolate mofetil (MMF). Figure 1 outlines a therapeutic approach algorithm for gout patients.

Finally, the urate-lowering potential of lifestyle modifications has been a matter of controversy over the years

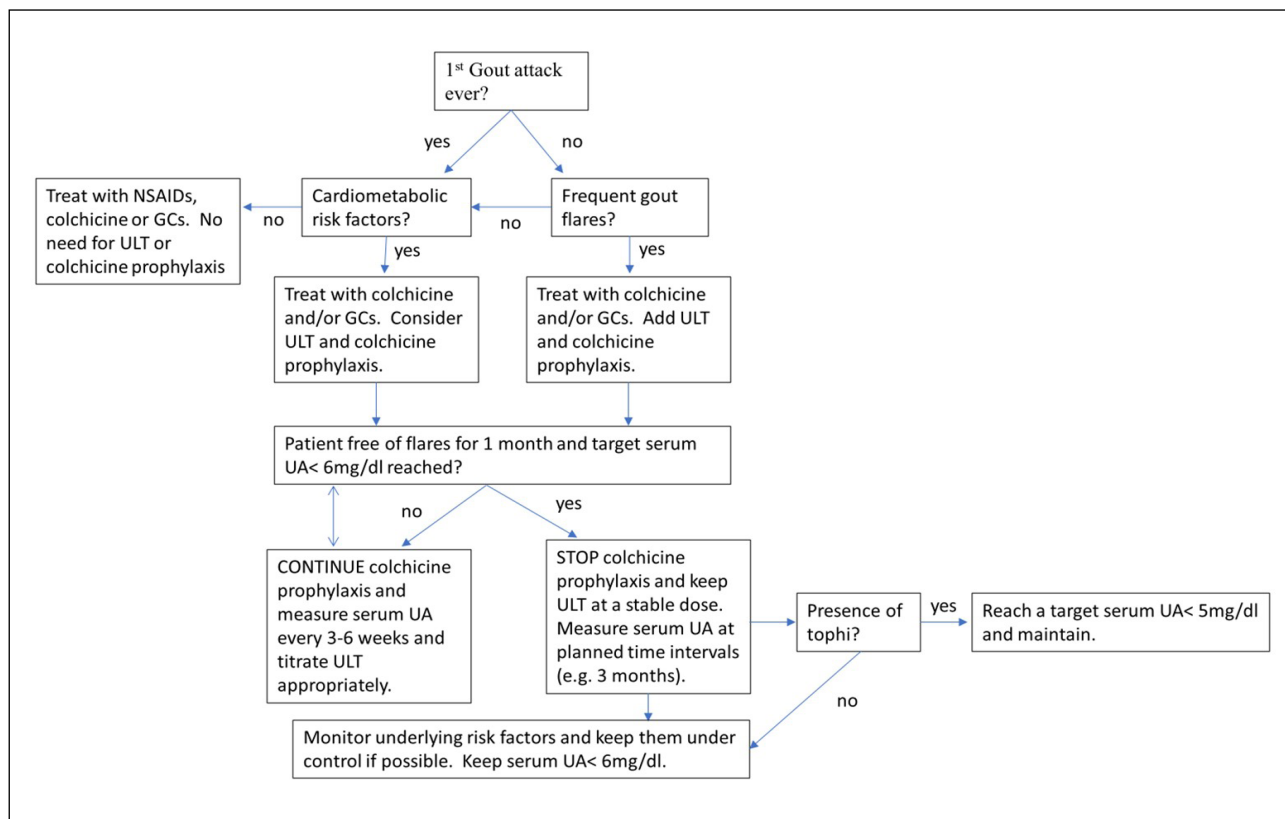


Figure 1. Gout Therapeutic Approach Algorithm.

Abbreviations: NSAIDs, non-steroidal anti-inflammatory drugs; GCs, glucocorticoids; ULT, urate lowering therapy; UA, uric acid.

