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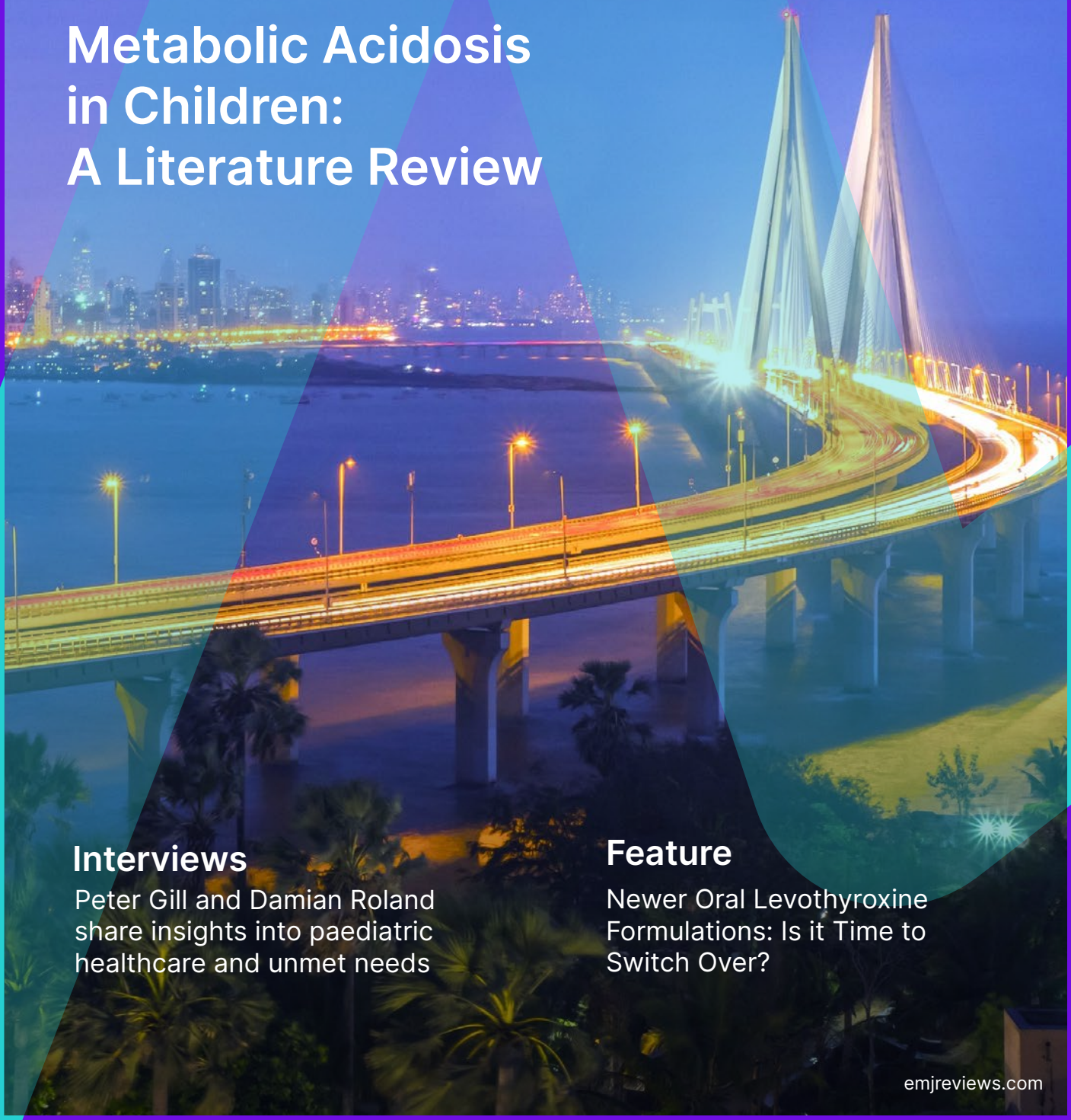
EMJ

Editor's Pick

Metabolic Acidosis in Children: A Literature Review



Interviews

Peter Gill and Damian Roland share insights into paediatric healthcare and unmet needs

Feature

Newer Oral Levothyroxine Formulations: Is it Time to Switch Over?

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 The cover photo is of Mumbai, India, the location of work for one of the authors of the Editor's Pick.

Front cover and contents photograph: Mumbai, India

Welcome letter

Koutsouki

Evgenia Koutsouki
Editor

Dear Readers,

Welcome to the first issue of the EMJ flagship for 2023! It is an immense pleasure to bring you this issue, which covers content from a number of areas of clinical practice, alongside curated content focusing on paediatric medicine practice across various disciplines. Part of this mini-focus on paediatrics is our report on paediatric radiology, covering a session from the recently held European Congress of Radiology (ECR), which took place in Vienna, Austria, in early March.

In line with this topic, we are proud to also bring you interviews with two experts in paediatric medicine, who discuss unmet needs, the value of eHealth, and paediatric emergencies. Our Editor's Pick for this issue is a systematic review of metabolic acidosis in children, exploring monitoring and therapeutic approaches.

As well as all of the above, the journal features a plethora of articles, ranging from a case report of a female with caseous mitral annular calcification, to a review of the impact of benzodiazepines on cognitive impairment in dementia.

This welcome would not be complete without a mention of our Editorial Board, our contributors, and peer reviewers, who have, as always, elevated the content quality we bring you in this issue. I hope you enjoy reading it and please do not miss our next issue, which will have a mini-focus on geriatric medicine.

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Foreword

Dear Colleagues,

Welcome to our latest issue of *EMJ*, which is, as always, filled with engaging, considered, and forward-thinking content. Topics such as the impact of using benzodiazepines as a treatment for symptoms of dementia, the importance of using a multidisciplinary approach when managing female patients presenting with chronic pelvic pain, and the potential role of a newer treatment for hyperthyroidism are covered in this journal.

The mini-focus of this flagship journal is paediatrics. Thus, my Editor's Pick for this issue is 'Metabolic Acidosis in Children: A Literature Review' by Zaki and Shanbag. This superb paper explores this acid-base disorder, a common diagnosis in the paediatric population, which can have detrimental consequences if severe or prolonged. Zaki and Shanbag's systematic literature review examines pathogenesis, diagnostic evaluations, and treatment modalities, as well as their potential side effects.

Our feature, written by Rajkumar, examines the role of newer formulations of oral levothyroxine in the treatment of hyperthyroidism and their potential for advancing patient care. The current common treatment for this condition is a form of levothyroxine sodium tablet, the side effects of which can cause suboptimal care for patients due to more frequent clinician visits and dosage changes.

This issue also showcases fascinating case reports on marantic endocarditis and lung adenocarcinoma alongside brain metastasis; a rare variant of mitral annular calcification, caseous mitral annular calcification, that presented as retinal artery occlusion; and a late complication in the treatment of a female patient with incontinence, who developed a urinary bladder stone following injection with a polyacrylamide hydrogel bulking agent.

Continuing with our mini-focus, EMJ carried out interviews with Damian Roland of the Children's Emergency Department, Leicester Royal Infirmary, and Honorary Professor in Population Health Sciences at the University of Leicester, UK; and Peter Gill, Associate Scientist and Assistant Professor at The Hospital for Sick Children, Toronto, and the Department of Paediatrics and Institute of Health Policy, Management and Evaluation at the University of Toronto, Canada.

As ever, I extend my heartfelt thanks to all of the authors, reviewers, interviewees, and Editorial Board members who have worked tirelessly on this issue. I hope that this journal will be an innovative and immersive read for healthcare professionals all over the globe.

Prof László Vécsei

Head of Neuroscience Research Group, Department of Neurology, University of Szeged, Szeged, Hungary

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Risks and Safety in Paediatric Radiology

Authors: Evgenia Koutsouki, Editor

Citation: EMJ. 2023;8[1]:10-14. DOI/10.33590/emj/10308469. https://doi.org/10.33590/emj/10308469.

In a highly engaging session at the European Congress of Radiology (ECR) in Vienna, Austria, which took place 1st–5th March 2023 and was chaired by Hans-Joachim Mentzel, experts came together to discuss risks and safety measures, including different radiology practices in children.

ECR 2023

RADIATION SAFETY IN PAEDIATRIC CT

When introducing the main risks involved in paediatric CT, Magdalena Maria Woźniak, Medical University of Lublin, Poland, explained that these include the risk of radiation, the risk linked to sedation, and the risk of use of contrast media, but that a lot can be done to reduce the risk of radiation, as many factors can be controlled by the radiologist.

Special attention needs to be given to the justification and optimisation of CT procedures in children, Woźniak explained, as the radiosensitivity of organs and the distribution of radiosensitive tissue differ in comparison to adults. However, the actual risk of developing cancer is still difficult to assess, meaning it is important to ensure that the radiation dose used does not exceed the necessary dose for an image of adequate diagnostic quality.

In terms of justification, Woźniak explained the importance of considering other imaging modalities, which do not involve ionising radiation, and for the radiologist to review every referral, ensuring criteria are met before deciding on the protocol and modality to be followed.

When optimising the procedures involved, there are a few factors to be considered. Woźniak emphasised the importance of keeping the patient immobilised, as this helps obtain a better image quality, thus reducing the risk of radiation intake. Using equipment specially designed for children is key, especially in facilities with a large population of paediatric patients, as is usage of pre-installed protocols for standard examinations tailored to paediatric patients. Woźniak also highlighted the importance of determining the used scan's field of view to cover the whole patient, thus avoiding artefacts, versus the smaller diagnostic field of view. When performing a scan, one should aim for the least acquisitions possible and the most reconstructions possible. The use of new technologies, including tube current modulation, organ based tube current modulation, automatic kilovolt selection, and adaptive collimation, can go a long way in reducing the radiation dose.

Woźniak concluded her talk by emphasising that the referrals for paediatric CT should be evaluated beforehand for justification and procedure optimisation. Furthermore, protocols should be adapted according to patient size and not age, except for brain CTs, and should take into consideration the clinical tasks. Looking

into the future, with the progress in medical X-ray technology, alongside the commitment of manufacturers to continued innovation, there is high potential for high dose reduction.

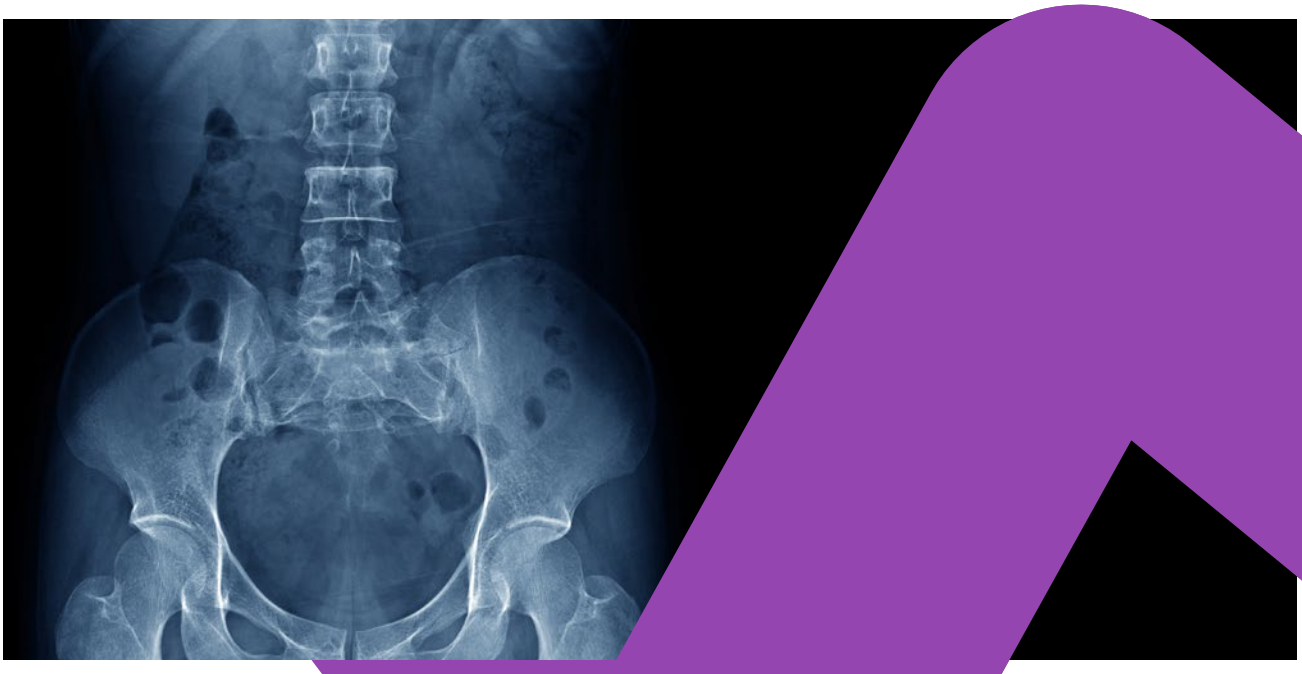
THE PROS AND CONS OF SHIELDING

In discussing the benefits of shielding in children, Rutger Jan A.J. Nievelstein, University Medical Center Utrecht, the Netherlands, explained that this is used in order to reduce the stochastic effects of radiation as well as its deterministic effects, such as skin erythema and cataract.

When thinking about shielding, Nievelstein explained it is important to consider factors such as obscure pathologies or anatomic structures, incorrect placement due to anatomic variations, interference with automatic exposure control systems, and beam hardening and streak artefacts, which can occur especially in CT.

A 2012 study[1] demonstrated that gonad shielding was placed incorrectly in 91% of females and 66% of males in pelvic radiographs of children aged 0–15 years. Given that the dose of pelvic radiograph is very low and the genetic risk without shielding is also very low, the risk reduction with shielding was calculated to be only 6% for females and 24% for males. According to the study, shielding does not add anything for risk reduction to the child and it is best left out, as when shielding is not done properly it increases the risk of retakes, which will actually increase the dose to the child. In fact, based on the European Consensus recommendation published in 2021, shielding is not recommended in any indications, except maybe in dental cone beam CT.

Exploring dose reduction strategies for conventional radiography and fluoroscopy, Nievelstein explained that good collimation, posterior anterior positioning, and removal of anti-scatter grids, especially in children under 12 years of age, are important. In radiography, focus-film distance that is as large as possible, use of filtration when applicable to remove the low energy radiation, and preferably avoiding usage of automatic exposure are also important. In fluoroscopy, factors to consider are increasing X-ray to skin distance, minimising the magnification, using image grabs instead of radiographs, and using pulsed fluoroscopy adapting pulse rate



to indication, preferably using as low a frame rate as possible.

In his concluding remarks, Nievelstein explained that shielding inside and outside the field of view is not recommended in almost all indications, and optimisation of technique and operator parameters in computed radiography and fluoroscopy are more efficient as a strategy for dose reduction. Nievelstein emphasised that using the European Diagnostic reference levels for a daily practice already results in very low doses of ionising radiation in computed radiography and fluoroscopy in children; however, there is room for further optimisation of these, as they are median values of doses used in different countries across Europe.

RISKS OF ULTRASOUND IN CHILDREN

In discussing the risks associated with ultrasound (US), Michael Riccabona, LKH University Hospital Graz, Austria, explained that the sound energy applied to the body during US might have both a mechanical impact on the body and thermal effects caused by molecular motion. The use of contrast agents also has risks associated with it. Unlike radiation, there is no stochastic effect in US and, therefore, the risk correlates to the amount of energy used, which can be managed by observing the output of the device. The energy output can be displayed on screen expressed as Watts, as a percentage of maximum output, as mechanic index, or as thermal index.

Quoting the European Federation of Societies for Ultrasound in Medicine and Biology (EFSUMB) guidelines, Riccabona explained that "diagnostic US can only be safe if used prudently and performed by trained and competent personnel." In explaining the risks of various US methods, Riccabona explained that harmonic imaging possibly has a higher mechanical index, whereas doppler involves more tissue heating and thus higher thermal index. Specifically, doppler applications need high intensities to obtain strong echoes from poorly reflecting blood cells for flow studies.

> **"Diagnostic US can only be safe if used prudently and performed by trained and competent personnel."**

With contrast enhanced US there are cavitation risks, even at relatively low mechanical index, and, finally, with elastography it is probable that more energy is used due to the stronger and longer acoustic pulse sequence. Riccabona emphasised the importance of observing the as low as reasonably possible (ALARA) principle, particularly in vulnerable organs and patient groups.

Ricabona also discussed the importance of cleaning and disinfecting to reduce the risk of viral and bacterial contamination, as well as the risk of nosocomial transmission of pathogens or cross infections between patients. Among items and areas that might require cleaning are the transducers, examiner's hands, investigation table, and keyboard. However, Ricabona emphasised that it is important to be careful about negative interaction with the transducer material, as disinfectant may destroy the surface, alter or impair imaging performance, and cause damage to the materials, or make the transducer electrically unsafe.

MITIGATING THE RISKS OF PAEDIATRIC MRI

Ruth O'Gorman Tuura, Center for MR Research, University Children's Hospital Zurich, Switzerland, discussed safety

in paediatric MRI. O'Gorman Tuura explained that the actual level of risk might differ between children and adults, not only due to differences in physiology, but also due to procedural differences, such as the involvement of additional staff, the presence of parents in scans, and difficulties with patient screening.

In MRI, the sources of risk arise from the static magnetic field, the radiofrequency pulses to excite the signal, and the time-varying magnetic field gradients used. Each of the magnets has projectile effects, and radiofrequency might cause heating of tissue and potential burns. Finally, peripheral nerve stimulation, acoustic noise, and interaction with devices are risks of the magnetic field gradients.

O'Gorman Tuura emphasised the importance of having local safety policies in place, and implementing access control to make sure that people without magnetic resonance (MR) training are not able to access the area to mitigate the magnetic field risk. It is also important to have adequate staff training, with clear roles and responsibilities outlined. She recommended always referring to national and international guidelines to stay informed and educated.

The most frequently reported adverse events arising from radiofrequency are the result of skin-to-skin contact or contact with the scanner bore radiofrequency coil. The ways to mitigate these are through specific absorption rate management; avoiding skin-to-skin contact and small points of skin contact; avoiding contact with the bore, ECG leads, or other electrically conductive objects; and using insulating pads. Changing patients into hospital provided gowns with no microfibres is also key in mitigating risk.

In children, due to differences in size, water content, and electrical properties, compared to adults, heat deposition and dissipation are altered, particularly in young children and neonates. Accurate estimation of heating depends on

"Changing patients into hospital provided gowns with no microfibres is also key in mitigating risk."

knowledge of child-specific parameters. In a simulation study investigating heating in neonates, additional hotspots were observed with child-specific values, meaning that heating risk is altered in children, particularly in neonates compared to adults. Cooling is also a concern, especially in neonates where the incubator temperature has been found to have dropped after scans, so excessively long scans can be problematic.

In terms of time varying gradient field risks, the magnitude of the switched gradient fields increases with distance from the isocentre, suggesting that the risk is smaller for children than adults. Adverse health effects have been linked to excessive sound pressure in preterm neonates. Neonatal earmuffs in combination with earplugs can reduce noise significantly.

Procedural challenges include the need for sedation in children, meaning that additional personnel and equipment are in the room and that there is no feedback available during the scan. In addition, parents may need to accompany unsedated children, meaning that procedures need to be put in place to screen the parents and document their answers to questions. Finally, teenagers might need double screening, with and without a parent, and there is an increased risk of foreign bodies.

In terms of solutions, O'Gorman Tuura explained that anaesthesia for neonates might not be necessary, as sedation can be done under natural sleep using the feed and wrap method. For older children, regular training for all staff involved in MRI is essential, but specific training for the anaesthesia team for practicing emergency procedures in the room is essential, as is building a strong safety culture.

In the final part of her talk, O'Gorman Tuura went through the procedures for imaging in people with implants. She highlighted the importance of looking for the MR label of safety in implants, confirming the model of implant from patient notes, looking up the latest guidelines from the implant manufacturers, and following MR conditional labelling. O'Gorman Tuura also explained that for cardiac implantable electronics a decided risk benefit analysis needs to be carried out, and there need to be defined responsibilities and procedures for monitoring the patient during the scan. For unlabelled implants for MR safety, O'Gorman Tuura emphasised the importance of assuming it is unsafe but gathering as much information as possible to assess the risk and carrying out a risk benefit analysis by the supervising radiologist. ●

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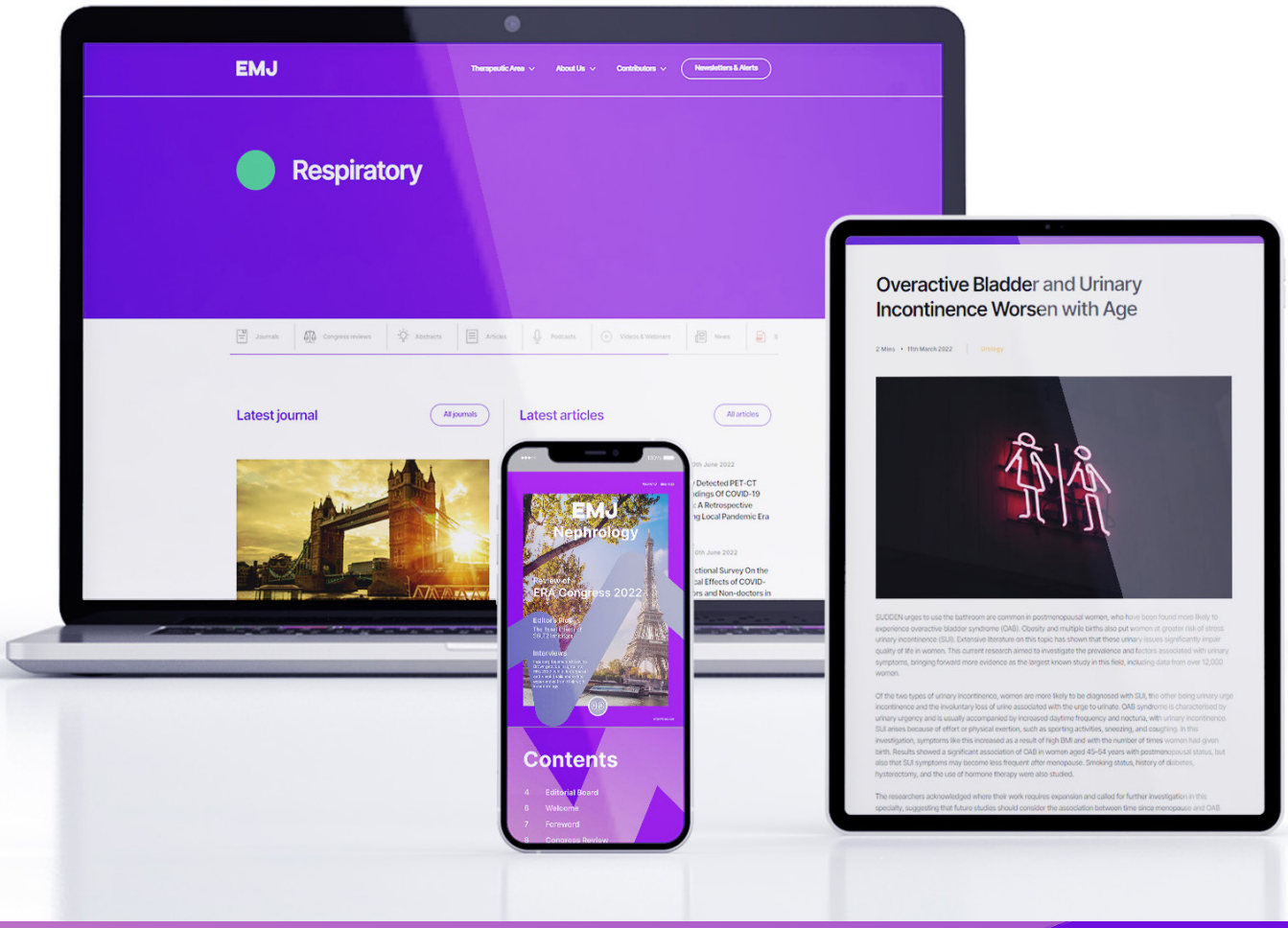
1. Franzen MJ et al. Gonad shielding in paediatric pelvic radiography: disadvantages prevail over benefit. Insights Imaging. 2012;3(1):23-32.



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The Role of Granulocyte-Colony Stimulating Factor Biosimilars for Supportive Cancer Care: A Year in Review

This year in review article covers the role of granulocyte-colony stimulating factor biosimilars for clinical care in breast, colorectal, and gynaecological cancers, featured at American Society of Clinical Oncology (ASCO), American Society of Hematology (ASH), European Society for Medical Oncology (ESMO), and San Antonio Breast Cancer Symposium (SABCS) 2022

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Disclaimer: Not all medicines and/or indications presented in this report may be approved for use in all countries.

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Keywords: Breast cancer, chemotherapy, colorectal cancer, febrile neutropenia, filgrastim, granulocyte-colony stimulating factor (G-CSF), G-CSF biosimilar, gynaecological cancer, pegfilgrastim, primary prophylaxis.

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Meeting Summary

This year-in-review article provides insights into clinical updates relating to granulocyte-colony stimulating factor (G-CSF) biosimilars research presented at five key congresses in 2022. These include the American Society of Clinical Oncology (ASCO) 55th Annual Meeting (3rd–7th June 2022, Chicago, Illinois, USA), European Society for Medical Oncology (ESMO) Congress (9th–13th September 2022, Paris, France), ESMO Asia Congress (2nd–4th December 2022, Singapore), San Antonio Breast Cancer Symposium (SABCS; 6th–10th December 2022, Texas, USA), and American Society of Hematology (ASH) 64th Annual Meeting and Exposition (10th–13th December 2022, New Orleans, Louisiana, USA). Alongside reviewing the current research presented at these key congresses, with a focus on the use of G-CSF agents and biosimilars in patients undergoing treatment for breast, colorectal, and gynaecological cancers, this article provides an overview of current guidelines on the use of G-CSF in supportive cancer care to manage chemotherapy-induced febrile neutropenia and explores trends in G-CSF biosimilars research.

INTRODUCTION

Chemotherapy-induced neutropenia is a frequent, severe, adverse haematological complication of myelosuppressive and immunosuppressive cytotoxic chemotherapy treatment.[1-5] Chemotherapy-induced neutropenia is defined by the National Comprehensive Cancer Network (NCCN) guidelines as a low white blood cell count (neutrophils), which can result in immunosuppression and is associated with an increased risk of infection that, when accompanied by fever, is termed febrile neutropenia.[5,6] Patients undergoing cytotoxic chemotherapy are, therefore, at a greater risk of contracting a life-threatening infection.

The occurrence of febrile neutropenia is associated with the intensity of chemotherapy and remains one of the most frequent and serious complications of chemotherapy.[1-5] Development of febrile neutropenia may compromise the treatment response, as it may necessitate dose reduction and treatment delay.[7,8] This imposes a substantial economic burden,[7,8] requiring hospitalisation and treatment with broad-spectrum antibiotics, and is associated with significant morbidity and mortality.[3,6] In patients with early breast cancer, neutropenia is reported to be the most common adverse event experienced, resulting in a reduction in relative dose intensity (RDI) for those receiving chemotherapy, reducing treatment efficiency and overall survival.[9]

A survey in the USA, presented during a poster session at ASH 2022, investigated the National Inpatient Sample (NIS) database in 2019 for the prevalence and clinical outcomes of febrile neutropenia in patients hospitalised with cancer.[10] Out of 118,965 patients hospitalised for febrile neutropenia or fever and neutropenia, 24,444 patients (88.1%) had a co-diagnosis of cancer and febrile neutropenia, including 24.5% (n=5,995) who were paediatric patients (<18 years). The severity of illness and risk of mortality was classified as 'moderate' in 57.2% (using the All Patient Refined Diagnosis Related Group [APR DRG] severity index). Among this sample of inpatients hospitalised with febrile neutropenia, the most common cancer types were haematological malignancies (59.4%), including non-Hodgkin lymphoma, acute myeloblastic or lymphoblastic leukaemia, myelodysplastic syndrome, and multiple myeloma. Other cancer types included breast cancer (7.8%) and gastrointestinal cancer (5.0%).[10]

GUIDELINES FOR GRANULOCYTE-COLONY STIMULATING FACTOR PRIMARY PROPHYLAXIS AND TREATMENT OF FEBRILE NEUTROPENIA

International febrile neutropenia guidelines from the European Organisation for Research and Treatment of Cancer (EORTC),[1] ASCO, and Infectious Diseases Society of America (IDSA) joint update,[2,3] ESMO,[4] as well as the NCCN,[5] aim to standardise the recommendations for the prevention, diagnosis, and treatment of febrile neutropenia (Table 1). The overall consensus is that febrile neutropenia is indicated by a fever above 38 °C, accompanied by an abnormally low absolute neutrophil count ($<0.5\times10^9$/L) and may also present with signs of infection, typically identified by physical examination, blood and urine cultures, and imaging, where necessary.[1-5]

Due to the high risk and frequency of febrile neutropenia associated with chemotherapy, current guidelines recommend analysing the risk before each chemotherapy cycle regimen,[4] and considering whether the use of primary prophylaxis to prevent chemotherapy-induced febrile neutropenia may be warranted.[1-5] The Multinational Association of Supportive Care in Cancer (MASCC) prognostic index is widely used to predict the prognosis of febrile neutropenia after chemotherapy in patients with cancer,[11] as well as the Clinical Index of Stable Febrile Neutropenia (CISNE) score.[12]

Primary prophylaxis is based on the use of G-CSF to stimulate granulocyte proliferation in the bone marrow and increase the number of circulatory neutrophils, supporting haematopoietic recovery following chemotherapy.[5,13] G-CSF may be used as supportive care for both solid and haematological tumours, typically administered 24–48 hours after the first cycle of chemotherapy.[14]

According to the ASCO/IDSA, EORTC, ESMO, and NCCN practice guidelines (Table 1),[1-5] G-CSF agents, including filgrastim or pegfilgrastim,

Table 1: Summary of the clinical practice guidelines for adult patients with cancer at risk of, or who require treatment for febrile neutropenia.[1-5]

Clinical Guidelines	Summary of recommendations for G-CSF for febrile neutropenia*	Reference to G-CSF biosimilar use†
ASCO[2]/IDSA joint[3]	• Prophylactic use of G-CSF to reduce the risk of FN is warranted when the risk of FN is approximately 20% or higher and no other equally effective and safe regimen that does not require G-CSFs is available. • Primary prophylaxis with a G-CSF starting with the first cycle and continuing through subsequent cycles of chemotherapy is recommended in high risk (≥20%). • Secondary prophylaxis with G-CSF is recommended for patients who experienced a neutropenic complication from a previous cycle of chemotherapy (for which primary prophylaxis was not received), in which a reduced dose or treatment delay may compromise disease-free or overall survival or treatment outcome. • In many clinical situations, dose reduction or delay may be a reasonable alternative. G-CSFs should not be routinely used for patients with neutropenia who are afebrile.	• Pegfilgrastim, filgrastim, tbo-filgrastim, and filgrastim-sndz (and other biosimilars, as they become available) can be used for the prevention of treatment-related FN.
EORTC[1]	• Recommends that patient-related adverse risk factors such as elderly age (≥65 years) and neutrophil count be evaluated in the overall assessment of FN risk before administering each cycle of chemotherapy. • It is important that after a previous episode of FN, patients receive prophylactic administration of G-CSF in subsequent cycles. • An expanded list of common chemotherapy regimens considered to have a high (≥20%) or intermediate (10–20%) risk of FN is provided. • Prophylactic G-CSF continues to be recommended in patients receiving a chemotherapy regimen with high risk of FN. • When using a chemotherapy regimen associated with FN in 10–20% of patients, particular attention should be given to patient-related risk factors that may increase the overall risk of FN. • In situations where dose-dense or dose-intense chemotherapy strategies have survival benefits, prophylactic G-CSF support is recommended. Similarly, if reductions in chemotherapy dose intensity or density are known to be associated with a poor prognosis, primary G-CSF prophylaxis may be used to maintain chemotherapy.	• Clinical evidence shows that filgrastim, lenograstim, and pegfilgrastim have clinical efficacy; the use of any of these agents to prevent FN and FN-related complications where indicated is recommended. • Filgrastim biosimilars are also approved for use in Europe. While other forms of G-CSF, including biosimilars, are administered by a course of daily injections, pegfilgrastim allows once-per-cycle administration. • Choice of formulation remains a matter for individual clinical judgement.
ESMO[4]	• The risk of complications related to FN should be assessed individually for each patient at the beginning of each cycle. • When assessing FN risk, the clinician should take into account patient-related risk factors (recommendation 1),* the chemotherapy regimen and associated complications (recommendations 2 and 3),* and treatment intent (recommendation 3).* • Prophylactic G-CSF is recommended when there is a ≥20% overall risk of FN. • When chemotherapy regimens associated with an FN risk of 10–20%, particular attention should be given to the assessment of patient characteristics that may increase the overall risk of FN.	• Filgrastim, lenograstim, and pegfilgrastim have clinical efficacy and ESMO recommends the use of any of these agents, according to current administration guidelines, to prevent FN and FN-related complications, where indicated. • Filgrastim biosimilars are now also a treatment option in Europe.

Table 1 contined.

Clinical Guidelines	Summary of recommendations for G-CSF for febrile neutropenia*	Reference to G-CSF biosimilar use†
NCCN[5]	• Patients in the high-risk group (risk of developing FN is greater than 20%) should receive prophylactic G-CSF (category 1).* • Prophylactic G-CSF should also be considered for patients in the intermediate-risk group (risk as a 10–20% probability of developing FN or a neutropenic event that would compromise treatment) based on patient-specific risk factors (see Patient Risk Factors for Developing FN).* • Patients in the low-risk group (as defined by an FN risk of less than 10%) should generally not receive prophylactic G-CSF.	• Filgrastim, tbo-filgrastim, pegfilgrastim, and biosimilars are FDA-approved options for FN prophylaxis in patients with solid tumours receiving myelosuppressive chemotherapy.

*Please refer to the complete guidelines for detailed information, recommendations, and further clinical tools and resources.

†Approval may have been granted from either the EMA or FDA but may not be authorised in all countries, and some agents may have been added or withdrawn from approval at the time of print.

