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EMJ

Interviews

Nicola Veronese, Tahir Masud, and Imran Ahman discuss geriatric medicine and innovation in surgery

Editor's Pick

Relationships of Chronic Kidney Disease and Thyroid Dysfunction in Patients with Stage 4 and 5 Chronic Kidney Disease: A Cross-Sectional Study

Infographic

Exploring the British Geriatrics Society's Blueprint for Preventing and Managing Frailty in Older People

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EMJ allows healthcare professionals to stay abreast of key advances and opinions across Europe.

EMJ aims to support healthcare professionals in continuously developing their knowledge, effectiveness, and productivity. The editorial policy is designed to encourage discussion among this peer group.

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Chair: *Prof. Ashley Woodcock*

SESSION	SPEAKER(S)
Welcome and introduction: The virtuous cycle of patient partnerships, improved outcomes, and sustainable respiratory care	Prof. Ashley Woodcock
Why climate change and environmental sustainability is everybody's problem	Prof. Rachel Huxley
How sustainable global pharmaceutical regulations are impacting supply chains: What this could mean for your patients	Dr John Pritchard
Combining sustainable interventions with optimal patient outcomes: Lessons learned from adult-onset asthma phenotypes	Prof. Hannu Kankaanranta
The UK view on sustainable clinical decision-making in respiratory care	Dr Alex Wilkinson
The Nordic view on sustainable clinical decision-making in respiratory care	Prof. Christer Janson

SCAN TO LEARN MORE ABOUT ORION'S ACTIVITIES AT ERS 2023

Abbreviations

CET: Central European Time; ERS: European Respiratory Society; Q&A: question and answer.

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ORION PHARMA

EMJ

Welcome letter

Evgenia Koutsouki
Editor

Welcome to the second issue of our flagship journal for this year. We are very proud to start this issue with a mini-focus on geriatric medicine, featuring interviews with geriatric medicine experts Nicola Veronese and Tahir Masud, alongside an infographic summarising the recently published British Geriatrics Society's Blueprint for Preventing and Managing Frailty in Older People. We have also interviewed Imran Ahmad, who gave a highly engaging interview discussing how surgical teams can be inspired by Formula 1 pit crews.

For the nephrologists among you, this issue includes a cross-sectional study investigating the relationship between chronic kidney disease and thyroid dysfunction in patients with Stage 4 and 5 chronic kidney disease. Another interesting article in the journal describes a study focusing on the prevalence of carbapenem-resistant *Enterobacteriaceae* in a tertiary care hospital in South India, aiming to help appropriate administration of antibiotics in carbapenem-resistant infections, potentially reducing mortality and morbidity from these infections. Finally, we feature a case report describing a rare case of cutaneous squamous cell carcinoma of the hand presenting as a tender dermal nodule on the dorsum of the hand. This is a useful article for dermatologists as it discusses the different presentations of cutaneous squamous cell carcinomas, as well as the risk of perineural invasion and its implications.

A big thank you goes out to all of our reviewers, Editorial Board members, contributors, and of course interviewees for helping to bring you this high-quality content. Please keep an eye out for our September issue, with more great content to come.

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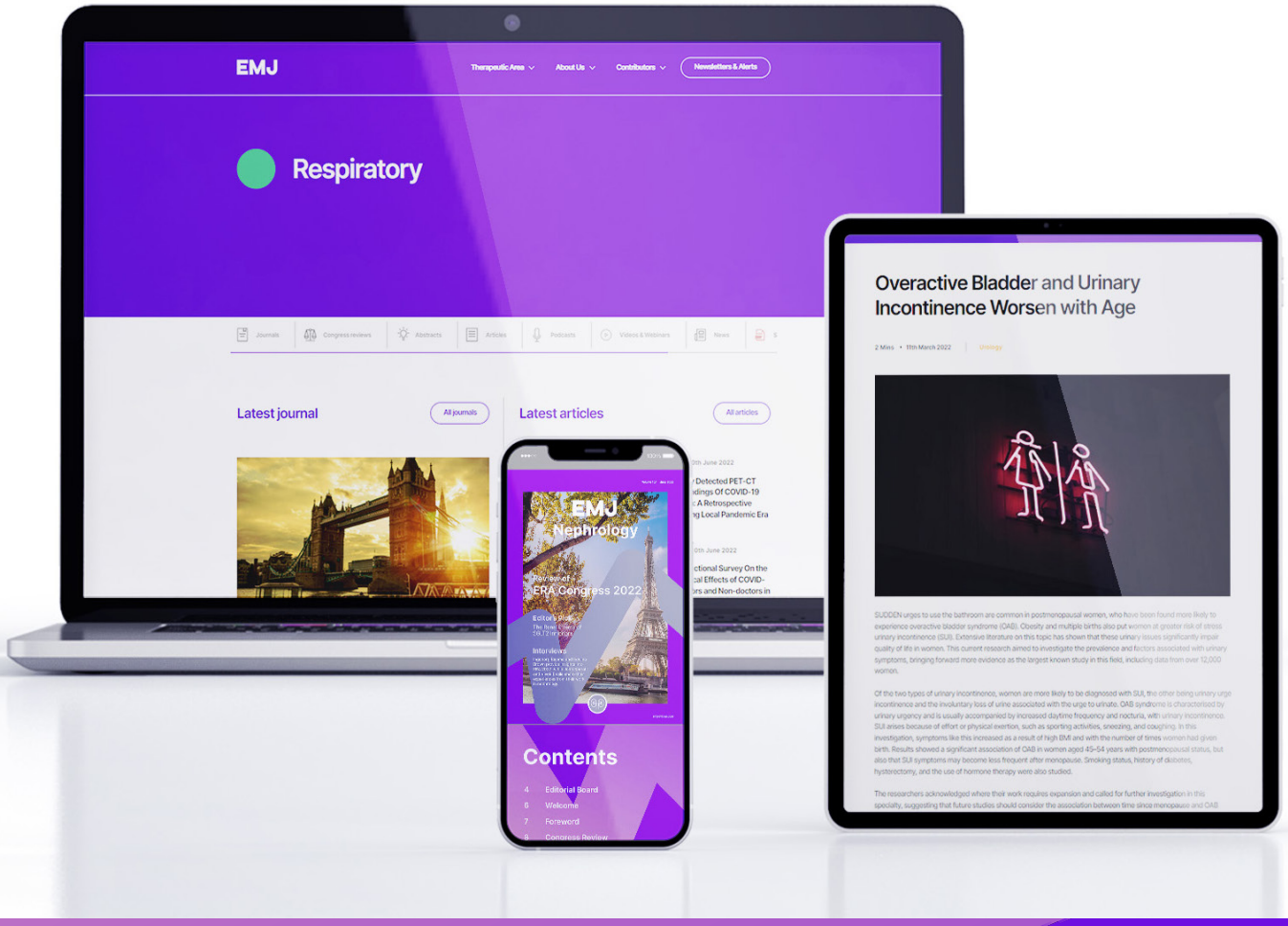

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EMJ

Foreword

Dear Colleagues,

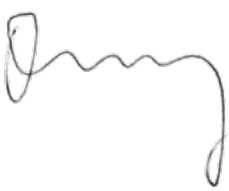
Welcome to the latest edition of our flagship journal *EMJ,* which is filled with engaging, practice-focused content from a wide range of therapeutic areas. Topics covered in this journal include bacterial antibiotic resistance in hospital settings, presentations of squamous cell carcinoma, and the relationship between chronic kidney disease (CKD) and thyroid dysfunction.

This edition of *EMJ* includes a mini-focus on geriatric medicine. Therefore, the Editor's Pick for this issue, by Bhuwania, is entitled, 'Relationships of Chronic Kidney Disease and Thyroid Dysfunction in Patients with Stage 4 and 5 Chronic Kidney Disease: A Cross-Sectional Study'. This study explores continual challenges of patients with Stage 4 and 5 CKD who are affected by thyroid problems, demonstrating the correlation of triiodothyronine, thyroxine, and thyroid-stimulating hormone with metabolic parameters of CKD; and how triiodothyronine and thyroxine syndrome progressively worsen estimated glomerular filtration rate.

This issue includes a range of fascinating case reports, including a nuanced diagnostic dilemma of distinguishing neurodegenerative disorders in older patients presenting with neuropsychiatric symptoms, and a case of severe refractory anaemia associated with *Helicobacter Pylori* infection, with authors exploring the optimal management with probiotics and haem iron supplementation.

Delving deeper into the selected mini-focus of geriatric medicine, this journal features interviews from experts in the geriatric field, Nicola Veronese and Tahir Masud. Veronese and Masud are Academic Board and Executive Council members, respectively, for the European Geriatric Medicine Society (EuGMS), and provide unrivalled insight into their careers in geriatric medicine. This journal also features an in-depth interview with Imran Admad, who provides insight into the development of high-intensity theatre lists for increasing the efficiency of urology surgery.

As always, I would like to extend my warmest thanks to all the authors, reviewers, interviewees, and Editorial Board members who have worked so tirelessly to make this edition of *EMJ* possible. I hope this journal proves to be an interesting and thought-provoking read for all healthcare professionals.

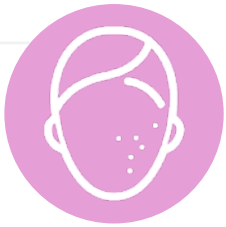


Prof László Vécsei

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

Elevating Aesthetics: Patient-Specific Treatment with Hyaluronic Acid Fillers to Improve Appearance and Psychosocial Wellbeing

This symposium took place on 26th January 2023, as part of the International Master Course on Aging Science (IMCAS) held in Paris, France



Author: Sabrina Shah-Desai,[1] Billur Sezgin,[2] Benji Dhillon,[3] Lee Walker,[4] Raymond Wu,[5] Patrick Trevidic[6]

1. Perfect Eyes Ltd., London, UK
2. Department of Plastic, Reconstructive and Aesthetic Surgery, Koç University School of Medicine, Istanbul, Türkiye
3. Define Clinic, Beaconsfield and London, UK
4. BCity Clinics, Liverpool, UK
5. Asia Pacific Aesthetic Academy, Hong Kong, China
6. Expert 2 Expert, Paris, France

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Keywords: Aesthetics, dermal filler, hyaluronic acid (HA), psychosocial wellbeing, quality of life.

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Meeting Summary

Perception of beauty is changing from a rigid concept (i.e., the universal idea of beauty) to a multifaceted and personalised view of one's appearance. One of the main concerns of patients is looking artificial and losing their unique facial expressions, which encourages them to seek aesthetic procedures that yield the most natural results. Patients also wish to increase their self-esteem and, ultimately, improve their quality of life. It is now well-established that treatment with hyaluronic acid (HA)-based dermal fillers improves the psychosocial state of patients. The assessment of facial anatomy and patient needs, accompanied by the proven holistic benefit and good safety profile of HA dermal filler treatment, is also a key factor for an optimal outcome. In addition, clear communication between patient and physician is crucial to manage patient expectations, maximise satisfaction, and minimise procedural risks. The availability of a wide range of HA dermal fillers, customised for specific anatomical areas and facial movements, allows physicians to develop patient-specific treatment plans.

This review of the 'Elevating Aesthetics' symposium held at the International Master Course on Aging Science (IMCAS) 2023 shares insights into the patient's facial

anatomy and possible danger zones presented during a cadaver workshop. Several successful treatment plans tailored to different patient profiles (i.e., patients seeking full-face aesthetic improvement, patients with facial asymmetry, low lip volume in mature and millennial women) were also implemented live. A comprehensive and patient-specific HA dermal filling treatment should be considered by physicians to achieve natural outcomes and improve the general wellbeing of the patient.