[25]. Often, patients prefer to try and modify their daily habits rather than taking ULT medication. Although alcohol cessation (and especially beer) is essential to avoiding gout flares, lifestyle modifications have been proven to have modest benefit at best [64]. That is not to say that patients should deviate from healthy eating, fat loss (where applicable) and comorbidities management, but one should not hope for a meaningful change in serum UA with lifestyle changes alone [65]. Maybe the best practice is reflected by a combination of ULT and daily habits alterations [66].

SPECIAL CONSIDERATIONS

In everyday clinical practice, there is a trend towards treating asymptomatic hyperuricemia without gout history [67]. Despite the rationale behind this practice, the benefit of ULT is not guaranteed to outweigh the cost, namely drug reactions [68], adverse events and interactions [69]. According to a meta analysis, patients with serum UA values higher than 10mg/dl had less than 50% chance of suffering a gout attack in 15 years, whereas the incidence at five-year-period was approximately 25% [70]. Of course, there is a time for exceptions and risk stratification, particularly in patients with metabolic syndrome, CKD or CVD, where hyperuricemia could act as a secondary cardiovascular risk factor [57]. Another important consideration is patient education regarding gout attack management [71]. Towards this direction, the “pill-in-a-pocket” approach has been proposed [72]. According to this method, the patient is literally prepared to face a gout flare, by having tablets of colchicine, corticosteroids or NSAIDs, readily available, ensuring timely intervention and a potentially faster flare resolution. Another topic of concern seems to be the place of allopurinol in CKD patients. Physicians are oftentimes reluctant to prescribe ULT therapy in such cases, confusing allopurinol with colchicine. Indeed, colchicine should be used cautiously in patients with estimated glomerular filtration rate (eGFR) lower than 30 ml/min. Wei et al found no worsening of renal function or reduced survival in moderate to severe CKD patients who took allopurinol [73]. With that in mind, CKD patients were found to have increased risk of allopurinol hypersensitivity reaction [74]. This is particularly true for people who are positive for a specific human leukocyte antigen (HLA), HLA-B*5801, commonly encountered in Asian and African American populations [75]. Allopurinol hypersensitivity reaction is characterized by diffuse rash, acute kidney or hepatic injury and high blood eosino-

phil count, usually in the context of drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [76]. In the event of such a reaction, topical or systemic corticosteroids should be administered, following immediate allopurinol cessation. Another topic reserved for last is the heart involvement in patients receiving febuxostat treatment. According to the 2018 CARES trial [77], increased CVD-related and all-cause mortality was noticed in the febuxostat versus allopurinol group, following randomization. This observation even led the FDA to issue a febuxostat black box warning for CVD patients. However, those findings were not replicated in the 2020 FAST trial [78], where no difference in CVD events or death were noted between the two groups. Results should be always taken with a grain of salt, since CARES trial had 50% loss to follow-up compared with 5.8% of the FAST trial. All in all, febuxostat appears to be safe in patients with heart involvement.

CONCLUSION

Gout management, albeit seemingly simple, requires a multifactorial and multidisciplinary approach. Frequent gout flares render ULT unavoidable, while lifestyle changes have modest benefits. Nevertheless, patient education remains crucial [79]. In any case, therapeutic approach plans for gout patients ought to be individualized, based on gout flare risk and comorbidity burden [80].

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- Abstract and Key Words
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Margins should be not less than 2.5 cm. Pages should be numbered consecutively.

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Do not use non-standard abbreviations. The use of abbreviations in the title and abstract should be avoided. Abbreviations should be defined on their first appearance in the text; those not accepted by international bodies should be avoided.

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- Conflict of interest disclosure.
- Declaration of funding sources.
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For Original Articles, structured abstracts should be 250 words or less and include the following sections: Background, Methods, Results and Conclusion. Review articles should carry an unstructured abstract which should not exceed 200 words.

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For the main body of the text, the recommended structure of

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Define abbreviations at first mention in text and in each table and figure.

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