ASCO: American Society of Clinical Oncology; ECORTC: European Organisation for Research and Treatment of Cancer; EMA: European Medicines Agency; ESMO: European Society for Medical Oncology; FDA: U.S. Food & Drug Administration; FN: febrile neutropenia; G-CSF: granulocyte-colony stimulating factor; IDSA: Infectious Diseases Society of America; NCCN: National Comprehensive Cancer Network.

and several biosimilar products associated with the reference (originator) drug (such as tbo-filgrastim, filgrastim-sndz, filgrastim-aafi, pegfilgrastim-jmdb, pegfilgrastim-bmez, and pegfilgrastim-apgf), are also approved for the reduction of neutropenia-related outcomes.[15] (These drugs may have been approved by either the European Medicines Agency [EMA] and/or the U.S. Food and Drug Administration [FDA] and may not be authorised in all countries, and some may have been added or withdrawn from approval at the time of print).

A retrospective, non-randomised, non-interventional study presented at ASCO 2022 presented data on the use of G-CSFs in clinical practice in Russia.[7] A total of 492 patients with solid tumours receiving myelosuppressive chemotherapy were included in the analysis. The majority of patients presented with breast (68%), colorectal (10%), and urogynaecological cancer (10%). In total, 30% of patients had at least one risk factor for febrile neutropenia and 14% had a high risk of febrile neutropenia based on the chemotherapy regimen. Primary prophylaxis was administered to 44% of patients with a high risk of febrile neutropenia, with 25% receiving filgrastim and 19% empegfilgrastim. A total of 3% of patients developed febrile neutropenia. However, 8% of patients had a reduction in their chemotherapy dose by 20–25%, and second-cycle chemotherapy was delayed in 27% of patients, suggesting that oncologists in Russia continue to use dose reduction or dose delays in clinical practice. Adherence to guidelines regarding use of primary prophylaxis is, therefore, poor.[7]

Practice Recommendations for the Use of Granulocyte-Colony Stimulating Factor for Febrile Neutropenia

Practice guidelines recommend the use of primary prophylaxis of G-CSF based on individualised patient-specific risk factors and the overall risk of developing febrile neutropenia by chemotherapy regimen (high [≥20%], intermediate [10%–20%], or low [<10%] risk [Table 1]).[1-5]

Typically, the use of G-CSF as a primary prophylactic is recommended in chemotherapy regimens when there is a high risk (≥20%) of febrile neutropenia, or for patients who receive chemotherapy with additional risk factors that place them at intermediate risk (>10% but less than <20%).[1-5] Risk factors are based on patient-, disease-, and treatment-related factors such as being elderly (aged 65 years and over), the presence of severe symptoms such as hypotension or invasive fungal infections, and these should be determined to establish if overall risk places them as high or low.[1-5] In those who are at low risk for febrile neutropenia (<10%), primary prophylaxis with G-CSF is not indicated.[1-5] Secondary prophylaxis is recommended following febrile neutropenia or when there is a dose-limiting neutropenic event. Off-label use of G-CSFs for afebrile neutropenia is not recommended.[2]

Interim Updates to the Granulocyte-Colony Stimulating Factor Primary Prophylaxis Guidelines for Febrile Neutropenia

Recently, in view of the COVID-19 pandemic and the potential risk of infection, multiple organisations (ASCO, ESMO, and NCCN) issued interim modifications to existing guidelines and recommendations to extend the use of G-CSF prophylaxis to include patients at intermediate-risk (10–20%) of febrile neutropenia, regardless of additional risk factors.[16-18]

In light of this, real-world evidence was presented at ESMO 2022, describing retrospective data from patients with solid tumours, including gastrointestinal (32.2%), lung (20.7%), and breast (7.8%) cancer, receiving anti-neoplastic chemotherapy prior to and during the COVID-19 pandemic (January 2019–December 2021; N=1,666) in Israel.[19] Rates of febrile neutropenia remained stable (2.45% pre-pandemic versus 2.35% during the pandemic; p=0.898), although, consistent with interim guidelines, more patients received G-CSF during the pandemic (16.00% versus 6.00% pre-pandemic; p<0.0001), and 1-year survival was higher during the pandemic period (p=0.021).[19] An ambispective, observational study, presented at SABCS 2022, indicated that patients with early breast cancer who had undergone neoadjuvant chemotherapy (N=183) in Spain, resulted in 13% being admitted to hospital for COVID-19 during March 2020 and May 2022, and found 41% (n=9) had received G-CSF. However, there was no association between the use of G-CSF and the occurrence of symptomatic COVID-19 infection, despite modified G-CSF guidelines being proposed to deter potential risk.[20] Therefore, the interim guidelines may need to be reviewed.

RECENT EVIDENCE FOR BENEFITS OF GRANULOCYTE-COLONY STIMULATING FACTOR PROPHYLAXIS

The use of G-CSFs has proven efficacy in the prophylaxis of chemotherapy-induced neutropenia and is associated with reducing the incidence of febrile neutropenia and hospitalisation.[8]

A Phase II clinical trial of adverse events in patients with human epidermal growth factor receptor2-positive (HER2+) metastatic breast cancer was presented at ESMO 2022.[21] The study reported that the occurrence of Grade ≥3 treatment-emergent adverse events of a decrease in white blood cell count and/or decrease in neutrophil count was less common in patients who had received G-CSF prophylaxis (23.3%; n=10/43), compared to those without G-CSF prophylaxis (36.1%; n=13/36).[21]

Interim results from a post-registration, prospective study that evaluated the impact of primary prophylaxis with empegfilgrastim on the ability to complete planned neoadjuvant chemotherapy courses in patients with early breast cancer (N=195) were presented at SABCS 2022.[9] An RDI of >90% was achieved in patients receiving dose-dense regimens for HER2+, hormone receptor-positive/HER2-negative or triple-negative breast cancer, with only one case of neutropenia (0.9%; n=1/111) leading to a drop in RDI in a patient with HER2+ breast cancer. Preliminary results suggest this may improve therapeutic efficacy, as pathological complete response rates in this study were higher than those seen in a historical control population; further data from this trial are anticipated.[9]

Regarding optimal therapy, a multicentre, prospective, observational, post-registration study conducted in Russia looked at the use of prolonged G-CSF empegfilgrastim in patients

with solid tumours (N=2,000), including breast cancer (n=350), colorectal cancer (n=63), and gynaecological tumours (n=35).[22] The study investigated the RDI of a single agent in at least one cycle of chemotherapy-based regimen combined with empegfilgrastim. While 22.4% (n=118) of patients had dose delays or dose reductions, only 1.1% (n=6) cited neutropenia as the reason for reduced RDI. The real-world evidence demonstrated that primary G-CSF prophylaxis with prolonged empegfilgrastim administration effectively maintained RDI ≥85% in the routine clinical practice of patients with solid tumours, including 96.3% of patients with breast cancer, 92.1% of patients with colorectal cancer, and 82.9% of patients with gynaecological tumours.[22]

A further study conducted in Spain between 2015–2021 investigated the efficacy of using filgrastim G-CSF prophylaxis as a useful and safe option in the neoadjuvant setting for HER2-negative breast cancer.[23] In total, 204 patients, including those with HER2+ (64%) and triple negative (25%) tumours, were included. Overall, G-CSF prophylaxis facilitated treatment compliance. Febrile neutropenia was reported in 18.1% of patients, with no significant difference in incidence between patients receiving pegfilgrastim or filgrastim (p=0.99). The outcomes indicated that although G-CSF facilitated treatment compliance, a risk of neutropenia was still present.[23]

An oral presentation delivered at ESMO Asia 2022 presented data from a real-world study in Nepal comparing filgrastim to single-dose pegfilgrastim in a cohort of patients with solid tumours (N=112) who were receiving high-risk or intermediate-risk chemotherapy regimens for febrile neutropenia.[14] The study found that febrile neutropenia was significantly lower with pegfilgrastim (43%) compared to filgrastim (70%), along with a reduction in hospitalisation. Overall, primary prophylactic treatment with G-CSFs (filgrastim and pegfilgrastim) minimised hospital stays, visits, and the frequency of admission in patients with cancer receiving chemotherapy. The authors concluded that patients require an adequate evaluation and determination of prophylactic G-CSFs to optimise their clinical care outcomes and reduce hospitalisation-related morbidities through the management of febrile neutropenia.[14]

GRANULOCYTE-COLONY STIMULATING FACTOR BIOSIMILARS ARE COMPARABLE TO THEIR REFERENCE PRODUCTS

Biosimilars have been approved for use in oncology as an alternative to reference products, as long as they have been approved for the registered indication.[15] Biosimilars offer increased accessibility to biologics without the financial implications to patients and the healthcare systems, and represent a safe, effective, and cost-effective alternative to reference products.[24] ASCO supports that biosimilars and reference products are considered equally efficacious for the purpose of inclusion in ASCO clinical practice guideline recommendations,[25] while ESMO recognises the potential of biosimilars to help achieve sustainable treatment in oncology, providing the manufacturing of biosimilars adheres to the stringent regulations and guidelines set out by regulatory authorities and the World Health Organization (WHO).[15]

Several filgrastim biosimilars were approved and have entered the USA market from 2015, followed by pegfilgrastim biosimilars in 2018.[24] Examples of current G-CSF biosimilars include filgrastim-sndz, tbo-filgrastim, filgrastim-aafi, pegfilgrastim-jmdb, pegfilgrastim-cbqv, pegfilgrastim-bmez, pegfilgrastim-apgf, and pegfilgrastim with on-body injector.

Granulocyte-Colony Stimulating Factor Biosimilar Use for Supportive Cancer Care

A health services survey conducted in the USA was presented at ASCO 2022.[26] The survey examined current trends in biosimilar use in oncology pharmacy practice. Results demonstrated a notable shift towards the use of biosimilars compared with the reference product.[26] The survey identified an 88% average utilisation of filgrastim and 55% average utilisation of pegfilgrastim, with 90% of the surveyed pharmacies indicating that they had a preferred biosimilar on the formulary. The key barrier to biosimilar adoption was associated with insurance reimbursement, and the survey identified that opportunities still exist to align formularies and consider the use of biosimilars to promote safe and cost-effective care.[26]

At SABCS 2022, a poster presentation provided an insight into population-based data from patients with breast cancer, comparing G-CSF biosimilar use with the reference products.[24] A retrospective analysis of data acquired from the Biologics and Biosimilars Collective Intelligence Consortium (BBCIC) distributed research network database of administrative claims for prophylactic G-CSF products between 2015–2019 was performed. Inclusion criteria included patients with breast cancer over the age of 20 years who were receiving their first cycle of chemotherapy. Of the patients included (N=11,788), 0.8% were male and 49.0% were aged 50–64 years. Based on those patients administered intravenous chemotherapy drugs, 93.0% (n=10,953) had a high risk for febrile neutropenia.[24] In addition, other risk factors associated with an increased risk of febrile neutropenia included 7.2% (n=850) with severe hepatic disease (i.e., hepatitis, non-alcoholic steatohepatitis, cirrhosis, and fibrosis), 3.2% (n=373) had open wounds, and 3.1% (n=371) had received surgery within 6 months prior to the first cycle of chemotherapy. Additionally, 7.0% (n=821) had used antibiotics during their first cycle of chemotherapy.

Febrile neutropenia events were low, occurring in 1.8% (n=218) of patients during their first chemotherapy cycle. Serious allergic reactions occurred in 6.7% (n=786) and other adverse events were observed in 4.1% (n=485). The majority of patients received a reference product, pegfilgrastim (92.0%; n=10,895), including 93.0% (n=10,162 out of 10,953) of those receiving high-risk chemotherapy. For biosimilar use, 3% received pegfilgrastim-cbqv, 2% pegfilgrastim-jmdb, 1% filgrastim-sndz, and <1% tbo-filgrastim or a combination of filgrastim plus a biosimilar. Despite guidelines recommending the use of G-CSF for high-risk chemotherapy,[1-5] 85% of patients who received low-risk chemotherapy (n=25) received pegfilgrastim. The administration of a reference G-CSF reduced from 97% to 76% between 2015–2019. By 2019, biosimilar administration had increased, with 13% having been administered pegfilgrastim-cbqv, and 8% pegfilgrastim-jmdb. The administration of reference products of filgrastim (n=156) decreased over 2016–2019 (3% versus <1%, respectively); however, in general, there was a low administration of tbo-filgrastim (n=<10), and 1% filgrastim-sndz. The increased use of pegfilgrastim biosimilars (2018 onwards) corresponded with the introduction of market availability.[24] This marks a slow but positive shift in the uptake of G-CSF biosimilars, but demonstrates that further opportunity exists.

Also presented at ASCO 2022 was a retrospective cohort study of patients in the USA receiving either the reference G-CSF or biosimilar G-CSF between 2018–2021.[8] The risk of hospitalisation for febrile neutropenia was compared between reference and biosimilar groups. Of the patients included (N=13,670), 49.2% were receiving a biosimilar G-CSF and the other half received a reference G-CSF.[8] Despite pegfilgrastim being the most common G-CSF medication overall (73.5%), filgrastim was used more commonly in the biosimilars group (43.2% versus 10.4% for pegfilgrastim; p<0.05). Of those receiving a G-CSF biosimilar, the key characteristics indicated that they were usually younger, male, had more G-CSF claims, and were more likely to use a specialist pharmacy.[8] The incidence of hospitalisation for febrile neutropenia was low (1.1% of patients), with no significant difference between biosimilar and reference products (1.0% versus 1.1%; p=0.39). This study, therefore, demonstrated similar effectiveness of G-CSF biosimilars in preventing hospitalisation due to febrile neutropenia in comparison with the reference G-CSF product.[8]

EMERGING TOPICS IN GRANULOCYTE-COLONY STIMULATING FACTOR PROPHYLAXIS RESEARCH

The method of delivery of G-CSF biosimilar pegfilgrastim-cbqv was the focus of a poster presented at ASCO 2022.[27] Pegfilgrastim-cbqv is normally administered via prefilled syringe 24–72 hours after a patient receives chemotherapy, necessitating a separate clinic visit. Delivery via an on-body injector applied on the day of chemotherapy would eliminate this need. A Phase II, open-label, cross-over study assessing the pharmacokinetic and pharmacodynamic bioequivalence and safety of pegfilgrastim-cbqv found that geometric mean ratios for pharmacokinetic and pharmacodynamic parameters for the two modes of administration fell within range, indicating bioequivalence.[27] Similar safety and immunogenicity profiles

between the two administration methods were demonstrated.[27] This study highlights a potential future approach to the administration of G-CSF biosimilars.

Furthermore, the timing of G-CSF administration was the focus of another poster presented at ESMO 2022.[28] The real-world evidence of G-CSF administration within 3 days in patients with breast cancer treated with chemotherapy, found those who received prophylactic G-CSF during their first cycle were highly effective in preventing febrile neutropenia in the following 3 weeks.[28] However, the authors indicated that the patients were largely unprotected during the first week of chemotherapy, with results demonstrating that the majority of febrile neutropenia occurred in the first week (81%; n=440 out of 546).[28] This has led to emerging insights into the use of a combination-therapy of pegfilgrastim with a novel chemotherapy-induced neutropenia-preventive agent to address the delayed onset of action of G-CSF in the first week of the chemotherapy cycle.[29] These studies identify the potential for additional approaches to prevent febrile neutropenia in the first week of the chemotherapy cycle.

Another potential application of G-CSF biosimilars as a primary prophylaxis was for sacituzumab govitecan (SG)-induced neutropenia and febrile neutropenia.[30] The SG label recommends G-CSF support only in response to severe neutropenia, rather than prophylactic use. However, a retrospective study of patients receiving SG for the treatment of metastatic triple-negative breast cancer (where 81% of patients developed SG-induced neutropenia), presented at SABCS 2022, found that patients who received G-CSF underwent more cycles of SG treatment (median five versus four).[31] This study identifies the potential application of G-CSF biosimilars for other neutropenia-induced instances, warranting future investigation.

Finally, the role of G-CSF to manage neutropenia induced by other agents besides chemotherapy warrants consideration. A new Delphi consensus amongst a French multidisciplinary steering committee considered the use of G-CSFs to treat neutropenia induced by poly (ADP-ribose) polymerase inhibitors, which are currently used in ovarian and breast cancer therapies.[32] The committee did not recommend the use of G-CSFs for this indication at the present time, due to the lack of efficacy data.[32] However, further research into this application may be warranted.

Such clinical trials indicate the potential direction of future G-CSF prophylactic approaches, and these recent highlights give an indication of the potential application of G-CSF biosimilars in future prophylactic therapy.

CONCLUSION

Given the importance of G-CSFs in providing supportive care and primary prophylaxis treatment to patients with breast, colorectal, and gynaecological cancers, the use of G-CSF biosimilars should be considered as a cost-effective means of supportive cancer care for the effective prevention of febrile neutropenia. Practitioners should consider the interchangeability of biosimilars for filgrastim and pegfilgrastim to replace reference products as an equally efficacious primary prophylaxis to chemotherapy-induced febrile neutropenia, to decrease overall healthcare cost, and improve patient access to supportive cancer care therapies.

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Ocedurenone: A Novel Therapy for Uncontrolled Hypertension in Advanced Chronic Kidney Disease

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Summary

Patients with advanced-stage chronic kidney disease (CKD) have a high burden of disease, which is compounded by serious comorbidities, including diabetes, cardiovascular disease (CVD), and, most commonly, hypertension. Control of hypertension is vital in patients with advanced CKD to reduce the associated risks of morbidity and mortality, but treatment options are limited, largely due to safety concerns for the use of existing antihypertensive agents in patients with poor renal function. During interviews conducted by EMJ in November 2022, two leading specialists in nephrology and cardiology, George Bakris, American Heart Association Comprehensive Hypertension Center, Department of Medicine, The University of Chicago Medicine, Illinois, USA, and Faiez Zannad, Clinical Investigation Centre (CIC 1493 Inserm-CHU), Université de Lorraine, Nancy, France; and Regional and University Hospital Center (CHRU) Nancy, France, discussed the challenges of treating uncontrolled hypertension in advanced CKD. These two experts described the complicated relationship between cardiovascular and renal disease, and identified significant unmet needs for patients with uncontrolled hypertension and advanced CKD. In this context, new agents in the field were viewed with interest, including the emerging class of non-steroidal mineralocorticoid receptor antagonists (MRA). The experts highlighted data from recent studies on the novel non-steroidal

MRA, ocedurenone (KBP-5074), and discussed its potential as a treatment for uncontrolled hypertension in patients with advanced CKD.

EPIDEMIOLOGY AND UNMET NEEDS IN ADVANCED CHRONIC KIDNEY DISEASE

Setting the scene, Bakris defined CKD as a reduction in kidney function (estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m^2), alongside the presence of albuminuria (≥30 mg/day) as an indication of kidney damage. The lower the eGFR, the more significant the disease, but Bakris emphasised: "Advanced CKD (Stages 3b, 4, and 5; or eGFR <45 mL/min/1.73 m^2) is really not just CKD, as the higher the stage, the higher the cardiovascular risk.[1] In the USA, there are close to 17 million people with Stage 3 CKD, but at Stage 4 there are just over 1 million. Why this discrepancy? It's easily put in a simple word: death. A huge number of people die from CVD before they get to Stage 4."

Zannad elaborated on the complex connection between CKD and cardiovascular conditions,[2] describing them as "two sides of the same coin of a common chronic heart–kidney disorder." They explained: "Most cases of CKD are related to risk factors shared with CVD. Hypertension and diabetes are the most frequent attributable risk factors for CKD, and they are also the most frequent attributable risk factors for CVD. If you realise that CKD is as much a consequence of these very common risk factors as CVD, then you realise how serious the intersection of CVD and CKD is. Hypertension is extremely frequent, especially in those above 65 years of age, amongst whom almost one in two inhabitants in the world have some sort of hypertension. Diabetes is on the rise exponentially, and more so in poorer countries in Africa, in the Middle East, and India.[3-5] Therefore, the combined effect of the rising epidemic of diabetes and a high prevalence of hypertension, make the CKD–CVD intersection one of the commonest conditions." Bakris agreed and also highlighted IgA nephropathy as the third most frequent cause of kidney failure, with a high prevalence in Asia.[6] Increasing age and ethnicity were also said to be influential risk factors, with CKD having higher rates in the African-American, African, and Middle Eastern populations.

Hypertension in Advanced Chronic Kidney Disease: An Unmet Need

The experts observed that milder forms of CKD may go undiagnosed for years, while treatment is focused on the more apparent problems of hypertension, diabetes, and other comorbidities. Indeed, diagnosis of CKD may only come following significant disease progression; thus the unmet needs of advanced CKD were described by Zannad as "issues of an 'end of the road' progression of risk factors." Better control of hypertension, and thus reduction in cardiovascular risk, was identified as a key unmet need in patients with advanced CKD. However, according to Bakris: "The higher the stage of CKD, the more difficult it is to control the blood pressure, and the more medications you're going to need. It's rare to find somebody with Stage 4 CKD (eGFR <30 mL/min/1.73 m^2) on one medicine. They're usually on three or four." Bakris went on to note that a patient with Stage 4 CKD linked to diabetes would likely be taking 12–14 different drugs per day for CKD- and CVD-related, and non-related conditions, and that overall, adherence with polypharmacy is a challenge in advanced CKD. Therefore, a simpler and more efficient means of controlling blood pressure is urgently required.

In addition to contributing to disease progression, uncontrolled hypertension was described as a "major contributor to morbidity", causing problems with sleep, the heart, and headaches. "Uncontrolled hypertension has direct effects on the heart," explained Bakris. "It makes the heart bigger, which contributes to the arrhythmia of atrial fibrillation, the most common arrhythmia in the world. It causes a lot of subtle changes as adaptation to these high pressures, which lead to future problems, even after blood pressure is controlled. That's a major issue." In addition, Bakris outlined the wider, indirect effect of uncontrolled hypertension on healthcare provision: "Apart from the impact on the patient and causing disease burden, there's a huge medical cost to the community and to governments because these people are more likely to go to the hospital or have serious

illnesses. To be clear, the majority of these costs are incurred not because of intensive care unit or [scheduled] visits to the hospital, they are driven by emergency room visits."

TREATMENT OF UNCONTROLLED HYPERTENSION IN ADVANCED CHRONIC KIDNEY DISEASE

The selection of treatments for uncontrolled hypertension in CKD is influenced by both general clinical guidelines on managing hypertension, and those specific to managing kidney disease. Considering treatment options in general, Zannad stated: "We have a very large number of antihypertensive medications. The most common medications are very effective, but they need to be combined." More specifically, for people with CKD, Bakris cited the 2021 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines:[7] "The recommendation is to have people on three different classes of drugs that work complementarily: a diuretic that's appropriate for kidney function; a calcium channel blocker; and a blocker of the renin-angiotensin system, so either an angiotensin receptor blocker or an angiotensin-converting enzyme inhibitor, and maximally titrated or tolerated."

Zannad clarified that for a diagnosis of uncontrolled hypertension, patients must have a systolic blood pressure ≥140 mmHg, despite having received the recommended combination of at least two antihypertensive medications and a diuretic.[7] He also explained that patients with uncontrolled hypertension are a mix of those with treatment resistance (i.e., those who required three or more drugs with complementary mechanisms of action, and taking all medications), and those who are poorly adherent. Considering patients with uncontrolled hypertension and advanced CKD, Bakris continued: "Once you've tried those three [medications], the question is, what's number four? The only data we have is per the American Heart Association (AHA) Scientific Statement on resistant hypertension.[8] Here, the fourth drug is considered to be spironolactone, an MRA. Why? Because the PATHWAY-2 trial showed that in people with resistant hypertension, spironolactone produced greater reduction in blood pressure than a β-blocker and an α-blocker.[9] However, the problem with that study is everybody had normal kidney function…"

Bakris explained that patients with advanced CKD (eGFR <45 mL/min/1.73 m^2) were excluded from the PATHWAY-2 study[9] due to the risk of hyperkalaemia with the steroid-based spironolactone. "If you try using [spironolactone] in people with advanced CKD, you're going to run into problems with potassium elevation. It works, but you've got to know what you're doing. Moreover, the dose used in the PATHWAY-2 trial was 25 mg/day, generally higher than used in heart failure. The other major limitation with spironolactone is that it is a prodrug. It gets metabolised to other drugs like canrenone that are active and actually cause gynaecomastia in males, breast tenderness in females, and, over time, intolerable side effects that preclude further use of the drug. So then you switch to eplerenone [another steroidal MRA] that does not have these problems, but you have to give it twice a day, and it has a much weaker effect for blood pressure reduction than spironolactone.[10] That's all we've got, so that's what people use. The hope is that with all these new agents coming out we can find a valuable substitute with far better tolerability in people with advanced CKD that can do the same job as spironolactone."

Emerging Treatments

Looking to the future, the two experts highlighted new drugs in development for the treatment of uncontrolled hypertension, but noted that data in patients with advanced CKD are very limited. "It's been 15–20 years since there's really been anything new in hypertension, and now there's an explosion of medications that are being looked at specifically for resistant hypertension," commented Bakris. "There's the aldosterone synthase inhibitor, baxdrostat, which has published very impressive Phase 2 data,[11] but in a normal kidney population. Also, the dual endothelin receptor antagonist, aprocitentan, is a contender. It showed very good blood pressure reduction in the Phase 3 PRECISION trial in patients with resistant hypertension,[12] but had oedema as a side effect, which is expected with endothelin receptor antagonists. There is the non-steroidal MRA, esaxerenone, approved for hypertension treatment in Japan,[13,14] but its efficacy in people with advanced CKD has not

been tested. There is also the non-steroidal MRA, ocedurenone, at an advanced stage of development. Ocedurenone shows clear promise because, regardless of kidney disease, it has been studied in people who are already taking a minimum of two or more drugs, and often three or more. Thus, the only drug that has consistently steadied resistant hypertension in people with advanced-stage CKD is ocedurenone."

Zannad shared this view: "The non-steroidal MRAs ocedurenone and finerenone are the main promising medications. I say promising because we know that finerenone has shown a cardiovascular and kidney protective effect in patients with diabetic kidney disease in the FIGARO-DKD and FIDELIO-DKD trials;[15,16] although the effect on blood pressure in these trials [in which mean systolic blood pressure at baseline was 136/138 mmHg] was relatively small, and we have no evidence in the non-diabetic population in uncontrolled hypertension. So we are hopeful for ocedurenone, because it has shown significant benefit in controlling blood pressure in uncontrolled hypertension, and notably in this group of patients with advanced CKD."[17]

OCEDURENONE: A NEW TREATMENT OPTION

As described above, several MRAs are already utilised as treatments for hypertension, and the number increases with the emergence of non-steroidal MRAs, including ocedurenone (KBP-5074).[18] Zannad discussed the background to the development of MRAs, which was built upon knowledge of the steroid hormone, aldosterone. Aldosterone is released by the adrenal gland and helps control blood pressure through the regulation of sodium and potassium exchange in the kidney, and exerts its action by binding to the mineralocorticoid receptor, affecting target gene expression.[19] The MRAs, also known as aldosterone receptor antagonists, were subsequently shown to block this effect.[20] "The very first use of MRAs was at high doses as diuretics, which eventually resulted in use as antihypertensive medication, as well as in the chronic congestive states associated with heart and hepatic failure," Zannad explained. "It wasn't until the late 1990s that smaller (non/mild diuretic) doses of MRAs were found to be effective in cardiovascular protection.[21] Since then, there has been a huge amount of work showing that there are mineralocorticoid receptors in a large number of tissues/organs, including the heart, brain, kidney, gut…alongside all the machinery for producing aldosterone in various organs. Aldosterone has very potent anti-inflammatory and anti-fibrotic effects to name just a few, and inflammation and fibrosis are the key common elements of progression of kidney failure and heart diseases. The very first MRAs were the steroidal MRAs, led by spironolactone. Later on we had eplerenone, which is still steroidal, but more specific to mineralocorticoid receptors, so avoided the main limitation of the first-generation agents off-target (e.g., sexual) side effects."

The more recently developed group of non-steroidal MRAs represents a novel approach to treatment and, as such, has been recognised by the U.S. Food and Drug Administration (FDA) as a distinct and new class of antihypertensive agents. Amongst these, ocedurenone is a highly selective agent with a higher binding affinity to the mineralocorticoid receptor than steroidal MRAs, and little or no binding affinity for the glucocorticoid, progesterone, and androgen receptors.[18,22] While ocedurenone has sometimes been referred to as a 'third generation' MRA, both experts felt that this term was highly misleading. "These are essentially different drugs," said Zannad. Bakris concurred: "Ocedurenone has very different chemistry from the steroidal agents. The binding characteristics are very different in terms of how it binds to the aldosterone receptor. The half-life is long, at approximately 60 hours, and is unaffected by dialysis.[17] It does not get into the brain. It does not have active metabolites. Also, because the receptor interaction is different, it produces different effects."[18]

Zannad added that non-steroidal MRAs have also demonstrated differences in their tissue distribution compared to steroidal agents. For example, spironolactone and eplerenone are concentrated in the kidney, impacting on the risk of hyperkalaemia, while finerenone has a more balanced distribution between the heart and kidneys,[18,23] and ocedurenone has a higher tissue concentration in the gastrointestinal tract (unpublished data, KBP). Therefore, the

distinctions between these categories of MRA are likely to be clinically meaningful in terms of efficacy and safety, as well as affecting practicalities such as dosing regimens. Bakris concluded: "A lot of people see ocedurenone as just an expensive spironolactone, but if you do that you're totally 'throwing the baby out with the bathwater'."

Clinical Support for Ocedurenone in Advanced Chronic Kidney Disease

The experts then considered the current clinical evidence for the efficacy and safety of ocedurenone in treating uncontrolled hypertension in patients with advanced CKD. In Bakris' opinion: "The strongest evidence is from the Phase 2b BLOCK-CKD study of ocedurenone,[17] which studied people with advanced CKD, many actually being in Stage 4. It is a unique study because it looked at the treatment of hypertension in the context of advanced CKD. There are two other drugs in the [non-steroidal MRA] class that produce blood pressure reduction. One is esaxerenone, approved exclusively in Japan,[13] for which there are no placebo-controlled comparisons,[14,24,25] and the other is finerenone.[26,27] The difference is that while finerenone reduces blood pressure (placebo subtracted) variously from 3 mmHg (ARTS-DN, FIGARO-DKD, and FIDELIO-DKD studies)[15,26,28,29] to approximately 8 mmHg (subset analysis from ARTS-DN study, eGFR of approximately 68, though office blood pressure from the same study showed around 3 mmHg reduction),[27] ocedurenone 0.5 mg reduces it by 11 mmHg (placebo subtracted),[17] and it's that [magnitude of] difference that made spironolactone the winner in the PATHWAY-2 study against β-blockers and α-blockers.[9] Although it doesn't sound like much, it's a big deal."

Bakris continued: "Ocedurenone 0.5 mg is a very low dose, but it has very powerful effects on precisely those people who have resistant hypertension. No other agent, so far, has steadied blood pressure as well in this group of patients. And the point is that these are the patients who need the most help, and these are the only data that I'm aware of that are unique to this patient group. As a dedicated study, BLOCK-CKD is really the only one." Importantly, Bakris also highlighted that the benefit observed with ocedurenone in this study appeared to be equal across all patients, unaffected by the presence of diabetes or older age, which are both common characteristics of patients with advanced CKD.

The opportunity to use ocedurenone at a low dose, due to its high affinity and specificity of receptor binding,[18,22] also has a favourable impact on safety, which limits the risk of hyperkalaemia as well as off-target (e.g., androgen) receptor side effects such as gynaecomastia. The higher concentration of ocedurenone in the gastrointestinal tract (unpublished data, KBP), compared to other MRAs that are more concentrated in the kidney,[18] may also lower the risk of hyperkalaemia. Considering clinical evidence from the BLOCK-CKD study, Bakris explained: "In terms of the safety signal for potassium, there was hyperkalaemia [0.5 mg ocedurenone 16.7% versus placebo 8.8%; no hyperkalaemia ≥6.0 mmol/L][17] but not at the frequency that you would expect of spironolactone. This has been looked at in detail with another non-steroidal MRA, finerenone, and it's been estimated that there's an approximately six-fold higher risk of hyperkalaemia with spironolactone than there is with finerenone [indirect comparison in patients with treatment resistant hypertension and advanced CKD].[30] So again, the distinct characteristics of binding and other factors contribute to this. Exactly how we don't know, but ocedurenone is behaving the same way as the other members of this non-steroidal MRA family."

Zannad reinforced the importance of these hyperkalaemia data for the clinical utility of ocedurenone: "The main limitation of the use of MRAs so far, in heart failure and in CKD, has been hyperkalaemia. Hyperkalaemia scares physicians because of the connection with the risk of sudden death and arrhythmias. Indeed, above approximately 5.5 or 6.0 mmol/L potassium, there is an increased risk of cardiovascular events and death. We now have pharmacological reason to believe that the non-steroidal MRAs may have a lower rate of hyperkalaemia, and this will give a major edge. With ocedurenone, for the first time ever we have an MRA that lowers blood pressure significantly, and may be safely used in advanced CKD."

However, Zannad also emphasised that further evidence was required to build on these Phase 2

findings: "We need to study many more patients [with ocedurenone] to know about the long-term and large population safety, and learn more about whether this promising effect on blood pressure is translated into hard outcome prevention. And that's the next step. We are very hopeful that ocedurenone may be a real addition in this space of uncontrolled hypertension in CKD." Bakris added: "A Phase 3 study of ocedurenone [in patients with uncontrolled hypertension and moderate or severe CKD] called CLARION-CKD[31] is ongoing, and I'm highly optimistic that it will show what the Phase 2 study showed, only with much greater numbers."

Further Patient Benefits

The experts moved on to consider the broader impact of ocedurenone for patients with advanced CKD, including on dosing, compliance, and quality of life. "There are a number of factors that affect compliance, and if you have a drug that has got this much impact on blood pressure, without profound side effects, the patients will notice it and stick with it," commented Bakris. Zannad agreed: "So far, there are no concerns about any safety issues that could make patients less likely to take ocedurenone." The convenience of a once-daily, or even potentially every other day (half-life approximately 60 hours), oral dosing regimen was identified as another factor in favour of ocedurenone, compared to eplerenone, which is taken twice a day, or sometimes once daily but with resulting loss of 24-hour coverage.

Bakris observed that effective control of hypertension would also benefit patients in terms of quality of life by relieving hypertension-associated effects such as headaches and poor sleep. Thus, reflecting on the overall profile of ocedurenone, they concluded: "There are a lot of things to be positive about with ocedurenone. I think if you have something that's got good tolerability and effectively lowers blood pressure in a very high-risk group, then you will have a big impact on morbidity. Yes, patients worry about mortality, but they also worry about morbidity because that's what's causing them all the problems right now. If you look at the profile of the non-steroidal MRAs in general, their morbidity index is far better than the steroidal MRAs. The only people arguing about this will be the ones who can't afford the non-steroidal MRAs, which is a real issue. Fundamentally, the cost question is going to be quite important, and is looming." Zannad agreed that much would depend on the availability and pricing of the medication. However, they concluded: "It's very likely that this class of drug is going to be effective in a large variety of cardiovascular and renal conditions, as has been shown with other MRAs. Indeed, mineralocorticoid receptors are so ubiquitous that we may have many more developments beyond CKD and cardiovascular conditions. I hope that this is just the beginning of a long story for ocedurenone."