Part 1: Impact of Hyaluronic Acid Dermal Fillers on Psychosocial Wellbeing

Sabrina Shah-Desai

During the 'Elevating Aesthetics' symposium, held at IMCAS 2023 and moderated by Patrick Trevidic, Expert 2 Expert, Paris, France, Sabrina Shah-Desai, Perfect Eyes Ltd., London, UK, presented the concept of individual beauty and how aesthetic treatments are not only about vanity, but also about improving the general wellbeing of the patient.

The ideal of classical beauty is changing. In Ancient Greece, beauty was defined in terms of harmonious proportion of facial features, and the 'perfect' human face was based on Plato's system of triads.[1] Although the Greek definition is still seen as the standard, the popularity of this prototype is influenced by social trends and historical events.[2] In fact, the notion of facial beauty is expanding nowadays into many different disciplines, such as psychology, evolutionary biology, sociology, cognitive science, and neuroscience.[3-7] It has been demonstrated that cultural intra- and interpersonal differences influence attractiveness perception in different ways,[7] which renders the concept of beauty more complex, but also more fluid and subject-specific.

The gradual shift to an 'individual beauty' concept is accompanied by the current trend of subtle enhancement in facial aesthetics, with an emphasis on natural-looking outcomes, maintenance of unique facial expressions, and popularisation of minimally invasive techniques.[8] Soft-tissue fillers are the second most preferred minimally invasive treatment and HA products are currently the most used soft tissue fillers.[9] The availability of a wide range of HA dermal fillers customised for specific anatomical areas with different facial movements allows physicians to elevate their treatment plans to achieve natural facial dynamism.[10-12] Panels of experts have defined key strategies to achieve natural-looking results when injecting HA fillers: patient assessment and individualisation of treatment plan, adequate knowledge of facial anatomy, proper injection techniques, good knowledge of the rheological properties and behaviours of different HA fillers, and a conservative treatment approach.[13,14]

Patients are not only looking to improve their appearance, but also their mental and emotional health, along with social wellbeing.[15] In a survey on patient motivations to undergo cosmetic procedures, psychosocial concerns were mentioned more than other identified themes, specifically the appeal for improved confidence, feeling depressed and anxious with current appearance, and feeling consumed by efforts to conceal undesirable physical features.[16] Other studies have demonstrated significant psychological and social benefits from HA filler treatment, in addition to considerable improvements in self-perceived appearance and age.[15,17] These results confirm that benefits from HA filler injections extend beyond mere physical improvements.[17]

Part 2: Live Demonstration– Patient Empowerment After Full-Face Injection

Billur Sezgin and Benji Dhillon

From a practitioner's perspective, it is essential to clearly explain the treatment plan to the patient and reach an agreement between the physician and the patient to manage the latter's expectations, maximise satisfaction, minimise procedural risks, yield the best aesthetic outcomes, and, ultimately, improve the patient's quality of life.

Full-Face Anatomy and Danger Zones

Proper knowledge and understanding of the facial anatomy and danger zones can mitigate risks during dermal filler injections, as well as potentiate natural-looking results. Billur Sezgin, Department of Plastic, Reconstructive and Aesthetic Surgery, Koç University School of Medicine, Istanbul, Türkiye, conducted a human cadaveric dissection to outline the multi-layered facial anatomy and summarise danger zones to avoid when injecting each facial region.

Sezgin displayed the facial arrangement in several layers that can be described from superficial to deep: layer 1, skin; layer 2, subcutaneous fat; layer 3, superficial musculoaponeurotic system; layer 4, deep fat; and layer 5, bone.[18] However, this general distribution needs to be adapted to each facial region, as there are regions composed of more (e.g., temple with 10 layers) or fewer layers (e.g., tear through with three layers).[18]

The subcutaneous fat layer extends throughout the facial surface, and its thickness and presence varies across facial region. As treatment with dermal fillers increases volume of tissue, knowledge on regional thickness and distribution of the facial superficial fat is essential to determine injection depth and layer.[19] Layer 2 is segmented by fibrous septae into different compartments, which serve as sheltered transit pathways for cutaneous nerves and vessels.[20] The superficial musculoaponeurotic system layer separates the superficial and the deep fat, and creates facial expression through transmission of the muscles' contraction to the skin.[21,22] The dynamism of the connection between superficial fat pads and the underlaying muscle plane should be well understood to avoid appearance of lumps upon muscle contraction.[22] The deep fat is also divided into distinct compartments, and their outline serves as conduits for facial nerve branches and for the branches of the facial artery and vein.[20] The facial skeleton support diminishes with age as the bones recede and remodel, which leads to the inferior and medial repositioning of fat pads and muscles over the bony foundation.[23,24] As deep fat compartments seem to be relatively stable during ageing, deep filler injection in this layer and in contact with the bone provides support for the overlying structures, and increases projection.[25]

Extensive knowledge of the location and pathway of facial blood vessels in the upper, middle, and lower face is essential to minimise the risk of complications associated with vascular injuries. Sezgin continued the cadaver dissection by reminding the audience about the facial vascular anatomy.[14,26-29] Three branches of the external carotid artery provide blood supply of the facial skin: the facial artery, superficial temporal artery, and transverse facial artery, which is a branch of the superficial temporal artery.[26] Over the neck, at the premasseter ligament region, two vascular structures enter the face: the facial artery and the facial vein. One of the facial artery branches, the submandibular artery, is located underneath the mandibular border. Another branch, approximately 6 mm lateral to the midline of the chin, is the submental artery. Following the course of the main artery, the inferior labial artery is found underneath the depressor anguli oris and enters the lower lip. The facial artery continues to follow its oblique tortuous course and reaches below the zygomaticus major muscle, accompanying the nasolabial fold, where it branches into the superior labial artery at the upper lip. After arriving at the nasal base, the facial artery continues superficially along the lateral wall of the nose and ends as the angular artery. It shares multiple connections and anastomoses with the internal carotid system, as well as with the supratrochlear and supraorbital artery. The transverse facial artery is close to the parotid duct, and the superficial temporal artery is found within the superficial temporal fascia. The latter supplies the forehead, the lateral portion, and the temple region. An additional branch, the infraorbital artery, is observed middle to the pupillary line and follows its counterpart nerve.

Sezgin highlighted the importance of mastering the facial anatomy when injecting, not only to avoid vascular compromise, but also to ensure the injection is performed in the desired and correct compartments. Superficial fat compartments that enlarge with age (e.g., nasolabial fat pads, jowl fat) should be avoided. Additionally, the infraorbital superficial fat pads should also be bypassed as this region comprises a very delicate lymphatic system, and its treatment can accentuate palpebromalar bags.

Patient Assessment

Benji Dhillon, Define Clinic, Beaconsfield and London, UK, introduced their 51-year-old female

patient who saw their confidence plummet over the years after experiencing several traumatic events. The patient was unhappy with age-related changes that rendered their cheeks more prominent and gave them harsh facial features. They were also self-conscious about their lips, which impacted their behaviour during social interactions. Tooth loss on the right side of the face further contributed to the increased concavity in their mid- to lower cheek and to the asymmetry between both sides of the face. Female patients tend to experience a decreased chin projection as they get older, since their mandibles rotate inferiorly and backwards toward the skull.[18,19] This age-related transition further accentuated the patient's retrognathic chin and overbite. By undergoing HA dermal filler treatment, the patient wished to feel more confident, stronger, and empowered.

Patient-Specific Full-Face Treatment

Temple

Dhillon injected the highly spreadable Teosyal RHA 1 (Teoxane, Geneva, Switzerland) at the temple region, into the inter-fascial plane. A product with high stretch was used since the deficiency of volume in this area was non-significant, and the treatment objective was only to improve the transition from the forehead towards the temple.[30,31] As the superficial temporal artery accompanies the hairline, a more posterior deposit of filler should be avoided. To treat the roof of the brow, Dhillon adjusted the depth of the cannula towards the deep fat compartment and injected small amounts of product moving towards the lateral canthus, at the lateral orbital rim, while avoiding the infraorbital superficial fat compartment. Treatment details are described in Figure 1.

Midface

Teosyal RHA 4 (Teoxane) was chosen for the cheekbone injection, a versatile volumiser with very high strength and good stretch, since the patient did not require a large volumisation in this region (Figure 1).[30,32] A small bolus was injected supraperiosteally with a cannula in the medial suborbicularis oculi fat compartment, entering from the zygoma. The same entry point was used to treat the superficial fat pad where a long thread of filler was injected, retrograding towards the entry point. At this stage, the patient showed inexistence of lumps and bumps, as well as animation deformities. Dhillon reminded the audience to avoid the infraorbital fat compartment when injecting this region as it has a rich lymphatic plexus, and also enlarges with time.

Tear trough

The tear trough was treated with Teosyal PureSense Redensity 2 (Teoxane; Figure 1). Its low hygroscopy and high spreadability are adapted for the correction of under-eye circles.[33,34] Using the same entry point as for the cheekbones, micro threads of product were injected supraperiosteally with a cannula while performing a fanning technique.

Mid- to lower face

Treatment of the inferior portion of the middle and lateral cheek fat compartment is normally avoided due to its closeness to the nasolabial and jowl fat compartments. However, treating this region could improve the patient's hollowing caused by missing teeth. Teosyal RHA 4 was injected with a cannula towards the medial cheek, at a superficial plane (Figure 1). Threads of product were deposited retrogradely to restore the transition to the lower face and soften patient features. A posterior tunnel from the previous entry point was created to minimise pain and bruising during the posterior injection. After treating the lateral fat compartments, threads of product were injected above the zygomatic arch to improve the mid-cheek to lower face transition.

Chin

The pogonion was treated with the highly cohesive and resistant to compression Teosyal PureSense Ultra Deep (Teoxane [Teoxane, unpublished data]; Figure 1), which is designed to provide deep structural support and maximum lifting capacity.[34] It was injected supraperiosteally with a needle to attenuate the patient's retrognathic chin and improve their facial profile.

Labiomental crease

Teosyal RHA 4 was injected with a cannula into the subcutaneous plane using a micro-fanning technique to decrease the shadowing observed in their lower face. Dhillon reinforced the flexible strategy of assessing the aimed outcome and adapting the treatment during injection, instead of rigorously following the planned injection volumes.

Figure 1: Full-face treatment of a mature female patient with low self-confidence.

C

	RHA 1	RHA 2	RHA 3	RHA 4				Ultra deep	Redensity 2
Treated indication	Temple/brow	*Lips/oral commissure	Marionette lines/oral commissure	Cheekbone	Cheek	Labiomental crease	*Jawline	Chin	Tear trough
Needle/ cannula	25-gauge 38 mm cannula	32-gauge 9 mm needle	Marionette lines: 25-gauge 38 mm cannula Oral commissure: 30-gauge 13 mm needle	25-gauge 50 mm cannula		25-gauge 38 mm cannula	25-gauge 50 mm cannula	27-gauge 13 mm needle	25-gauge 50 mm cannula
Injection	Temple: interfascial Brow: deep fat compartment	Mucosa	Marionette lines: superficial fat Oral commissure: subcutaneous	Supraperiosteal injection into the medial SOOF; superficial fat pad	Superficial injection into the lateral and medial cheek	Subcutaneous	Superficial fat	Supraperiosteal	Supraperiosteal
Volume	0.50 mL per side	Lips: 0.40 mL Oral commissure (right): 0.10 mL	Marionette lines: 0.50 mL per side Oral commissure: 0.15 mL per side	Supraperiosteal: 0.20 mL per side Superficial fat: 0.30 mL per side	Right side: 0.50 mL medial; 0.20 mL lateral Left side: 0.40 mL medial; 0.10 mL lateral	0.80 mL	Left side: 0.80 mL Right side: 0.90 mL	0.25 mL per side	0.30 mL per side

A) Front facing and **B)** profile before and after photographs of a mature female patient with low self-confidence, who received full-face treatment with TEOSYAL (Teoxane, Geneva, Switzerland) fillers. **C)** Treatment summary.