SUMMARY

During the interviews, Bakris and Zannad highlighted the complications and significant unmet needs surrounding the treatment of uncontrolled hypertension in patients with advanced CKD. Despite the many antihypertensive drugs and combinations available, the experts acknowledged that their use in advanced CKD is limited by safety concerns, hyperkalaemia in particular, and compounded by an overall lack of clinical evidence. After decades with little advancement, the emergence of non-steroidal MRAs was viewed as an important development for the treatment of uncontrolled and resistant hypertension. Amongst this new class of agents, ocedurenone was identified as a promising drug for use in patients with hypertension and advanced CKD. In the first dedicated study of patients with uncontrolled hypertension and advanced CKD, ocedurenone demonstrated efficacy in lowering blood pressure, together with a favourable safety profile. The experts were optimistic that it could provide a much-needed treatment option for this group of severely ill patients, with potential for reduction in the risk of cardio-renal outcomes.

Biographies

George Bakris

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George Bakris is a Nephrologist/Certified Hypertension Specialist, and is Professor of Medicine and Director of the American Heart Association (AHA) Comprehensive Hypertension Center at the University of Chicago Medicine, Illinois, USA. They have published over 900 peer-reviewed articles and book chapters in the areas of diabetic kidney disease, hypertension, and nephropathy progression. They have served on the Cardiorenal Advisory Board of the U.S. Food and Drug Administration (FDA), as well as many national guideline committees. Bakris is the past President of the American College of Clinical Pharmacology (ACCP) and the American Society of Hypertension (ASH). They serve on more than 15 editorial boards and are current Editor-in-Chief of the American Journal of Nephrology, and UpToDate (Nephrology and Hypertension Sections). Bakris is the recipient of the Irvine Page-Alva Bradley Lifetime Achievement Award-American Heart Association BP Council (2019) and National Kidney Foundation of Illinois Lifetime Service Award (2020).

Faiez Zannad

Clinical Investigation Centre (Inserm-CHU), Nancy, France

Faiez Zannad is Professor Emeritus of Cardiology and Therapeutics, and Past Director of the Inserm Clinical Investigation Center at the Université of Lorraine, Nancy, France. They have significantly contributed to building the evidence supporting modern heart failure therapy, including MRAs, β-blockers, sodium-glucose co-transporter-2 inhibitors, and anticoagulants, as well as in major comorbid conditions in heart failure such as diabetes, hyperkalaemia, CKD, and central sleep apnoea. Zannad is past Chairman of the French Society of Hypertension, and of the European Society of Cardiology (ESC) Working Group on Pharmacology and Drug Therapy. They are also founder of the Global CardioVascular Clinical Trialists (CVCT) Forum and Workshop, a thinktank meeting dedicated to the science of clinical trials. Zannad has published more than 1,000 peer-reviewed papers, and received the Paul Milliez Award of the European Society of Hypertension (ESH), the Lifetime Achievement Award from the ESC-HFA (2017), a Eugene Braunwald Scholarship at Harvard Medical School, and the Heart Failure Society of America (HFSA) International Honorary Fellowship (2022).

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Interviews

EMJ are delighted to introduce Peter Gill and Damian Roland, who provided fascinating insights into paediatric medicine, focusing on unmet needs, the value of eHealth, and the future of the field.

Featuring: Peter Gill and Damian Roland

Peter Gill

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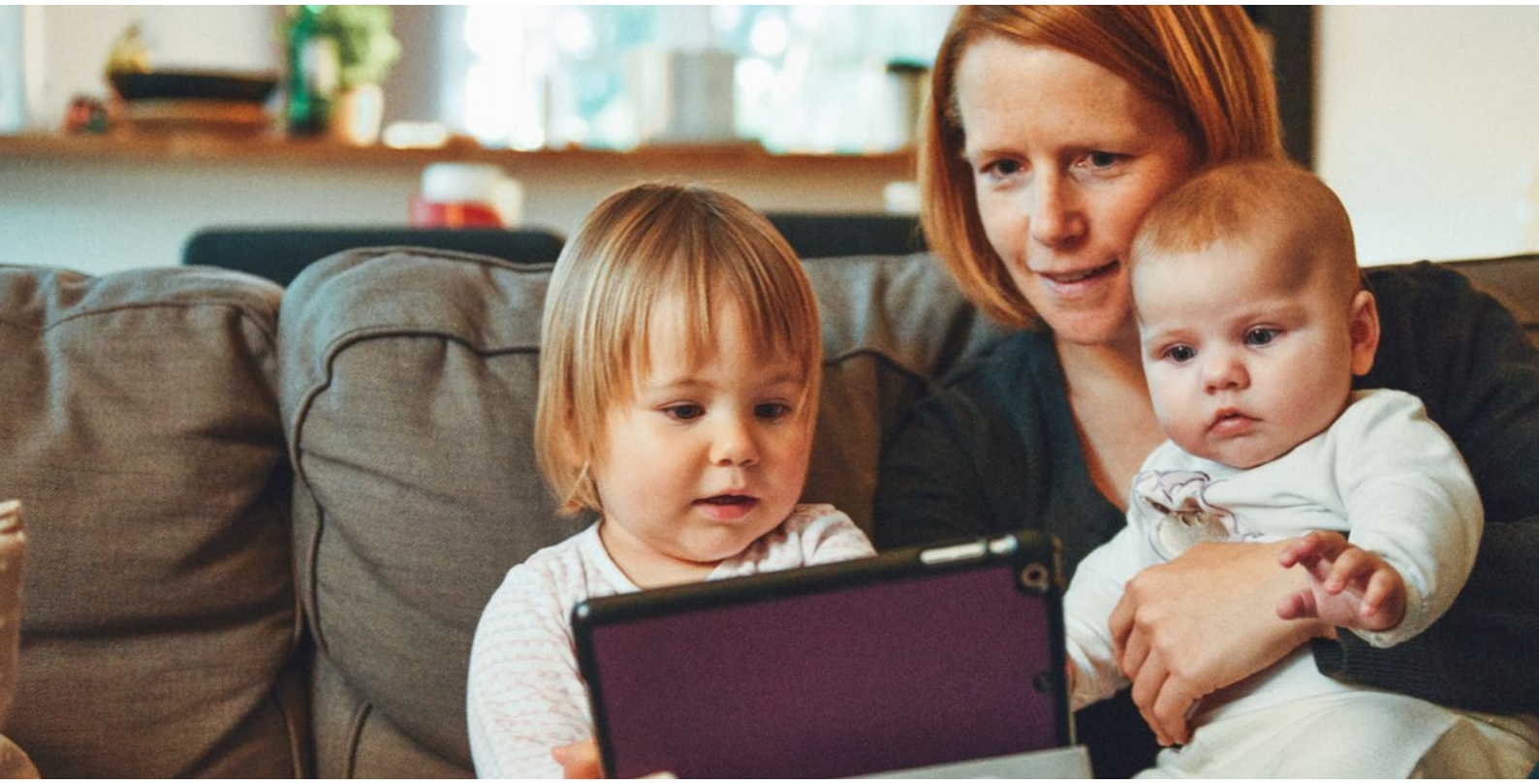
Q1 What led you to pursue a career in medicine and what made you decide that paediatrics was the specialty for you?

Ever since I was young, I have wanted to be a paediatrician. I had a fantastic paediatrician as a child, who made going to the doctor fun, exciting, and interesting. As I teenager, my passion grew for science, leadership, and medicine. I have always loved working with children, from coaching football camps to running programmes and summer camps for children with disabilities. These passions continued when I started university and I have not looked back since!

Q2 Your research programme focuses on improving the evidence base for children hospitalised in general paediatric settings, particularly for conditions that have important long-term impacts. Can you explain what this research involves?

My research focuses on improving the care and outcomes for hospitalised children on the general paediatric ward. I lead an outcomes-based research programme, which focuses on comparative effectiveness of clinical care in real-world settings, the patient perspective, and system performance. I co-lead a research group with Sanjay Mahant, where we focus on large, multicentre studies to generate evidence on effectiveness and patient-oriented outcomes. We also conduct studies using large health administrative databases, evaluating the cost and health system impact of common and highly prevalent conditions. Lastly, we work closely with patients as partners, to ensure that we understand and focus on outcomes that matter most to children and families.



Q3 What are some of the paediatric conditions that have a long-term impact and need more attention?

As general paediatricians, we take care of hospitalised children and youth on the general paediatric ward, which represents approximately one-quarter of all hospital admissions. In this setting, we care for a range of conditions, including previously healthy children hospitalised for acute, common illnesses like bronchiolitis, children with a chronic disease like asthma, and children with medical complexity who are hospitalised for a variety of reasons. Some of the specific conditions which have may long-term impacts include acute illnesses such as urinary tract infections, orbital cellulitis, and severe acute respiratory syndrome coronavirus 2 infection. There are still many important gaps on long-term impacts for these and other conditions.

Q4 What does some of your current research involve, and how will this impact future patient care?

My research focuses on several different conditions, reflecting the breadth of children cared for on the general paediatric ward. For example, a major focus is bronchiolitis, the most common reason children under the age of 2 are hospitalised. I lead a multicentre study that aims to understand parent involvement in decision-making related to the choice of supplemental fluids, either intravenous (IV) or a nasogastric (NG). Both IV and NG fluids are safe and effective, yet in North America over 90% of hospitalised infants receive IV fluids. Interestingly, surveys of parents whose children have had both IV and NG show that NG fluids are preferred. Why is there a discrepancy? Our study will provide important information on safety and effectiveness of IV and NG fluids in bronchiolitis, a condition with a major health system impact, but will also inform how we can increase parent involvement in decision-making.

Q5 What inspired you to start the open-source paediatric medical education website PedsCases?

When I started medical school in 2006, we had 30–40 hours of mainly didactic lectures. The curriculum was also longitudinal, where most paediatric content was interspersed throughout courses. This inspired me to co-found PedsCases, an open-source website that uses various learning modalities to assess and teach paediatric knowledge. By challenging students to personalise learning, to contribute to the learning of others, and by providing a creative integration of evidence-based medicine, PedsCases sought to fill the gap between theory and practice, while generating free content for others to use. Currently, PedsCases is embedded in undergraduate paediatric education curricula across Canada, with over 5 million podcast downloads of over 150 podcasts.

Q6 You also co-founded the Canadian Paediatric Inpatient Research Network (PIRN). What is the aim of this network and what is your role in this organisation?

The Canadian PIRN is a hospital-based research network that aims to improve the evidence base and outcomes for hospitalised children in general paediatric settings. Established in 2019, PIRN includes all 17 academic paediatric hospitals across Canada and 4 large community hospitals in Ontario, Canada. The network conducts multicentre patient-oriented research to serve patients and their families, clinicians, researchers, and health system decision makers. I co-founded PIRN with my colleague Sanjay Mahant, and helped establish the initial Executive Council, of which I am Vice-Chair. I also led a foundational priority setting partnership that identified the top 10 unanswered research questions in paediatric hospital care, and helped to establish partnerships with key stakeholders, including patient and family advisory groups.

Q7 Tell us about your role in Canadian Institutes of Health Research (CIHR) Institute of Human Development, Child and Youth Health Advisory Board, and how this translates into policies in paediatric healthcare.

I have actually just finished my term as a member of the Institute Advisory Board (IAB) of the CIHR Institute of Human Development, Child and Youth Health, which has been an absolute privilege. As member of the IAB, my role was to represent the scientific and research community, and act in an advisory capacity to the Scientific Director of the Institute. This included providing feedback on potential research priorities and strategies, and implementation plans for engaging the broader research community.

Q8 What are the current gaps in knowledge in paediatric healthcare that should be addressed in the near future?

Evidence-based medicine, as coined by the late David Sackett, is the integration of the best available evidence, clinical expertise, and patient

perspective. With the growing focus on data science, artificial intelligence, and machine learning, we cannot lose sight of the importance of the voice of children, youths, parents, caregivers, and families. There are major gaps in how we integrate the patient perspective into medical decision-making with the growing complexity of healthcare, and these need concerted efforts to address. Further, there are major limitations to conducting clinical trials in paediatrics, ranging from regulatory, cost, complexity, and scale. Without major investments in clinical trial infrastructure, including comparativeness effectiveness research on routinely used but off-label medications, paediatrics will continue to fall behind adults in new treatments.

Q9 How do you see the future of the field and where can we expect to see your focus lie in the coming years?

The future of paediatrics is exciting, with a growing focus on developing novel therapies, the integration of data sciences into clinical care to identify prognostic factors or predictors of response to therapy, and the recognition of health equity. However, the past few years have also highlighted the threat of misinformation, poorly conducted research, and the implementation gap. As a general paediatrician, I am continually reminded and humbled by patients and families of what matters to them. I will continue to focus on questions driven by patients and families, including the better integration of the patient perspective and voice into medical decision-making, and how we can bring the best available research evidence to patients to improve care.

Q10 Throughout your career so far, what has been your proudest achievement?

After establishing the Canadian PIRN, we felt it was important to have our work informed by parents and families.

"Both IV and NG fluids are safe and effective, yet in North America over 90% of hospitalised infants receive IV fluids. Interestingly, surveys of parents whose children have had both IV and NG show that NG fluids are preferred."

With support from a large team, I obtained grant funding from the CIHR to seek broad input from parents, caregivers, children, youths, and clinicians on the top research priorities for paediatric hospital medicine, using the James Lind Alliance Priority Setting Partnership methodology. This seminal work, which was overseen by a steering group of parents, youth, paediatricians, and nurses, identified the top 10 most important unanswered research questions. The project was published in *JAMA Network Open*[1] with a commissioned editorial,[2] and highlighted nationally by CIHR as an exemplar of partnering with parents and patients.[3] I am proud of this project, which put the voice of patients and front-line clinicians at the forefront of guiding where research should focus.

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Q1 What first sparked your interest in working in paediatric medicine, specifically in paediatric emergency medicine?

I'd gone to medical school thinking I was going to be an orthopaedic surgeon. I demonstrated a number of attributes which meant it become quickly apparent this wasn't where my career was destined. It wasn't until I did my paediatric attachment as a fourth year student that I found I had an aptitude for spot diagnosis, which is essentially about 95% of acute paediatrics.

I was then lucky enough to go to Perth, Western Australia, for my pre-registration house officer (intern) year. I was placed on a 2-month paediatric emergency secondment, and realised that the fast-paced nature of the work, combined with an absence of need for high level technical skill (I just don't have the patience for surgery), was a perfect vocation for me.

Q2 You are an educator who has developed and evaluated educational resources, particularly with regard to digital (eHealth) technologies. Could you speak about a couple of the resources you have worked on, and why these are so important for clinicians?

My PhD involved testing the educational outcomes of an e-learning platform. This was a bespoke website which used video clips of unwell febrile children to teach junior doctors how to risk assess them according to the National Institute for Clinical Excellence (NICE) guidelines. Paediatrics is a visual specialty, and it's very difficult to teach via text book or in the lecture theatre without audiovisual tools. It is important to note that children relatively infrequently present seriously unwell to emergency care. Paradoxically, while you may think this means that staff may miss serious illness without suitable training, it also means many children with only moderate disease are overtreated, as this will be the most sick child that healthcare professional has ever seen. This overtreatment and overdiagnosis is not good for patients, families, or health systems. Given the reduction in presentations of children during 2020, education and training in normal, moderate, and serious cases is even more important for the next generation of paediatricians. I'm on the lookout all the time for good examples of children with a range of conditions. A child with a classic grunt on my YouTube channel has had 4.7 million views.

Q3 You are recognised for using scoring systems in your work, and personally developed the Paediatric Observation Priority Score (POPS). Why do you feel that such systems are an important communication tool in healthcare settings, and how can they improve the care of younger patients? How has your score impacted the field?

I've been on a long journey with scoring systems in paediatric emergency care, and while I am a fervent advocate for

them, the reasons why I think they work have almost reversed since I started researching them. Ultimately, acute and emergency care paediatrics is a high intensity and high-risk specialty, with large volumes of patients who don't need treatment but serious consequences result from not treating the small proportion who do. There are too many cognitive biases for clinicians alone to make the right choices all the time, and there need to be systems in place to mitigate for environments where decision-making is impaired.

Conversely, an over-reliance on scores is equally dangerous, as it switches off the Gestalt that is needed in clinical practice. Ultimately, we are still looking for the perfect balance between subjective but flexible human decision-making, and objective but inflexible scores. I hope my work with POPS has demonstrated the need for bespoke emergency care tools; POPS is not a Paediatric Early Warning System (PEWS), and doesn't really work for ward care, in the same way PEWS isn't specific enough for emergency care. I hope the need for scoring systems to be cognitive prompts rather than decision making aids has started to percolate through health system thinking.

Q4 You recently co-authored a study entitled 'Time to change the reference ranges of children's physiological observations in emergency care?' What were the aims, and did you find out anything surprising?

My colleagues and I for a long time have felt reference ranges for heart and respiratory rates were not specific enough in emergency care. This work, using hundreds of thousands of patient data points, I hope puts to rest the argument about the need to alter the upper limits of heart rate values, especially in preschool children. In our study, for those children below 1 year of age, 23.3% had what NICE considers to be a high-risk heart rate. Interestingly, the respiratory rate values weren't quite as variable compared to Advanced Paediatric Life Support guidelines as we had predicted.

Q5 What do you feel are the unmet needs in paediatric healthcare, and what is the most important thing that should be implemented into the field on a global level?

Without a doubt, inequality, deprivation, and poverty are a leading cause of childhood ill heath, morbidity, and mortality. It is a sobering thought that while we can spend huge sums on health services and systems to treat children, it would probably be better if we could just move more children out of poverty, and concentrate less on expensive hospitals and complex technologies.

Q6 You are a strong proponent of using social media in a medical context, and you have over 19,000 followers on Twitter alone. In which ways do you feel yourself, and your readership, benefit from this particular communication tool?

I must confess, I feel, sadly, Twitter is becoming a less powerful tool now that it is increasingly commercialised. However, Twitter has been instrumental for me in developing a large community of a practice and learning network, without which I would have spent far longer making collaborations and researching dead ends. I've published

a number of papers with colleagues I have never met face-to-face, and have been involved in a few communication strategies which I think have effectively reached the public. The recent invasive group A streptococcal disease surge in the United Kingdom is a good example. I created a short video to help parents understand the risks of this disease, and through Twitter and other mediums, it had over 50,000 views in a week.

Q7 You wrote on your Twitter feed recently that the COVID-19 pandemic 'has accentuated the importance of symptoms over signs'. What is the difference between symptoms and signs, and how do you feel clinicians could better communicate this to the public?

There has always been an issue with 'Fever Phobia', a concern that fever alone is harmful even in the absence of other features of illness. COVID-19 has accentuated this, as for 18 months having a fever and/or mild cough would have significant implications for your ability to go to work or go to school. I increasingly recognise that parents and carers become fixated by the symptom their child has (fever, vomiting, diarrhoea), and don't really concentrate on their behaviours. We have a generation of work to do on helping parents and carers focus on the signs of illness their child has (level of alertness, amount of urine they have produced, the work of their breathing, etc.), rather than symptoms alone.

Q8 In early 2022, you co-authored the paper 'Development, implementation and evaluation of an early warning system improvement programme for children in hospital: the PUMA mixed-methods study'. Could you let us know what this study uncovered, and why an early warning system is so important for your patient cohort?

This was a long piece of work, over 5 years, in which we studied the impact of a focused PEWS implementation programme at four hospitals. We undertook pre-, during, and post-implementation evaluations, using both quantitative and qualitative methods. This approach had not been taken before, and led us to a few unique findings. We were able to develop a bespoke assessment tool that predicted, fairly accurately, the maturity of a hospital in managing the deteriorating child. We were also able to confirm a previously known supposition that the system (staff training, communication tools, reduction of hierarchy) is more important than any one score alone. Finally, we also discovered that demonstrating impact from these systems is very difficult, and across the four hospitals, fluctuations in relevant outcomes (death, ICU transfer) are very small. We have highlighted the need for a broader range of outcome measures to test PEWS systems, and this work is being taken up by the NHS England, Royal College of Paediatrics and Child Health (RCPCH), and Royal College of Nursing (RCN) National PEWS programme.

Q9 What advice would you give to those considering a career in paediatric medicine?

Don't get put off by media reporting and the current challenges all health systems are facing. Paediatrics will challenge you, but it is a highly rewarding career. Try to get some early years experience as a medical student or early years doctors. Rotations in emergency medicine are usually highly rated; while they may be hard from a rota point of view, you will get to see and manage a greater range of patients than on the wards. There are lots of simple things you can do, such as reducing a pulled elbow, that provide almost instant relief to children, and will leave you with a smile inside all day.

Newer Oral Levothyroxine Formulations: Is It Time to Switch Over?

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Abstract

Primary hypothyroidism is a frequent presentation in primary care, and is treated with levothyroxine sodium tablets once daily in the morning in the fasting state. With an adequate dose, the goal is to achieve a thyroid stimulating hormone in the normal range in 6–8 weeks. Medications, foods, and gastrointestinal conditions can interfere with the absorption of the levothyroxine tablet. This can lead to increased visits to the laboratory and physician, necessitating frequent dosage changes, and causing suboptimal care. The newly-introduced oral solutions and soft gel capsule formulations received approval for use by regulatory authorities. This article describes the kinetics of levothyroxine, examines the available evidence from the literature, and summarises the rightful place of the levothyroxine solution from the perspective of the clinical practitioner. At the end of the analysis, it is evident that more robust trials with this new formulation are needed to consider a switchover from tablet form for millions of patients, in order to justify the cost. The newer levothyroxine formulations may have a role in selected patients with resistant hypothyroidism.

INTRODUCTION

Hypothyroidism is a common condition encountered in primary care and is prevalent worldwide. Primary hypothyroidism due to autoimmune thyroid disease is the most common aetiology, followed by thyroidectomy and radioiodine therapy. Secondary and tertiary hypothyroidism due to pituitary and hypothalamic diseases, respectively, are rare in primary care. Hence, only primary hypothyroidism is discussed. Thyroid hormone replacement therapy is the treatment for hypothyroidism of any cause. In the remote past, preparations extracted from dried animal thyroid were used. Subsequently, the categorisation of the hypothalamic-pituitary-thyroid axis, the discovery of thyroid hormones, their structure, kinetics, and feedback regulation led to levothyroxine (LT4) as the standard replacement therapy. A newly diagnosed patient is started on therapy given as a tablet once daily in the morning. A thyroid stimulating hormone (TSH) level in the normal range is the goal of therapy which takes 6–8 weeks to attain when adequately dosed. A log-linear relationship exists between TSH and free T4 (FT4). For small changes in FT4, there is a large inverse shift in TSH, qualifying the latter as a more sensitive test for diagnosis and follow-up.[1,2]

Natural Thyroid, Levothyroxine, and Combination Therapy

The normal thyroid secretes both thyroxine (T4) and triiodothyronine (T3) in a ratio of 13:1. T4 acts as a pro-hormone and is deiodinated to T3 in peripheral tissues like the liver. Most of the T3 in the body (around 80%) is obtained from peripheral deiodination of T4. The latter is the effector hormone in all tissues. It is this fact that the proponents use for advocating T4 monotherapy.[3] Although suitable for most patients, some 10–15% continue to suffer symptoms and a poor quality of life, despite achieving therapeutic goals. Opponents of sole therapy with LT4 have advocated more physiological therapy using a combination of T4 and T3. While natural thyroid preparations contain both T4 and T3, these animal products have a much higher T3 content (T4 to T3 ratio of 4:1). Moreover, there is variation in the contents between batches that provide erratic levels, leading to suboptimal care.[3] This therapy is, therefore, not recommended by experts.

Studies using a combination of T4 and T3 have failed to prove superiority over T4 monotherapy.[4] The T3 used in these studies was short-acting, and dosed one to three times daily. This produces high levels shortly after dosing, and low trough levels before the next dose. This fact is used for refuting these studies. To mimic the bodily kinetics, a long-acting T3 is a solution. The Phase I trials with long acting T3 (T3 LA) have shown some promise.[3,5] Until definite results are obtained from more robust trials with a combination of T4 and T3 LA, LT4 will remain the standard of care for hypothyroidism.

Depending on the clinical scenario, LT4 is used by oral, intravenous, intramuscular, subcutaneous, or rectal routes. Nasal spray formulations are being studied.[6] Although the other routes are useful for certain clinical situations, such as with patients who are critically ill, oral LT4 in tablet form (LT4tab) is the choice for patients who present to primary care.[7]

Levothyroxine Preparation and Kinetics

LT4 itself is very unstable and rapidly degraded in the milieu of the stomach. Treatment with alkali in the manufacturing laboratory yields LT4 sodium, which is more stable in the gastric environment. After ingestion, the stomach acid helps disintegrate the LT4tab. An optimal pH of the gastric contents delivered to the duodenum is essential for proper absorption in the duodenum, jejunum, and ileum via specific transporters in the intestinal epithelial cells. The absorbed LT4 reaches the liver. Here, apart from deiodination to LT3, some of the LT4 gets converted to sulfates and glucuronides via alternative routes of metabolism. Some of these metabolites reach the gut via biliary excretion. Here, they are converted to free T4 by intestinal bacteria and reabsorbed to complete the enterohepatic cycle. Between 60–80% of an oral dose of LT4tab is bioavailable. Given the complexities involved in the kinetics of LT4tab, many factors can interfere with its smooth absorption (Table 1). The consequences are frequent laboratory and physician visits that result in constant dosage changes, increased expense, and suboptimal care. The development and testing of novel oral formulations raise hope for a solution to this problem.[8]

What is in an levothyroxine tablet?

Apart from LT4 sodium, each tablet contains many inactive ingredients. These include binding agents, preservatives, and permitted colouring agents, among others. They serve various functions, including binding the active ingredient, improving stability, and facilitating disintegration, dissolution, and dispersion. There are variations in the type and amount of these excipients that may explain some differences in bioequivalence between different brands and generics. Manufacturers are constantly trying to improve the quality of their products by manipulating these substances.[7] Table 2 compares characteristics of levothyroxine tablet with the newer formulations.

In the quest for a solution to the problems with LT4tab described, investigators have ventured into levothyroxine solution (LT4sol) and levothyroxine soft gel capsules (LT4gelcap) as suitable alternatives.[8,9]

What is in the levothyroxine solution and levothyroxine soft gel capsules?

LT4 sodium, glycerol, and water are the constituents. Some previous LT4sol preparations included alcohol or propylene glycol in small quantities. In the LT4gelcap, a gelatin outer covering is present in addition, which quickly dissolves in the stomach.[10]

Table 1: Factors affecting absorption of oral levothyroxine.

Dietary factors	Medications	Diseases/conditions
Soy protein	Calcium salts	*Helicobacter pylori*
Milk	Aluminium antacids	Achlorhydria
Some fruit juices	Lanthanum	Gastrectomy
Papaya	Sevelamer	Atrophic gastritis
Coffee	Raloxifene	Gastroparesis
Dietary fibre	Bile acid sequestrants	Giardiasis
Enteral feeds	Quinolones	Lactose intolerance
	Atorvastatin	Gastric bypass (bariatric)
	Potassium binding agents	Coeliac disease
	Iron salts	Intestinal parasitosis
	Chromium supplements	Small bowel resection
	Orlistat	Short bowel syndrome
	Proton pump inhibitors	Inflammatory bowel disease
	H_2 receptor antagonists	Small intestinal bacterial overgrowth
	Simethicone	Exocrine pancreatic disease
	Vitamin C*	

*Increases levothyroxine absorption.

Bioequivalence, a prerequisite for new formulations

The U.S. Food and Drug Administration (FDA) and other regulatory agencies have mandated bioequivalence tests before approval of new drugs. For LT4, the area under the curve and maximal concentration achieved, measured as the FT4 concentration after administering 600 mcg as a single dose in the fasting state, should be close to that of a standard LT4 preparation. Initial tests performed showed that the newer compounds achieved bioequivalence to standard LT4tab.[11] The FDA approved the LT4sol in 2017, whereas it was approved earlier in Europe. Yue et al.[9] studied the kinetics of LT4sol and showed the earlier time to maximum concentration and greater area under the curve for LT4sol. This fact alone may be the main contributor to its advantages when administered with food or medications.[9] It is not surprising that the LT4tab needs time to dissolve and attains blood levels later. Yamamoto[12] reported three patients in whom powdered LT4 tablets solved the absorption issues with the whole tablet. If similar results are obtained in many different clinical situations in a larger population, it could be a much cheaper alternative to the much-touted and more expensive LT4sol.

Table 2: Comparison of levothyroxine tablet and oral solution/soft gel capsule.

LT4 preparation	LT4 tablet	LT4 solution/gelcap
Additional contents	Inactive excipients	Glycerol, water, (gelatin)*
Cost	Low	High
Availability	Universal	Restricted
Familiarity with providers	Very familiar	Less familiar
Duration in use	Many years	A few years only
Shelf life	Long	Short
Storage temperature	25 °C; maximum 30 °C	25 °C; maximum 30 °C
Interaction with food/drugs	Present	Absent†
Intolerance/allergies to ingredients	Present in some patients	Not reported
Ease of administration	Swallowing discomfort in some	Easy to swallow (solution)‡

Blue depicts advantages.

Red depicts disadvantages.

*Gelatin outer shell in soft gel capsule dissolves and releases liquid levothyroxine.

†Claimed by studies; however, product leaflet suggests spacing with food and medications.

‡Soft gel cap needs to be swallowed, and may cause discomfort in some susceptible patients.

LT4: levothyroxine

EVIDENCE IN LITERATURE

Summary of Studies with Concomitant Food, Medications, or Conditions

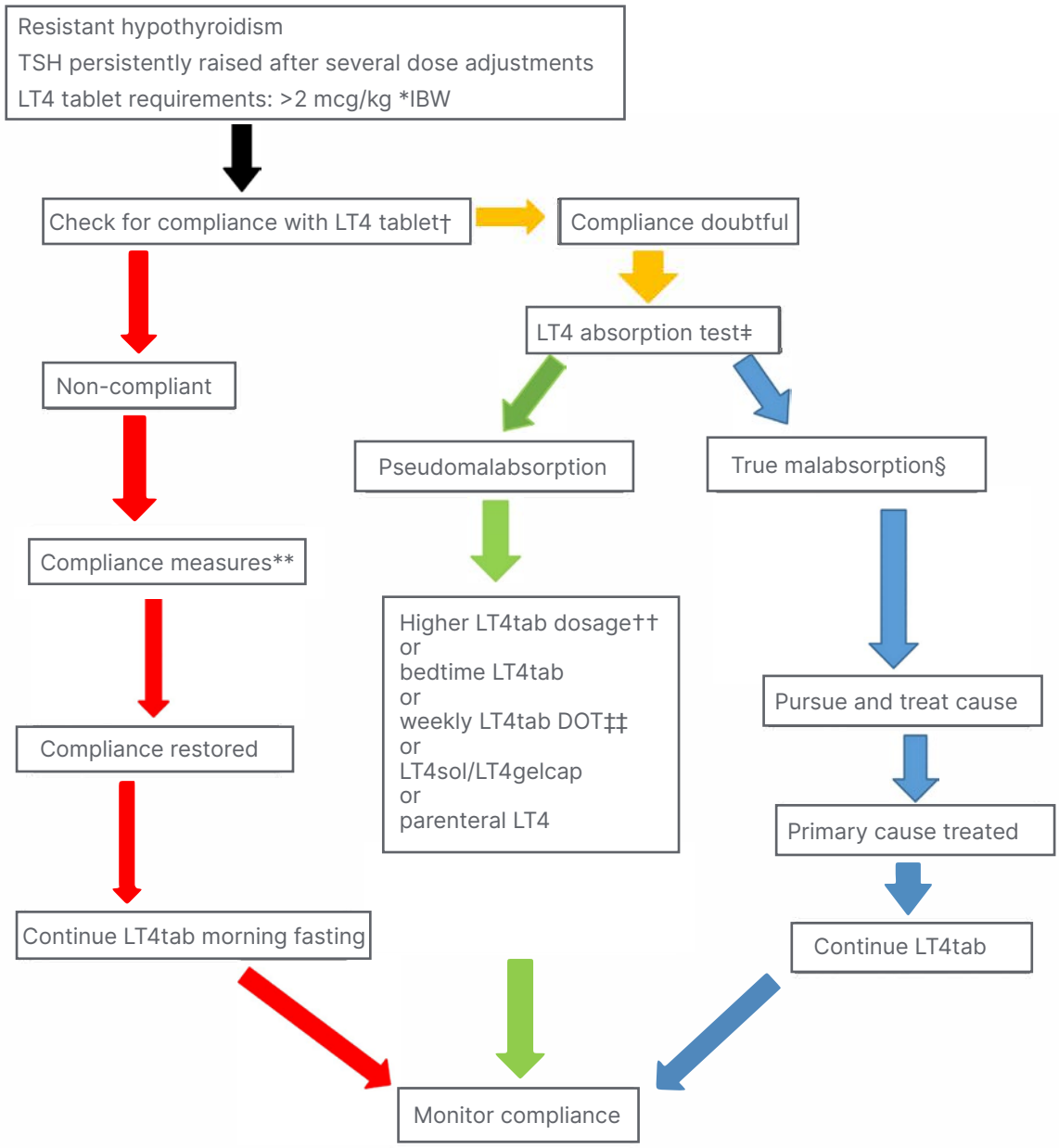
There are numerous case reports involving a single or a small number of subjects. Many examined the effects of food, concomitant medications, gastrointestinal disease states, bariatric surgery, radioiodine thyroid ablation, and thyroidectomy. Most results rated LT4sol as superior or equivalent and none inferior to LT4tab. All studies had one or more deficiencies: insufficient power (small number of subjects), not blinded, unmatched, insufficient washout periods, retrospective and non-uniform design, and a strong component of compliance bias in favour of LT4sol during the crossover.[13,14] Among the various studies, the TICO study was prospective, placebo-controlled, double-blind, and well designed. It showed that LT4sol was not influenced by both food and medications. The drawbacks of this study were that it included subjects from a single country partaking a standard diet, and the absence of a comparative LT4tab arm to prove its superiority over the latter in a head-to-head comparison.[15]

Studies Addressing Temperature Stability and Storage Issues

Boulton et al.[16] studied the effects of temperature and preservative on liquid thyroxine prepared by compounding crushed tablets. They concluded that a prepared LT4sol was least stable with added preservative and most stable at 4 °C with no added preservative.[16] Benvenga et al.[17] described the instability of LT4tab when stored in less than optimal conditions (proximity to room heaters, clear bottles, and transfer from

blister packs into alternate storage). Subjects who took these poorly-stored pills reported abnormally high TSH levels. Subsequently, when these patients took properly stored pills, the TSH returned to normal.[17]

Figure 1: Author's approach to resistant hypothyroidism.



*Correlates better than actual body weight for computing LT4 dose.

†Ask open-ended non-judgemental questions, interview caregivers, and check mood and cognition.

‡Many versions available; consult Endocrinology.

§May need alternative modalities of LT4 until primary malabsorption resolves.

**Use education tools tailored to literacy; use all available resources.

††Any one of the modalities may work; personalised approach needed.

‡‡Total weekly LT4tab requirements as single weekly dose.

DOT: directly observed therapy; IBW: ideal body weight; LT4: levothyroxine; LT4gelcap: levothyroxine soft gel capsules; LT4sol: levothyroxine solution; LT4tab: levothyroxine tablet.

Bernareggi et al.[18] added LT4sol to breakfast beverages, warmed them, and analysed LT4 levels in these foods by reliable methods. They showed good retrieval, even after subjecting the LT4sol to temperatures as high as 50 °C.[18] While this may prove convincing, no one is going to add LT4 in whatever form into their foods and heat it before consumption, nor is a temperature of 50 °C ever attained in the body. A better alternative is to test whether LT4sol is stable in the slightly higher temperatures that occur in the milieu of the tropical pharmacy for its entire shelf life. Most drug manufacturers recommend a storage temperature of 25 °C or less. It is the room temperature in most temperate climates. In warm climates like tropical countries, the average ambient temperature in most pharmacies is 30 °C or more. They invariably have no air conditioners, only ceiling fans. The LT4tab stored in these 'hot' areas has withstood high temperatures and generally seems effective given the on-target TSH levels with the usual replacement doses in most patients (Rajkumar, unpublished data). There are very few 'real-world' studies on the effects of sunlight, artificial room light, and temperature on levothyroxine tablets.[19,20] These studies suggested that sunlight exposure, but not room light or heat exposure, degrades the drug. This corroborates the author's observations on heat exposure. A careful reading of the prescribing information of a standard brand of LT4tab gives the answer. In the product insert, the upper limit of the storage temperature is stretchable to 30 °C. It begs the question: how stable is LT4sol in higher temperatures, and for how long? The LT4sol supplied in single-dose ampoules is not stable beyond 2 weeks after opening. The package insert also cautions on spacing with food and medications.[21]

CONCLUSION

The most common reason for poor control is non-compliance. The patient, caregiver, and practitioner should partner in ensuring compliance. There may be a role for LT4sol in selected patients to justify the cost. Figure 1 outlines the approach to 'resistant' hypothyroidism proposed by the author. This approach is line with the expert consensus panel from Europe.[22] A good history and evaluation for correctable causes should be undertaken. However, there will remain a handful of patients where a levothyroxine absorption test may be necessary. Here the art of convincing the insurers will win over clinical competence.

A large, double-blind, multicentre, prospective, randomised, crossover trial comparing LT4tab with LT4sol will answer many burning questions. There is a need to represent paediatric and geriatric groups, all races, and geographical regions in these studies. The difficulty in blinding because one product is a tablet and the other is a solution is solved by utilising a double-dummy model: a placebo tablet that looks exactly like the LT4tab given with LT4sol, and a placebo solution that looks, feels, and tastes like the LT4sol used with the LT4tab for the study. After an adequate washout period, a crossover can be done, and an analysis performed.

Presently, there is insufficient evidence to justify a switch to LT4sol from LT4tab for millions of patients with hypothyroidism. The results of studies with the LT4sol, LT4gelcap, combination therapy of LT4 with LT3 LA, and nasal spray, will decide the future of LT4 replacement therapy. Like all new medications, the prices of LT4sol may become competitive in the future. At that time, LT4tab and LT4sol may become interchangeable. Recombinant human insulin has practically replaced animal-sourced insulin. LT4sol has to wait, at least for now.

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Metabolic Acidosis in Children: A Literature Review

Editor's Pick

Metabolic acidosis, acute or chronic, is a frequently observed condition that can have a deleterious effect on cellular function, leading to increased morbidity and mortality. It is a pathologic process in which H^+ concentration increases and $HCO3^-$ in the blood is reduced. Severity can range from mild to moderate and severe, and a methodical approach to its diagnosis and treatment is essential. This systematic review of the literature discusses the prevalence, manifestations, cause, and outcomes of metabolic acidosis in children, providing details on the best treatment options.

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Abstract

Metabolic acidosis is characterised by a primary decrease in the serum bicarbonate concentration, a secondary decrease in the arterial partial pressure of CO_2, and a reduction in blood pH. Metabolic acidosis, acute or chronic, may have deleterious effects on cellular function and cause increased morbidity and mortality. A systematic review of the available literature was performed to identify data on the prevalence, manifestations, cause, outcomes, and treatment of metabolic acidosis in children. Online databases (Ovid Medline, Embase, and PubMed), commercial search engines (including Google), and chapters on metabolic acidosis in the standard textbooks of paediatrics and medicine were reviewed.

Systematic approach to acute metabolic acidosis starts with proper history taking and examination. This is followed by assessment of acid-base parameters, including pH, partial pressure of CO_2, and bicarbonate concentration in arterial blood. Blood gas is needed to differentiate primary metabolic acidosis from compensated respiratory alkalosis. Once the diagnosis of a metabolic acidosis has been confirmed, serum electrolyte values are used to determine the serum anion gap. The various causes of increased and normal anion gap metabolic acidosis have been discussed in the article. The main aim of treatment in metabolic acidosis

is to reverse the primary pathophysiology. In acute metabolic acidosis, sodium bicarbonate therapy is not beneficial due to potential complications and is reserved for specific situations. Base therapy is used in chronic metabolic acidosis where it ameliorates many of its untoward effects. Other modalities of treatment of metabolic acidosis include peritoneal or haemodialysis and tris-hydroxymethyl aminomethane.

Key Points

1. Metabolic acidosis is frequently observed in clinical practice, especially in patients who are critically ill and/or have renal failure.

2. Complex mechanisms are involved; in most cases, they are identifiable by medical history, pathophysiology-based diagnostic reasoning, and measures of some key acid-base parameters, which are easily available or calculable.

3. The therapeutic approach should be first aimed at early correction of concurrent clinical problems (e.g., fluids and haemodynamic optimisation in case of shock), in parallel to the formulation of a diagnosis. In case of severe acidosis, the administration of alkalising agents should be carefully evaluated, taking into account the risk of side effects, as well as the potential need of renal replacement therapy.

INTRODUCTION

Acid-base disorders are commonly seen in the paediatric intensive care unit (PICU). Severe metabolic acidosis is connected with adverse clinical outcomes. Of these, metabolic acidosis may occur due to a primary disease or as a result of secondary complications in patients with critical conditions. Metabolic acidosis is a pathological process defined by a decrease in the serum bicarbonate (HCO_3^-), an increase in the hydrogen ion (H^+) concentration, and a secondary decrease in the partial pressure of carbon dioxide ($PaCO_2$).[1] It can be acute (occurring over minutes to days) or chronic (occurring over several weeks).[1] Noor et al.[2] found that approximately 44% of PICU admissions had metabolic acidosis. A similar study by Kim et al.[3] reported that 60% of PICU admissions had metabolic acidosis. They concluded that regardless of underlying aetiology the corrected anion gap (AG) at PICU admission may predict mortality in children. Acute or chronic metabolic acidosis may affect cellular function adversely and result in increased morbidity and mortality.[4,5]

This article will review the approach and management of metabolic acidosis in children. The causes of metabolic acidosis will be addressed only briefly due to the constraints of space.

METHODS

The authors reviewed literature to identify data on the prevalence, manifestations, causes, outcomes, and management of metabolic acidosis in children. They searched the online databases (Ovid Medline, Embase, and PubMed) to identify relevant English language articles using combinations of (child OR children OR adolescent OR infant) AND (metabolic acidosis OR acidaemia). The authors also scanned the World Health Organization (WHO) website for further references. They screened abstracts of articles identified in this search strategy for relevance and obtained the full text of the electronic copies. They further scanned the cross references from each relevant article. Commercial search engines, including Google, were also used to check for any publications missed in the above searches. The authors also reviewed chapters on metabolic acidosis in the standard textbooks of paediatrics and medicine.

Definitions

Metabolic acidosis is defined as a pathologic process characterised by an increase in the H^+ concentration and a reduction in the blood HCO_3^- concentration (<22 mmol/L). It can be acute or chronic.[1,6]

The severity of metabolic acidosis has been divided into three levels based on the systemic arterial blood pH: mild (pH: 7.30–7.36), moderate (pH: 7.20–7.29), and severe (pH: <7.20).

Acidaemia (as opposed to acidosis) is defined as a low arterial pH (<7.35), which can result from a metabolic acidosis, respiratory acidosis, or a combination.[1,6]

PATHOGENESIS OF METABOLIC ACIDOSIS

Under physiologic conditions, children produce 1–3 mmol/kg/day of non-volatile acid, predominantly sulfuric acid, derived from sulfur-containing amino acid metabolism. Acid-base balance is initially maintained by buffering of the acid load followed by urinary excretion. The HCO_3^- in the extracellular fluid and proteins, and phosphate in the cell provide the initial buffering,[7,8] the net effect of which is a fall in serum HCO_3^- concentration. The renal excretion of the daily acid load then restores the serum HCO_3^- concentration to normal.

Two basic processes are involved, mediated by tubular H^+ secretion: absorption of the filtered HCO_3^- and H^+ secretion. These combine with either titratable acids, mainly phosphate ($HPO_4^- + H^+ = H_2PO_4^-$) or ammonia (to form ammonium).[7,8] In normal circumstances, the rates of titratable acid and ammonium excretion are roughly equal to the daily dietary acid load. The kidney compensates, primarily by increasing ammonium excretion when the acid load is increased.

There are three basic pathophysiologic mechanisms leading to metabolic acidosis, including[1,9] an increase in acid concentration. This occurs either due to increased acid generation (endogenous production or exogenous ingestion/infusions) or decreased excretion of acid by the kidney (e.g., renal failure and distal or Type 1 renal tubular acidosis [RTA]). It also includes the loss of HCO_3^-, which occurs with a loss of serum HCO_3^- via the gastrointestinal tract (diarrhoea) or abnormal drainage from the small bowel/pancreas or from the kidneys (e.g., proximal or Type 2 RTA). The loss of serum bicarbonate is matched with a concomitant increase in serum chloride (hyperchloremic metabolic acidosis). Finally, it also includes the dilution of serum HCO_3^- concentrations, which pertains to a drop in serum HCO_3^- concentration due to intravascular fluid volume expansion with a large volume of non-HCO_3^-/acetate/lactate-containing solutions with a resultant rise in blood H^+ concentrations. It is usually seen in children who receive parenteral fluids following trauma or in those undergoing surgery. Dilution-induced metabolic acidosis is generally mild and often occurs with clinical signs of fluid overload.

Adverse Effects of Metabolic Acidosis

Involvement of the cardiovascular system is most critical, though acute metabolic acidosis can affect a number of organ systems. The adverse effects of metabolic acidosis can be classified into those primarily occurring with acute metabolic acidosis and those with chronic metabolic acidosis.[1,9]

Clinical Features

There are no distinguishing symptoms of metabolic acidosis in children. Most features are non-specific, as detailed below.

Acute metabolic acidosis typically presents with symptoms related to the underlying condition and may also have signs/symptoms of compensatory respiratory alkalosis. Respiratory compensation can result in tachypnoea and deep respiration (e.g., Kussmaul breathing). The lack of an appropriate hyperventilatory response may be indicative of a significant underlying neurologic and/or respiratory disorder.[9] Neurologic effects such as lethargy and confusion have been observed in patients with severe acute metabolic acidosis,[1,10] as well as cardiac effects. Data from animal and tissue studies have shown myocardial depression and arrhythmias when the pH falls below 7.1.[11]

Chronic metabolic acidosis can be asymptomatic or present with multiple-system manifestations, depending on how long the underlying condition has lasted and how severe it has been. Findings in children with long-standing uncorrected metabolic acidosis (e.g., RTA) include poor growth and skeletal muscle wasting. Poor growth and skeletal muscle wasting are attributed to aberrant growth hormone secretion, resistance to insulin-like growth factors, and rickets due to

bone abnormalities.[12] These can result in poor growth and skeletal muscle wasting. It can also include rickets, where the release of calcium and phosphate from bone due to bone buffering of some of the excess H^+ results in a decrease in bone mineral content and rickets.[1,9,13] Another finding is nephrolithiasis and nephrocalcinosis. Increased mobilisation of calcium out of the bone results in an increased renal load of calcium leading to hypercalciuria. Additionally, hypocitraturia occurs in response to metabolic acidosis with enhanced proximal tubular citrate reabsorption. This limits the ability to reabsorb tubular calcium leading to nephrolithiasis and nephrocalcinosis.[1,9,14]

APPROACH TO METABOLIC ACIDOSIS

History and Physical Examination

History should be first evaluated in a child with metabolic acidosis. The clinical context will often point to the underlying disorder leading to metabolic acidosis. For example, metabolic acidosis in a child with severe diarrhoea suggests an acute HCO_3^- loss through the gastrointestinal tract, while recent-onset polyuria, polydipsia, weight loss, and hyperglycaemia suggest new-onset diabetes with ketoacidosis. A more detailed laboratory evaluation will be needed to determine severity, chronicity, and treatment options.[1]

Laboratory Evaluation

A diagnostic evaluation that includes serum electrolytes, blood glucose, renal function tests, serum lactic acid, serum AG (SAG), and urine AG usually suffice to specify the aetiology of the metabolic acidosis and direct therapy. In some cases, a blood gas measurement is needed to differentiate primary metabolic acidosis from compensated respiratory alkalosis.

Blood Gas

If metabolic acidosis is tentatively identified by a low total CO_2 on an electrolyte panel, an arterial or venous blood gas sample may be needed to differentiate metabolic acidosis from compensated respiratory alkalosis. This eliminates the possibility of a primary respiratory alkalosis where the bicarbonate is decreased due to a compensatory renal response. If the patient has a simple metabolic acidosis, then the patient will be acidaemic with a pH of <7.35. If the patient has respiratory alkalosis with compensated metabolic acidosis, the patient is alkalemic with a pH >7.42.

An arterial blood gas also helps in evaluating for a co-existing mixed acid-base disturbance.[1] As discussed above, acidaemia due to metabolic acidosis causes compensatory respiratory alkalosis. Documentation of the presence and magnitude of the respiratory compensation should be done. In uncomplicated metabolic acidosis, a predictable relationship exists between the change in (Δ) $PaCO_2$ and Δ HCO_3^- concentration once a steady state is established. This can be derived using the Winter's formula: predicted $PaCo_2$=1.5 (HCO_3^-)+8±2.

A Δ $PaCO_2$ higher than expected indicates a co-existing respiratory alkalosis.[1,15] On the other hand, if the Δ $PaCO_2$ is lower than expected, a co-existing respiratory acidosis is present.[15] Once it has been established whether metabolic acidosis is present in isolation or in association with respiratory disturbances, the aetiology of metabolic acidosis should be investigated.

Anion Gap

Once metabolic acidosis has been confirmed, serum electrolyte values are used to calculate the SAG.[1] The SAG is the difference between the serum concentrations of the primary measured cations namely sodium (Na^+) and the measured anions, chloride (Cl^-), and HCO_3^-.[1,9]

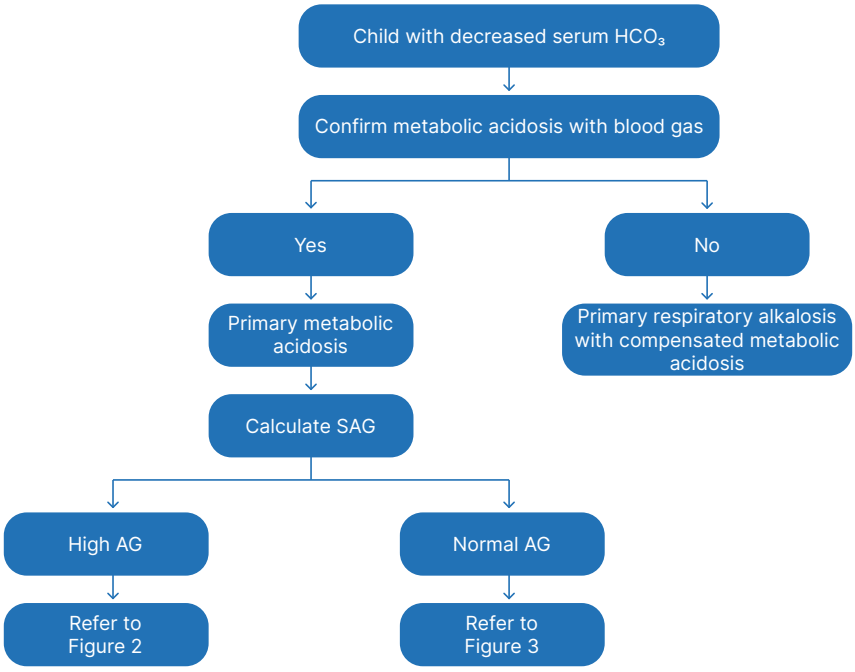
SAG=(Na^+)–($C1^-$+HCO_3^-).

The normal SAG is 8–16 mEq/L (or mmol/L in SI units).[9]

The SAG, composed of unmeasured anions, is generally due to negatively charged plasma proteins. Negatively charged plasma proteins account for the normal AG, and, hence, normal values should be modified for patients with hypoalbuminaemia.[16]

Corrected SAG=(Na^+)–([$C1^-$+HCO_3^-)+2.5x[4.0-measured albumin g/dL).

Figure 1: General approach to a child with metabolic acidosis.



AG: anion gap; SAG: serum anion gap; HCO_3: bicarbonate.

The AG further divides patients into two groups: those with normal AG metabolic acidosis and those with increased AG metabolic acidosis. This allows an algorithmic approach to diagnosis. Figure 1 shows the algorithms for the initial approach to primary metabolic acidosis.

Increased anion gap metabolic acidosis

Increased AG metabolic acidosis occurs when there is an increase in the number of both H^+ and unmeasured anions.[1,9] For example, in diabetic ketoacidosis (DKA), β-hydroxybutyrate and acetoacetate are the unmeasured anions. In lactic acidosis, lactic acid is composed of negatively charged lactate ions and positively charged H^+. The H^+ are buffered by serum HCO_3^- until reserves are depleted, at which point the residual H^+ will lower the serum pH, while lactate anions will raise the AG. Results from the initial basic metabolic tests and the history and physical examination are typically helpful in determining the underlying cause and in some circumstances, guide further diagnostic evaluation. For example:

- Elevated blood glucose and a history of polyuria with or without weight loss, abdominal pain, and vomiting, point to DKA.
- Elevated blood urea nitrogen (BUN) and serum creatinine suggest uraemia and impaired renal acid excretion.
- Evidence of poor tissue perfusion (shock) with elevated lactic acid is seen in sepsis, cardiac failure, and severe hypoxia, as well as in severe crush injuries.
- Neurologic signs and symptoms: a history of severe hypotonia, seizures, developmental delay, or apnoea in a new-born infant may be suggestive of an inborn error of metabolism. Elevated lactic acid is observed in patients with mitochondrial disorders and organic acidurias. A serum ammonia level and a lactic acid and pyruvic acid ratio may be helpful in the differentiation of the inborn error of metabolism.
- History of accidental or intentional ingestion such as ethylene glycol, ethanol, or methanol ingestion (results in a high SAG and osmol

gap); and elevated levels of iron, cyanide, carboxyhaemoglobin, salicylates, cocaine, or amphetamines, which are associated with high AG metabolic acidosis but with a normal osmol gap.

Osmolar Gap

The metabolites of certain toxic alcohols and glycols can generate a high AG metabolic acidosis. The accumulation of these alcohols, because of their low molecular weight, substantially elevates the serum osmolality and causes a disparity between the estimated and measured serum osmolality.[17] Serum osmolality can be calculated using the following formula:

Calculated serum osmolality=2[Na^+]+[Glucose]/18+[BUN]/2.8' where [glucose] and [BUN] are measured in mg/dL.

Serum osmolality should be measured using a freezing point depression osmometer, not a vapour pressure osmometer, in conditions where the elevated osmol gap is generated by a volatile solute such as ethanol or methanol.[17] The measured osmolality and the calculated osmolality should be similar (generally within approximately 6 mosmol/kg). An elevated serum osmol gap exists if the measured osmolality is more than 10 mosmol/kg greater than the calculated osmolality and suggests components such as methanol or ethylene glycol.[1]

Co-existence of Other Disorders

The presence of an elevated AG acidosis does not rule out a concomitant normal anion gap acidosis or a metabolic alkalosis. The delta ratio must be calculated to screen for mixed disorders and confirm that whatever acidaemia is present is completely explained by an elevated AG acidosis.[18]

Delta ratio=Δ AG/Δ HCO_3

$$\text{Delta ratio} = \frac{\text{measured anion gap} - \text{normal AG}}{\text{Normal } HCO_3^- - \text{measured } HCO_3^-}$$

OR

$$\text{Delta ratio} = \frac{AG - 12}{24 - [HCO_3^-]}$$

Factors determining this relationship include the rates of urinary anion excretion and renal HCO_3 generation, the spaces of distribution of the anions and protons, and the quantity of chloride-containing fluids infused.

In general, the Δ HCO_3 is associated with an equivalent change in the Δ AG and this 1:1 relationship has been used to establish co-existing acid-base disorders, such as metabolic alkalosis or normal AG metabolic acidosis. A delta ratio of less than 1 suggests a concomitant normal AG metabolic acidosis, whereas a delta ratio of >1–2 suggests a concomitant metabolic alkalosis. The delta ratio is typically 1:1 in patients with keto-acidosis and often more than 1:1 (often as high as 1.6-1.8:1.0) in patients with lactic acidosis. It is usually less than 1:1 in patients with mixed non-AG metabolic acidosis and a high-AG metabolic acidosis in conditions where renal functions are preserved and the acid anion is readily excreted into the urine, for example with toluene ingestion and some cases of DKA.[18]

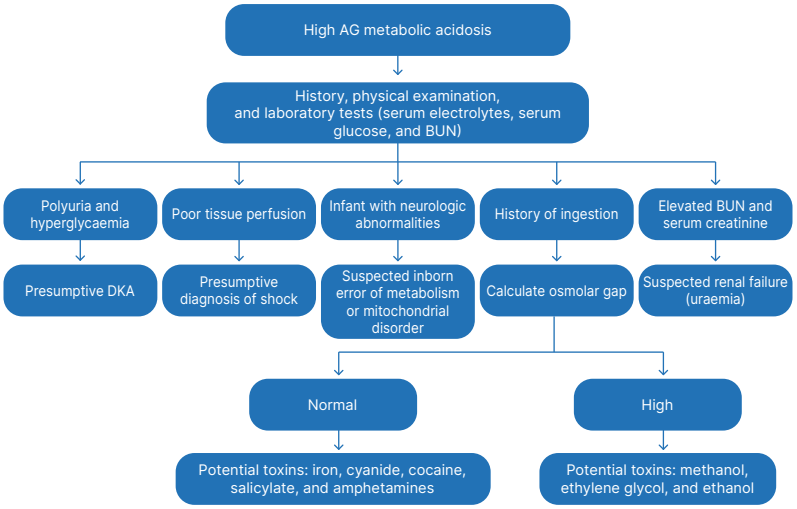
The algorithm for the evaluation of children with increased AG metabolic acidosis is given in Figure 2. A frequently used mnemonic to identify the more common causes of high AG metabolic acidosis in children is MUDPILES (where M is methanol; U is uraemia; D is DKA; P is paraldehyde; I is iron, isoniazid, and inborn metabolic errors; L ia lactic acid; E is ethylene glycol; and S is salicylates).[9]

Normal Anion Gap Acidosis

Also referred as non-AG metabolic acidosis, this occurs with a loss of serum HCO_3^-. This loss of HCO_3^- is balanced by a concomitant rise in serum Cl^- (hyperchloremic metabolic acidosis) to maintain electrical neutrality. Loss of serum HCO_3^- can occur via the gastrointestinal tract (diarrhoea) or abnormal drainage from the small bowel/pancreas or the kidneys (e.g., Type 2 or proximal RTA).[1,9]

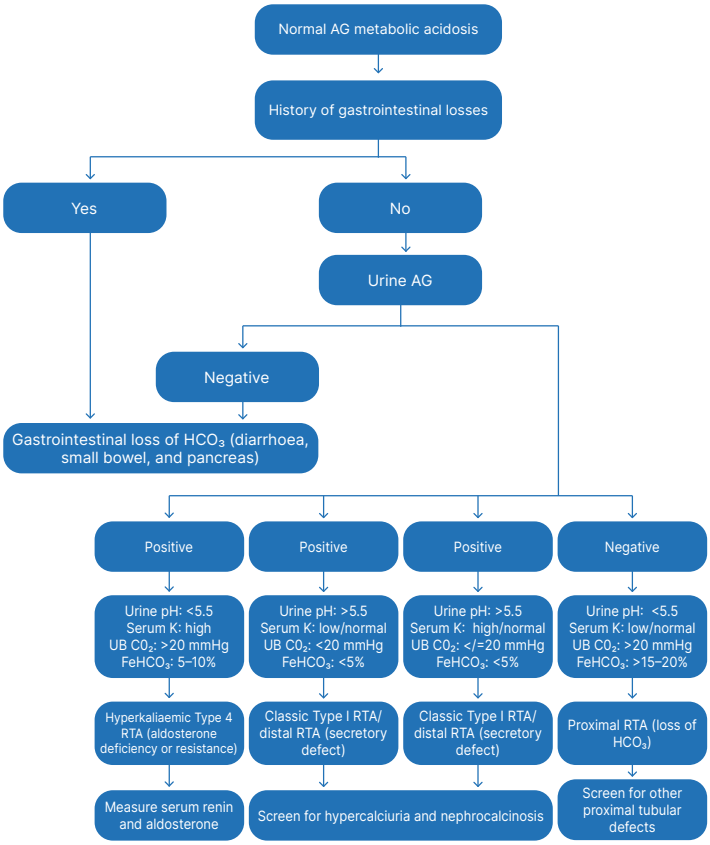
If the aetiology of the normal AG remains unclear clinically, a urine AG may be useful. In the presence of metabolic acidosis, a positive value for urine AG is indicative of impaired ammonium excretion, such as is seen in distal (Type 1) and hypoaldosteronism (Type 4) RTA. Conversely, a negative value is consistent with intact urinary

Figure 2: Approach to high anion gap metabolic acidosis in children.



AG: anion gap; BUN: blood urea nitrogen; DKA: diabetic ketoacidosis.

Figure 3: Approach to normal anion gap metabolic acidosis in children.



AG: anion gap; $FeHCO_3$: fractional excretion of bicarbonate; HCO_3: bicarbonate; K: potassium; RTA: renal tubular acidosis; UB CO_2: urine-blood CO_2 tension gradient.

ammonium excretion as seen in children with metabolic acidosis due to proximal (Type 2) RTA and gastrointestinal losses.[1,9,19]

The urine anion gap can be determined using the equation: (Na+potassium [K])-Cl.[1,9,19]

The algorithm for the assessment of RTA is given in Figure 3.

MANAGEMENT

The primary focus of therapy for metabolic acidosis, both acute and chronic, is directed at reversing the underlying pathophysiologic process.[1,9,19,20] Specific therapy of acidosis depends on whether metabolic acidosis is acute or chronic, and the severity of acidosis.

Acute Metabolic Acidosis

Mild metabolic acidosis is generally well tolerated but severe acidaemia can be life-threatening. In hypovolemic shock, restoring haemodynamic stability should be the priority. Similarly, delivering fluids and insulin to a patient in DKA remains the first-line therapy not only for the underlying condition, but also for the associated metabolic acidosis.

Intravenous bicarbonate therapy

When metabolic acidosis occurs due to loss of intracellular and extracellular buffers, it is compelling to administer $NaHCO_3$ to shore up HCO_3 stores. However, neither better clinical outcomes nor decreased mortality have been reported from the use of base therapy in cardiac arrest, lactic acidosis, DKA, and septic shock.[21]

Base therapy is disputed for several reasons. First, in conditions where HCO_3 serves to buffer an increased acid load such as DKA or lactic acidosis, the use of HCO_3 forms an anionic base known as potential HCO_3, that can lead to overcorrection alkalosis.[21,22] This in turn can result in dangerous degrees of hypokalaemia, hypophosphataemia, and ionised hypocalcaemia.[22] Additionally, through the carbonic anhydrase-mediated reaction, HCO_3 freely converts to CO_2, which diffuses freely across cell membranes, and leads to a paradoxical intracellular acidosis and deranged cellular function.[23] Besides, frequent $NaHCO_3$ administration increases fluid overload and hypernatraemia risk, which can further worsen pulmonary oedema.[21] In DKA, administration of base therapy increases the risk of cerebral oedema and delayed resolution of ketosis. Therefore, the risks of base therapy, in the conditions mentioned earlier, must be examined against the potential dangers of uncontrolled acidaemia.

Indications for sodium bicarbonate therapy

Severe metabolic acidosis affects the cardiovascular system most critically. A blood pH drop to below 7.1–7.2 is accompanied inevitably by a fall in cardiac output,[24] a predisposition to ventricular arrythmias, and a resistance to the inotropic and vasoconstrictive effects of infused catecholamines.[1,9] The use of intravenous (IV) $NaHCO_3$ is reserved for the following cases:[1,21]

- IV HCO_3should be used very cautiously if the pH is <7.1 with cardiovascular compromise. The aim is to raise the pH to 7.2. Since the PCO_2 is expected to rise after $NaHCO_3$, administration the patient should be adequately ventilated; severe hypokalaemia should be avoided with $NaHCO_3$ therapy.
- IV HCO_3 may be given when the blood pH is <7.2 in patients with impaired renal excretion such as those with RTA, acute kidney injury, and chronic kidney disease (CKD).
- IV HCO_3 may be used in patients where urine alkalinisation is required therapeutically, as in patients with tumour lysis syndrome or rhabdomyolysis.
- In salicylate poisoning, base therapy increases renal clearance of salicylates and decreases the associated cognitive toxicity. Base therapy in salicylate poisoning is therefore recommended irrespective of the arterial pH.[25]
- Similarly, base therapy is also recommended to maintain a pH of 7.3 following the ingestion of ethylene glycol or methanol. Base therapy keeps the metabolites of these ingested substances in a charged form, limits their diffusion into end organs, and thereby reduces their toxic effects. Moreover, urinary alkalisation helps to increase renal clearance.[25]

Pre-administration considerations

Effect of $NaHCO_3$ on the level of serum/plasma ionised calcium and compatibility with other IV medications should be taken into consideration prior to HCO_3 therapy. Pre-treatment with calcium is advised if the corrected calcium is less than 8 mg/dL or ionised calcium is less than 1 mmol/L. This is important because an acute decrease in the ionised calcium concentration can cause cardiac dysrhythmias, seizures, and/or even tetany.[9]

Dose of intravenous bicarbonate

In the emergency setting, an 8.4% $NaHCO_3$ solution is infused at a dose of 1 mEq/kg (maximum: 50 mEq), as an IV slow push. Blood gas, ionised calcium, and serum electrolytes are obtained after 15 min to determine therapy effectiveness and/or if there has been an adverse effect of bicarbonate therapy.[9]

In a non-emergency setting repletion, the dose of $NaHCO_3$ is determined by the calculated estimated bicarbonate deficit using the following formula:[9] estimated HCO_3deficit=(target HCO_3-current HCO_3)xweight (kg)x0.4-0.5.

Half of the estimated HCO_3 deficit is infused intravenously over 2–4 hours. The remaining half of the HCO_3 deficit is infused over the following 6–24 hours. A longer course of infusion should be prescribed when the $NaHCO_3$ deficit is large (>3 mEq/kg).

During and after repletion of the HCO_3 deficit, blood gas, ionised calcium, and serum electrolytes are obtained to determine whether additional HCO_3 therapy is required and to detect any adverse effect of HCO_3 therapy.

When the patient can tolerate oral medications, maintenance administration should be changed to an oral alkali.

Chronic Metabolic Acidosis

Several studies in patients with chronic metabolic acidosis, with and without renal impairment, have shown that alkali therapy decreases the progression of bone disease, improves growth, reduces muscle degradation, and retards the progression of CKD.[26]

Oral Bicarbonate Therapy

Use of long-term base therapy is earmarked for children with disorders such as RTA and chronic renal failure. Oral HCO_3 therapy is given in the form of $NaHCO_3$, Na citrate, or K citrate. The choice of therapy depends on the underlying cause of chronic metabolic acidosis, availability and cost of the specific medication, and the experience of the prescribing clinician.[9]

Proximal/distal RTA can be effectively treated with $NaHCO_3$/Na citrate. Citrate is actively metabolised to bicarbonate in the liver. The use of citrate solutions has been reported to ameliorate the harmful effects of chronic metabolic acidosis such as poor bone quality.[26] For children with Type I and II RTA who are hypokalaemic, K citrate provides an added benefit. For those in renal failure, use of Na citrate prevents an added K load. Base therapy may exacerbate pre-existing hypertension and cause volume overload. Hence, care must be taken to maintain neutral sodium balance.

Treatment can be started at 1–2 mEq/kg/day of base in three to four divided doses. Some conditions like proximal RTA may require up to 20 mEq/kg/day of base for correction of acidosis. When alkali therapy is initiated, the smallest dose should be used and increased in a stepwise fashion until the targeted total CO_2/HCO_3 level is reached.