*Lip and jawline treatment was not demonstrated live.

Marionette line and oral commissure

A strong and highly stretchy product (Teosyal RHA 3 [Teoxane]) was used to guarantee the dynamic volumisation of the marionette lines.[30,35] The techniques applied to treat this region should respect the correct placement of the filler to avoid weighing down a superficial fat compartment. Treatment injection was performed medial to the mandibular ligament, progressing up towards the oral commissure, and depositing long and short threads of product retrogradely with a cannula. Dhillon superficially injected a small bolus of Teosyal RHA 3 in the oral commissure using a needle. Lastly, they injected the inferior vermillion border close to the oral commissure, acknowledging the position of the inferior labial artery, which enters the lip medial to the injection site.

Before and after photos can be seen in Figure 1, with visible improvement of the anterior midface projection, decreased infraorbital hollowing, and improvement of their middle to lower face transition and profile.

Patient satisfaction after 1 month of treatment

The patient was requested to answer a short survey 1 month after treatment, which combined questions on injection experience, impact of HA fillers on quality of life, and overall treatment satisfaction. They experienced no pain during injection. Although their improvement in self-esteem has been gradual, they felt more comfortable during social interactions, and more inclined to look at their own reflection. They also declared feeling more confident, beautiful, and

empowered while still looking like themself and maintaining their defining facial features.

Part 3: Patient-Tailored Lip Treatment

Lee Walker

Lee Walker, BCity Clinics, Liverpool, UK, kickstarted this session by accentuating how lip treatments can visually impact facial aesthetics. The lips are an essential component of the symmetry and aesthetics of the face,[36] with full lips being historically associated with female youth, beauty, and voluptuousness.[37] The perioral tissues increasingly deteriorate with age.[38] Prominent signs of labial ageing include the lengthening of the cutaneous upper lip, development of rhytids, collapse of the oral commissures, inversion of the red vermillion, drooping mouth corners, and flattening of cupid's bow and philtrum columns.[39]

Lip augmentation procedures are increasingly popular, with nearly 2.6 million injections (e.g., soft tissue fillers) performed in 2018, and a total increase of 312% between 2000 and 2017.[9] According to Walker's clinical experience, lip treatments are even the most requested dermal filler procedures. Once again, most of the patients (73%) requesting dermal fillers wish to achieve natural and healthy-looking lips. Nonetheless, a natural look requires a thorough knowledge of the perioral anatomy, the range of products that better suit this region, and technique.[37] The main goal when treating this area is to create a shape that aesthetically harmonises with the patient's unique facial features, and considers their age and ethnic background.[37]

Live Demonstration: Patient Self-Confidence After Lip Treatment

Raymond Wu and Patrick Trevidic

Mature lip

Raymond Wu, Asia Pacific Aesthetic Academy, Hong Kong, China, continued the session by treating a 59-year-old female patient with age-related loss of lip volume. The patient acknowledged an offset between their sportive physique and their thin lips, which made them look older than they felt. They wished to improve the appearance of their smile and lips and regain their self-confidence.

Assessment of the patient anatomy revealed an obvious depletion of the upper and lower lip volume, as well as downturned mouth corners. They lost all their upper teeth and wore a dental prosthetic. Shortening of the lower third of the face, deeper wrinkles, and prolapse of the labial commissure are examples of facial soft tissue collapse in subjects with edentulism.[40] Wu emphasised the importance of assessing the perioral area in a mature lip, such as the existence of barcode lines.

Wu started the treatment with an HA filler (TEOSYAL RHA 3) combining high strength and good stretch, which ensures dynamic lip volumisation. With a cannula, they entered the corner of the oral commissure and injected the subcutaneous plane of the lip with small droplets of product to anaesthetise the region. Afterwards, the treatment injection was performed very slowly but dynamically (i.e., back and forth movements) to avoid any vascular compromise.

To provide more definition to the vermillion border and cupid's bow, Wu used a needle to inject superficially and retrogradely the vermillion border from the corner of the mouth, at two different entry points. Subsequently, they treated the cupid's bow by applying a mini fanning technique at the midline to achieve more natural results in the upper lip. The product of choice was an HA dermal filler with high stretch and moderate strength (TEOSYAL RHA 2 [Teoxane]), which allows dynamic lip reshaping.[30,41] Lastly, two boluses were injected in the vermillion border, at each side of the lower lip, to improve contouring.

A product with very high stretch (TEOSYAL RHA 1) that adapts uniformly to superficial dynamic wrinkles was applied to the perioral lines. Small boluses of product were placed laterally and intradermally with a needle to improve barcode lines, but also the skin quality of this region.

Wu manoeuvred through a wide range of products that can be used in several indications of the perioral region. The treatment yielded a visible improvement of perioral rhytids, lip

volume, and contour, while retaining an age-appropriate outcome (Figure 2).

One month after treatment, the patient described no pain during injection and no evident bruising or swelling. The treatment was unnoticed by their acquaintances, which supports the natural outcome of HA filler treatment. Dermal filler injections improved their appearance, boosted their self-confidence, and led them to elevate their posture during social interactions. Overall, this procedure evidently improved the patient's quality of life.

Millennial lip

Trevidic introduced a 23-year-old female patient who demonstrated volume imbalance between the upper and lower lip, with the upper lip being much thinner than its counterpart. They have been mocked because of the lack of upper lip volume, which took a toll on their self-esteem. For this patient, conservative dermal filler treatment could change the way others perceive their appearance and, most importantly, it could boost their self-confidence and complement their already radiant personality.

In conjunction with the low upper lip volume, Trevidic identified an asymmetry between the left side and the right side of the upper lip, with the latter showing less volume. As the cupid's bow and the vermillion border were well defined in this patient, Trevidic reinforced two important points to be considered when defining this patient's treatment plan: maintain the balance of the upper and lower lip and avoid over-volumising the lips. Treatment details are described in Figure 3.

The injection was performed with the dynamic filler TEOSYAL RHA 3. Entering the cupid's bow in the vermillion border, small amounts of product were injected slowly with a needle in the mucosa to allow the lidocaine to anaesthetise the region before volumisation injection. Trevidic emphasised the dangers of injecting the submucosa. Injections should be less than 3 mm deep, with an intermediate or low-G filler, at the vermillion cutaneous border or within the red dry vermillion.[42] Using the same anaesthesia entry point, Trevidic injected the submucosa horizontally and in a retrograde manner. They then used a second entry point oblique to the first to further volumise the lips.

With conservative amounts of product, the patient's lips were volumised to a natural-looking degree and the asymmetry between the right and left upper lip was corrected (Figure 3).

On their 1-month post-congress testimonial, the patient described having barely any bruising and that the swelling disappeared after a couple

Figure 2: Lip treatment of a mature female patient.

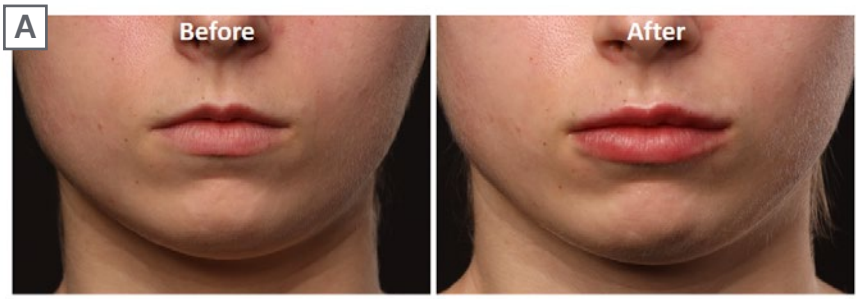
C

	RHA 1	RHA 2	RHA 3
Treated indication	Perioral lines/smiling lines	Vermilion border/cupid's bow/lower lip	Upper/Lower lip
Needle/ cannula	30-gauge 13 mm needle		25-gauge 38 mm cannula
Injection	Intradermal	Subcutaneous	Subcutaneous
Volume	0.20 mL per side 0.80 mL total	Vermilion border upper: 0.10 mL Vermilion border lower: 0.10 mL Cupid's bow: 0.01 mL Lower lip: 0.20 mL	Upper lip: 0.30 mL left side; 0.40 mL for the right side Lower lip: 0.30 mL per side

A) Front facing and **B)** profile before and after photographs of a mature female patient who received lip treatment with TEOSYAL (Teoxane, Geneva, Switzerland) fillers.
C) Treatment summary.

Figure 3: Lip treatment of a millennial female patient.

A



B

	RHA 3
Treated indication	Upper/lower lip
Needle/ cannula	30-gauge needle
Injection	Submucosal
Volume	Upper lip: 0.30 mL left side; 0.40 mL for the right side Lower lip: 0.15 mL per side

A) Before and after photographs of a millennial female patient who received lip treatment with TEOSYAL (Teoxane, Geneva, Switzerland) fillers. **B)** Treatment summary.

of days. The treatment outcome was natural and aesthetically pleasing, while maintaining lip mobility and facial expressions. It also enabled them to behave comfortably and confidently during social interactions. The patient was fulfilled with the treatment plan adapted to their concerns and expectations, and would recommend it to anyone with self-confidence issues.

Conclusion

Beauty perception is evolving from an ancient, rigid, and 'universal' perspective to a multidisciplinary and individualised concept. No matter the indication, patients seek subtle facial enhancement procedures that yield natural-looking outcomes in harmony with their unique facial expressions but, most importantly, treatments that will ultimately improve their psychosocial well-being. Extensive evidence has demonstrated the positive impact of HA dermal fillers on the patient's quality of life. The holistic benefit and safety of these products, coupled with comprehensive and patient-specific treatment plans, should be considered by physicians to achieve natural outcomes, and improve the general wellbeing of the patient.

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Interviews

Nicola Veronese and Tahir Masud sat down with EMJ to delve into their individual careers in geriatric medicine. The interviews focus on the nuances of the specialism and key issues to be addressed in the future. Imran Ahmad provides insight into how he developed high-intensity theatre lists to increase the efficiency of urological surgery.

Featuring: Nicola Veronese, Tahur Masud, and Imran Ahmad.

Nicola Veronese

Senior Researcher, Geriatrics and Internal Medicine, University of Palermo, Italy; Member of the Academic Board of the European Geriatric Medicine Society (EuGMS) 2022–2023; Member of the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis, and Musculoskeletal Diseases (ESCEO) Board

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Q1 You are a renowned expert in many aspects of geriatric medicine, including osteoporosis, sarcopenia, and frailty. What initially led you towards this specialty?

Initially, I was student in endocrinology; however, after some years, I understood that the holistic approach to complex patients such as older individuals was more adapted to my attitude. I believe that the geriatrician has the privilege to face important non-medical aspects such as end-of-life issues or social isolation, and needs to have the competencies to face these aspects. Today, several younger colleagues feel that geriatric medicine is somewhat less important than other medical specialties, but I hope that they will change their mind, since having prepared geriatricians is of critical importance.