Mineralocorticoid therapy is indicated for the treatment of chronic metabolic acidosis in children with hyporeninemic states but should be used judiciously in those with antecedent hypertension.[27] In such patients, diuretics or Na polystyrene sulfonate may be used for control of acidosis and hyperkalaemia.[28]

In patients with CKD on chronic haemodialysis (HD), dialysate with a high HCO_3 concentration (approximately 40 mmol/L) usually suffices to correct metabolic acidosis.[29] Similarly, in children on chronic ambulatory peritoneal dialysis (PD) a dialysate with a high base concentration is usually efficacious.[29]

Haemodialysis or Peritoneal Dialysis

Refractory acidosis is an indication for renal replacement therapy (HD or PD). The decision to perform dialysis may be dictated

by concomitant electrolyte disturbances, especially hyperkalaemia. Besides providing base, HD is effective in removing toxins such as ethylene glycol or methanol. Continuous renal replacement therapy is superior to peritoneal dialysis or intermittent HD to finely control fluid and electrolyte derangements especially in haemodynamically unstable patients.[30]

PD using bicarbonate-buffered PD fluid may be required in children with seriously compromised liver functions and acute kidney injury.[31] HCO_3-based PD fluid may also be used for metabolic acidosis arising out of inborn errors of metabolism.[31] The use of HCO_3 as a buffer in the dialysate results in better correction of acidosis, lower lactate levels, and improved haemodynamic stability. HCO_3-buffered dialysate cannot be stored; hence, it should be prepared just prior to use. Adding 260 mL of 5.0% dextrose and 40 mL of 8.4% $NaHCO_3$ to 700 mL of normal saline gives a dialysate containing Na 147 mEq/L and HCO_3 40 mEq/L).

OTHER TREATMENT MODALITIES

Tris-hydroxymethyl Aminomethane

Tris-hydroxymethyl aminomethane (THAM) is a reasonable alternative to HCO_3 therapy in patients with acidosis and adequate renal function, particularly if associated with severe hypernatraemia and CO_2 retention. THAM is a weak alkali that reduces arterial H^+ without producing CO_2. THAM, available as an IV formulation, can buffer acid by directly binding to protons without an associated increase in CO_2.[32,33] Another advantage of THAM is that it has the potential to optimise pH for cellular function since its diffusion intracellularly is slow.[32] Adverse reactions of THAM include respiratory depression and hypoglycaemia due to insulin release, especially if infused rapidly. Though THAM has been tried in children with DKA and gastroenteritis, and in neonates with acute respiratory distress syndrome in the 1960s, there is limited published literature thereafter of its use in paediatrics or neonatology.[32,33]

Metabolic Acidosis as a Predictor of Mortality in Children

A variety of models exist for the prediction of mortality in patients of PICU, including the Pediatric Risk of Mortality (PRISM and PRISM III) and the Pediatric Index of Mortality (PIM and PIM 2) scores.[34] These scores are a quantification of physiologic status using predetermined physiologic variables to facilitate accurate estimation of mortality risk. These scores have been validated in several studies, and help physicians to provide optimum patient management with the available resources. It is important to note that both the PRISM III and PIM 2 score use HCO_3 levels and base excess as a variable for prediction of mortality. Kim et al.[3] concluded in their study that an elevated corrected AG at admission was associated with higher mortality in PICU. They also suggested that corrected AG at admission may be used to predict mortality in PICU, regardless of underlying aetiology. Thus, metabolic acidosis plays an important role in determining the patient outcome and should be promptly addressed.

Effect of Metabolic Acidosis on the Quality of Life

Chronic metabolic acidosis can occur secondary to several conditions as mentioned above. It is important to study the quality of life in children affected with chronic conditions as it helps in providing a holistic, multidimensional, and comprehensive management.[35,36] Some of these chronic conditions have associated metabolic acidosis. For example, studies on quality of life have been done in children suffering from CKD. Several of the clinical manifestations seen in CKD are due to underlying chronic metabolic acidosis.[36-38] Ruidiaz-Gómez et al.[36] did a meta-analysis on the impact of CKD on health-related quality of life in the paediatric population. They concluded that paediatric patients with CKD have lower health-related quality of life than healthy patients, specifically in the school, physical, emotional, and social dimensions. Amongst the affected dimensions, the most affected was the school attendance due to frequent visits to the doctor and the symptoms of the disease. Complications of the disease also reduced the opportunities for social interaction with peers and to carry on recreational activities, thereby affected the social dimension.

CONCLUSION

Metabolic acidosis is a common disorder in children and may present acutely or chronically. Diagnosis requires a methodical approach starting with the history and physical examination followed by laboratory investigations. The SAG plays a crucial role in differentiating the different causes of metabolic acidosis. Severe and prolonged metabolic acidosis has detrimental effects on cellular function and is related to increased morbidity and mortality. The main aim of treatment in metabolic acidosis is to reverse the primary pathophysiology. In acute metabolic acidosis, $NaHCO_3$ therapy is not beneficial due to potential complications and is reserved for specific situations. Base therapy is used in chronic metabolic acidosis where it ameliorates many of its untoward effects.

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Heated Tobacco Products and Chronic Obstructive Pulmonary Disease: A Narrative Review of Peer-Reviewed Publications

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Abstract

An estimated 65 million people worldwide have moderate or severe chronic obstructive pulmonary disease (COPD), an umbrella term used to describe a group of progressive lung diseases that obstruct airflow such as emphysema and chronic bronchitis. Smoking contributes to an estimated 90% of COPD cases, as the harmful chemicals produced during tobacco combustion damage the lungs and airways. Although smoking cessation is the only intervention shown to improve COPD prognosis in smokers, many patients who try to quit continue to smoke. The continued use of conventional cigarettes exacerbates COPD symptoms, and globally more than 3 million people die from the disease every year. The last two decades have seen the introduction of combustion-free nicotine delivery alternatives that produce significantly lower levels of the harmful components in cigarette smoke, and researchers have begun to assess the impact of switching from cigarettes to these products. Several studies have examined how patients with COPD use e-cigarettes as assistance for quitting, but few have examined how heated tobacco products (HTP) may reduce risk. This narrative review summarises results from pre-clinical, clinical, and real-world evidence studies showing possible harm reduction benefits for patients with COPD who switch to HTPs rather than continuing to smoke cigarettes. Epidemiological studies, real-world data analyses, and randomised clinical trials must be conducted to determine whether switching from cigarettes to HTPs can improve health outcomes in patients with COPD who would otherwise continue to smoke combustible cigarettes.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is a preventable lung condition that represents a major and growing cause of global morbidity and mortality, and is primarily due to cigarette smoking.[1,2] The World Health Organization (WHO) cites it as the third leading cause of death after ischaemic heart disease and stroke.[3] The mortality risk from COPD is 12–13 times greater in smokers of combustible cigarettes,[4] and an estimated 80–90% of patients with COPD smoke(d).[5] Beyond the 3 million deaths attributed to COPD annually, the condition also has a major impact on healthcare systems: all smoking-related diseases, including COPD, are responsible for 1.5–6.8% of national health system expenditures worldwide.[6]

COPD is not a singular respiratory disease; it encompasses a range of treatable (but not curable) chronic lung conditions (including chronic bronchitis and emphysema) characterised by respiratory symptoms, progressively worsening airflow limitation, and resultant airway inflammation. According to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines,[7] lung function evaluation via spirometry testing (e.g., forced expiratory volume in one second [FEV_1] and forced vital capacity) is the gold standard for diagnosing COPD and tracking disease progression. However, COPD is widely thought to be underdiagnosed, and many current smokers who do not meet the diagnostic standards do have respiratory symptoms without airflow obstruction.[7]

The symptoms of COPD are induced and exacerbated by exposure to cigarette smoke,[8] which causes inflammation and oxidative stress.[9] There is no question that smoking cessation is by far the best approach to reduce disease progression in patients of any age. Most subjects with COPD are or were smokers and therefore have first-hand experience with the detrimental effects of cigarettes, but multiple studies reported that roughly half of smokers with COPD attempted to quit smoking in the past year.[10-12] Unfortunately, only approximately 20% of patients with COPD are successful for 1 year,[13] and many eventually relapse. Considering this small percentage, complementary tobacco harm reduction approaches should also be considered for this specific population of adult smokers.

Chronic Obstructive Pulmonary Disease and Cigarette Smoke

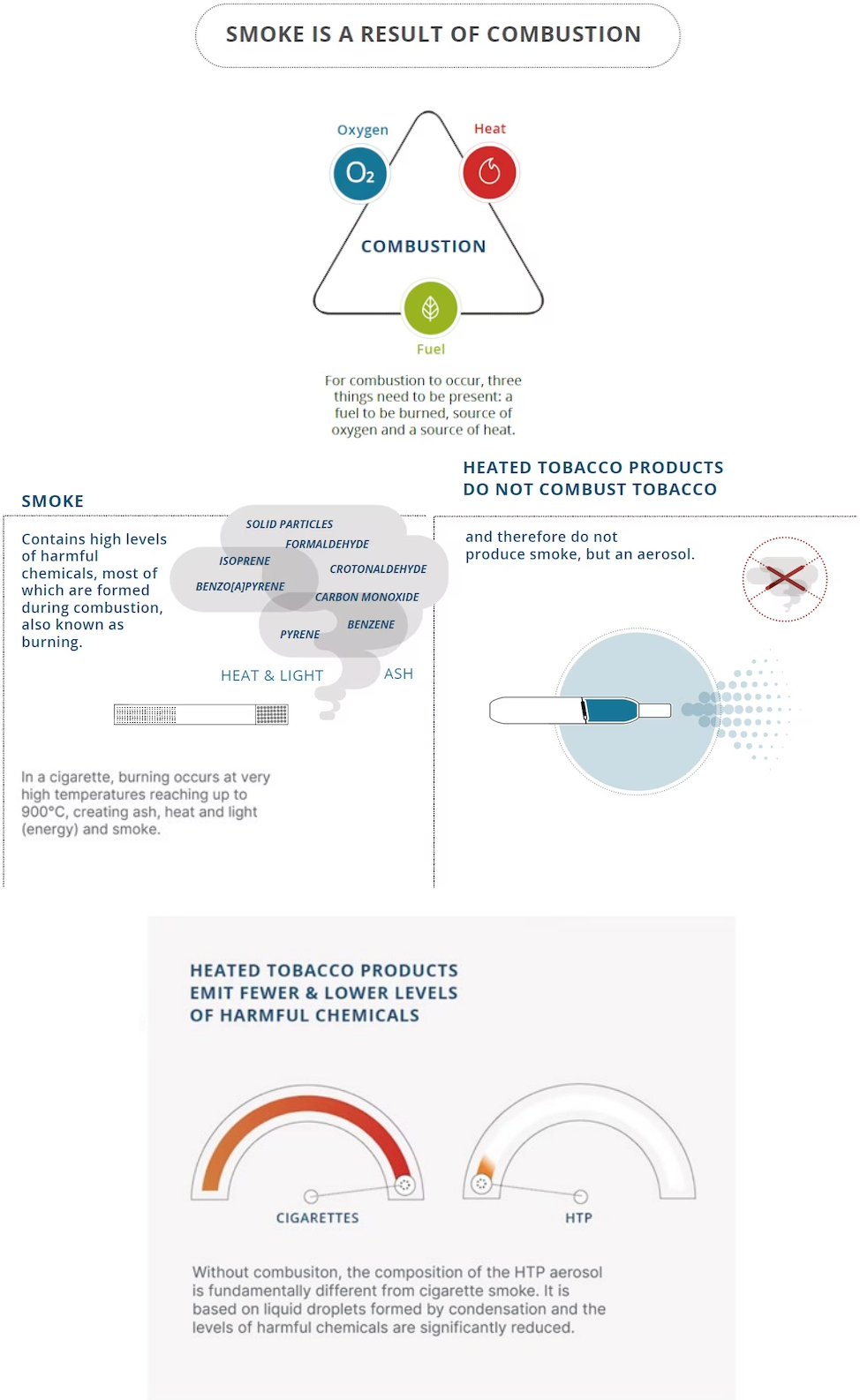
The primary cause of smoking-related disease and mortality is the harmful and potentially harmful constituents (HPHC) formed during tobacco combustion. A burning cigarette releases a complex mixture of ultrafine solid and gaseous particles, and more than 6,000 chemical constituents, approximately 100 of which have been identified by public health authorities as HPHCs linked to smoking-related diseases. These include particulates, oxidising chemicals, polycyclic aromatic hydrocarbons, acrolein, butadiene, metals (e.g., cadmium), and carbon monoxide (CO). These HPHCs are deposited throughout the respiratory tract, leading to cilia toxicity, oxidative stress, inflammation, impairment of lung defences, and irritation.[9] Their continued presence causes changes in airway and alveolar cells, and affects tissue functions. This adversely impacts overall pulmonary function, eventually leading to the development of COPD. The most common symptoms are dyspnoea, increased sputum or mucus production, and chronic cough.

Smoke-Free Products

Although the best way to reduce the risks of developing COPD and other smoking-related diseases is to quit tobacco altogether, many people still want to continue using products with similar taste, ritual, and nicotine uptake.[14] Recent scientific and technological advances have facilitated the development of innovative smoke-free products (SFP) that have the potential to be less harmful than continued smoking and are acceptable to and may be used by current adult smokers. The most widely used SFPs are e-cigarettes and HTPs. The former vaporises an e-liquid solution when it is puffed, while the latter heats real tobacco. E-cigarettes and HTPs operate differently, but they share the absence of combustion while still providing a satisfactory sensory experience for adult smokers.[15-17]

HTPs are designed to generate a nicotine-containing aerosol by heating tobacco to temperatures sufficient to release nicotine and flavours from the tobacco (<350 °C), but low enough to prevent the tobacco from burning (400–800 °C in conventional cigarettes).[18] As a result, HTP aerosol contains fewer and lower levels of HPHCs than cigarette smoke (Figure 1).[19]

Figure 1: Differences between cigarette smoke and heated tobacco product aerosol.



HTP: heated tobacco product.

Adapted from PMIscience.[19]

Philip Morris International (PMI, New York, USA) launched the first iteration of the current generation of HTPs in 2014. It was developed as Tobacco Heating System (THS, version number 2.2), commercialised under the IQOS (PMI) brand name, and explicitly marketed to adult smokers unable to quit.[20] As of September 2022, it was available in 68 countries. British American Tobacco (BAT, London, UK) launched glo in 2016 and Japan Tobacco (JTI, Tokyo, Japan) launched the HTP Ploom in the same year. Korean Tobacco and Ginseng (KT&G, Daejeon, South Korea) entered the HTP market with the launch of lil in 2017.

APPROACH AND PURPOSE OF THIS NARRATIVE REVIEW

There are a myriad of systematic literature reviews and meta-analyses on the topics of smoking and COPD, with extensive high-level evidence supporting the causal relationship between the habit and disease.[13,21-23] Although SFPs are increasingly used by adult smokers, there are fewer studies on the effects of HTPs compared to e-cigarettes. A simple query on PubMed for "e-cigarette" returns 5,495 results, versus 180 for "heated tobacco product." Some groups have investigated health effects in smokers who switch to e-cigarettes.[24,25] Fewer publications are related to HTPs. There is one systematic literature review on heat-not-burn tobacco products,[26] and a Cochrane meta-analysis examined the use of HTPs for smoking cessation and reducing smoking prevalence.[27] Almost no studies have assessed the individual and population health benefits from tobacco harm reduction for people with COPD and other chronic conditions who switch to SFPs instead of continuing to smoke. As more data are gathered, it is important to understand how alternatives like HTPs may reduce risk in patient populations.

This literature summary contains three sections. The first two describe the studies that support HTP harm reduction based on HPHC levels and a brief overview of pre-clinical findings. These publications are complemented by references to statements from regulatory bodies. The third section describes findings from the above-described literature search that identified published clinical data of HTP effects on HPHC exposure and smoking-related respiratory diseases. The narrative review concludes with a discussion of the cited studies, limitations of the data, and gaps in the literature to be addressed.

The goals of this narrative review were to provide a high-level summary of the studies performed to demonstrate that HPHC levels are lower in HTPs compared to cigarettes; and to identify studies on health outcomes in patients with COPD who switch from combustible cigarettes to HTPs. The publications were identified in the PubMed, Scopus, Embase, Google Scholar, and SciFinder databases using the following search string: (((chronic obstructive pulmonary syndrome[Title/Abstract]) OR (COPD[Title/Abstract])) AND (heated tobacco product[Title/Abstract])) OR (tobacco heating system[Title/Abstract]). The authors also searched the reference lists of relevant reviews and meta-analyses.

LITERATURE SUMMARY

Harmful and Potentially Harmful Constituents Levels

The absence of combustion during THS use and the fact that THS aerosol is not smoke have been validated by leading scientific experts in the fields of combustion, fire safety, and thermochemistry from numerous countries, including Italy, the UK, Japan, Poland, the USA, Australia, Germany, and Switzerland, as well as by an independent research organisation in New Zealand.[28]

By avoiding combustion, THS generates an aerosol that contains significantly fewer harmful chemicals. Relative to smoke from a reference cigarette, the levels of International Agency Research on Cancer (IARC) Group 1 carcinogens in THS aerosol are reduced on average by >95%.[29,30] Compared to cigarettes, THS also emits >94% lower levels of free radicals[31] and 85% lower levels of reactive O_2 species.[32] A 2022 review concluded that SFPs, including e-cigarettes and HTPs, had a reduced effect on oxidative stress compared to cigarette smoking, with the caveat that more investigation is needed to clarify the long-term toxicological impact.[33]

The significant HPHC reduction in THS aerosol was confirmed by various public health authorities and independent laboratories around the world. In April 2019, the U.S. Food and

Drug Administration (FDA) Center for Tobacco Products (CTP) issued a marketing order[34] for PMI's IQOS Tobacco Heating System to allow its introduction in the USA market. In its scientific review of the regulatory application,[35] the FDA "found that the aerosol produced by the product under consideration 'contains fewer toxic chemicals than cigarette smoke', and many of the toxins identified are present at lower levels than in cigarette smoke. For example, the CO exposure [resulting from this product] is comparable to environmental exposure, and levels of acrolein and formaldehyde are 89–95% and 66–91% lower than from combustible cigarettes, respectively." In July 2020, the FDA authorised the marketing of IQOS as a modified risk tobacco product with the following information: the IQOS system heats tobacco but does not burn it; this significantly reduces HPHC production; and scientific studies have shown that switching completely from conventional cigarettes to the IQOS system reduces user exposure to HPHCs.[36]

The German Federal Institute for Risk Assessment (BfR) also conducted an independent analysis of THS and found that the "levels of major carcinogens are markedly reduced in the emissions of the analysed [heat not burn] product in relation to the conventional tobacco cigarettes, and that monitoring these emissions using standardised machine smoking procedures generates reliable and reproducible data, which provide a useful basis to assess exposure and human health risks."[37]

Published research on existing HTPs available in various markets confirms the reduction in the number and levels of HPHCs.[38-42] This is in line with the statement from Public Health England (PHE, now under the UKHSA) that, "compared with cigarette smoke, heated tobacco products are likely to expose users and bystanders to lower levels of particulate matter, and harmful and potentially harmful compounds. The extent of the reduction found varies between studies." In addition, "[t]he available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes, and more harmful than e-cigarettes."[43] However, it is important to note that this potential HPHC reduction should be assessed on a product-by-product basis.

Pre-Clinical Findings

COPD is characterised by airway inflammation, damage, and remodelling.[1,4] High levels of HPHCs in cigarette smoke irritate the lungs, introduce free radicals, and stimulate the production of proinflammatory chemokines and cytokines.[10] Several *in vivo* studies have shown that the reduced exposure to HPHCs following THS use translates into lower levels of biomarkers of exposure and significantly reduced biological impacts on the rodent respiratory tract.[44-47] These effects of lower exposure manifest as reduced disturbances in biological processes associated with COPD (including oxidative stress, inflammation, and apoptosis), less severe adaptive changes in respiratory tissues, absence of alveolar destruction (emphysema), and reduced pulmonary dysfunction.[44,47] Emma et al.[33] recently published a detailed review on how HTPs may also impact oxidative stress. They concluded that HTPs appear to have a better safety profile than cigarettes but suggested further long-term studies.[33]

While aerosols from HTPs appear to be less harmful than cigarette smoke, they may still induce changes. One group reported that HTP exposure induced apoptosis-mediated pulmonary emphysema in mouse lungs.[48] Another recent study concluded that HTP aerosol altered rat ultrastructural lung airways and DNA.[49] Gu et al.[50] found that mice exposed to HTP aerosol exposure for 24 weeks had increased proinflammatory cytokine levels in the lung, impaired pulmonary function, and lung tissue damage. However, many of these changes were not as significant as those induced by cigarette smoke.[48-50]

Clinical Findings

Human clinical trials with THS indicate that reduced HPHC exposure may have a lower impact on smokers' health compared to continued combustible cigarette use. However, most studies focused on measuring biomarkers of exposure to toxicants or potential harm as proxies to assess cardiovascular and respiratory disease, and cancer.[51] Only a handful of publications have actually examined lung function in smokers. In a clinical trial in Japan, healthy smokers who were not willing to quit switched from menthol cigarettes to menthol THS for 5 days in confinement and 85 days in

ambulatory settings, and showed improved lung function (i.e., higher FEV_1), similar to that measured in subjects who stopped smoking.[52] The authors proposed that this was due to decreased lung inflammation after switching from cigarettes. In a 6-month clinical study in the USA, smokers who switched from smoking cigarettes to predominant THS use showed significant improvements in clinical risk endpoints associated with O_2 delivery (decreased carboxyhaemoglobin levels), inflammation (reduced white blood cell count), and COPD (increased FEV_1), although their plasma nicotine levels remained similar to that in smokers.[53]

A longitudinal epidemiological study[54] of a Kazakhstani population showed that adult smokers who switched to HTPs showed less decline in health-related parameters than subjects who continued to smoke combustible cigarettes after 1, 2, and 4 years of follow-up. Although the study did not specifically assess subjects with COPD, the cohort included individuals aged 40–59 years with a minimum 10 pack-year smoking history. Smokers who switched to HTPs had fewer respiratory symptoms, better lung function (forced vital capacity and FEV_1) and physical exercise capacity (assessed with a 6 Minute Walk Test [6MWT]), and healthier metabolic syndrome parameters (waist circumference, high-density lipoprotein cholesterol levels, and systolic blood pressure) than cigarette smokers.[55-57]

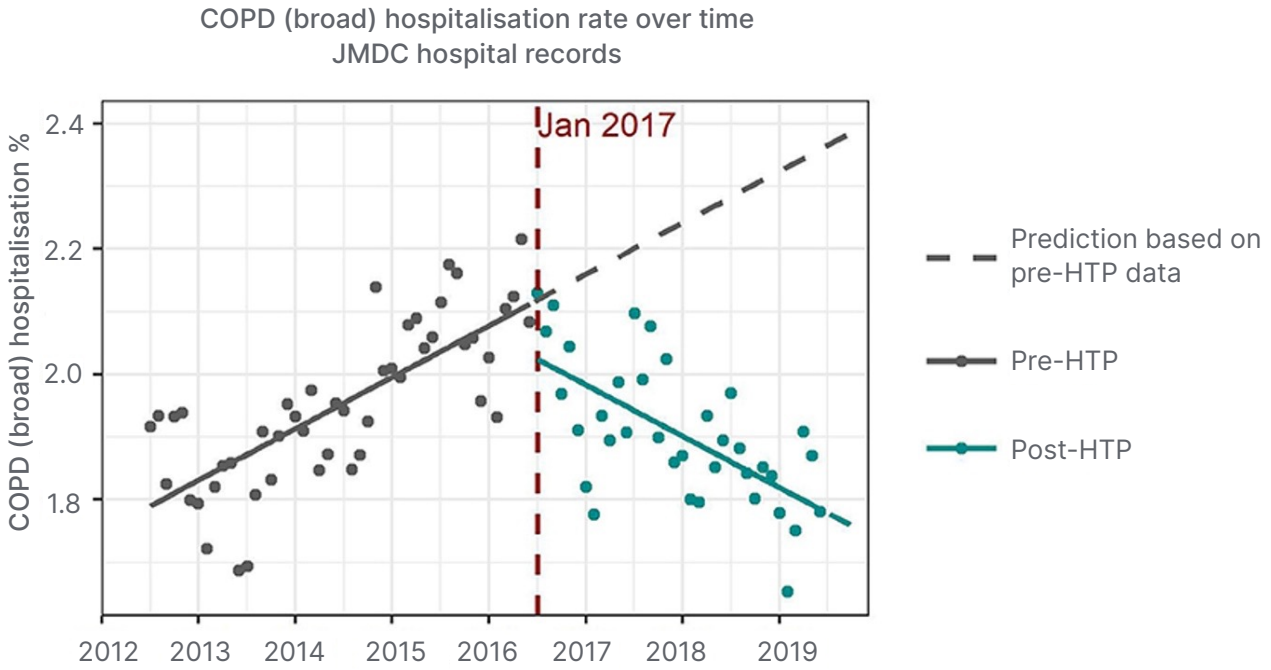
One group specifically analysed data from a COPD cohort for 3 years after smokers with COPD switched to HTPs. Despite the small number of patients in their study (n=38), Polosa et al.[58] found that patients with COPD using HTPs experienced fewer COPD exacerbations and significant improvements in symptoms, exercise capacity, and overall health-related quality of life than patients who continued to smoke cigarettes.[58] Importantly, the authors performed a subgroup analysis of dual users who continued to smoke combustible cigarettes in addition to HTPs (n=8) and found a marked reduction in the number of cigarettes smoked per day (confirmed by exhaled CO measurement).[58,59] A cross-sectional study from the same research group[60] analysed mucociliary clearance, a known biomarker of early respiratory health changes, by measuring the saccharin transit time after SFP use. The median saccharin transit time was almost twice as long in cigarette smokers (13.15 min) compared to never (7.24 min) and former smokers who had abstained for at least 3–6 months (7.26 min). Subjects in the HTP study group had a saccharin transit time (8.00 min), similar to former and never smokers. Based on these findings, the authors concluded that switching from cigarettes to HTPs has a beneficial impact on mucociliary clearance, which could be considered an early respiratory health change.

After their introduction to Japan in 2014, the prevalence of HTP use increased 50-fold from 2015–2019, from 0.2% to 11.3%.[61] This coincided with a rapid decrease in cigarette sales in the country, from 186.2 billion sticks in 2014 to 120.9 billion in 2019.[62] A recent real-world evidence study analysed hospitalisation numbers associated with COPD using data from the Japanese Medical Data Center (JMDC) over this same time period.[63] Careful evaluation of all available data from the JMDC database revealed a significant reduction in the number of hospitalisations for COPD and a non-significant reduction in hospitalisations for COPD plus lower respiratory tract infections after the 2014 THS introduction (Figure 2).

DISCUSSION

Although HTPs have only been marketed for a decade, there is a considerable body of evidence from industry and independent studies that HTPs generate lower levels of HPHCs. A Cochrane meta-analysis on 13 clinical studies involving HTPs concluded that there was moderate-certainty evidence that HTP users are exposed to lower levels of HPHCs than smokers.[27] There are also numerous pre-clinical studies supporting their relative safety compared to cigarettes.[44-50] However, the clinical picture is less clear. A systematic review on HTP exposure and adverse health effects found just 17 studies investigating the effects of HTPs on human health, most of which were short term.[64] The authors' review of the literature identified a small number of studies[55-58] that longitudinally assessed lung function in middle-aged subjects who continued to smoke or switched to HTPs, but they were not specifically recruited from a patient population with COPD. In patient-focused studies, the actual numbers of subjects with lung disease or COPD

Figure 2: Chronic obstructive pulmonary disease hospitalisation rate over time in Japan (data acquired from the Japanese Medical Data Center [JMDC] database).



The increasing trend of COPD hospitalisations turned downward in 2017, shortly after the introduction of HTPs to Japan.

COPD: chronic obstructive pulmonary disease; HTP: heated tobacco product; JMDC: Japanese Medical Data Center.

Adapted from van der Plas et al.[63]

were very low: n=51 (continued smoking) and n=25 (switched to HTPs) in Sharman et al.[57] and n=19 in both arms of Polosa et al.[58] Real-world evidence studies such as the publication by van der Plas et al.[62] can provide some insight into how these products affect population health, but there are many limitations to this type of research. While the results highlight associations, they cannot be used to infer a causal relationship. Longer studies with different designs will ultimately determine whether these findings reflect a reduction in COPD morbidity.

This narrative review also highlights a significant literature gap regarding HTP use by patients with chronic conditions, including COPD. A recent survey on HTP use by subjects with chronic conditions only included 42 patients with COPD out of 9,008 respondents,[64] and 33.3% were using HTPs in conjunction with conventional cigarettes. Clearly, more information is needed to determine if completely switching to HTPs improves the quality of life and health outcomes of patients with COPD who would otherwise continue to smoke. This will require multiple lines of evidence from surveys of patients with chronic conditions, continued surveillance of real-world evidence, and the completion of Phase IV trials that will take several years. As noted in a recent meta-analysis,[26] only 11 randomised controlled trials have assessed HTP safety and the median follow-up was just 13 weeks. A clinical trial sponsored by PMI is currently recruiting subjects for a 3-year study to assess the effect of switching from cigarette smoking to THS on disease progression in subjects with mild to moderate COPD with chronic bronchitis;[65] the estimated study completion date is June 2027.

It is worth noting that HTPs were only recently authorised for sale in the USA (in 2019) and they are currently only available in a few cities. Presumably, more researchers will study their effects as HTP uptake increases in the USA and around the globe.

CONCLUSIONS

The congruence of recent scientific findings indicates that adult smokers who completely switch to HTPs could have a lower risk of COPD development and progression than those who continue smoking. However, the paucity of studies on this specific topic limit the strength of this conclusion. Further epidemiological studies, additional follow-up of real-world data, and prospective clinical trials are needed to understand the impact of switching to HTPs on health outcomes in COPD.

In closing, it is important to state that HTPs are not risk-free and contain nicotine. Although nicotine is addictive, it is not the primary cause of smoking-related diseases.[14] The best choice any smoker can make continues to be quitting cigarettes and nicotine altogether. If they choose to switch to HTPs, they should be informed that dual use with conventional cigarettes is not advised.

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Oral Corticosteroids for Patients with Eosinophilic Diseases: An Expert Panel View on Use, Overuse, and Strategies to Reduce Use

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Summary

Severe asthma (SA), chronic rhinosinusitis with nasal polyps (CRSwNP), and eosinophilic granulomatosis with polyangiitis (EGPA) are three conditions driven by IL-5 and eosinophilic inflammation. As these conditions have high use of healthcare services, as well as lifestyle and psychological burdens, well-tolerated treatment to achieve optimal control is key. In all three conditions, as for many other eosinophilic diseases (ED), oral corticosteroids (OCS) are often used for both acute and maintenance treatment where disease activity is high. While, in general, OCS are very effective, their use is limited by a well-recognised high potential for adverse effects (AE). Moreover, cumulative exposure to OCS may not be acknowledged in many patients, especially for those predominantly treated in primary care, exposing patients to potentially damaging long-term OCS-related AEs. To discuss the use of OCS for these eosinophilic diseases, as well as to provide guidance on how to help limit their use, a board of European experts within each field was gathered. The experts completed questionnaires regarding treatment and referral pathways for patients with SA, CRSwNP, or EGPA; then, in an online meeting, discussed a number of issues in regard to OCS use. Here, the authors present the key recommendations from the expert advisory panel alongside some background to these conditions regarding treatment with OCS.

INTRODUCTION

Globally, systemic corticosteroid use for EDs is widespread.[1] An expert panel of advisors was convened to discuss OCS use, overuse, and ways to limit use for patients with EDs such as SA, CRSwNP, and EGPA, all populations where cumulative OCS doses may be high. Discussion included how such use depends on several factors, including disease severity and phase, organ involvement, comorbidities, responsivity to therapy, and treatment adherence. These discussions have implications for other EDs such as hypereosinophilic syndrome. This typically multi-organ and tissue damaging disease is also predominantly treated with OCS, kinase inhibitors, and biologics; and similar issues with long-term use of OCS, as discussed below, may apply to this and all EDs where such treatment is common.[2] Unless specifically referenced, the opinions shared here are those of the advisors.

ORAL CORTICOSTEROID DOSE AND ADVERSE EVENT PROFILE

As with most illnesses, treatment decisions regarding OCS use should be individualised to the patient's needs and account for disease, behavioural, comorbidities, and environmental factors. There is no standard definition of what constitutes a low or high dose of OCS, or an acceptable lifetime cumulative dose, the advisors discussed, so there may be misconceptions in clinical practice with detrimental consequences regarding morbidity and mortality, even for patients receiving a low OCS dose. Recently, a European League Against Rheumatism (EULAR) task force deemed that for maintenance OCS use, there was a low risk of harm at a dose of ≤5 mg/day, a need for individual harm assessment at >5–10 mg/day, and an elevated risk of harm at >10 mg/day.[3] However, the advisors stressed how cumulative exposure, including for other

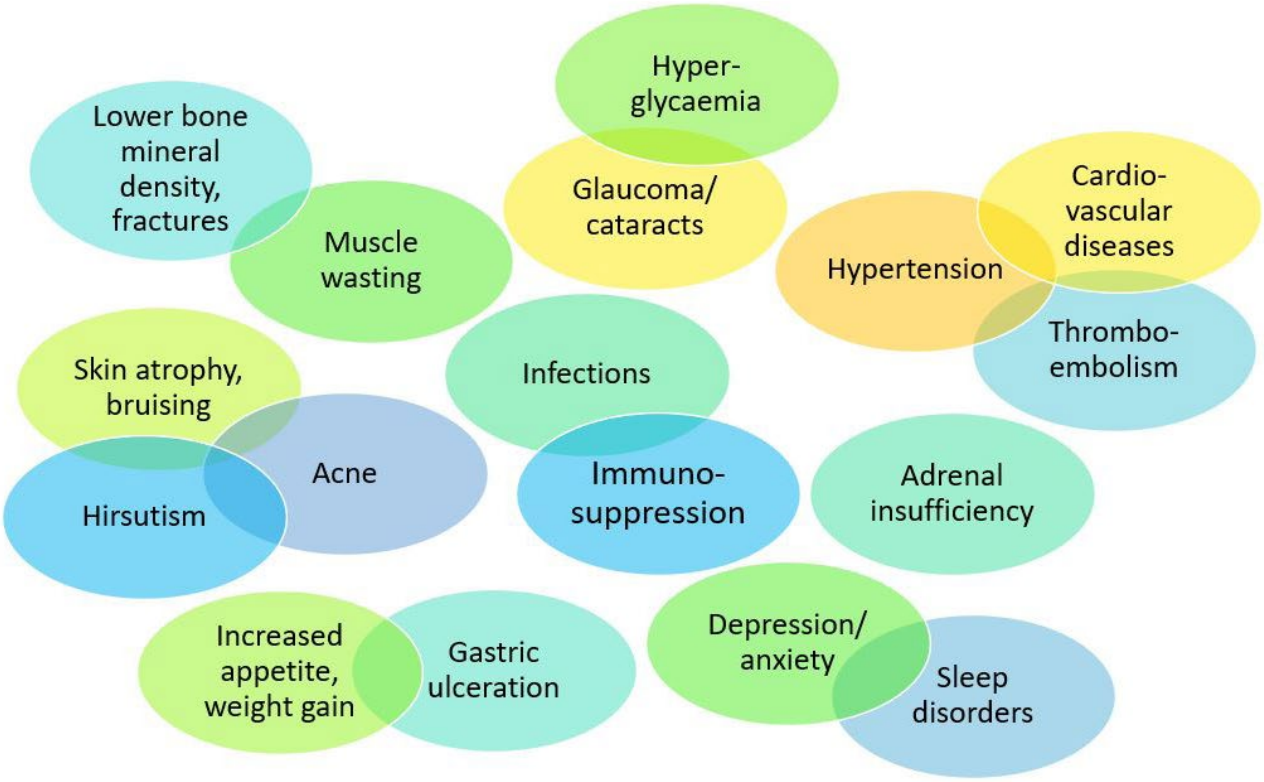
inflammatory conditions, must be taken into account, as in one long-term study including 24,117 adults with SA, adverse outcomes began with cumulative OCS exposures of 500–1,000 mg, equivalent to four OCS courses over a lifetime,[4] and, pointed one of the advisors, lower than the annual dose for a patient on 5 mg/day.