Q2 Can you talk about some of the unique challenges that doctors face when working in the geriatrics specialty?

Geriatricians have several unique challenges. The most important one is that medications traditionally used in adults were not experimented in older people; therefore, having the capacity to adapt medications in terms of dosages and indications is an important challenge. Another important daily clinical practice challenge is the approach to nutritional issues, in particular those related to artificial nutrition, which includes not only clinical problems, but also ethical issues. A final relevant challenge is facing the medical and non-medical problems of patients that are often unable to communicate their symptoms. Therefore, the geriatrician should be prepared as a specialist in internal medicine, while also having competencies such as comprehensive geriatric assessment.

Q3 Can you tell our readers about some of the key conclusions that you and your co-authors found in your 2022 article, 'Healthy Aging and Dietary Patterns'?

Increasing research is showing the importance of geriatric medicine not only for the treatment of the complex older patient, but also for the primary prevention of medical conditions typical of older age such as cancer and cardiovascular diseases. In this regard, our article reports that dietary factors may influence specific pathways regulating the aging process and the extension of life, which makes longevity a multidimensional process. Recently, dietary patterns have increased in importance in nutritional epidemiology, since we have observed a multifaceted, synergistic interplay among nutrients, other dietary constituents, and whole foods. In this article, we described some specific dietary patterns such as the Mediterranean diet, with evidence of associations with reduction in the incidence of chronic diseases, allowing older adults to live not only longer, but also healthier.

Q4 One of the lasting impacts of the pandemic has been the remaining effects of long-COVID in the population. Can you speak to the specific impact that long-COVID has had upon the geriatric community?

We have recently reported in a large systematic review and meta-analysis that long-COVID can affect approximately one in two people, after several months of follow-up, and that the therapeutic options are really limited. These findings, in my opinion, clearly indicate that long-COVID is a public health priority. In older people, we have observed a dramatical decrease in several domains and, in particular, in cognitive and functional aspects. Often, older people with long-COVID have important memory issues and respiratory problems that can lead to disability. Finally, another undervalued problem is the importance of mood disorders in older people after having COVID-19.

Q5 Can you tell our readers about the importance of vaccination in the elderly?

Several medical conditions typical of older people, such as dementia, are not preventable. Therefore, having weapons such as vaccinations, that can avoid the onset of infectious diseases, is of importance for geriatricians. Moreover, vaccinations may have further pleiotropic effects. For example, we have increasing evidence that vaccination against flu is able to decrease the incidence of dementia or other cognitive disorders. Most importantly, geriatricians should feel comfortable in indicating vaccinations, but some education is still needed.

Q6 You are currently a member of the Academic Board of the European Geriatric Medicine Society (EuGMS). Can you give us any insight into areas of focus for the society currently and looking forward?

I am extremely honoured and proud to be part of the Academic Board of the EuGMS, a society that faces the problems of geriatricians and older people. At the moment, among all the projects that we are leading, we are preparing some guidelines regarding the importance of physical activity and exercise in mild cognitive impairment and dementia, covering this topic from prevention to treatment. Of course, several other important projects are ongoing, including European projects in which EuGMS has the role of coordination and development.

Q7 Can you talk about any significant changes you have seen in the field of geriatric medicine in your time practicing in the specialty?

It is very hard to answer to this question. I believe that, unfortunately, very little was done for older people in terms of changes and improvements. The problems that we have today are very similar to those that were present several years ago.

"The geriatrician has the privilege to face important non-medical aspects such as end-of-life issues or social isolation."

Maybe, from a geriatric perspective, one of the most interesting changes is the safe use of some anti-diabetic medications in frailer patients. More should be done in several aspects of importance in geriatrics such as dementia, frailty, and sarcopenia, for which the current therapy is still limited to a few options.

Q8 How have you seen the advent of new technologies impact the field of geriatrics in recent years?

The COVID-19 pandemic has indicated the importance of new technologies in facing the problems of older people better. For example, the use of telemedicine is of importance, since it could permit patients to have a medical and non-medical assistance, even in case of social isolation. I hope that in the near future we will have a better integration of technologies, particularly those inherent to the communication of different systems such as administrative data, medical records, and insurance information.

"More should be done in several aspects of importance in geriatrics such as dementia, frailty, and sarcopenia."

Q9 As a researcher, educator, and physician, where can we see your focus lying in the coming years?

Actually, when we think about geriatricians, we think about a physician dedicated to disability and its consequences such as bedridden syndrome. I sincerely believe that in the coming years geriatricians will have an important role in prevention and in public health themes. Moreover, another important topic of the future is to integrate the work of geriatricians in primary care, an important setting that often requires specialist competencies.

Tahir Masud

Consultant Physician in Geriatric and General Medicine, Nottingham University Hospitals NHS Trust, UK; Secretary of the Clinical Section of the International Association of Geriatrics and Gerontology (IAGG)-European Region; Member of the Executive Council of the European Geriatric Medicine Society (EuGMS); Former President of the British Geriatrics Society (BGS); Former President of the European Union of Medical Specialists (UEMS)-Geriatric Medicine Section

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Q1 When did you first decide on your specialism of geriatric medicine, and what sparked your interest in this area of medicine?

I was inspired to go into geriatric medicine in the late 1980s and early 1990s, when I was a registrar in medicine in Newcastle, UK. I worked with some truly inspirational geriatricians at the time, which I think was a major factor in my decision. What I liked about geriatric medicine was the holistic and multidisciplinary approach to older people. I really enjoyed working in a close team of different healthcare professionals, and I can't underemphasise the role played by the people that you work for, who inspire you.

Q2 Do you think that there are any misconceptions about geriatric medicine?

I think many people still believe that a lot of the conditions that occur in older people are due to ageing, and that we can't do too much about them. However, nothing could be further away from the truth. Let's take falls as an example. When we look at the risk factors which might contribute to an older person falling, we find that often there is something we can do to address many of them, allowing us to start a programme of management or treatment that can help to prevent further falls. That's just an example of misconceptions that people have.

Q3 You have previously mentioned that education surrounding geriatric medicine can be nuanced and challenging. Can you explain why this is the case?

Geriatric medicine overlaps with all other medical fields, and in effect, we're really the only old-style general physicians left, alongside maybe the specialty of acute medicine. The nuances are that we really need to think about not only the physical aspects of health in older people, but also the psychological and social aspects of the older person, as well as considering their frailty status, which often determines how we're going to manage them. I think these are some of the nuances which we need to improve upon.

> "What I liked about geriatric medicine was the holistic and multidisciplinary approach to older people."

Q4 In your 2022 article, 'The giants of education in geriatric medicine and gerontology', you highlight the need for wider knowledge of gerontology in both patients and the public. Can you explain some of the key gaps you see in geriatric knowledge?

Given the demographic trends and the ageing population, geriatricians will not have the capacity to look after everyone, due to the growing size of this age group. You would need a vast increase in geriatric specialists, which I don't think is realistic. We do need to increase the

number of geriatricians, but more importantly, we need to educate and train our colleagues in other specialties. And that's a challenge. Bernard Isaacs coined the so-called 'geriatric giants', or the four 'I's: intellectual impairment, incontinence, immobility, and instability. In the article, my colleagues and I fashioned four 'I's in other areas. For example, in education, we have investment, inspiration, integration, and interprofessionality; and in research, there is interest, income, innovation, and impact. I think these are some of the gaps in trying to improve healthcare for older people which we need to work more on.

Q5 You contributed to 'World guidelines for falls prevention and management for older adults: a global initiative' in 2022. Can you enlighten our readers about some of the key recommendations you and your colleagues concluded?

Falls have a major impact on older people across the world. We put these guidelines together because there was inconsistency in approaches across different countries. We thought it was important to try and harmonise this approach, recognising that we still must consider differences in healthcare and socio-economic level. But this was a mammoth project, with 96 world experts from 39 countries. There were 12 working groups looking at different aspects of falls, with one working group looking at patient perspective, which were not considered by previous falls guidelines. Another patient-focused working group made sure that other working groups would be relevant to what the needs were. Some of the themes were the problems caused by polypharmacy, where people are having side effects from taking too many medications; this can cause falls. We then came out with some recommendations regarding how we should think about this issue, and how we should think about deprescribing some of the more harmful medications, which might contribute to the falls. Another example was the importance of exercise. One working group looked closely at the benefits of exercise in reducing falls, and outlined what type of exercises are important for older people. Another working group looked at how we could reduce falls in care homes and hospitals. These are just a few examples of important issues that merit more attention.

Q6 You are a member of, and have been associated with, multiple congresses focusing on geriatric medicine, including a term as President of the British Geriatrics Society and a role on the Executive Council of the European Geriatric Medicine Society (EuGMS). What impact do you believe that membership with these societies has, both directly on physicians and indirectly on patients?

It has an important role, as it allows us to learn from each other. There are lots of innovations going on in different parts of Europe, and the world. One of the greatest methods to keep up to date with these developments is to go to congresses, meet people from other areas and other countries, see what they're doing, and try to apply it in your own country. As an example, there's a lot of development in technology, and how that might be useful in treating older people; we have some interesting data from Denmark and the Netherlands looking at this. Likewise, there are some innovations in the UK on frailty and assessing frailty through electronic databases, which could be very useful in other countries.

Q7 Sarcopenia is one of the most common geriatric diseases. Have you seen much improvement in its treatment over the last few years?

I think this is an area of ongoing research and development. We are beginning to recognise sarcopenia better, and it's got an International Classification of Diseases (ICD) code now, which is helpful. However, we still have a long way to go in terms of treating and preventing sarcopenia. We know that resistant exercise is probably the most effective intervention, but there is also a lot of research going on with proteins. Some of these research findings are positive, some are not, and some are contradictory, so there's still work to do in that area. We are also learning a lot about deconditioning, so we now know that it doesn't take very long to be in hospital and bedbound to develop sarcopenia and become deconditioned. We really need to try and prevent this by getting patients out of bed as soon as possible. Innovative research trials in Denmark are looking at robots who try to prevent deconditioning and sarcopenia in

older people. We are also learning about the concept of acute sarcopenia; it doesn't take very long after an operation to start developing sarcopenia. A great development in this field has been trying to standardise the definition. There are many different definitions, so a European group has been researching this, and they have developed guidelines on how to diagnose sarcopenia. There is also an initiative to develop global guidelines on sarcopenia, which would be very useful.

Q8 Over the years that you have been practicing in the field of geriatrics, how have you seen the specialty change?

I've seen it change a lot, actually. When I first started in geriatric medicine, it had just come out of the era where geriatrics was considered a bit of a 'Cinderella speciality', a U.K term for an under-appreciated, under-funded, and underdiscussed speciality, but this has changed a lot. Geriatric medicine is now one of the more popular specialties that young junior doctors want to get trained in. I think is a testament to the geriatricians who really brought the field forward over the last few decades. Another great change has been that geriatricians are beginning to sub-specialise into different areas in treating older people. As well as having general geriatric specialists, we now have surgical liaison specialists, geriatricians with an interest in movement disorders or rehabilitation geriatrics, community geriatrics, and even onco-geriatrics. These are just some examples of how we've become much more diversified, and that I think this is very exciting going forward.

> "We are beginning to recognise sarcopenia better."

Q9 What are some points of emphasis you incorporate into practice to be the best physician in geriatric medicine you can be?

I've always felt that in my position it is very important to be a good role model for trainees and colleagues. When I have trainees with me, I try my best to make sure that they see that. I also try to treat my patients with the highest dignity and respect, giving them time, and not just to thinking of their physical illness, but also the psychological, social, and functional impact. If you can put all those things together, I think you can be a good role model, and hopefully the trainees will be inspired by that.

Q10 Are there any innovations on the horizon in the field of geriatric medicine that you think are particularly noteworthy?

The implementation of technology could be very useful in geriatrics going forward. In Denmark, they are doing some great work with 'hospital at home' schemes, where technology can help to prevent admissions to hospital. When older people come into hospital, they come to get better, but quite often they can also come to harm. Treating them at home requires technology; for example, to assess blood pressure, heart rate, and oxygen saturations. These systems are now being developed and trialled to see if they can prevent admission, or allow earlier discharge from hospital.

We also learnt a lot about virtual consultations during the COVID-19 pandemic. Sometimes it may not be necessary for the older person to come into hospital for every visit, and some of the consultations could potentially be done virtually. Another example is that there's a group in Nottingham, UK, who are looking at putting fibre optics into socks to measure oxygen saturations, heart rate, and blood pressure. People can then wear the socks and send signals to a central hub from their home. There are some exciting developments going on, and it will be incredibly interesting to see what the field looks like in 10–20 years.

Imran Ahmad

Consultant Anaesthetist and Deputy Clinical Director for Theatres, Anaesthetics and Peri-operative Medicine, Guy's and St Thomas' NHS Foundation Trust, UK; President, Difficult Airway Society (DAS); Honorary Clinical Lecturer, King's College London, UK

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Q1 Since your appointment at Guy's and St Thomas' Hospital, what has been your proudest achievement?

First of all was being appointed in the first place. I did all my training in Oxford, being from London originally, and I wanted to work in a major London teaching hospital. Having a lot of connections and contacts within Guy's and St Thomas', it was always somewhere that I really wanted to work. I tried as an A&E doctor many years ago, but wasn't offered a post; however, after I finished my anaesthetic training, the first place I tried to work was Guy's and St Thomas'. When applying for a consultant job, the interview needs to be within 6 months of your certificate of completion of training date, and I realised very late on that I was actually eligible for the job advertised. Honestly, I was so happy and proud to be offered a job there.

While I've been here, I have increased my roles and responsibilities. The biggest involvement I have now is with difficult airway management, becoming the lead, and training about 30 consultants over 12 years to become experts. We are now recognised as one of the best training centres in the world. I'm also the President of the DAS on the back of this; we have quite a large presence and write national guidelines.

Finally, I think it's the work I've done as a Deputy Clinical Director. During the first wave of the pandemic, I helped set up the intubation and medical emergency response incident teams (MERIT) to manage critical care. We progressed to developing the high-intensity theatre (HIT) lists. This has been a really big achievement because it's something that has not only done well locally, but regionally, and we are now looking at it hopefully becoming a national program.

Q2 What was the goal you set out to achieve when you designed the HIT lists? Is it true the idea was inspired by Formula 1 motor-racing pit stops?

It all started with me thinking about it on my bike on a Saturday morning in February 2022. When you think about elite teams, they are very good at doing what they do very quickly and efficiently, and the best example I can give is a Formula 1 pit crew. By chance, I have actually anaesthetised quite a few crew members over the years with their injuries, working with a surgeon they go to, and speaking to quite a few of them. They have a team of individuals who work well as a team by being very good individually, and then practising so they are also very good collectively. We used this as the basis of our intubation teams, trying to get the best people managing the sickest patients, where quite often it can be the trainees on the front line.

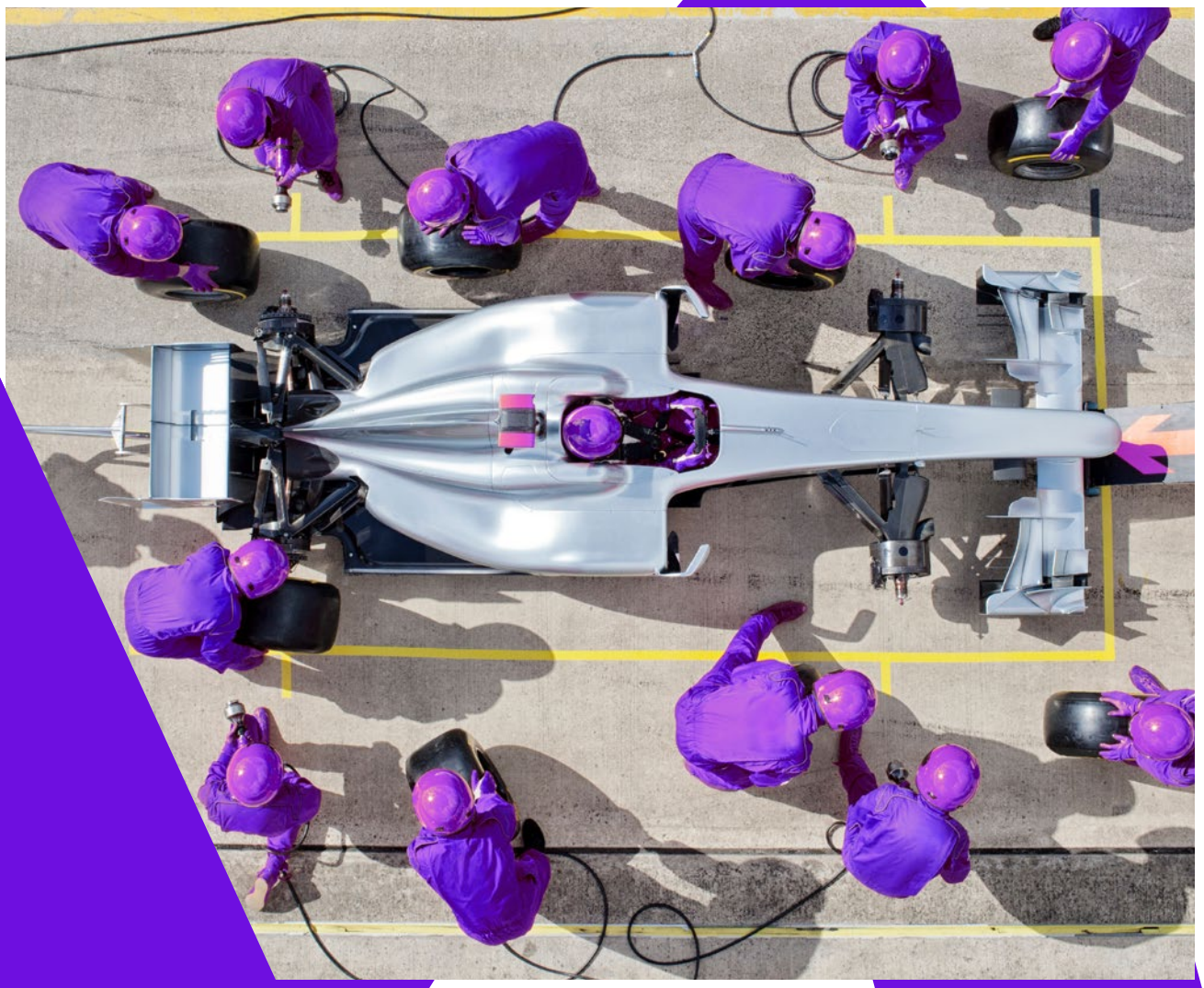
"When you think about elite teams, they are very good at doing what they do very quickly and efficiently, and the best example I can give is a Formula 1 pit crew."

At the time, we didn't know about personal protective equipment (PPE), and about the risk to healthcare workers themselves, but the teams were brilliant; we saved many lives, especially because of where we are geographically, as we received so many patients at the beginning. Using the same principle, I thought, "Why can't we do the same thing with the next problem?", which is surgical backlog and theatre lists. "Why can't we create teams that deal with the backlog of a specific problem very efficiently?"

Focusing on a specialty, urology, for example, you get all the individuals together, making sure everyone knows their roles with multiple planning meetings. Then running the HIT list itself, which is an execution of all our planning and preparation. The other analogy we use is a football team; you see them playing a match for 90 minutes, and you see the end result. But actually, there's training, tactics, discussion, and so much other preparation work happening in the background which we don't see, all done to deliver on the day.

Q3 What are some of the challenges you have encountered and had to overcome in rolling out the HIT list initiative? Are there any exclusive to urological procedures?

The biggest challenge is that you're working in a different way to convention. Normally, you have an operating list and a theatre team; the patients are allocated; you see the patients on the list; and then you go home. This is a completely different but efficient way of working; you involve everybody that contributes to a patient's pathway regularly and meet to plan a list, using more staff than normal, and more theatres.



Any time you want to change culture within the NHS, it's a real challenge. When I first came up with the idea, I had to really convince people that this was the right thing to do, and that it was something that would work. The biggest challenge was to get it started, and then to overcome sceptics in the form of managers, surgeons, anaesthetists and nursing teams. A lot of people thought, "this is never going to work", or "it's not safe", or "it's too expensive".

But the more we have done, the more the remit has expanded. At first, it was going to be quick, high-turnaround cases like cystoscopies and circumcisions, where you can do 20 or 30 cases in a day. But, as time has gone on, we have expanded to more complex, longer operations, like robotic prostatectomy and Aquablation therapy. The more we have done, the more other surgeons have seen this and said, "If you can do it for them, can you do it for us?" Off the back of our urology HIT list, I've had a head and neck surgeon approach me, so now we are planning one involving cochlear implants.

So, from quick and easy hernias and circumcisions, we have now progressed to doing those, as well as more complicated operations. Trying to roll things out and scale things up is our next challenge.

> **"The biggest challenge is that you're working in a different way to convention."**

Q4 How do you see practice changing specifically for urologists in the near future? Should they expect to become more and more familiar with overlapping surgeries?

One thing to note is that overlapping surgery is not a new concept. I'm not saying we've invented something new, it's just that we do it very differently. I think it's absolutely possible that this could become business as usual.

In terms of changing practice, when there is a HIT list scheduled, surgeons have begun allocating patients specifically to this ahead of time. The HIT lists are performed on top of what is already happening in a usual week for a surgeon. This might shift a month's worth of operating to 1 day. Once a HIT list is scheduled, in 6 weeks, for example, surgeons can begin to allocate patients to this. Or, if they have a large waiting list, they will carry on with their weekly work and take out 20 or 30 patients in one go.

So there are multiple ways to utilise HIT lists, and I do think it will change practice if we can incorporate them as a more regular occurrence. We are hoping to do these more regularly in high-volume, low-complexity centres being built in Lewisham, in the UK. We're working towards conducting a week's worth of HIT lists, covering a month's worth of operating, on top of what is already happening.

Q5 Procedures like robot-assisted prostatectomies currently have long waiting lists. Does the use of innovative technology in surgery and artificial intelligence (AI) in research complement the enrolment of HIT lists? If so, how?

What's interesting is, if you look at the average console time surgeons spend conducting surgery, say a robotic prostatectomy, its normally up to 2 hours. Looking at the data from our recent HIT list with similar cases, the console time was exactly the same, between 90–120 minutes. The only difference was that we managed to eliminate all the other times to zero; the operative time itself is exactly the same, there is no additional stress on the surgeons, and a procedure still takes as long as it takes.

Can technology help with this? Absolutely. In terms of planning, AI can be used to select the right patients, and have them pre-assessed remotely. On the day, technology can be harnessed to help things run smoothly, and then post-operatively too, in terms of collecting data and analysing this to help us improve our processes. Doing this across multiple hospitals and multiple sites allows improvement and learning from each other through comparison of this data; for example, why turnaround times for certain cases were longer.