While efficacious, there are myriad AEs associated with OCS exposure (Figure 1), as they regulate inflammation and immune function; lipid, carbohydrate and protein metabolism; brain function; calcium and bone metabolism; and cardiovascular homeostasis.[5,15,16] For example, OCS action on the anterior pituitary gland and hypothalamus leads to decreased release of associated hormones and, subsequently, potentially iatrogenic adrenal insufficiency.[6,17] Another example is psychological effects, with one study finding a high incidence rate difference for depression and anxiety between OCS and non-OCS users with asthma, even in those with low OCS cumulative exposure. Of note though, this may not be a direct causative effect.[18]

Also of concern to the advisors is mortality associated with OCS use. Most studies here have been carried out in patients with asthma. For example, in a South Korean study including 16,668 OCS-dependent and matched OCS-independent adults with asthma, there was a hazard ratio (HR) of mortality of 2.17 (95% confidence interval: 2.04–2.31) with HR increasing with dose.[19] A Swedish study including 217,993 patients with asthma aged ≥6 years found an HR for mortality of 1.34 (95% confidence interval: 1.24–1.45) for regular OCS users compared to non- or periodic-OCS users.[20]

Patients themselves have concerns regarding OCS use due to AEs, with one study of adult patients with asthma reporting that 44% of 268 patients had a 'negative image' of OCS, with 26% reducing or stopping OCS treatment, and 42% and 34%, respectively of 230 patients, saying they would try to find an alternative treatment and would ask advice from another healthcare professional (HCP).[21]

Figure 1: Adverse events associated with oral corticosteroid use.[5-15]



TREATMENT OF EOSINOPHILIC DISEASES WITH ORAL CORTICOSTEROIDS

Severe Asthma

Approximately 5–10% of the 300 million people worldwide with asthma are diagnosed with SA, which may involve frequent exacerbations and hospitalisations, or have at least one severe exacerbation per year.[22-25]

Morbidity and mortality rates are high in SA and burdens include healthcare costs, corticosteroid-induced comorbidity, psychological factors, and work-related difficulties.[23,26-29] SA assessment and management should preferably be carried out in a specialised centre, in an individualised step-wise approach, with validation of diagnosis and attention to comorbidities. The Global Initiative for Asthma (GINA) has SA treatment goals, including good symptom control and risk reduction with minimal treatment side-effects. For patients aged ≥12 years old they recommend medium/high dose maintenance inhaled corticosteroids (ICS) plus formoterol or, as an alternative reliever, long-acting β-2 agonists, and considerations for adding a long-acting muscarinic antagonist and a biologic treatment if needed. They recommend only short courses of OCS for severely uncontrolled asthma, with maintenance OCS 'as last resort', and place high priority on OCS minimisation strategies.[30]

Studies investigating OCS use for patients (>5 years) with SA show that OCS mean daily maintenance doses range from 4.0–21.4 mg prednisolone equivalent,[1] with daily doses of 5.5–7.5 mg for patients prescribed OCS for ≥2 years.[31] Major reasons healthcare professionals (HCP) state for maintenance OCS prescription include relative resistance to ICS and other controller medications, increased numbers of exacerbations, and increased disease severity.[1] The advisors highlighted the need to perform routine inhaler adherence and use checks, and discussed how worsening symptoms may be automatically attributed to poor asthma control when there are other potential causes. In these latter situations, patients have a high risk of being prescribed a rescue course of OCS without objective signs of worsening such as a decline in lung function.

Despite biologic treatment availability for SA, the advisors discussed how OCS use continues to be high.[1,32] For instance, a survey including 4,990 adult patients from the International Severe Asthma Registry (ISAR) found that 63.1% of patients in Italy, 59.6% in the UK, 23.3% in the USA, 24.7% in Australasia, and 20.7% in South Korea received maintenance OCS treatment at registry; although, the advisors noted, many of these patients will have subsequently proceeded to biologic therapy in specialist centres.[24] A study including 1.7 million Spanish patients (≥12 years) showed that of the 5.5% of the study population who had asthma, 7.7% of these had SA, with nearly a third of these patients being OCS-dependent.[25] In a Portuguese study, 91.3% of 46 physicians with a SA speciality thought that OCS use was necessary to control SA, and approaching two-thirds did not consider that there was maintenance OCS overuse.[33]

Both long- and short-term OCS use is associated with increased healthcare costs for people with asthma compared to no use, as is long-term use compared to short-term.[1] For instance, in one study, patients on maintenance OCS had 43% more costs than those not receiving this, partially due to cost of medications to manage OCS-related AEs.[34] Indeed, another study showed such costs to be higher in patients with SA with high OCS exposure compared to patients with mild/moderate asthma with low OCS exposure.[35]

Chronic Rhinosinusitis with Nasal Polyps

In CRSwNP, which has an estimated global prevalence of 1–4%, nasal inflammation can be accompanied by loss/reduction of smell; nasal blockage, discharge, and congestion; facial pain/pressure; and polyps that can lead to partial or complete nasal obstruction.[36-39] CRSwNP, compared to people without this disease and people with chronic rhinosinusitis without nasal polyps, is associated with greater symptom burden and medication use, along with missed workdays and decreased productivity and quality of life (QoL).[36,38,39] CRSwNP and asthma are often comorbid, occurring in around 40% of people with either condition.[40,41] Such comorbidity is associated with higher OCS use, including number of courses per year and rate of maintenance therapy.[40]

Surgery may be needed for severe CRSwNP; however, post-operative polyp recurrence is high, particularly in those with eosinophilic polyps and patients with comorbid asthma.[36,42] More recently, biologic therapy with anti-IL4Rα has been recommended in some patients, including those who need ≥2 courses of OCS/year or OCS therapy >3 months.[36] While localised, intranasal, steroid treatment is routinely prescribed for CRSwNP, short courses of OCS may reduce polyp size.[36,43-45] The advisors noted though that in recent years, this has not been recommended, even if limited to 1–2 courses/year. Studies of 7–21 days of OCS for CRSwNP, usually additional to intranasal corticosteroids, show that therapy led to reduced symptoms, including improved sense of smell and nasal flow, and decreased nasal polyp scores. The latter can remain decreased for several weeks after therapy initiation; however, symptoms typically relapse.[36,44,46,47] Evidence is conflicting as to whether OCS compared to nasal corticosteroids following CRSwNP surgery is beneficial, with some studies showing greater effects and lower recurrence rates, and others not showing an advantage.[48-50]

According to the advisors, OCS use for CRSwNP is generally symptom-driven, not preventative. Such therapy is infrequent in some countries, with OCS being prescribed only prior to surgery or as rescue medication for severe uncontrolled symptoms.[51] However, an Italian study including 437 otorhinolaryngologists found that 94% prescribed a short course of OCS for CRSwNP re-exacerbation, with only 41.1% saying they do not exceed two courses/year and 13.4% not exceeding four courses/year. While 35.0% considered 4 weeks/year to be the cut-off point for high risk for AEs, 16.9% considered the cut-off to be 8 weeks/year. Total yearly dose considered dangerous was 1,000 mg for 23.1% of respondents and 2,000 mg for 11.2% of respondents.[52]

Eosinophilic Granulomatosis with Polyangiitis

The immune-mediated inflammatory disease EGPA, a form of small-vessel, necrotising, anti-neutrophil cytoplasm antibodies-associated vasculitis, has an estimated annual incidence of 0.5–6.8 cases/million.[53-56] While disease course may differ between patients, EGPA typically progresses slowly from early phase asthma, sinusitis, and rhinitis, followed by tissue infiltration by eosinophils and vasculitis. There can be pulmonary, renal, and gastrointestinal involvement; peripheral nervous system damage; and eosinophilia-driven cardiomyopathy.[53,57]

The advisors saw the primary goal of EGPA therapy to be to induce remission and prevent tissue/organ damage. Subsequent management goals include relapse prevention, minimisation of OCS and immunosuppressant use, and QoL improvement. In EGPA guidelines, OCS therapy recommendations include starting with 2–3 weeks' 1 mg/kg/day prednisolone, tapered to 0.3, then 0.15 mg/kg/day after 3 and 6 months, respectively, to achieve a minimally effective dose or withdrawal.[55] While maintenance doses are ideally <7.5 mg/day prednisolone,[55] one study found that a maintenance daily dose of 12.9±12.5 mg was needed to control EGPA symptoms.[58] Such OCS therapy is associated with improved remission and survival rates.[56,59-62] Intravenous steroids may be administered in life or organ-threatening cases.[56,62] For those with more severe EGPA, therapy may include cytotoxic agents such as cyclophosphamide, anti-IL-5 agents, B cell depletion therapies, or other biologics.[55,56,62,63] Asthma symptoms in EGPA, a major cause of chronic OCS use in these patients, are treated as for this condition, according to GINA recommendations.[30,56,62]

The advisors highlighted that in general, high doses of OCS for maintenance treatment potentially result from a lack of early referral to the appropriate specialist. As such, there is a need for education among HCPs regarding EGPA screening, early diagnosis, and treatment and risks of prolonged OCS use. OCS can be used for emergency EGPA treatment, but there should be no minimal level considered non-harmful as this may 'encourage' OCS prescription, albeit at a low level. However, one advisor noted that it is difficult to avoid OCS use for some patients due to recurrence of symptoms and exacerbations. Another advisor stressed that the need for an OCS course should trigger HCPs to review other potential causes of disease recurrence (e.g., incorrect inhaler technique, infection, or poor treatment adherence).

INITIATIVES TO REDUCE BURDEN OF ORAL CORTICOSTEROIDS

Overall, the advisors agreed that OCS use for these EDs should be reserved for intermittent/rescue therapy only, at the lowest dose possible if there are disease flares (e.g., 1–2 courses a year at 0.5–1.0 mg/kg prednisolone or equivalent for 2 weeks maximum). OCS should be eliminated in the maintenance setting or, if unavoidable due to the need for disease control, prescribed at the lowest possible dose. Measures of success regarding OCS reduction included either no maintenance OCS or reduced OCS use (by 50–70%; 1–2 courses/year), and reductions in symptom and adverse QoL measures.

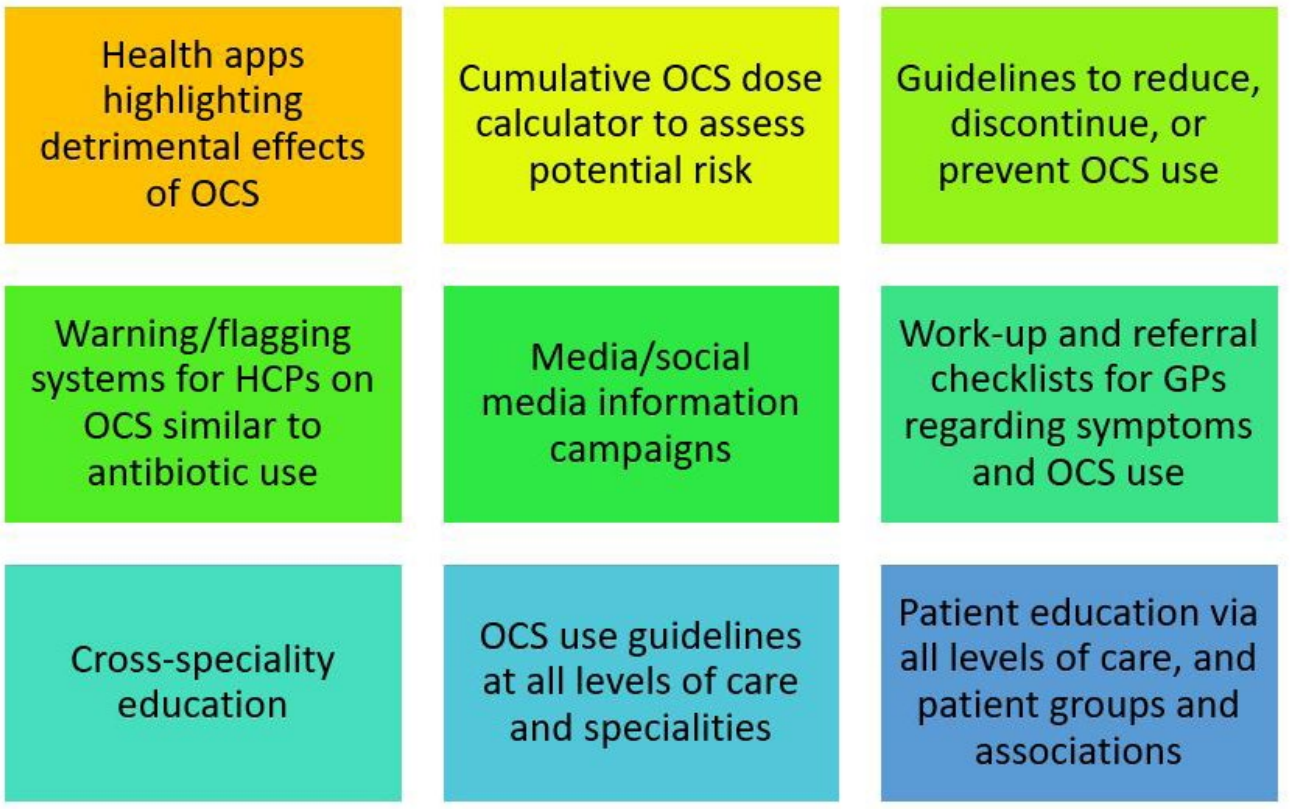
As can be seen from Figure 2, the advisors suggested several initiatives to reduce OCS burden.

Cumulative Dose Risk

While there is a lack of evidence as to what an acceptable cumulative OCS dose is, most advisors agreed that the maximum lifetime dose should be 500–1,000 mg and that the ideal is no more than three courses over a lifetime (depending on length of course) to mitigate severe AEs. For patients who do require long-term treatment, concerns especially included administering a dose >5.0–7.5 mg/day, although even lower doses were of concern; or using OCS for patients with comorbidities that may be aggravated by such OCS use.

The more a patient is exposed to OCS over their lifetime, the advisors discussed, the more complications they may experience later in life. This is important as it was noted that patients may not be asked about, or properly recall, previous OCS use. Therefore, calculating cumulative lifetime exposure may be problematic.

Figure 2: Potential initiatives to reduce oral corticosteroids burden.



GP: general practitioner; HCPs: healthcare professionals; OCS: oral corticosteroids.

While a patient's maintenance OCS prescription history may be checked with electronic prescribing records, as-needed OCS use may be harder to track as the patient may not report it, and one advisor noted that OCS are available over the counter and/or patients self-administer in some countries. Tracking of cumulative OCS exposure also becomes harder where there is countrywide heterogeneity of electronic patient records and patients move hospital and/or primary care provider (PCP). Additionally, the advisors discussed, not all countries have electronic recording, so patient reporting may be the main way to evaluate OCS use. This can also be difficult as patients may not always know medication details. For example, one advisor discussed a patient who was administered what was described by their PCP as an 'allergy vaccination', which was actually an OCS.

Healthcare Professional Education and Policy Maker Involvement

A large need was seen by the advisors to educate all HCPs, especially in primary care, regarding treatment options other than OCS for these EDs. However, one noted, OCS are cheap and easy to prescribe, so other options such as biologics could be seen to impact a PCP's budget. Additionally, some countries prohibit PCPs from receiving direct information from manufacturers regarding biologics. Another problem the advisors highlighted was how non-specialists may prescribe OCS more broadly due to lack of awareness regarding cumulative negative impact on health outcomes. OCS may also be prescribed for an acute exacerbation of an ED, but the patient is not always followed-up to assess frequency of such OCS prescription or potential AEs. This may be due to restricted capacity within primary care. In these cases, the advisors discussed how specialists need to work with and inform a patient's PCP to help reduce the dose or withdraw OCS use, and, ultimately, the advisors recommended that SA, CRSwNP, and EGPA are treated in specialist centres to avoid indiscriminate OCS administration.

Further discussion centred on the need for multidisciplinary team patient care networks, with PCP and specialist involvement, and broad HCP meetings and educational initiatives regarding OCS use. This could include multidisciplinary team workshops and round table discussions, structured patient interviews by expert clinicians at symposia, and collaborative programs with PCPs seeing patients together with a specialist.

One strategy suggested by the advisors to improve awareness regarding reducing OCS use in these EDs included educating policymakers regarding unmet needs, to facilitate changes on a national level. Organisers of healthcare systems and insurance companies, where applicable, also need to be aware of the need to use drugs with more favourable safety profiles than OCS, and data is needed to show the impact of using therapies other than OCS.

Referral Checklists

One issue with OCS use, according to the advisors, may be because secondary referral pathways for eosinophilic diseases are not optimal. For instance, a UK study revealed that 72% of 16,409 patients (≥16 years) identified with potential SA in primary care had not been referred to a specialist in the past year.[64] Referral checklists could be beneficial to ensure that patients requiring specialist care are referred appropriately and early during the disease course. One advisor suggested developing protocols to ensure patients are referred to specialists before being prescribed maintenance OCS.

Monitoring parameters or triggers for specialist referrals could include not only disease-related factors, but also, according to the advisors, OCS-related prompts, including repeat prescription of OCS and/or injectable steroids, potential steroid-associated AEs, and high-dose OCS use. A warning system could be linked to a patient's electronic medical records to notify PCPs when patients receive, for example, more than two courses of OCS/year, as is done in the UK to flag excessive short-acting β2-agonists use. However, it was discussed how the feasibility of such initiative is not clear due to variability between healthcare systems in their ability to have a red-flag system on a patient level basis and, in some cases, heterogeneity in software packages used across a country.

Patient Education

Including patients in OCS reduction initiatives is key, as withdrawal effects such as adrenal suppression can keep patients dependent on OCS.[33] Suggestions from the advisors included

patient education via videos in a clinic/PCP waiting room, and patient congresses and online meetings. Patients should also be advised on ways to minimise AE risks (e.g., avoiding weight gain, exercising to aid bone protection, and cardiovascular AEs).

The advisors suggested that patients could complete an AE symptom checklist under supervision of their PCP, as many patients recognise OCS-related AEs but may not be aware of alternative treatments. The Glucocorticoid Toxicity Index (GTI), for example, can track changes in several domains, including glucose tolerance, bone mass index, skin toxicity, bone density, infection, and neuropsychiatric symptoms.[65] Patients reporting symptoms and OCS use via health apps is feasible; however, one advisor reported how such apps had not engaged their patients, with many only using them for a couple of days. Such health apps, it was discussed, are also burdened with complexity around data protection and relevant analysis being carried out by commercial companies.

Oral Corticosteroids Limitation More Specific for severe Asthma, Chronic Rhinosinusitis with Nasal Polyps, or Eosinophilic Granulomatosis with Polyangiitis

In specific regard to SA, the advisors noted how, with the advent of biologics, it is possible to maintain disease control without the use of OCS or using only the smallest dose that maintains disease remission in combination with QoL. They proposed a systematic approach to OCS dose limitation that assesses and improves medication adherence, provides education on ICS device technique, provides an asthma self-management plan, optimises asthma treatment, and manages comorbidities. Such a strategy is associated with exacerbation reductions, greater symptom control, increase in lung function, improved QoL, and significant reduction in OCS dose.[66] Once OCS use was reduced/eliminated, the advisors discussed how ICS use should also be tailored to individual needs.

While OCS are recommended in CRSwNP guidelines,[36,45] the advisors noted that there is little information regarding dose regimens and duration of treatment, and there are few studies regarding minimal dose for maintenance treatment. Although some advisors reported they would consider alternative treatment options if patients with CRSwNP have >2 courses of OCS/year, others indicated that one course is sufficient to warrant treatment change or escalation to biologics, and it was underlined how HCPs need to be more aggressive about limiting OCS use. However, one advisor warned against complete 'steroid phobia' as OCS are relatively inexpensive and effective in cases with respiratory airway involvement. Another suggestion was that PCPs managing CRSwNP should attend specialist-led training events to educate them regarding OCS use.

In cases of EGPA with clear vasculitis manifestations, the advisors discussed how OCS use, plus biologics such as anti-IL-5 or immunosuppressive agents, may be necessary for maintenance therapy. A dose of ≤5 mg/day prednisolone was deemed potentially acceptable (although, it was noted, this is still a large cumulative dose) or the minimal dose needed so a patient has <3 exacerbations/year, and a view to tapering off when possible. Increased awareness is needed regarding comorbidities that could represent disease treatable traits and, if there is other vital organ involvement, careful OCS dose tapering to a minimal dose is required. Age is also a factor of concern for the advisors as younger patients may have a higher risk of being on maintenance treatment for longer time periods. One advisor highlighted how, "in anything but EGPA, rheumatologists do not accept long term OCS treatment." As such, alternatives to OCS use should be examined for all patients and there is a need for early, steroid sparing pathways. Of note though, complete OCS removal for some patients is not feasible as this may lead to exacerbations.

CONCLUSION

Although there are alternatives to OCS treatment, the advisors discussed that for SA, CRSwNP, and EGPA, many patients are prescribed intermittent and/or maintenance OCS therapy despite the known AE profile. They stressed how education and initiatives are needed to increase awareness regarding OCS AEs and underline the necessity to focus on optimal efficacy with minimal toxicity. These will help reduce OCS use to only when necessary and, if needed, then at the lowest dose possible to maintain an effect and limit AEs.

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Benzodiazepines in the Treatment of Behavioural and Psychological Symptoms Associated with Dementia and Their Impact on Cognitive Impairment: Review of Clinical Evidence

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Abstract

Alzheimer's disease (AD) is the most common form of progressively disabling degenerative dementia. In dementia in general, there are, unfortunately, even from the earliest stages of the disease, associated behavioural and psychological symptoms of dementia (BPSD), and even more pronouncedly in AD, in addition to cognitive impairment. There are no specific drugs for the treatment of BPSDs. Therefore, there remains an unmet medical need. To date, despite side effects, benzodiazepines, anti-psychotics, mood stabilisers, and anti-depressants continue to be used in the clinic. The aim of this research work is to provide an understanding of the role of benzodiazepines when used for the treatment of BPSD and cognitive impairment in AD.

Key Points

1. This article is a clinical review centred on behavioural and psychological symptoms of dementia and their treatment with benzodiazepine (BDZ), which is widespread but unsafe.

2. It is a study with the aims to stand as a guide for finding the right BDZ to give to a patient with dementia, and also the different pharmacokinetics of these drugs.

3. The study expresses the possibility of treating a patient with dementia with the right BDZ, along with adjuvant therapies.

INTRODUCTION

In the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), Alzheimer's disease (AD [named after the German psychiatrist and neuropathologist, Alois Alzheimer, who first described it]), is considered as a major or mild neuro-cognitive disorder. It is estimated that about 50–70% of total dementia cases are due to this condition, while 10–20% are due to vascular dementia, and it is the fourth leading cause of death in industrialised countries.[1]

The lesions caused by AD can mainly be considered as two types: neurofibrillary tangles, consisting of paired helical filaments (pairs of tubulin associated unit), and senile or neuritic plaques, consisting of a protein called β-amyloid. In dementia, in addition to cognitive impairment there are, from the earliest stages of the disease, associated behavioural and psychological symptoms, which are grouped together as behavioural and psychological symptoms of dementia (BPSD).[2] These can be anxiety disorders such as generalised anxiety disorder, psychomotor agitation, social phobia, and wandering, and they are often very severe and difficult to manage. Usually, BPSDs are not isolated but tend to appear in certain clusters. Clusters can be classified, according to the main symptoms of dementia, into predominantly affective, psychotic, hyperactive, and apathetic.

Several drugs have been found, and are in common use today, for the treatment of cognitive decline; however, the same cannot be said regarding the search for drugs for the management of behavioural and psychological disorders for patients with dementia. In fact, to date, there are no drugs that meet the efficacy and security pair for the treatment of BPSD. Drugs for the treatment of BPSDs, therefore, remains an unmet medical need.

To date, benzodiazepines (BDZ), anti-psychotics, mood stabilisers, and anti-depressants continue to be used in the clinic, despite their side effects.[3] BDZs are among the most widely used psychotropic drugs; however, their use in the treatment of BPSDs appears to be an off-label regimen, as this treatment for BPSDs is not considered an authorised therapeutic, as indicated in their datasheet. The administration of BDZs, particularly in an elderly patient with dementia, can accelerate cognitive impairment, as the authors detail in this article.

This work is innovative as it focuses attention to the behavioural symptomatology that is associated with dementia, which is just as important to the symptomatology of cognitive impairment, which is studied more often. The review lends itself as a possible guide to follow for the treatment of BPSDs with BDZs and for choosing the right BDZ in relation to different pharmacokinetic parameters, in combination or not with adjuvant therapy.

MATERIALS AND METHODS

The present experimental thesis work consists of a systematic literature review by consulting the two medical-scientific databases: PubMed and Cochrane. The material is between the date of the first available article (1965) and the end of the search (August 2020). The search strategy was to use the following keywords: "benzodiazepines and dementia" and "benzodiazepines and Alzheimer's disease."

Inclusion Criteria

All available clinical trials concerning BDZs used for the treatment of BPSD and their possible involvement in increasing cognitive impairment were considered. No filter was applied regarding the date and duration of the study, or its possible follow-up. The focus was on clinical trials where the role of BDZs was observed specifically in Alzheimer's dementia. The papers were selected based on tests for assessing the stage of dementia such as Mini-Mental State Examination (MMSE), as well as the Global Deterioration Scale (GDS), National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Criteria, and International Classification of Diseases ninth revision (ICD9), etc. The last selection was made considering studies in which the age of patients was over 65 years.

Exclusion Criteria

The following were not considered for this review article: narrative and systematic reviews; meta-

analyses; conference communications; book chapters; studies on forms of dementia other than Alzheimer's dementia; studies in which the assessment of patients' dementia stage was not done in relation to a particular rating scale or diagnostic criteria, as mentioned above; studies including patients with early-onset dementia (under 65-years-old). Duplicates were eliminated, as were papers that were not open access in the above databases and also papers that were written in a language other than Italian and English.

RESULTS

The search of the study material yielded a total of 792 scientific articles, including 183 from Cochrane and 609 from PubMed. First, all the duplicate articles were eliminated. Then, the authors proceeded to consider the remaining articles (693) according to the inclusion criteria. The authors only included clinical trials, such that narrative and systematic reviews, meta-analyses, conference communications, and book chapters were excluded. The authors considered clinical trials that were only concerned with AD; however, they did not consider other forms of dementia. The number was thus reduced to 89 clinical trials. These were then analysed in relation to the remaining inclusion criteria (articles in which patients are classified according to MMSE or other diagnostic criterion such as GDS or NINCDS-ADRDA and also articles where the patients were over 65 years old). Therefore, a total of 28 articles were included. Further analysis of the remaining clinical trials was completed according to the exclusion criteria, where unavailable articles or those written in a language other than English were not considered; thus, the authors found three clinical trials for qualitative synthesis (Table 1). Cognitive impairment was assessed by means of several rating scales (Table 2).

DISCUSSION

It is estimated that BDZs belong to a class of medications called probable inappropriate medications (PIM), which are inappropriate in the elderly.[4,5]

According to data from the Italian Medicines Agency (AIFA),[7] 50 daily doses of BDZ are prescribed per 1,000 patients, a trend that is increasing; it is approximately 8% higher than the previous year. In daily clinical practice for the pharmacological treatment of BPSDs, 'short-acting BDZs' (i.e., BDZs with a shorter half-life such as Lorazepam), are mostly used. In some cases, however, the authors also refer to the use of 'long-acting BDZs' and their major representatives such as diazepam. The former is mainly used for the treatment of insomnia, while the latter for the treatment of anxiety.[8,9]

For this systematic review, the authors have focused on 3 studies, two of which are longitudinal studies by Koyama et al.[4,5] and the other is a cross-sectional study by Lopez et al.,[6,10] with longitudinal follow-up.

The aforementioned drugs cause a significant increase in cognitive decline, according to a study by Koyama et al.,[4] in addition to a worsening of other comorbidities in different ways that were associated with age-related changes in pharmacodynamics and pharmacokinetics. This cognitive decline and worsening of other comorbidities is also due to the use/abuse of multiple classes of inappropriate psychotropic drugs, resulting from the consequent problems arising from their interaction,[11] despite the fact that guidelines are already available regarding polyadministration.[12]

According to Koyama et al.,[4] as inappropriate drugs for older patients, BDZs might not only result in worsening cognitive decline of patients with AD; Koyama et al.[4] indicate that the drugs may be a cause of it, or even result in both. To assess the role that BDZs play, worsening cognitive decline and the reached stage of dementia were observed through the MMSE in the former, and the latter was correlated with the Anticholinergic Cognitive Burden (ACB) scale. In fact, an increase in GABAergic tone, as determined by BDZs, may result in a decrease in cholinergic tone.[13]

Regarding the first rating scale, an MMSE score of less than 9 was obtained; while in regard to the ACB, the score was 2–3. These scores confirm the close association between the use of these PIMs and the net worsening of cognitive function of the patients under consideration, plus

Table 1: Key features of the studies included in the qualitative synthesis.

Name	Studies design	Number of patients	Age	Administration	Outcome
Koyama et al. (2013)[4]	Longitudinal study	1,484 females living in the community, with a 10-year follow-up	Average age of 75 years	Administration of PIM class drugs, including BDZs	23.9% of females taking at least one drug belonging to PIMs had an initial ACB score of 1.41 (1.699). The most reported drugs belonging to PIM class were BDZs (8.6% in total). Of the latter, the most widely used were lorazepam (n=43 in the PIMs list); alprazolam (n=30); temazepam (n=27). After 10 years of follow-up and administration of PIMs drugs, the MMSE was <9 and CBA was 2–3, demonstrating a worsening cognitive decline (the stage of dementia was later determined according to the DSM-5).
Koyama et al. (2014)[5]	Longitudinal study	4,606 females, with follow-up of 5 years	Average age of 75 years	Administration of PIMs, including BDZs	1,227 patients of the total recruited females died and 911 saw a worsening of their cognitive and functional status. In terms of CBA, an increase in CBA of 1.6 1.9 was obtained. Therefore, the authors concluded by saying that: 24.8% developed dementia after administration of BDZs (n=98) belonging to the PIMs class. Of the BDZs administered, 90% were lorazepam (n=28; 7.1%), temazepam (n=21; 5.3%), and alprazolam (n=20; 5.1%) Patients who were administered the above BDZs manifested not only dementia but also falls, exacerbation of their comorbidities (existing conditions), and there was regression of their activities of daily living such as playing sports. The regression of activities of daily living associated with the administration of PIMs, in terms of ORs, was 1.33 (1.05–1.70) in un-adapted models and 1.36 (1.06–1.75) in post-adapted models (adaptation to age, race, education, tuxedo, and physical activity). Cognitive impairment was observed after 7 different cognition assessment tests, including: CVLT-II, where there was a reduction of a significant number of words, and verbal and memory reduction; Trails B, where subjects administered BDZs took longer to complete the test and had decreased attention and speed in processing information; 3MS, where a reduction in MMSE score in terms of SE: 0.170.08; p=0.03; and the CFT, which saw a significant reduction in verbal fluency equal to SE=-0.530.21; p=0.01

Table 1: Key features of the studies included in the qualitative synthesis. (Continued)

Lopez et al. (1999)[6]	Transversal study with longitudinal follow-up	179 patients with probable AD enrolled at the University of Pittsburgh, Pennsylvania, USA, from 1983–1988	Age 73.9±5.9	Administration of classes of psychotropic drugs, including BDZ (23% of patients were taking at least one at the beginning of the study)	41% of the 179 patients were institutionalised. Of these, 42% (76 patients) obtained an MMSE score of 9 or lower; 31% (55 patients) obtained a BDRS score of 15 or higher; and 56% (101 patients) died.

ACB: Anticholinergic Cognitive Burden; AD: Alzheimer's disease; BDRS: Blessed Dementia Rating Scale; BDZ: benzodiazepine; CFT: category fluency test; CVLT-II: California Verbal Learning Test, second edition; DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth edition; IADL: impairment activity of daily living; MMSE: Mini-Mental State Examination; OR: odds ratio; PIM: probable inappropriate medication; SE: side effect.

Table 2: Techniques used in the studies of these systematic reviews.

Name	Diagnostic criteria
Koyama et al. (2013)[4]	NINCDS-ADRDA, MMSE, and ACB
Koyama et al. (2014)[5]	7 tests to rate cognition include Trails B, 3MS, CVLT, CVLT-II (short form), DSB, CFT, and VFT
Lopez et al. (1999)[6]	MMSE and BDRS

ACB: Anticholinergic Cognitive Burden; BDRS: Blessed Dementia Rating Scale; CFT: Category Fluency Test; CVLT: California Verbal Learning Test; CVLT-II: California Verbal Learning Test, second edition; DSB: Digit Span Backwards; MMSE: Mini-Mental State Examination; NINCDS-ADRDA: National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association; VFT: Verbal Fluency Test; 3MS: Modified Mini-Mental State Examination.

the worsening of psychological comorbidities at a high stage of dementia, which was later confirmed by a diagnosis made by a team of experts in accordance with the Diagnostic and Statistical Manual of Mental Disorders (DSMMD), created by American Psychiatric Association in 1994. In confirming the PIMs–BDZ association and increased cognitive decline, however, the authors ultimately failed to understand whether BDZs, in addition to leading to worsening cognitive status, may also be the cause, on par with previous studies.[14,15]

The 2014 study by Koyama et al.[5] is a 'continuation' of the 2013 study, confirming that BDZs result in a high rate of adverse effects, both short-term[16,17] and long-term.[15] The focus is no longer on the dual risk of worsening cognitive impairment and mortality in older patients, but rather on the dual risk of worsening cognitive

impairment and regression of activities of daily living (impairment of activities of daily living),[18] associated with an increased anticholinergic load.

The worsening cognition of the patients considered was determined by assessment of the MMSE and correlated with the CBA; however, other cognitive status assessment tests were also used such as Trails B, Modified Mini-Mental State (3MS), California Verbal Learning Test (CVLT) second edition CVLT short form (CVLT-II), Digit Span Backwards (DSB), Category Fluency Test (CFT), and Verbal Fluency Test (VFT). These demonstrated worsening in terms of reduced attention and readiness in response to a test (Trials B); reduced verbal fluency and semantic memory (CFT and VFT); and reduced visual-spatial ability and orientation (3MS).

Regarding anticholinergic load (ACB), other recent studies have shown that worsening cognitive function in patient with AD may be associated with reduced cholinergic tone.[15,19] Cholinergic neurotransmission is critical for cognition as the 'pyramidal' neurons of the septus or basal nucleus of Meynert communicate with cortical areas and the hippocampus by means of terminals that release acetylcholine. Some drugs used in the clinic for slowing cognitive decline are indirect cholinomimetics such as donepezil, rivastigmine, and galantamine.

Cognitive impairment is also increased by BDZ use through interference with neurodegeneration. It has been shown in a transgenic mouse model that chronic BDZ use can result in an increase in α42, a form of amyloid that is insoluble and thus capable of forming the senile plaques typical in AD.[20] Despite this, the characteristics of the experimental studies still do not allow for definitive conclusions.

A study by Lopez et al.[6] highlights the importance of treating BPSD for a patient with AD, as symptoms such as insomnia, psychosis, and agitation are predictive of functional decline, hospitalisation,[10,21,22] cognitive decline,[10,23,24] and even death. In the latter case, symptoms associated with an increased risk of death are depression;[25] wandering and behavioural problems;[26] and selected behavioural symptoms such as agitation, wandering, and hallucinations, which appear to play a predictive role in death.[27]

The findings of the study of Lopez and colleagues[6] on the use of BDZs and their consecutive alteration of the normal course of AD pathology are similar to that of the study by Koyama et al.[5] This is in terms of cognitive decline (cognitive impairment) due to reduced cholinergic tone and anticholinergic activity; and regression of activities of daily living, secondary parkinsonism, orthostatic hypotension, and sedation.

The dual risk of cognitive impairment and regression of activities of daily living is consolidated by identification of an advanced stage of dementia. An assessment is conducted by considering the MMSE score, which turns out to be very low indeed. For the assessment of reduced activities of daily living (such as the inability to play sports), the Blessed Dementia Rating Scale (BDRS), which turns out to be high, is considered instead. BPSDs are, therefore, important symptoms to be treated in a patient with AD due to the increased risk of cognitive impairment, functional impairment, and hospitalisation that these symptoms result in; however, BDZs are not so safe that they can be prescribed for dementia.

Some relatively recent studies[8,9] have pointed out the increased risk of dementia after chronic exposure to BDZs, which is when a patient takes a BDZ for more than 3 consecutive months of drug therapy. In addition, the risk of increased cognitive impairment following chronic BDZ use may also be different according to the different BDZs considered (i.e., the risk of increased cognitive impairment varies according to the different pharmacokinetics of BDZ).[8,9] In fact, several studies note that a meeting point between efficacy and safety of these drugs in the treatment of BPSD should be found in the use for short periods of time for short-acting BDZs such as lorazepam or oxazepam.[28-30]

Increased cognitive impairment after higher doses and prolonged times of drug therapy with long-acting BDZs such as diazepam has been demonstrated by several studies. Of particular relevance is the study conducted by Billioti de Gage et al.,[9] in which a markedly different risk of acceleration of cognitive impairment is

observed between the administration of a short-acting BDZ and a long-acting BDZ, as well as the difference between shorter drug therapy times and much more protracted times instead. In the present case, regarding the difference in pharmacokinetics, this pivotal study reports that the risk of increased cognitive impairment in patients with AD is 70% in those who are given long half-life BDZs, and the risk of increased cognitive impairment in patients with AD is 43% in those given short half-life BDZs. In terms of timing of drug therapy, however, it is reported that the risk of worsening and existing cognitive impairment is 50% in patients given BDZ for 3 months, and the aforementioned risk is even greater in patients treated with BDZ for 6 months (as high as 84%).

In the study by Sunderland et al.,[31] a short half-life BDZ such as lorazepam at low doses and for a few weeks of treatment (2 weeks) did not result in accelerated cognitive decline.

Other more recent studies have shown that it is necessary to provide individualised treatment for patients with BPSDs.[32] The latter could also include non-pharmacological therapies[33] such as aromatherapy and music therapy,[28,34,35] which, according to latest clinical data, present efficacy in managing agitation in dementia patients without the side effects of psychotropic drugs.

CONCLUSION

BDZs represent a widely used class of psychotropic drugs in the treatment of BPSD in patients with AD. They are very effective in treating these symptoms but, at the same time, they do not appear to be safe drugs. The clinical trials identified in this systematic literature review support that BDZs result in increased cognitive impairment in the AD patient. The possible reasons for this include a high rate of side effects such as amnesia, confusion, and sedation; increased GABAergic tone that, in turn, results in decreased cholinergic tone due to reduced acetylcholine release; possible increase in neurodegeneration due to increased synthesis of α42 (a form of amyloid predisposed to senile or neuritic plaque formation); an increased dual risk of worsening cognitive impairment and impairment in activities of daily living, patient mortality, and falls with potential hip fracture; and significantly increased risk of worsening cognitive decline due to the wrong choice of BDZ from a pharmacokinetic point of view, dosage (high), and timing of drug therapy (prolonged for 3 or even 6 months).

For the reasons stated above, BDZs are effective but unsafe drugs, which is why they are still administered for the treatment of BPSDs as an off-label regimen. Without resolving this for older patients with AD, this remains an unmet medical need. Subsequent studies are needed to determine the right choice of BDZ, a short acting BDZ, to be administered to an older patient with AD in the right doses and for an appropriate treatment period. In addition, individualised therapy should be preferred, including complementary therapeutic approaches (see aromatherapy and music therapy), which demonstrate efficacy in the absence of side effects.

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Marantic Endocarditis and Lung Adenocarcinoma with Brain Metastasis: A Diagnostic Conundrum

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Abstract

Neurological symptoms such as headache and blurring of vision could be a manifestation of an underlying lung adenocarcinoma. The objective of this case report is to unveil the possible differentials and processes involved in the diagnosis of marantic endocarditis. A 57-year old male with blurring of vision and brain CT revealing multiple abscesses, sterile on culture, was treated as per guidelines. However, the patient had recurrent complaints that reinforced recurrent admissions and the patient was found to be COVID-19 positive during the pandemic when a routine test was performed in the emergency department. Suspicious lesions on the chest X-ray were further scrutinised and the patient was diagnosed with lung adenocarcinoma. To further investigate the sterile cultures in the brain, a cardiologist's opinion was taken and a transthoracic echocardiogram was done, which was unremarkable. The increased suspicion for non-infective endocarditis necessitated a transoesophageal echocardiogram, which was positive for vegetations on the aortic valve. The patient was treated with anticoagulants and chemotherapy. In conclusion, in patients with CT findings of abscesses and sterile cultures, it is crucial to investigate the possible differentials in a meticulous fashion, as there could be an undiagnosed lung cancer in a non-smoker and there is a rare possibility of a sterile vegetation on the aortic valve, as was seen in the authors' case.

Key Points

1. The case highlights the importance of a comprehensive evaluation and a high degree of suspicion in the evaluation of patients with some peculiar features for non-bacterial thrombotic endocarditis such as lung adenocarcinoma, sterile cultures, and a positive transoesophageal echocardiogram.

2. The case also demonstrates the conundrums that arose while evaluating a patient for a headache and blurring of vision. Thus, one of the differentials for headache with a CT scan demonstrating 'abscesses' that should be considered, if sterile, is the possibility of non-bacterial endocarditis.

3. Transoesophageal echocardiogram shows higher accuracy in detecting non-bacterial thrombotic endocarditis compared to transthoracic echocardiogram.

INTRODUCTION

Non-bacterial endocarditis (also known as marantic endocarditis), a term coined by Gross and Fiedberg in 1936,[1] encompasses the non-infectious (sterile) vegetations on structurally normal or superficially damaged cardiac valves in the absence of blood stream infection.[2] Studies have postulated that local physical damage or cytokine mediated damage leads to platelet consumption, activation of clotting factors, and interlacing of fibrin strands that could be contributing to the vegetation formation.[2,3]

Embolic spread is seen in approximately 50% of patients with non-bacterial thrombotic endocarditis (NBTE), while 42% of NBTEs are associated with malignancies and 33% with neurological manifestations.[4] Other commonly involved vessels include cerebral, coronary, mesenteric, and digital vessels.[5,6] Being a non-inflammatory vegetation, the emboli are released with minimal changes in the valves, further making the diagnosis challenging.[3]

Lung adenocarcinoma, which is considered one of the potential causes of marantic endocarditis, has been explored in the case report. When diagnosed at advanced stages, the prognosis of patients with lung cancer is very poor, with a 5-year survival of 12%, while the more distant metastases lead to a survival rate of less than 5%.[7]

The presenting complaint of patients with marantic endocarditis could be a distant metastasis.[8] Thus, the authors present complexities of a case of lung adenocarcinoma, which was incidentally suspected while screening for COVID-19. Marantic endocarditis increased suspicion and the foremost clue to the quandary, a simple headache proving to be a brain metastasis, instigated the whole investigative process.

CASE PRESENTATION

A 57-year-old male patient, known to have hypertension, presented with complaints of blurring of vision involving both eyes for 3 weeks. They also had an episode of loss of consciousness after a fall from a vehicle approximately 15 days previously. After the episode, they had a headache and an episode of vomiting. They were haemodynamically stable.

On ophthalmological examination, the uncorrected visual acuity of the right and left eye was 6/18 P (the smallest row of letters that a normal eye could discern at 18 m is what the tested eye can discern at 6 m) and 6/12 P (the smallest row of letters that a normal eye could discern at 12 m is what the tested eye can discern at 6 m), respectively. Non-contact tonometry revealed a pressure of 15/16 mmHg, pupils were round and reactive, and fundoscopic examination and extraocular movements were unremarkable. Neurological examination revealed no focal deficits.

CT of the brain reported two hypodense ring enhancing lesions with disproportionate oedema at the post-parietal region with mass effect. Differential diagnosis included abscesses or secondaries from a malignancy. Subsequently, a neurosurgical evaluation required a surgical

approach by a burr hole bilaterally in the occipital region. With the patient in prone position, a bilateral linear incision was traced and a burr hole was marked. Under navigation guidance, the abscess was drained and sent for cultures. Wound closure was done in layers. The cultures, both in aerobic and anaerobic media, revealed no growth. On a follow-up visit after 1 week, complaints of headache and blurring of vision persisted.

A repeat brain CT at this time reported a persistent perifocal oedema along the bilateral parieto-occipital region with hypodensities (residual abscess). No interval change in the mass effect on the underlying brain parenchyma was seen, although a midline shift to the left by approximately 8 mm was reported. No other significant abnormalities were observed. The following day, bilateral exploration of the abscess was performed with the patient in prone position, with head placed on a horse shoe. Bilateral incision was deepened and under navigation guidance, the abscess was drained. A thorough vancomycin and gentamicin wash was given until fluid appeared unremarkable. Bilateral scalp wounds were sutured and dressed. Consequently, the patient reported a complete recovery of their initial symptoms. The cultures performed in both aerobic and anaerobic media revealed no growth. Gram stain and acid-fast bacilli were negative as well.

On their visit to the emergency department after approximately 1 month, the patient reported complaints of blurring of vision, headache, and a generalised weakness. In view of the ongoing pandemic of COVID-19, they were tested for the same, and turned out to be positive. They were then admitted to the COVID-19 ward. Chest X-ray revealed mediastinal lymphadenopathy (Figure 1), which necessitated a high resonance CT (HRCT) of the chest. This further revealed a neoplastic right hilar and right lower lobe soft tissue, enlarged mediastinal adenopathy, and multiple pulmonary metastases along with mild pericardial effusion (Figure 2).

A whole body CT scan with contrast revealed a neoplastic right hilar and right lower lobe soft tissue and mediastinal lymphadenopathy with multiple pulmonary metastases. Well defined, ring enhancing lesions in bilateral parietooccipital lobes with surrounding oedema and mass effect were seen, possibly neoplastic (Figure 3).

In view of multiple recurrent occipital-parietal abscesses with sterile cultures (blood and drainage fluid) and the underlying lung adenocarcinoma, in consultation with the cardiologist, a possibility of marantic endocarditis was considered.

A 2D echocardiography did not show the presence of vegetations. However, increased suspicion of marantic endocarditis encouraged a further investigation and thus a transoesophageal echocardiogram was performed, which revealed vegetations on the aortic valve prolapsing into the left ventricle outflow obstruction (4 mm). The report was suggestive of grade 1 aortic regurgitation with good left ventricular function.

The patient was treated with anticoagulants for the marantic endocarditis and chemotherapy for the lung adenocarcinoma. The patient was discharged in a clinically and haemodynamically stable state.

DISCUSSION

NBTE refers to vegetations on the cardiac valve composed of thrombin and platelets. The age group most commonly susceptible to NBTE is 40–80 years.[9] The clinical manifestations can be quite ambiguous; moreover, the initial manifestations are usually embolic manifestations such as focal neurological deficits, myocardial infarction, etc. However, a triad could aid in the diagnosis of NBTE, including underlying disease processes associated with NBTE such as connective diseases, malignancies, etc.; new onset of heart murmur; and evidence of multiple systemic emboli.[10]

In patients presenting with an embolus, the commonly involved arteries include cerebral, coronary, renal, and mesenteric arteries. Systemic emboli are evidenced as the primary presenting complaint in up to 50% of the cases of NBTE.[5,10] However, the authors' case presented with metastasis from a primary lung cancer, an atypical manifestation of marantic endocarditis.

Chest X-ray is the initial modality of investigation and further imaging studies are necessary if the following features are detected: bulky mediastinal lymphadenopathy or bony lesions,

Figure 1: Chest X-ray showing right sided hilar lymphadenopathy.

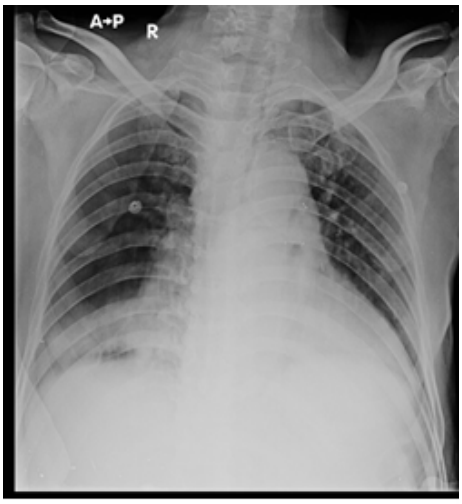


Figure 2: High resolution CT of the chest showing neoplastic right hilar lymphadenopathy and right lower lobe soft tissue and pericardial effusion.

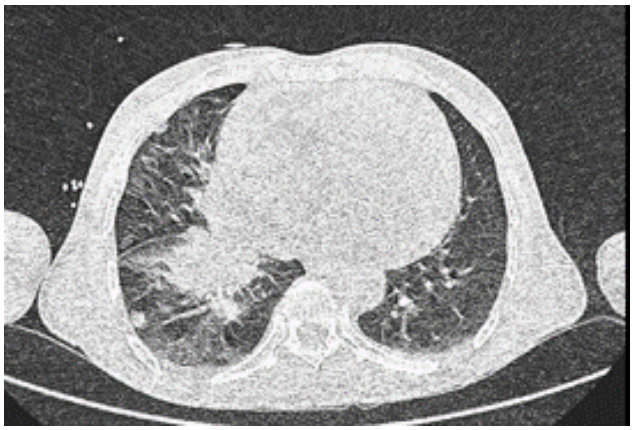
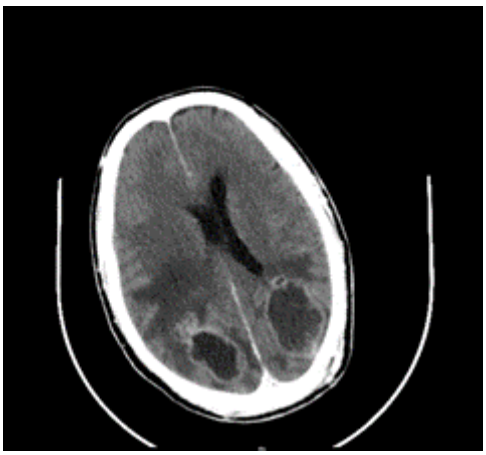


Figure 3: CT of the brain demonstrating well defined ring enhancing lesions in the parieto-occipital lobe with surrounding oedema.



as this has a low sensitivity.[11] A HRCT scan can identify lesions that are small, guide the placement of a needle for a lung biopsy, and guide the staging of lung cancer as well.[12] In concordance with the authors' case, the hilar lymphadenopathy showed on chest X-ray was recognised on HRCT, which revealed a comparatively comprehensive description of the adenocarcinoma.

Biopsy of the lung can be done to further confirm the diagnosis of adenocarcinoma. Up to 95% of malignant lesions and 91% of benign lesions can be detected by a transthoracic lung biopsy.[13] The use of a CT-guided lung biopsy further strengthened the authors' suspicion of lung adenocarcinoma as the possible cause of the marantic endocarditis. A few other differentials include secondaries from the lung adenocarcinoma, fungal abscess, and embolic event disseminating from the cardiac valves.

Further scrutiny by chest X-ray, CT scan, and additional lung biopsy revealed lung adenocarcinoma, which could be an inciting factor for the development of marantic endocarditis (Figure 4). This is demonstrated by the release of tissue factors in mucinous cancers such as adenocarcinoma of the lung, ovary, etc.[14]

The reported cumulative incidence of brain metastasis was 16.3% in patients with lung cancer after a 5-year period in a cohort of patients with melanoma, colorectal cancer, lung adenocarcinoma, and renal carcinoma in a study conducted with a sample size of 2,724, 232 (8.5%) of whom were found to have brain metastasis. There was also an increased frequency of detection of brain metastasis with lung cancer compared to other primary tumours.[15] As reported in the literature, the authors' case also had recurrent lesions in the brain, possibly due to metastasis from the lung cancer, as suggested by the findings on the CT scan of the brain.

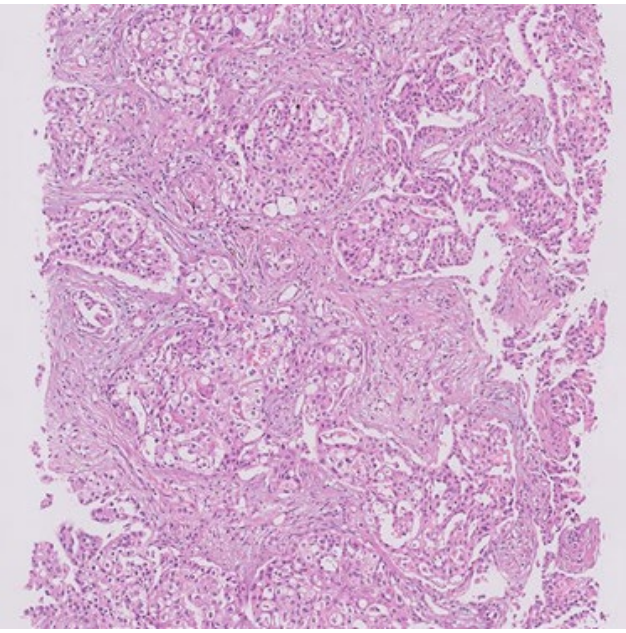
Transoesophageal echocardiography (TEE) has been more sensitive and specific in the diagnosis of NBTE,[5] particularly if the lesions are small (less than 5 mm) and irregular in shape compared to TTE. A study of 200 patients demonstrated the involvement of left sided heart valves, particularly the mitral and aortic valves in NBTE. Of the 200 patients studied, 19% had well established vegetations and, of this 19%, 19 patients had vegetations in the mitral valve compared to 18 patients who had vegetations in the aortic valves. Furthermore, valvular lesions were found in 28% of those with carcinoma of the lung.[16] The formation of vegetations in case of NBTE is quite rare as the damage that occurs is very superficial and may not be visible on TTE.[9] As seen in the authors' case, the vegetations unperceived by TTE were detected by TEE as a small vegetation on the aortic valve, emphasising the increased sensitivity of TEE.

Cytokines such as IL-1 and TNF found circulating in the blood stream of these patients further contributes to the damage to the valve, contributing to the vegetations on the valve.[14] Another possible inciting factor in the authors' case could be the COVID-19 positive status, well investigated for its hypercoagulability, which could possibly also explain the valvular damage, endothelial damage, activation of the coagulation cascade, and deposition of fibrin on the valves.[17] The authors postulate that the vegetations that formed on the cardiac valve could be attributed to the above explanations.

Marantic endocarditis being onerous, probably due to its association with cancer, it preliminarily requires a high degree of suspicion followed by treatment of the underlying cause of the condition. Marantic endocarditis is composed of fibrin and platelets and therefore requires treatment with anticoagulation. Most commonly used anticoagulants in the treatment of such cases are the activators of antithrombin (i.e., heparin, particularly low molecular weight heparin). The role of warfarin in patients with NBTE has not demonstrated efficacy due to its increased risk of thromboembolism. Anticoagulants in NBTE are continued indefinitely provided there are no contra-indications. Newer anticoagulants such as factor Xa inhibitors can also be used.[11,18] The authors' case was treated with low molecular weight heparin.

To the authors' knowledge, the essence of this case lies in the presenting neurological complaint, which was later found to be a secondary/metastasis from a primary lung adenocarcinoma, associated with marantic endocarditis.

Figure 4: Lung biopsy showing adenocarcinoma



Future prospective studies to determine the incidence and pathophysiology of marantic endocarditis presenting with metastasis are needed. Imaging studies on lesions in the brain could be done to fathom the various presentations in marantic endocarditis.

CONCLUSION

The presented case has its uniqueness in terms of presentation in the form of a neurological manifestation due to a metastasis from a lung adenocarcinoma. Thus, an extensive workup of the case of a pre-eminent neurological complaint uncovers a possible differential of an underlying process such as cancer, with a high degree of suspicion for marantic endocarditis, given the background of sterile cultures.

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Caseous Mitral Annular Calcification Presenting as Retinal Artery Occlusion

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Abstract

Caseous mitral annular calcification (CMAC), sometimes called liquefaction necrosis of mitral annular calcification (MAC), is a rare variant of MAC, a chronic degenerative process that progresses with age. It is a degenerative abnormality of the fibrous tissue and typically involves the posterior annulus, appearing as a smooth mass with no flow or acoustic shadow artefacts. It can be differentiated from other cardiac masses by CT and MRI. Whilst benign in nature, it is associated with a range of pathologies, such as mitral valve dysfunction, arrhythmias, and systemic embolisation. Given the risk of systemic embolisation, surgery may be appropriate, but there is no clear consensus in the literature in patients who are asymptomatic. This case highlights a case of CMAC presenting with a retinal artery occlusion, and was managed conservatively.

Background

The mitral annulus is a key component of the mitral valve, ensuring appropriate function by facilitating complete closure of the leaflets during systole. With age, MAC can occur, potentially resulting in mitral valve dysfunction, infective endocarditis, and arrhythmias. CMAC is a rare variant of MAC, typically involving the posterior annulus. Whilst benign, the risk of complications, such as systemic embolisation, may indicate a surgical approach to management, even in patients who are asymptomatic.

Case Presentation

A 60-year-old female, presenting with sudden loss of vision in the lower part of her left eye due to a branch retinal artery embolus, was admitted from ophthalmology services. An outpatient transthoracic echocardiogram showed an abnormal mass on the posterior annulus of the mitral valve. Transoesophageal echocardiography identified a calcified posterior aspect of the mitral annulus with normal leaflet mobility and trivial regurgitation, and an echogenic mass attached to the ventricular aspect of the mitral annulus (at the level of posteromedial commissure), 9×4 mm in size. A cardiac CT showed a caseous mitral valve with evidence of rupture of the calcified shell. Discussion with the surgical multidisciplinary team resulted in a conservative approach, with follow-up echo for monitoring.

Conclusion
Whilst a benign and rare variant of MAC, CMAC is associated with a range of pathologies, including mitral valve disease, arrhythmias, and systemic embolisation. Currently, there is no standardised management approach for CMAC. Surgery is currently recommended in the context of already known surgically indicated pathologies, such as severe mitral valve disease or systemic embolisation. However, this conservatively-managed patient has had no further complications with stable echocardiographic appearance on repeat echo 3 months following initial exam.

Key Points

1. Caseous mitral annular calcification (CMAC) should be considered in the differential when assessing mitral annular masses, and can be differentiated with CT and MRI.

2. Whilst a benign and rare variant of mitral annular calcification, CMAC is associated with a range of pathologies, including mitral valve disease, arrhythmias, and systemic embolisation.

3. Currently there is no standardised management approach for CMAC. Surgery could be considered in good surgical candidates who are asymptomatic, given the reported prevalence of cardioembolic events associated with CMAC.

BACKGROUND

The mitral annulus is a key component of the mitral valve, ensuring appropriate function by facilitating complete closure of the leaflets during systole. With age, calcification of the annulus can occur, termed mitral annular calcification (MAC), and is a chronic degenerative process that can result in mitral valve stenosis and/or regurgitation, infective endocarditis, and arrhythmias. Caseous mitral annular calcification (CMAC) is a rare variant of MAC, typically involving the posterior annulus. Whilst a benign mass in nature, the risk of complications, such as systemic embolisation, may indicate a surgical approach to management, even in patients who are asymptomatic. This case highlights a patient who was identified to have CMAC following presenting with a retinal artery occlusion, and was managed conservatively.

CASE PRESENTATION

A 60-year-old female presented to local eye services, reporting a 4-day history of new 'floaters', followed by a sudden loss of vision in the lower part of her left eye. They were identified by the ophthalmology services to have an embolus in a branch retinal artery on fundus photography, and was referred to the acute inpatient medical team for further assessment.

The patient's past medical history included a previous left knee replacement, BMI of 43, non-medicated hypertension, and vertigo.

Observations on admission were normal, with a respiratory rate of 17, O_2 saturation 96% on air, blood pressure 118/65 mmHg, and heart rate of 75 beats per minute. The patient was afebrile, though on repeat observations they were noted as mild hypertensive with average blood pressure 130–140 mmHg systolic. Examination demonstrated no positive findings, with no evidence of irregular pulse or abnormal cardiac auscultation.

Initial haematology and biochemistry results were as follows: haemoglobin: 149; white cell count: 8.6; neutrophil: 5.18; calcium: 2.5; creatinine: 70; estimated glomerular filtration rate: 77; alanine transaminase: 18; bilirubin: 12; total cholesterol: 6.3; non-high-density lipoprotein cholesterol: 4.9; low-density lipoprotein: 4.1; and HbA1c: 39. CT head demonstrated small vessel disease but no evidence of acute infarction. Chest X-ray was normal.

Following inpatient assessment, the patient was discharged for outpatient transient ischaemic attack clinic review, provided with aspirin and statin therapy with outpatient echo, and carotid Dopplers and Holter were arranged. Outpatient carotid and vertebral Doppler were unremarkable with minimal disease, and outpatient 7-day Holter demonstrated sinus rhythm with no evidence of atrial fibrillation.

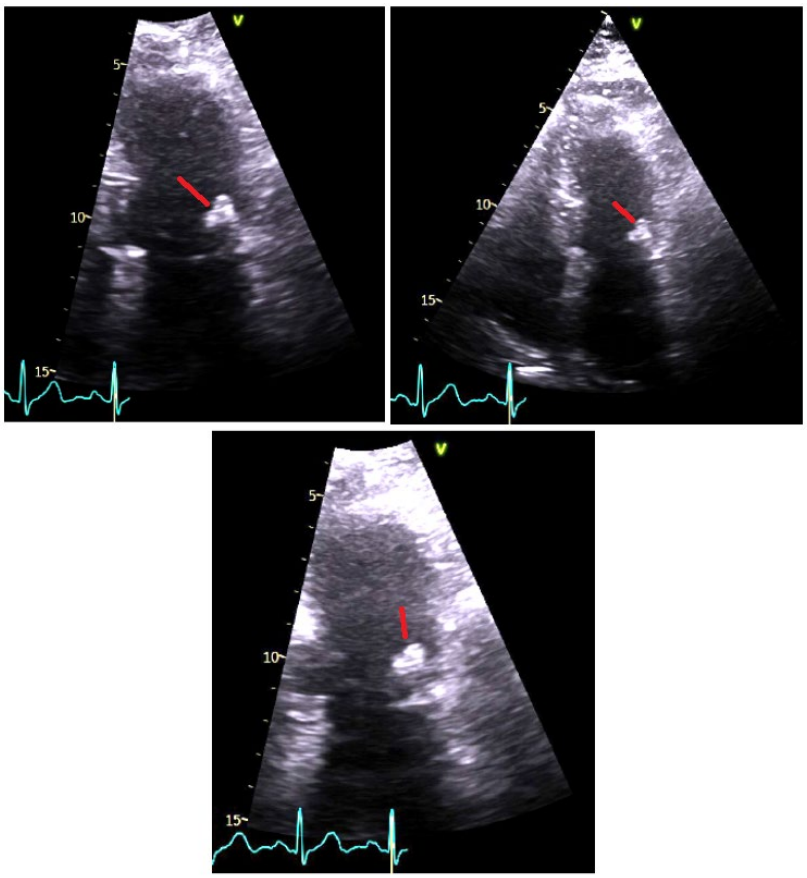
However, outpatient transthoracic echocardiogram (TTE) demonstrated an echogenic nodular anomaly closely related to the posterior mitral annulus with a mobile linear structure attached, possible vegetation or extension of caseous calcification (Figure 1). Normal left ventricular dimensions with visually normal systolic function were noted, with a visually estimated left ventricular ejection fraction 55–60%. In addition, the report stated a visually normal right heart size and normal systolic function, mildly dilated ascending aorta with no other significant valvular abnormalities.

The patient was admitted from outpatient echo following the report for urgent inpatient transoesophageal echocardiogram (TOE) and assessment for infective endocarditis. However, further blood investigations and microbiology cultures were all unremarkable, with no evidence of raised infection markers or positive microbiology results.

TOE demonstrated an echogenic posterior aspect of the mitral ring with normal mitral leaflet mobility with trivial mitral regurgitation. An echogenic mass was seen attached to the ventricular aspect of the mitral annulus at the level of posteromedial commissure, 9×4 mm in size, that was initially thought to represent a fibroma, or less likely an old vegetation (Figure 2). There was no thrombotic lesion attached to it.

The case was discussed with the regional cardiothoracic multidisciplinary team with an outcome of repeat TTE in 3 months time, which if demonstrated change for re-discussion at

Figure 1: Transthoracic echocardiogram images.



the multidisciplinary team for consideration for surgical intervention.

An outpatient CT coronary angiogram revealed severe calcific atheroma, but was unable to fully evaluate the coronary arterial lumens (Figure 3). The CT also showed mixed calcific and soft tissue related to the mitral valve annulus. Caseous degeneration was diagnosed with evidence of rupture of the calcified shell.

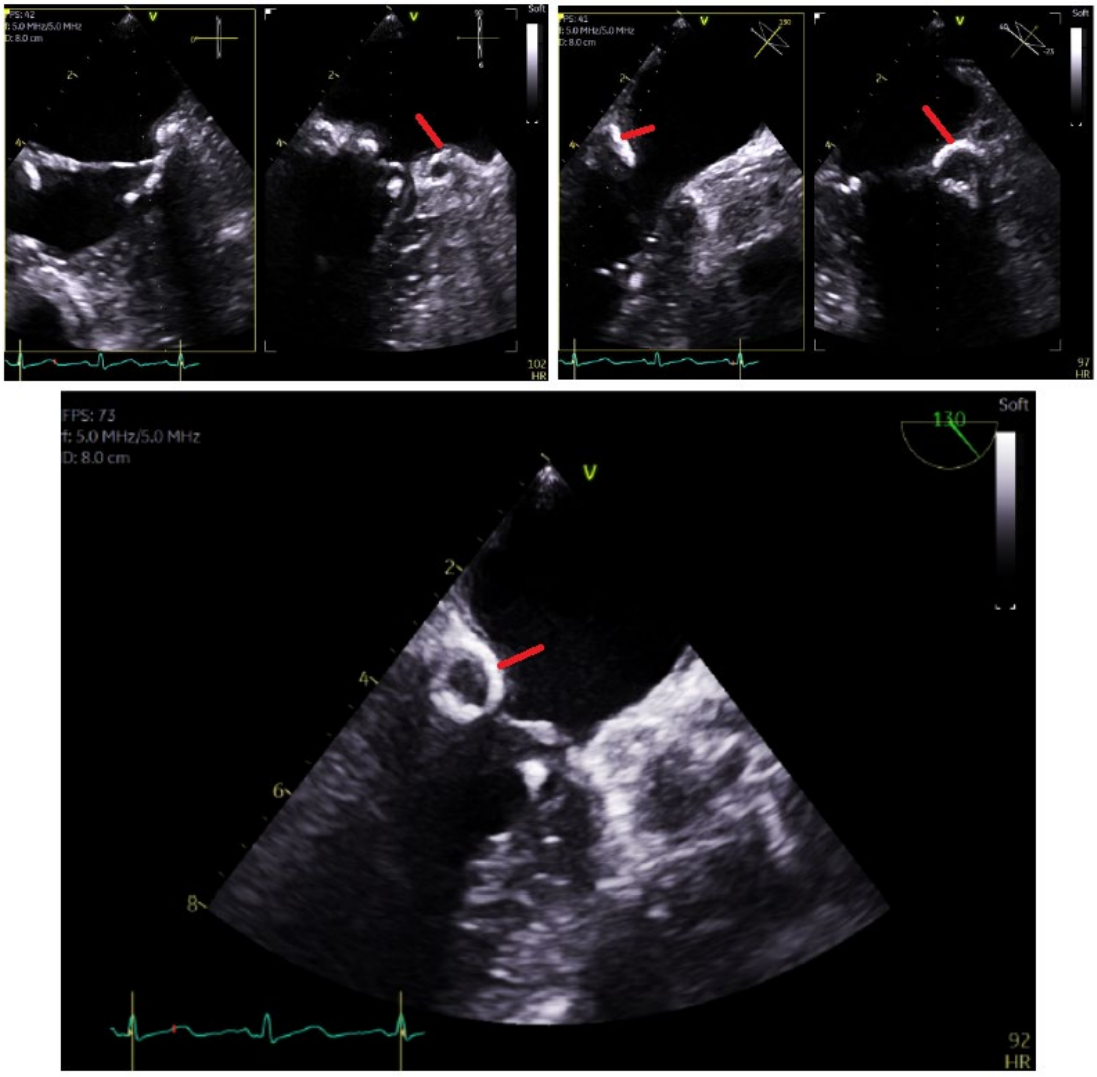
Repeat TTE demonstrated the known caseous calcification of the posterior mitral annulus as previously reported, though the previous mobile attachment noted was not readily identified, possibly seen in the subcostal window with no significant increase in size.