The Backbone of Mobility: Interconnected Musculoskeletal Health

The publication of this infographic was supported by Nestlé Health Science. EMJ. 2023;8[2]:28-29. DOI/10.33590/emj/10306291. https://doi.org/10.33590/emj/10306291.

Infographic

MOBILITY ISSUES ARE AN INCREASING CHALLENGE AND A GLOBAL PUBLIC HEALTH CONCERN

1.71 billion people have musculoskeletal conditions worldwide

- Leading contributor to global disability
- Significantly limits mobility and dexterity reducing QoL and ability to participate in society

Due to our ageing population the number of people living with musculoskeletal functional limitations is rapidly increasing

>1 in 4 adults do not meet the global recommended levels of physical activity, with even greater prevalence in higher income countries

Those who are insufficiently active have

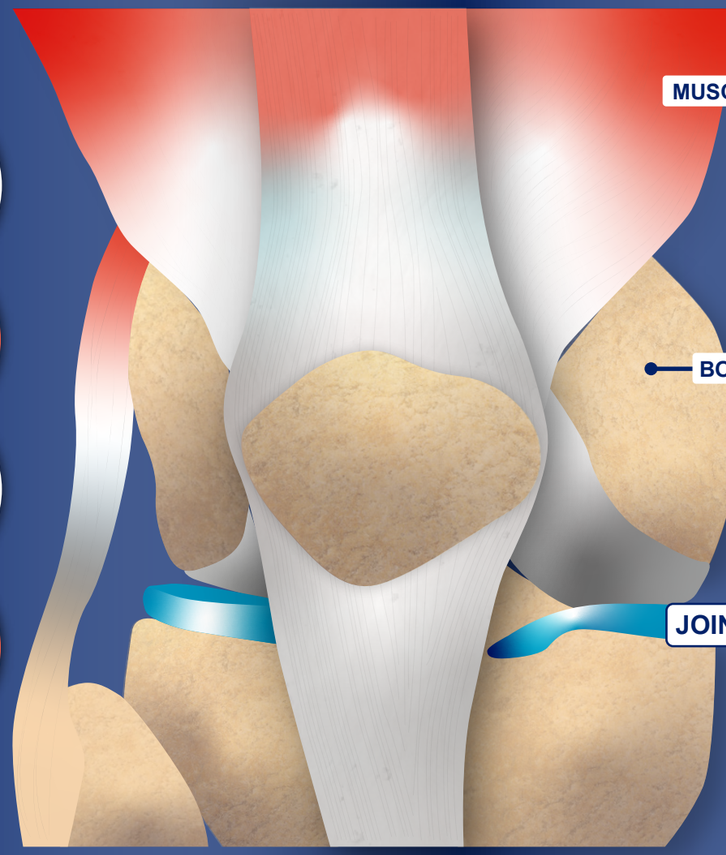
20%–30%

increased risk of death

IMPROVING MOBILITY DURING AGEING THROUGH EVIDENCE-BASED COMPLEMENTARY APPROACHES

Physical activity

- Aerobic exercises / walking
- Resistance training
- Balance exercises / gait training
- Power exercises



- **MUSCLE** — High quality protein intake, with 20–35g per meal
- **BONE** — Optimise vitamins and minerals such as Ca, Vit D, Phos, and Mg
- **JOINTS** — Adequate and safe pain management e.g., with oral enzyme combinations
- Support cartilage through collagen, glucosamine, and chondroitin

International Expert Groups Recommend Higher Protein Intake for Adults >65 years

Protein levels

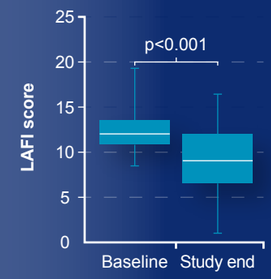
Current Recommendation for Adults: **0.8 g/kg**

Expert Recommendations: ↑ **25–50%** → **1.0–1.2 g/kg** minimum protein intake for healthy people

kg: body weight

Maximise Protein Synthesis with Even Distribution of Protein Throughout the Day's Meals

Comparable Efficacy with a Superior Safety Profile: Oral Enzyme Combination with Bromelain/Trypsin/Rutin



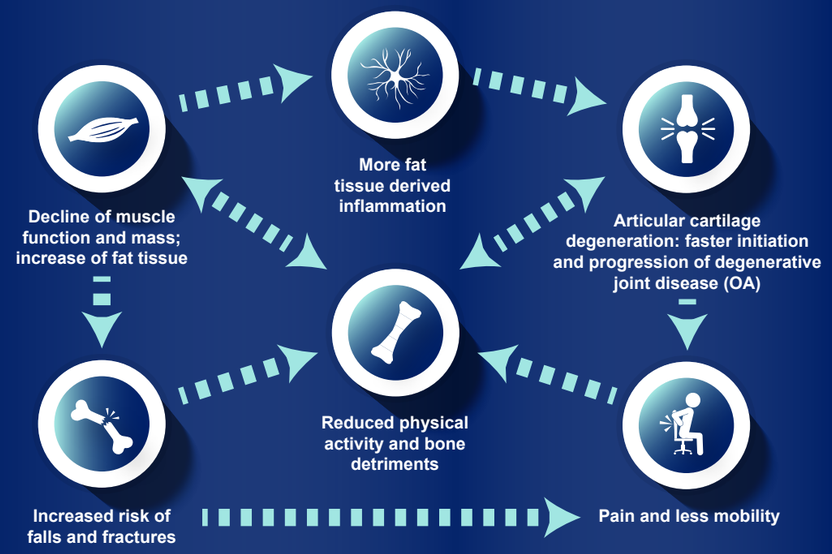
	Baseline	Study end
Mean±SD	12.6±2.4	9.1±3.9
95% CI	12.3–12.9	8.7–9.6

Diclofenac (NSAID)

	Baseline	Study end
Mean±SD	12.7±2.4	9.1±4.2
95% CI	12.4-13.0	8.7-9.7

LAFI: self-assessment of OA-related joint pain and functional disability in daily life

ADDRESSING ALL ASPECTS OF THE MUSCULOSKELETAL SYSTEM IS NECESSARY TO BREAK THE VICIOUS CYCLE



THE IMPACT OF AGEING CAN BE SEEN AS EARLY AS 40Y

20–30 years old

Peak muscle and bone mass

40–50 years old

Approximately 1%/year average loss of muscle mass begins

2–5 times faster loss of muscle strength

50–60 years old

Bone loss with a decline in mineral density; prevalent in females due to menopause

30% of post-menopausal females have osteoporosis, and over **40%** of them will have fragility fractures in their lifetime

60–70 years old

Cartilage that lines the joints tends to thin and efficiency of repair mechanisms are reduced

Ligaments and tendons become less elastic and weaken

Over 70 years old

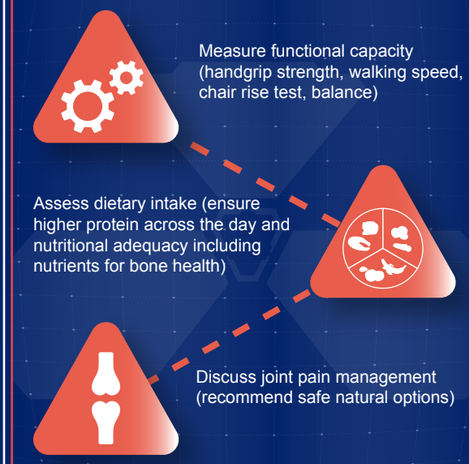
Significant muscle and strength loss, declining to **<50%** in the 80s compared with peak

Percentage of body fat increases, along with risk of health problems such as diabetes

Food intake often declines, increasing risk of calorie-protein malnutrition

A poor diet, sedentary lifestyle, comorbidities, or injuries will hasten this progression

TOP RISKS TO SCREEN FOR:



ACRONYMS

Ca: calcium; CI: confidence interval; LAFI: Lequesne Algofunctional Index; Mg: magnesium; NSAID: non-steroidal anti-inflammatory drug; OA: osteoarthritis; Phos: Phosphorus; QoL: quality of life; SD: standard deviation; Vit D: Vitamin D.

Please **click here** for references.

Summary of the British Geriatrics Society's Blueprint for Preventing and Managing Frailty in Older People

EMJ

Citation: EMJ. 2023; DOI/10.33590/emj/10301433. https://doi.org/10.33590/emj/10301433.

Frailty and Ageing

Older people have complex and diverse health and care needs.

Frailty is NOT an inevitable part of ageing and measures can be put in place to slow its onset and progression.

Frailty may affect up to half the population aged >85 years and costs the UK healthcare system £5.8 billion GBP per year.

Preventing frailty allows people to live independently for longer, reducing the demand on healthcare services.

Comprehensive Interdisciplinary Assessment and Person-Centered Care Planning

1. Family, friends, and social network
2. Integrated primary and community care
   - ICT and equipment
   - Care manager or care navigator
3. Specialist assessment, treatment, rehabilitation, and long-term care
   - Hospitals
   - Pharmacies
   - Care homes
   - Hospices
   - Ambulatory care and community hospitals
4. Age-friendly environment and community
   - Day centres
   - Leisure
   - Place's of worship
   - Learning
   - Transport
   - Restaurants and shops

BGS's Recommended 7 System Touchpoints

Investing in all these touchpoints creates a comprehensive wrap-around system of care that supports older people to age well and live well for longer.

1. Population-based proactive anticipatory care
2. Reimagined outpatient and ambulatory care
3. Enabling independence and promoting wellbeing
4. Frailty-attuned acute hospital care
5. Enhanced healthcare support for long-term care at home and in care homes
6. Co-ordinated, compassionate end of life care
7. Integrated urgent community response, reablement, rehabilitation, and intermediate care

Conclusions

Older demographics are the main users of health and social services, mainly due to frailty and multimorbidity.

Implementing of a sustainable integrated model, recommended by the BGS, improves how services work for this age group, extending healthy living years, delaying frailty, and alleviating pressure on healthcare.

Key

BGS: British Geriatrics Society ; ICT: information and communications technology.

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EMJ

Relationships of Chronic Kidney Disease and Thyroid Dysfunction in Patients with Stage 4 and 5 Chronic Kidney Disease: A Cross-Sectional Study

Editor's Pick

This novel study explores the continual challenge of patients with Stage 4 and 5 chronic kidney disease who are affected by thyroid problems, and demonstrates the correlation of triiodothyronine, thyroxine, and thyroid-stimulating hormone with metabolic parameters of chronic kidney disease. The article then investigates how triiodothyronine and thyroxine syndrome progressively worsen estimated glomerular filtration rate.

Markus Peck-Radosavljevic
Professor of Medicine, Chairman, Department of Gastroenterology and Hepatology, Endocrinology, Rheumatology and Nephrology, Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

Authors:	*Puneet Bhuwania Department of Nephrology, Wockhardt Hospitals Ltd., Mumbai, India *Correspondence to punit101.pb@gmail.com
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Received:	09.03.23
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Keywords:	Chronic kidney disease (CKD), dyslipidaemia, euthyroid sick syndrome (ESS), hypothyroidism, low-tri-iodothyronine (T3) syndrome.
Citation:	EMJ. 2023; DOI/10.33590/emj/10306741. https://doi.org/10.33590/emj/10306741.

Abstract

Introduction:
Chronic kidney disease (CKD) affects the pituitary-thyroid axis and peripheral metabolism of thyroid hormones, thereby causing dysfunction of thyroid hormones. This study aimed to highlight the correlation between thyroid dysfunction and the staging of chronic kidney disease.

Methods:
Fifty patients with CKD were studied between 2014–2017 in a tertiary care centre in Western India. These patients were split into a subgroup for Stage 4 and 5 CKD, based upon estimated glomerular filtration rate as per the Kidney Disease Improving Global Outcomes (KDIGO) guidelines. Thyroid function tests and lipid levels were compared in the different CKD subgroups by analysis of variance. Pearson's

correlation coefficient was used to evaluate the thyroid dysfunction with respect to degree of renal dysfunction in the study population.

Results:
Thyroid abnormalities were seen in 68% of the author's patients. Euthyroid sick syndrome (ESS) was the most prevalent thyroid hormonal abnormality seen in 32% (n=16), followed by hypothyroidism category seen in the remaining 36% (n=18) of the study population. Of these, 18% (n=9) of the patients had subclinical hypothyroidism, while the remaining 18% (n=9) manifested overt hypothyroidism. Results showed that ESS had a positive correlation with estimated glomerular filtration rate ($r=0.822$; $p<0.001$). No significant differences were found between groups in thyroxine or thyroid-stimulating hormone ($p>0.05$). Linear regression in unadjusted analysis revealed that deranged low-density lipoprotein levels was found to be significantly associated negatively with hypothyroidism ($p<0.001$) in patients with CKD.

Conclusion:
Patients with Stage 4 and 5 CKD have many hormonal disturbances, of which ESS is a common occurrence, and has a significant association with dyslipidaemia, increasing morbidity in these patients. Hypothyroidism is more prevalent in patients with severe renal dysfunction, as a result of higher uremic milieu in these patients.

Key Points

1. The association between chronic kidney disease (CKD) and thyroid has been well studied, but its impact in patients with Stage 4 and Stage 5 CKD remains an unsolved problem.

2. In this study, the author demonstrated the correlation of tri-iodothyronine, thyroxine, and thyroid-stimulating hormone with metabolic parameters of CKD.

3. The study showed that low tri-iodothyronine and low thyroxine syndrome progressively increased as the severity of chronic kidney disease increased, which may impact progressive worsening of estimated glomerular filtration rate.

INTRODUCTION

A spectrum of various pathophysiological processes associated with a progressive worsening in estimated glomerular filtration rate (eGFR) and abnormal kidney function are encompassed in chronic kidney disease (CKD).[1,2] Despite various aetiologies, irreversible destruction of nephrons ultimately culminates into CKD, resulting in alteration of the internal milieu that affects each and every system in the body, including the thyroid hormonal system. In the clinical scenario of patients with CKD, thyroid gland disorders such as hypothyroidism and euthyroid sick syndrome (ESS) occur very often, especially in Stage 5 CKD.[3-5]

However, the directionality of the association and mechanistic link between kidney disease and ESS remain widely unknown. In patients with CKD, a pivotal role is played by the inflammatory cytokines and oxidative stress in the pathogenesis of ESS. A study by Lo et al.[3] indicated the increasing prevalence of subclinical primary hypothyroidism from 5.4% to more than 20.0% when the eGFR reduced from >90 mL/min/1.73 m^2 to <60 mL/min/1.73 m^2. In addition to the above, Song et al.[4] indicated the morbidity of low tri-iodothyronine (T3) syndrome to be increased in patients with CKD. In patients with hypothyroidism, clinically and statistically important reductions in eGFR are seen, which could be attenuated by using adequate thyroid hormone replacement therapy.[6,7]

Studies also demonstrated the clinical and subclinical hypothyroidism states to be independent risk factors for cardiovascular death and all-cause mortality, which could be the effects of worsening atherosclerosis in coronary and peripheral vessels and hyperlipidaemia.[8-10] Due to the dearth of available data to prove the relationships between thyroid hormones and eGFR, gender, age, and various other biomarkers such as haemoglobin, electrolytes, and lipid profile in patients with Stage 4 and 5 CKD, the author performed such kinds of analysis to explore the relationships between these biomarkers in patients with Stage 4 and 5 CKD and thyroid hormones.

MATERIALS AND METHODS

Study Design

A prospective, cross-sectional study was conducted between 2014–2016 at a tertiary healthcare centre, in patients who were admitted and registered into the system. After approval by the Institutional Review Board, the study was performed in accordance with the Declaration of Helsinki. An informed consent was sort and obtained from all participants on admission to the hospital, and prior to the required investigations.

Study Population

A total of 50 patients hospitalised with CKD, and not on dialysis, were recruited. These randomly chosen participants had Stage 4 and 5 CKD (i.e., GFR <30 ml/min), and were patients who fulfilled the criteria for CKD (uraemic symptoms for ≥3 months, with decreased eGFR and ultrasound evidence of chronic kidney disease), and who were on conservative management. The author excluded patients younger than 18 years of age; females who were pregnant; patients with acute kidney injury, or undergoing renal replacement therapy; patients who were receiving concurrent treatment with drugs that could affect thyroid hormones (amiodarone, lithium, methimazole, iodine, oestrogen pills, or phenytoin); or with known thyroid illness in the past. Outpatients were also excluded to prevent acute kidney injury (acute illness) causing confounding results on thyroid panels, and to prevent dropouts during follow-up.

Laboratory Measure

The electrochemiluminescence assay (Siemens, Munich, Germany) was used to test thyroid function. The normal reference range of the author's institution was T3 (60–200 ng/dL), thyroxine (T4; 4.5–12.5 mcg/dL), 'free' T4 (FT4; 0.8–2 ng/dL), and thyroid-stimulating hormone (TSH; 0.3–5.5 mIU/L). Clinical hypothyroidism was defined as a condition with increased TSH, along with decreased FT4 and decreased or normal T3. Clinical hyperthyroidism was defined as a condition with a lowered TSH, along with a raised FT4, T4 and/or T3. Subclinical hypothyroidism was defined as a condition with raised TSH along with a normal FT4, T4, and/or T3. Subclinical hyperthyroidism was defined as a condition with a lowered TSH, along with a normal FT4, T4, and T3. ESS was defined as a condition with normal or a low TSH, along with low T3 and/or a low FT4 and TT4. Serum sodium, potassium, calcium, urea, and creatinine were measured by an enzymatic method called the isotope dilution mass spectrometry.[11] Haemoglobin was detected by an automated haematology system. Serum lipid profile analysis (triglycerides, low-density lipoprotein [LDL] and high-density lipoprotein) using an enzymatic colorimetric method. Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) method was utilised to calculate the eGFR.[12,13]

Statistical Analysis

Analysis was conducted using the PASW 18.0 software (SPSS Inc., Chicago, Illinois, USA). The following was the expression of eGFR equation in software: eGFR=141 x min $(Scr/\kappa,1)^{\alpha}$ x max $(Scr/\kappa,1)^{-1.209}$ x 0.993^{age} x 1.018 (if female). κ was 0.9 for males and 0.7 for females; α was -0.411 for males and -0.329 for females; max indicates the maximum of Scr/K or 1, and min indicates the minimum of Scr/κ or 1. CKD Stage 4 and 5 definitions were in accordance with KIDGO guidelines (Stage 4: eGFR <30 mL min/1.73 m^2–≤15 mL/min/1.73 m^2; Stage 5: eGFR <15 mL/min/1.73 m^2). Data were expressed as mean±standard deviation. Different thyroid diseases prevalence were calculated by χ^2 test. One-way analysis of variance was used to compare the levels of various biochemical markers in different CKD stages and thyroid hormones. Association between categorical factors and groups were tested using the χ^2 test.

For any statistical significance, a p-value of ≤0.05 was fixed. Spearman correlation analysis was used to analyse the correlations between various kidney biomarkers and thyroid hormones. Multivariate logistic regression was used to assess the adjusted effect of the factors on incidence of hypothyroidism. Factors that are statistically significant at 10% level of significance from univariate analysis and clinically significant were included in the model.

RESULTS

Patient Characteristics in Various Chronic Kidney Disease Groups

Characteristics of 50 patients recruited are depicted in Table 1. The mean age of the patients was 49.5 years, with an equal distribution of all patients above and below 50 years of age (p=0.199), and 80% of the total patients were males. The mean age of the patients in both Stage 4 and Stage 5 CKD groups did not show any statistical difference (p=0.199), with a similar distribution of patients of age above and below 50 years in Stage 4 and 5 groups (p=0.239). Similarly, the gender distribution of the patients in the Stage 4 and 5 groups were not statistically different (p=0.440). There were significant differences among the two groups in eGFR, urea, creatinine, T3, haemoglobin, sodium, potassium, and calcium (p<0.001). Patients in the Stage 5 group had a lower T3, haemoglobin, sodium, calcium, and a high potassium (p<0.001). No significant differences were found in TSH, T4, FT4, and LDL (p>0.05).

Prevalence of Different Types of Thyroidism and Dyslipidaemia in Chronic Kidney Disease Groups

Subclinical and overt hyperthyroidism were not seen in either CKD group. However, there was a high prevalence of euthyroid state (normal: 32%) and ESS (32%), as compared with subclinical (18%) and overt hypothyroidism (18%) in CKD groups. The euthyroid state was more prevalent in the Stage 5 group, but this was not statistically significant (p>0.05), while ESS had a similar prevalence in both groups. The morbidity of overt hypothyroidism was 18%, and was especially high in patients with Stage 5 CKD (p<0.026). There was a high prevalence of patients with undesirable high LDL cholesterol, high triglycerides, and low HDL cholesterol levels in these groups, with no significant differences between either (p=0.948, p=0.810, and p=0.087, respectively; Table 2).

Correlation Analysis of Thyroid Hormone and Chronic Kidney Disease

The analysis between thyroid hormone and urea, creatinine, and eGFR were shown in Table 3. With urea and thyroid hormones, Pearson's correlation coefficient (R) was -0.658 between T3 and urea, which had a significant statistic negative correlation (p<0.001). R was -0.302 between T4 and urea, and 0.211 between TSH and urea, both of which were statistically non-significant. With creatinine and thyroid hormones, R was -0.792 between T3 and creatinine, which had a significant statistic negative correlation (p<0.001). R was -0.305 between T4 and creatinine, and 0.231 between TSH and creatinine, both of which were statistically non-significant. With eGFR and thyroid hormones, R was 0.822 between T3 and eGFR, which had a significant statistic positive correlation (p<0.001). R was 0.309 between T4 and eGFR and -0.263 between TSH and eGFR, both of which were statistically non-significant.

Analysis of Other Covariates with Chronic Kidney Disease Staging and Hypothyroidism

Association analysis were also conducted between the biomarkers and CKD staging. None of the covariates showed any significant association with CKD staging. Lower levels of haemoglobin showed association with CKD staging in unadjusted models, but it was not statistically significant (odds ratio [OR]: -0.334; 95% confidence interval: -0.382–0.015; p=0.073). None of the other kidney biomarkers, which included urea, creatinine, and other electrolytes showed any association with CKD staging in unadjusted models (p>0.05). Similarly, no association was seen between lipid profile and CKD staging in unadjusted models (p>0.05). LDL cholesterol demonstrated a significant negative correlation in unadjusted analysis with hypothyroidism (OR: -0.759; p<0.001), but after adjustment with other kidney biomarkers no

Table 1: Characteristics of patients with chronic kidney disease in different groups.