Single antiplatelet therapy was initiated given the evidence of non-obstructive coronary artery disease, but anticoagulation therapy on risk–benefit balance was not initiated. The patient has had no further admissions suggestive of ongoing complications due to this pathology.

DISCUSSION

The mitral valve has a marginal fibrous ring known as the mitral annulus. This is an extension of the cardiac fibrous skeleton to which the mitral valve leaflets are attached. Its function is to reduce the surface area during systole to facilitate complete closure of the leaflets.

Figure 2: Transoesophageal echocardiography images.



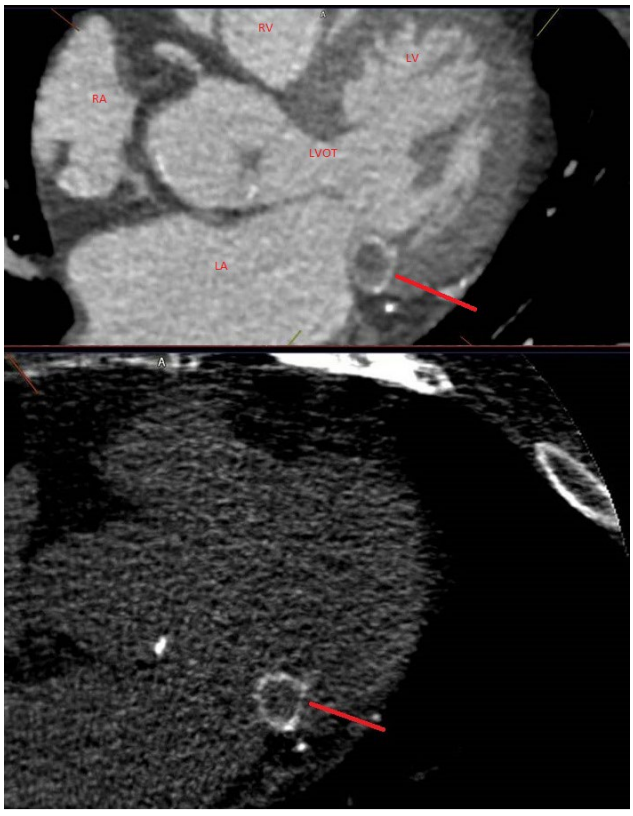
MAC, most common in elderly females, is a chronic degenerative process that progresses with age and can result in mitral valve disease (both stenosis and regurgitation), infective endocarditis, atrial arrhythmias, and high-grade block.[1] It is more commonly found in patients with systemic hypertension, mitral valve prolapse, raised left ventricular systolic pressure, aortic valve stenosis, chronic kidney disease, secondary hyperparathyroidism, atrial fibrillation, and risk factors for the development of coronary artery disease.[2]

CMAC, sometimes called liquefaction necrosis of MAC, is a rare variant of MAC. It typically involves the posterior annulus, appearing as a smooth mass with a surrounding hyper-echogenic rim, with no flow or acoustic shadow artifacts.[3] The mass typically consists of calcium, fatty acids, and cholesterol, and though benign can cause significant clinical concern, such as mitral stenosis or regurgitation, left ventricular outflow obstruction, or systemic embolisation, such as in this case study.[4]

The prevalence of CMAC amongst echocardiographic studies has been reported as 0.640% of patients with MAC, and 0.068% of the general population, though incidence amongst an autopsy series was 2.700%, possibly suggesting prevalence may be higher.[5] Most cases are incidentally found on echocardiograms or during catheterisation with fluoroscopy of the annulus. However, cases can present following investigation for embolic causes, or as work-up for possible cardiac tumours, possibly presenting as new murmurs.

Echographically, CMAC appears as a round or semilunar bright echogenic mass in the peri-annular region of the mitral valve. Typically, it contains a central echolucent area reflecting liquefaction, but with no acoustic shadowing artefacts such as in MAC, which presents with a posterior echo shadow.[3] On 3D echo imaging, it appears similarly.[6] Whilst TTE can be helpful in identifying CMAC, it is well known to be limited in accuracy and diagnostic value in some patients due to poor acoustic windows, and therefore TOE can provide high-quality visualisation.

Figure 3: CT coronary angiogram image.



Differentiation of CMAC from other cardiac masses, usually tumour or thrombus, can be done with CT or MRI. On CT, CMAC typically appears as well-defined oval or crescent shaped calcified mass, with peripheral calcification with high Hounsfield units, and lacks contrast enhancement. The central hypodensity is considered to be due to the liquefactive material within the centre of the mass.[6] On cardiovascular MRI, T1/T2 steady-state free precession and post-gadolinium sequences will be required, and the calcium is low signal on all sequences, the centre area is more fluid, so low on T1 and high on T2 and steady-state free precession without avid vascularity.

Currently, there is no standard treatment protocol for CMAC. Given the benign nature of CMAC, some authors have recommended a conservative management for asymptomatic cases.[7] However, a literature review by Dietl et al.[9] suggested elective surgical resection in good operable candidates in asymptomatic cases, given the risk of embolic strokes unrelated to atrial fibrillation. Dietl et al. reported prevalence of cardioembolic events associated with CMAC as 19.2% amongst literature they reviewed.[8,9] Though, if the embolism is more consistent with a fat embolism, then anticoagulation is unlikely to be effective. However, surgery is generally considered in good surgical candidates, where the clinical situation is in the context of other established surgical indications, such as severe mitral valve disease or systemic non-embolisation, especially if embolisation is in the context of established anticoagulation.

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Incidence of Chronic Pelvic Pain in Females Attending a Gynaecology Outpatient Department

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Abstract

Background and Aims: Chronic pelvic pain (CPP) is a persistent pelvic pain that leads to reduced work performance and impaired quality of life in females. Nearly 15% of females report time off from paid work and around 45% report reduced work productivity. There is a paucity of studies to address the issue, especially with a multidisciplinary and multifactorial view. Various gynaecological disorders are associated with CPP such as endometriosis, adenomyosis, adhesions, chronic pelvic inflammatory disease, and pelvic congestion syndrome. The objective is to determine the frequency of CPP in females attending gynaecologic outpatient departments.

Materials and Methods: A total of 201 patients aged 14–48 years attending the gynaecologic outpatient department for gynaecological disorders with complaints of lower abdominal pain were included in this study. Patients enrolled in the study were assessed by a detailed history and pelvic examination, and a structured questionnaire was filled out. Data were analysed using the statistical package for social sciences version 23.0 (International Business Machines Corporation, Armonk, New York, USA).

Results: The mean age of the patients was 32.39±6.98 years. The frequency of CPP in females was observed as 95.52% (95% confidence interval: 91.67–97.93%) The rate of CPP was significantly high in females with parity ≤5 and those who had a duration of pain lower than 36 months. In multivariate analysis, adjusted odds ratio by stepwise logistic regression model showed that parity (parity 0–1) and duration of pain (≤36 months) were significantly associated with CPP in females.

Conclusion: The study indicates that the most common gynaecological causes of CPP in females attending the outpatient department were those with endometriosis followed by adenomyosis. The management of CPP needs patient-centred care with a multidisciplinary approach. This will lead to early and effective management.

Key Points

1. Chronic pelvic pain (CPP) is an often ignored complaint that plagues females for years before a diagnosis is made. Patients are advised of many unnecessary investigations and treatments, which hinder proper care.

2. The authors' research shows that most causes of CPP can be managed with a thorough and complete history. A multi-disciplinary approach is the best for such patients.

3. Physicians must have an open mind when patients present with CPP. Their concerns and fears should be validated and all-out efforts should be made to ease symptoms from this disregarded complaint.

INTRODUCTION

Chronic pelvic pain (CPP) affects up to 25% of females of reproductive age, and 15% of all females worldwide.[1] It is a common complaint of females visiting the gynaecology outpatient department. The annual prevalence of CPP was found to be 38/1,000, a rate comparable to asthma (37/1,000) and back pain (41/1,000).[2] Among sparse population-based studies, the prevalence of CPP was found to be 25.4% in New Zealand and 21.5% in Australia.[3] Among South East Asian countries, a 44.2% prevalence of CPP was reported in Thailand.[4] CPP is also one of the most frequent indications for gynaecological laparoscopies, accounting for approximately 40% of cases.[5]

CPP is defined by the Royal College of Obstetrics & Gynaecology (RCOG) as an intermittent or constant lower abdominal pain of greater than 6 months' duration, not occurring exclusively with menstruation or intercourse and not associated with pregnancy.[6] It arises from structures within the pelvis. The differential diagnoses of CPP include gynaecological causes (endometriosis, adenomyosis, adhesions, chronic pelvic inflammatory diseases, remnant ovary syndrome, trapped ovary syndrome, or pelvic congestion syndrome), gastrointestinal causes (irritable bowel syndrome, inflammatory bowel disease, or coeliac disease), urinary causes (interstitial cystitis or urethral syndrome), neurological causes (pudendal neuralgia, trigger points, or nerve entrapment), and musculoskeletal causes.[7] The pain is caused by a single, or often a combination of different disorders with overlapping symptomatology, making it difficult to diagnose.

Patients with CPP have a long history of pain, marked psychiatric effects, work and physical impairment, and distrust of treatment,[8] leading to a burden on healthcare expenditure and work productivity loss. Every year, 881.5 million USD is spent on outpatient department management in the USA, and an estimated 158 million EUR is spent on the UK National Health Service.[5] In total, 550 million USD is lost each year in the USA due to absence from work.[8] In the United Kingdom in 2001, 15% of affected females reported lost working days and 45% reported reduced working capacity. A study showed that 43% of individuals with CPP reported that their activities were restricted by pain.

Without a medical prescription, 58.4% of females use analgesics or nonsteroidal anti-inflammatory drugs weekly or daily for pain relief.[5] Females who have had pelvic pain for longer develop strong associations with disability, distress, poor general health, low satisfaction levels, a sense of helplessness, and negative coping responses.[9,10] The purpose of this study is to obtain insight into the scope of a problem that leaves many females crippled with an often misunderstood diagnosis.

MATERIALS AND METHODS

This descriptive cross-sectional study was conducted at the Department of Obstetrics and Gynecology Unit-2 of Dr Ruth K.M. Pfau Civil Hospital Karachi, Pakistan, from March 2019 to January 2020. Data were collected from females attending the gynaecology outpatient department who fulfilled inclusion criteria, after taking their informed consent. Females aged 14–48 years with complaints of lower abdominal

pain greater than or equal to 6 months' duration were enrolled in the study. Menopausal females and those with a history of hysterectomy were excluded from the study. Age, parity, duration of pelvic pain, history of past sexual abuse, family history of CPP, education, marital status, employment status, use of pain-relieving medications, diagnosed gynaecological cause, and pain analysis on the visual analogue scale were recorded in a structured questionnaire.

Females who met the inclusion criteria were asked detailed questions to ascertain whether pain was of pelvic origin or due to other causes. Data were analysed using the statistical package for social sciences (SPSS) version 23.0 (International Business Machines Corporation, Armonk, New York, USA). The quantitative variables of age, parity, duration of pelvic pain, and pain score on visual analogue scale were represented by mean and standard deviation. The qualitative variables of ethnicity, history of past sexual abuse, family history of CPP, education, marital status, employment status, pain-relieving medications, and diagnosed gynaecological cause were represented as frequency and percentage.

Effect modifiers such as ethnicity, history of past sexual abuse, family history of CPP, education, marital status, employment status, pain relief, and diagnosed gynaecological cause were addressed through data stratification. A post-stratification chi-square test was applied, and a p-value ≤0.05 was considered significant.

RESULTS

A total of 201 patients with lower abdominal pain were included in the study. The mean age of the patients was 32.39±6.98 years. More than two thirds of these females were married (81.6%), 25 (12.4%) were single, 8 females were separated and 4 females were widows. Almost 55% of the females had multiparity. More than half (109; 54.2%) of the females were illiterate, 62 (30.8%) had attended primary education and 30 (14.9%) had attended secondary education.

Out of 201 patients, 192 (95.5%; 95% confidence interval: 91.67%–97.93%) had experienced CPP. Ten (5%) females reported sexual abuse and 65 (32.3%) patients had a history of pelvic pain complaints in the family. There were 128 (63.7%) females who used analgesics or nonsteroidal anti-inflammatory drugs for relief of pain, 44 (21.9%) females used hormonal methods for pain relief and 29 (14.4%) were taking other forms of medications and therapies for symptom control. Endometriosis (60; 29.9%) and adenomyosis (56; 27.9%) were the top two most common diagnoses in females.

Parity (parity ≤5) and duration of pain for less than 36 months were significantly associated with CPP in females, yet was not statistically significant with age groups, marital status, education, employment, past sexual abuse, family history of pelvic pain, use of pain-relieving medicine, and diagnosis, as shown in Table 1. In a multivariate analysis, adjusted odds ratio by stepwise logistic regression model showed that parity (parity 0–1) and duration of pain (≤36 months) were significantly associated with CPP in females, as shown in Table 2.

DISCUSSION

The quality of life of patients with CPP is severely affected, and current known therapies are adopted for relief from pain and an aetiological diagnosis. This imparts a huge burden on the healthcare system, as patients experience repeated hospital admissions, surgical procedures, and emergency and general physician visits to obtain a definitive diagnosis, as well as to relieve CPP symptoms causing distress, disability, and affecting daily activities.[11-12] This also develops a strain in relationships and often requires absence from work.[13,14]

CPP has a multifactorial aetiology; therefore, a multidisciplinary approach is advised to reach a diagnosis. Treating patients with medical and surgical therapies, as well as reassuring them, gaining trust and providing psychological support for pain relief results in better cure rates compared to pharmaceutical and interventional options alone.[15] One of the main causes of CPP is endometriosis, which can make management even more challenging. Illness imparted to the affected individual by pain intensity is ignored by many clinicians and endometriotic foci are put into consideration.[16,17]

Table 1: Univariate analysis showing factors associated with chronic pelvic pain in females (n=201).

Variables	Cut-off	N	Chronic Pelvic Pain Presence	Odds Ratio (95% confidence interval)	p-value
Age Groups (Years)	≤30	115	110 (95.7%)	1.07 (0.27–4.1)	0.9180
	>30	86	82 (95.3%)	Ref**	
Parity	0–1	91	89 (97.8%)	13.69 (2.27–82.36)	0.0040*
	2–5	93	90 (96.8%)	9.23 (1.85–45.99)	0.0070*
	6–7	17	13 (76.5%)	Ref**	N/A
Duration of Pain (months)	6–36	187	183 (97.9%)	25.41 (5.81–111.1)	0.0005*
	>36	14	9 (64.3%)	Ref**	
Marital Status	Single	25	23 (92.0%)	0.47 (0.09–2.43)	0.3100
	Married/ Separated/ Widow	176	169 (96.0%)	Ref**	
Education	Primary	62	57 (91.9%)	0.32 (0.07–1.39)	0.1310
	Secondary	30	29 (96.7%)	0.82 (0.08–8.19)	0.8600
	Illiterate	109	106 (97.2%)	Ref**	
Employment	Employed	55	53 (96.4%)	1.33 (0.27–6.63)	0.7230
	Unemployed	146	139 (95.2%))	Ref**	
Past sexual abuse	Yes	10	9 (90.0%)	0.39 (0.04–3.49)	0.3740
	No	191	183 (95.8%)	Ref**	N/A
Family history of chronic pelvic pain	Yes	65	60 (92.3%)	0.36 (0.09–1.40)	0.1520
	No	136	132 (97.1%)	Ref**	N/A
Use of pain relieving medication	Analgesic/ nonsteroidal anti-inflammatory drugs	128	122 (95.3%)	0.87 (0.21–3.59)	0.9990
	Hormonal/ Others	73	70 (95.9%)	Ref**	N/A
Diagnosis	Endometriosis	60	58 (96.7%)	1.28 (0.17–9.51)	0.8030
	Adenomyosis	56	53 (94.6%)	0.78 (0.13–4.91)	0.7960
	Adhesions	38	36 (94.7%)	0.80 (0.11–5.96)	0.8280
	Others	47	45 (95.7%)	Ref**	N/A

N/A: not applicable.

* Significant <0.01

** Reference group: comparison category equal to 1

Table 2: Multivariate stepwise logistic regression model showing factors associated with chronic pelvic pain in females.

Variables	Cut-off	Adjusted Odds Ratio (95% confidence interval)	p-value
Parity	0–1	10.91 (1.42–84.13)	0.0220
	2–5	4.55 (0.69–29.75)	0.1140
	6–7	Ref*	N/A
Duration of Pain (months)	6–36	22.16 (4.27–115.11)	0.0005
	>36	Ref*	

Model Accuracy: 96.5%

Nagelkerke R Squared: 0.341

Hosmer–Lemeshow Test: p=0.951

Age, education, marital status, employment, past sexual abuse, family history of chronic pelvic pain, use of pain-relieving medication, and diagnosis were excluded from the model. Stepwise Forward Wald logistic regression model was applied.

*Reference group: comparison category equal to 1

Mood disorders such as anxiety and depression accompanying such a diagnosis have a negative impact on the perception of pain. These concurrent diagnoses of CPP, endometriosis, and mood disorders disrupt pain inhibitory pathways, which makes the patient more sensitive to nociceptive stimuli.[17-19] These have a profound impact on the severity of pain, which is directly proportional to low output and absent days from work.[20,21] Diagnostic delay is a significant factor and fatigue is a major complaint in direct correlation with the severity of pain, leading eventually to absenteeism from education, academics, and work. Social and sexual relations are impaired and patients live a socially isolated life.[22] The miscommunication, inadequate treatment for relief of pain, and negative attitude by doctors can further aggravate detrimental psychological effects.[23-25]

In their study, Yasmin et al.[26] demonstrated that 40% of laparoscopies performed for evaluation of CPP aetiology remained inconclusive. In such patients, other factors such as childhood sexual abuse and non-gynaecological pathologies should be considered. However, the reassuring effect of negative laparoscopy improved their quality of life. The authors did not perform any laparoscopies for the patients, which was a limitation of the study.[26] Facchin et al.[27] demonstrated in their study that mood dysfunction, anxiety, depression, and stress all negatively influence the immune system. The resulting imbalance between pro- and anti-inflammatory cytokines flares inflammatory response. A vicious cycle is started with increased disease severity and increased mental upset and depression. Therefore, the author insists upon psychological therapy along with medical and surgical treatment for better outcomes.[27] The study conducted by Centini et al.[28] suggests that when patients are reassured and made to understand their disease, they are found to get positive improvement in quality of life. Cognitive therapy is an integral part of CPP treatment. Reduced stress, reduced mental anxiety, improved quality of life, and feeling of well-being indirectly reduce ongoing stress response within their body and inflammatory process, and therefore the disease. Centini et al.[28] divided patients with CPP into two groups, with and without endometriosis. They found that those with endometriosis generally had a poorer

prognosis and a more severe disease overall. The authors made a similar observation intheir study.[28]

Petrelluzi et al.[29] reported altered metabolism of cortisol, hypothalamic pituitary adrenal axis malfunctioning, and hypocortisolism in patients affected with chronic fatigue syndrome.[29] Tripoli et al.[30] stated that surgical and medical treatment for CPP is not sufficient. Other aspects should also be addressed to improve patient quality of life. Patients with CPP are frustrated and socially isolated, with disrupted marital and sexual life because of long intervals in achieving a definitive diagnosis. Sexual, social, psychological, emotional, and mental well-being is entirely neglected by physicians while treating underlying disorders, which is why optimal therapeutic results are not achieved.[30]

A significant amount of healthcare costs are borne by insurance companies and governments due to the extensive workup and continuous doctor's visits needed for CPP.[31,32] It also requires more frequent visits to the psychiatrist, and sometimes surgery such as a hysterectomy does not improve pain.[33-35]

If the underlying cause is endometriosis, it results in even more workup and reproductive challenges.[36] There is a complex and altered interplay between the central and peripheral nervous systems for the generation, transmission, and aggravation of pain in endometriosis.[37,38] The pain of endometriosis is resolved with hormonal treatment, but can recur as soon as therapy is stopped.[39-42] Another significant cause of CPP is adenomyosis, which affects around 30% of females in their late reproductive years.[43] Adenomyosis presents with abnormal uterine bleeding and chronic pelvic, but is not routinely diagnosed clinically or even radiographically. The diagnosis is mostly concluded from hysterectomy specimens.[44,45]

Mathias et al.[46] reported that females older than 35 years of age are slightly less prone to the risk of developing CPP when compared to females of a younger age group. Females separated from their partners and widowed females were found to have an increased prevalence of CPP compared to single females.[46] In the study conducted by the authors, over two thirds of females were married (81.6%). This raises the association of CPP with marital status. Mathias et al.[46] found no significant relationship between the educational level of patients and CPP frequency in their study.

Facchin et al.,[47] when observing an association between CPP impact on the employment status of affected females, found a potential connection between the severity of pain of endometriosis and unemployment and absence from work. Symptomatic patients with endometriosis were more likely to be unemployed compared to asymptomatic patients. The author concluded that severe incapacitating CPP caused by endometriosis disrupts patients' professional life and career, and renders them helpless.[47]

Mackey et al.[48] studied 262 participants with CPP. Compared to the control group, patients affected with CPP had lower literacy levels, lower monthly income due to unemployment, an inability to perform work, days off from work, and expenses on frequent physician's visits. Associated co-morbidities were also more common in disease affected group.[48]

The highest pain intensity reported in the authors' study was a visual analogue score of 8 (4% of patients) leading to an inability to perform at work, the feeling of helplessness about pain relief, and unemployment, as well as patients feeling unable to take care of family and to do household chores. Roth et al.[49] studied the correlation between the level of educational achievement and pain perception, quality of life disruption, and disability. The study included a total of 187 participants. Educational achievement was grouped into five categories ranging from primary school to graduation level. A direct relationship was observed between higher educational levels and the severity of pain. The author concluded that greater educational status makes patients susceptible to perceiving the increased intensity of pain sensation, disability, and distress. The level of education was also found to be inversely related to favourable treatment outcomes. Roth et al.[49] emphasised the importance of treating chronic pain with a bio-psychosocial approach that considers multidimensional aspects of clinical factors together with socio-economic parameters, which are beyond physiological impairment.[49]

Day et al.[50] examined the association between demographics and psychosocial variables with chronic pain in 115 patients. The study

illustrated that race and ethnicity could be potentially linked to pain severity and disability. Pain intensity score found was far greater in African-American patients compared to White Americans. The author reported satisfaction with living as a contributing factor to favourable pain tolerability and favourable treatment outcome scores in White Americans, whereas African-American patients were living in rural areas with low monthly income, poor socio-economic status, low literacy level, and poor access to appropriate treatment. All these factors played part in contributing to further aggravating their pain perception and associated illness. Life satisfaction plays a protective role against negative mindset and affectivity.[50]

The main limitation of this study was a limited sample size and sample collection from a single centre, which was a government-run hospital. The population presenting to the hospital belonged to the lower socio-economic class, hence some bias may be expected in the extrapolation of the results.

CONCLUSION

In conclusion, CPP is an important but overlooked health morbidity that has been disregarded for a long time. It has a huge impact and burden on healthcare economics, patient quality of life, and almost every aspect of the affected individual's life. There is a need to emphasise effective management protocols, multidisciplinary and multi-dimensional approaches, and to aim every effort to obtain an accurate diagnosis for pelvic pain from the first day of presentation. This would avoid unending referrals, investigations, and procedures, and the trial of different and inappropriate therapies which often do not address the pathology for symptom relief. There is a need to allocate healthcare resources and address the disease in future research for better treatment and care of females with from debilitating diseases such as CPP.

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Urinary Bladder Stone: A Late Complication of Bulkamid® Periurethral Bulking Injection

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Abstract

Polyacrylamide hydrogel bulking agent (Bulkamid® [Axonics, Irvine, California, USA]) injection is used as a minimally invasive treatment for stress and mixed urinary incontinence in females. Several studies have demonstrated the short- and medium-term efficacy and safety of Bulkamid. However, there are limited data available on the long-term safety of this procedure. The authors report an unexpected and late complication associated with Bulkamid periurethral injection.

An 80-year-old female, who had undergone Bulkamid periurethral injection for stress urinary incontinence 10 years previously, was referred to the authors' clinic with recurrent lower urinary tract symptoms and dysuria. Investigations with ultrasound and cystoscopy confirmed a single 2 cm bladder stone adhered to an exposed Bulkamid agent at its injection site.

Exposed intravesical Bulkamid can act as a foreign body with lithogenic potential to cause urinary bladder stone formation. This article highlights urinary bladder stone formation as a late potential complication of Bulkamid periurethral injection.

Key Points

1. Urethral bulking therapy has provided a minimally invasive alternative to treating mixed/stressed urinary incontinence with limited short- and medium-term complications. There is, however, little publication on long-term complications associated with bulking therapy.

2. The authors describe an unexpected finding of a bladder stone adhered to an exposed urethral bulking agent, Bulkamid® (Axonics, Irvine, California, USA), which was injected 10 years prior. Bulkamid is non-toxic and inert in tissue; however, once exposed to intravesical urine for prolonged periods, it acts as a foreign body and a nidus for calculi formation.

3. Exposed bulking agents, extruding from its injection sites, have the potential for urinary stone formation with prolonged urine exposure. Care should be taken to ensure adequate depth of Bulkamid injection, to prevent later extrusion and complications.

INTRODUCTION

Polyacrylamide hydrogel (PAHG) Bulkamid® (Axonics, Irvine, California, USA) was introduced in Europe as a promising periurethral bulking agent for the treatment of female stress and mixed urinary incontinence in 2006.[1] Composed of 2.5% polyacrylamide and 97.5% water, it benefits from being non-biodegradable and stable long-term. Its efficacy is widely published, with growing interest as a minimally invasive treatment option. Subjective symptomatic improvement rates have been reported to be as high as 82.8% at 3-year (3–60 months) follow-up.[2] Its side effect profile includes mild to self-limiting symptoms. However, there are limited data available on the long-term safety of this bulking agent injection. Here, the authors highlight an unexpected 10-year late complication of Bulkamid periurethral bulking injection.

CASE REPORT

An 80-year-old female patient was referred to the urology clinic with recurrent cystitis in October 2020. They previously had Bulkamid periurethral injection under local anaesthesia in 2009 with good outcomes; however, over the recent 9 months, the patient presented with dysuria, increased urinary frequency and urgency, and subsequently became incontinent, especially during the last 3 months. Urine tests and cultures confirmed *Escherichia coli* infection, which was resistant to trimethoprim and amoxicillin. Despite having repeated courses of antibiotics, the patient remained symptomatic. The patient was otherwise in excellent health, with no significant comorbidities.

INVESTIGATIONS

Urinary bladder ultrasound imaging revealed a single 2 cm mass with acoustic shadow, suggestive of a bladder stone. There was no significant postvoid residual volume. Subsequent flexible cystoscopy confirmed the presence of a stone, which was fixed to the previous Bulkamid injection site at 9 o'clock of the bladder neck. The bladder mucosa close to the trigone was inflamed, but the rest of the bladder looked healthy, with no signs of chronic cystitis. The patient was then given further antibiotic treatment and put on the waiting list for litholapaxy.

TREATMENT

As planned, the patient was admitted a few weeks later and had the urinary bladder stone removed under general anaesthesia. From the findings, the 2 cm stone (Figure 1) was adherent to the exposed Bulkamid agent at the bladder neck. This was dislodged and fragmented with lithoclast; all stone fragments were removed. The remnant exposed Bulkamid at the 9 o'clock site was also completely removed endoscopically (Figure 2). The patient's urinary symptoms and urinary tract infection resolved post-operatively with the completion of an antibiotic course.

DISCUSSION

Periurethral bulking injections are a less invasive alternative treatment for female stress urinary incontinence compared to the gold standard treatment of surgical repair with a synthetic mid-urethral sling (MUS), with its long-term efficacy and durability. In a recent systemic review comparing both treatment options, MUS was two- to five-times more likely to result in a cure compared with periurethral bulking injections.[3]

There has, however, been a growth in controversies surrounding the long-term complications of MUS, including long-term pain, urethral erosion, and medical-legal implications. This has led to an increasing shift towards the use of bulking agents in recent years.[4]

There are currently a variety of bulking agents marketed in different countries. While no study directly compares polyacrylamide hydrogel (Bulkamid) to the other bulking agents, its safety and effectiveness profile has been demonstrated in numerous short- and medium-term studies.[5]

Polyacrylamide hydrogel has widely been used in other medical specialities, including breast augmentation and facial fillers for cosmesis. Its suitability for *in vivo* soft tissue injection is owed to its non-biodegradability, non-toxicity, and resistance to migration and calcification long-term.[6]

Figure 1: Endoscopic images of a urinary bladder stone at the bladder neck.

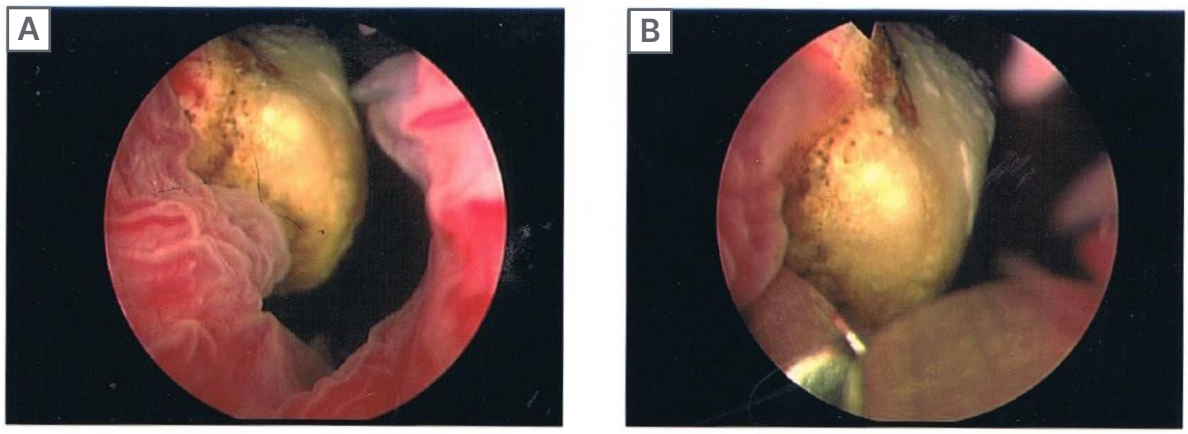
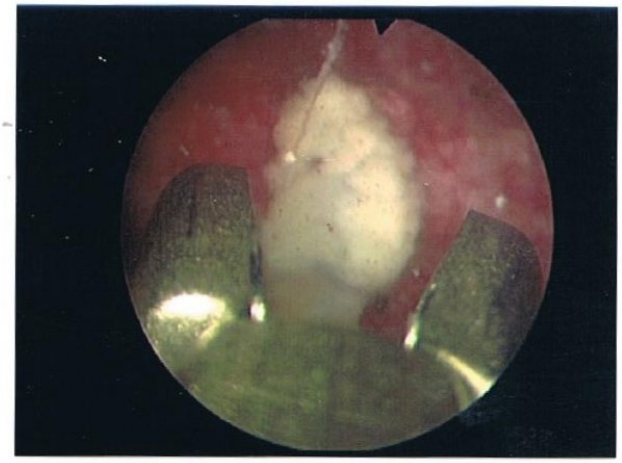


Figure 2: Endoscopic image of exposed Bulkamid® (Axonics, Irvine, California, USA) bulking agent at the urinary bladder neck.



Despite its safety profile, Bulkamid injection for stress urinary incontinence has some reported adverse effects. The most frequently reported adverse effects were pain at the injection site and urinary tract infections. This was followed by haematuria and transient urinary retention. One study reported a serious adverse effect of a periurethral abscess.[7]

To the authors' best knowledge, there were no reported cases of urinary bladder stones associated with Bulkamid periurethral injections until this case. While the reason for this stone formation is unclear, this article postulates a number of possible mechanisms for stone formation based on the exposed bulking agent.

Virtually all foreign bodies in the urinary bladder are lithogenic with the potential to act as a nidus for stone formation. This is seen regularly with retained iatrogenic and non-iatrogenic objects, including ureteric stents, long-term urinary catheters, retained suturing materials, and inserted domestic items.[8] While Bulkamid has demonstrated long-term resistance to calcification within soft tissue in a previous study,[6] there are no experimental reports with long-term exposure of Bulkamid to urine. Bulkamid exposure to the intravesical urine long-term may have the potential to accumulate minerals from urine over time, thus allowing for layered stone formation. This is evident in this case with the stone's adhesion to the exposed Bulkamid agent.

Secondly, this patient presented with recurrent cystitis and confirmed antibiotic-resistant *E. coli*, a bacteria capable of forming biofilm. Bacteria and biofilm on a foreign body in the urinary system create an environment preferential for calcium and struvite stone formation through ureolysis.[9] Unfortunately, stone analysis was not performed in this case to confirm the composition.

To avoid the complication of bulking agent extrusion from the injected urethral site, proper technique must be adhered to. Bulking agents can be injected either via a periurethral or transurethral route, both of which have similar efficacy and safety outcomes.[10] Emphasis is placed on slow advancement of the needle to avoid accidental urethral mucosa injury, while ensuring adequate depth in the submucosa. The recommended number of submucosa injection sites is three or more, usually at 3, 6, and 9 o'clock, and within 1 cm distal to the bladder neck. Good coaptation of the urethral wall is achieved with no more than 0.5 ml of Bulkamid injected at each of the injection sites.[2]

CONCLUSION

The authors report an unexpected finding of a urinary bladder stone adhered to an exposed Bulkamid agent as a late complication of periurethral bulking injection. Given the limited data available on the long-term safety of Bulkamid, this is a potential complication to be considered in patients presenting with new and recurring symptoms years after undergoing periurethral injection. The injection procedure should aim for adequate submucosal depth to reduce the risk of Bulkamid extrusion, and thus prevent subsequent stone formation.

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