Parameters	All patients (N=50)	Stage 4 CKD (n=15)	Stage 5 CKD (N=35)	p value
Age (years)	49.5 (25.0–76.0)	48.0 (25.0–76.0)	52.0 (27.0–68.0)	0.199
Age groups (years), n (%) ≤50 >50	27 (54.0) 23 (46.0)	10 (66.7) 5 (33.3)	17 (48.6) 18 (51.4)	0.239
Sex, n (%) Males Females	40 (80.0) 10 (20.0)	13 (86.7) 2 (13.3)	27 (77.1) 8 (22.9)	0.440
Laboratory parameters				
eGFR (mL/min)	11.1 (2.7–29.0)	21.4 (16.0–29.0)	9.0 (2.7–14.5)	<0.001
Urea (mg/dL)	94.0 (65.0–175.0)	75.0 (65.0–175.0)	106.0 (70.0–172.0)	<0.001
Creatinine (mg/dL)	5.0 (2.5–15.0)	3.2 (2.5, 4.0)	6.4 (3.5–15.0)	<0.001
T3 (ng/dL)	53.0 (15.0–200.0)	80.0 (50.0–180.0)	31.0 (15.0–200.0)	<0.001
T4 (µg/dL)	6.0 (1.5–9.6)	6.0 (4.6–9.0)	5.6 (1.5–9.6)	0.270
TSH (µlU/mL)	4.6 (0.8–26.0)	4.7 (0.8–14.0)	4.6 (0.8–26.0)	0.207
FT4 (ng/dL)	1.4 (0.8–2.1)	1.6 (1.1–2.1)	1.3 (0.8–2.1)	0.427
Haemoglobin (g/dL)	8.9 (1.1)	10.0 (0.4)	8.5 (1.0)	<0.001
Sodium (mmol/L), mean (SD)	134.7 (3.6)	137.6 (2.3)	133.5 (3.3)	<0.001
Potassium (mmol/L), mean (SD)	5.0 (0.4)	4.6 (0.2)	5.1 (0.4)	<0.001
Calcium (mg/dL), mean (SD)	7.9 (0.7)	8.4 (0.4)	7.6 (0.7)	<0.001
LDL (mg/dL), mean (SD)	124.6 (20.7)	120.0 (18.1)	126.8 (21.7)	0.271
HDL (mg/dL), mean (SD)	44.3 (8.0)	46.7 (8.4)	43.3 (7.8)	0.171
TG (mg/dL), mean (SD)	134.9 (12.6)	133.1 (7.6)	135.7 (14.3)	0.499

Data shown as median (range), unless otherwise specified.

CKD: chronic kidney disease; eGFR: estimated glomerular filtration rate; FT4: free thyroxine; HDL: high-density lipoprotein; LDL: low-density lipoprotein; SD: standard deviation; T3: triiodothyronine; T4: thyroxine; TG: triglyceride; TSH: thyroid-stimulating hormone.

Table 2: Thyroid dysfunction and dyslipidaemia in different stages of chronic kidney disease.

Parameters	All patients (N=50)	CKD Stage 4 (n=15)	CKD Stage 5 (N=35)	p value
Thyroid status Euthyroidism Overt hypothyroidism Subclinical hypothyroidism ESS	16 (32.0) 9 (18.0) 9 (18.0) 16 (32.0)	3 (20.0) N/A 4 (26.7) 8 (53.3)	13 (37.1) 9 (25.7) 5 (14.3) 8 (22.9)	0.026
Low HDL cholesterol (HDL cholesterol <40 mg/dL)	17 (34.0)	5 (33.3)	12 (34.3)	0.948
Undesirable LDL cholesterol (LDL cholesterol >100 mg/dL)	41 (82.0)	12 (80.0)	29 (82.9)	0.810
Hypertriglyceridaemia (triglyceride >150 mg/dL)	6 (12.0)	N/A	6 (17.1)	0.087

Data shown as n (%).

ESS: euthyroid sick syndrome; HDL: high-density lipoprotein; LDL: low-density lipoprotein.

Table 3: Correlation between thyroid hormones and parameters of renal function.

Thyroid parameters	Kidney parameters	R	p
T3 (ng/dL)	Urea (mg/dL)	-0.658	<0.001
	Creatinine (mg/dL)	-0.792	<0.001
	eGFR (mL/min)	0.822	<0.001
T4 (µg/dL)	Urea (mg/dL)	-0.302	0.033
	Creatinine (mg/dL)	-0.305	0.031
	eGFR (mL/min)	0.309	0.029
TSH (µIU/mL)	Urea (mg/dL)	0.211	0.140
	Creatinine (mg/dL)	0.231	0.106
	eGFR (mL/min)	-0.263	0.065

eGFR: estimated glomerular filtration rate; R: correlation coefficient; T3: tri-iodothyronine; T4: thyroxine; TSH: thyroid-stimulating hormone.

significant correlation was found between LDL and hypothyroidism in patients with CKD (OR: 1.002; 95% confidence interval: 0.998–1.007; p=0.296).

DISCUSSION

Of the 50 patients recruited, patients were predominately males (80%), which reflects the gender discrepancy in healthcare seeking-behaviour in Western India. The analysis revealed that T3 levels change in accordance with urea, creatinine, and eGFR. Urea and creatinine negatively correlated with T3, while eGFR positively correlated with T3 levels. The most common thyroid disorder in Stage 4 and Stage 5 CKD groups is ESS. In this analysis, it was found that the frequency of ESS demonstrated a rising trend in patients with Stage 4 and 5 CKD, the number being around 32% with equal representation in both CKD groups. Stage 5 patients had an increasing trend in frequency of overt hypothyroidism of around 26%. Additionally, overt hypothyroidism had correlations with LDL. However, adjustment and multivariate analysis revealed overt hypothyroidism to be independent of LDL.

Multiple reports have shown that thyroid glands and kidneys have a close relationship,[11,14,15] and that thyroid hormones play an important role in the metabolism and development of the kidneys.[12] Thyroid gland dysfunction induces disorders of electrolytes, water, and lipids, amongst others. Den Hollander et al.[13] demonstrated the kidneys to be influenced by the thyroid status during both of its stages (i.e., embryonic development and maturation), directly by altering kidney structure, glomerular function, tubular absorptive, and secretory capacities of the electrolyte channels, and indirectly influencing the renal blood flow via its effects on the cardiovascular system.

In another micropuncture study, proximal tubules of thyroidectomised rats showed a more than 65% increase in isotonic fluid reabsorption after treatment with T3.[16,17] Studies carried out in rats and humans indicated that there was an increase in eGFR by up to 18% due to hyperthyroidism,[13,18] while some studies also showed hyperthyroidism to cause decrease in serum creatinine and an increase in serum cystatin C.[19] Inversely, the decline in eGFR was commonly seen in patients with subclinical or overt hypothyroidism.[13,18] This analysis demonstrated a linear relationship between T3 and eGFR, indicating the fact that T3 decreased with declining eGFR, which has been linked and attributed to a reduction in the peripheral synthesis of T3 from T4. Such change in thyroid hormone balance could be attributed to a self-protecting mechanism in cases of severe levels of disease to diminish the metabolic requirement, the underlying mechanisms of which still remain unknown. Some studies predicted a higher prevalence of ESS or hypothyroidism in the CKD population.[4] Song et al.[4] demonstrated an increasing trend of low T3 population in accordance to the increasing CKD stage with normal TSH levels (eGFR <15: 78.6%; 15 ≤eGFR <30: 60.6%; 30 ≤eGFR <60: 20.8%; 60 ≤eGFR <90: 10.9%; eGFR ≥90: 8.2%).[4] Similarly, in the author's analysis, a large proportion of patients with Stage 4 and 5 CKD were also found to have ESS (32%). Meanwhile, the low T3 syndrome has become a marker of severe disease.[20] Carrero et al.[21] indicated, due to its intimate association with inflammation, the low T3 levels to be independent predictors of cardiovascular disease and all-cause mortality in patients with ESS.

Although this study did not test for inflammatory markers in the Stage 4 and 5 CKD population, it did show a high prevalence of hypothyroidism in these patients. Therefore, higher levels of inflammation in patients with Stage 4 and 5 CKD induce an increased frequency of euthyroid. Case reports, pilot studies, and meta-analyses carried out in humans have documented worsening levels of serum creatinine with hypothyroidism.[22-25] Similar to the above-mentioned reports, a big proportion of the author's patients with Stage 4 and 5 CKD also had hypothyroidism (18%), with significant predominance in the Stage 5 group. Understanding the impact thyroid dysfunction has on kidney functions and its importance have been highlighted in recent studies, which indicate clinical and subclinical hypothyroidism to be common in patients with eGFR <60 mL/min per 1.73 m^2, leading to the question of whether hypothyroidism could be one of the contributing factors to a lower eGFR in some of these individuals.[3] Hypothyroidism has been attributed to patients with serum creatinine

levels exceeding 6 mg/dL, with a few even being described to have end-stage kidney disease.[26]

Many reviews have tried to establish or illustrate the interplay between the organs, and to establish the cause and effect relationship between the thyroid gland and the kidneys, or vice versa. Echterdiek et al.[27] indicated in their review the positive effect of treating subclinical hypothyroidism in paediatric patients who are non-dialysis dependent and dialysis dependent.[27] While mortality analysis was not conducted in this review, high TSH levels in patients with Stage 4 and 5 CKD had a higher mortality rate compared to normal TSH levels.[28] Although data analysing the use of thyroid hormone supplementation and its outcomes in the patients with kidney disease are scant, a recent analysis carried out in veterans in the USA with Stage 3 CKD showed that patients with undertreated and untreated hypothyroidism have a higher mortality risk compared with those with euthyroid, whereas veterans who were treated to target hypothyroid had a better survival.[29] Patients with CKD, when compared with the general population, have a higher incidence of cardiovascular deaths even in early stages, which increases significantly with declining or worsening of renal function. This causes a higher mortality, which increases many times in the presence of thyroid dysfunction, the pathologic basis of which are not only the haemodynamic changes, but also due to the increased endothelial damage and vascular calcification in conjunction with atherosclerosis. Atherosclerosis is also accelerated due to the presence of dyslipidaemia, causing alterations in the ion channel expression of the cardiac myocytes, leading to QT interval prolongation which heightens the risk of arrhythmias and sudden cardiac death in these patients.[30-35]

CONCLUSION

Of the patients with Stage 4 and 5 CKD, 68% had some kind of thyroid dysfunction. Hypothyroidism had an increased prevalence in patients with CKD. Patients with low T3 and T4 syndrome progressively increased as the severity of chronic kidney disease increased. eGFR negatively correlated with T3 levels, and positively with TSH. Thyroid dysfunction had an increased prevalence in patients with CKD in the age group of 31–60 years, but did not show any increased incidence in either male or female patients with CKD.

LIMITATIONS

This study is not without its limitations, some of which have been highlighted here. The patient pool was comprised only of patients with Stage 4 and 5 CKD, none of whom were undergoing dialysis, as it impacts the thyroid profile of these patients due to metabolism, systemic acidosis, chronic inflammation, etc. A small sample size was used, which included a relatively older population that may have significant impact on thyroid panels. A single centre study often has a crowd bias; however, this analysis included patients with CKD irrespective of aetiologies, thereby providing believable results. Lastly, as happens with all observational analysis, it is difficult to exclude all confounding factors and establish a causal relationship.

FUTURE RESEARCH

Prospective analysis is necessary to determine the influence supplementation of thyroid hormone has in patients with high TSH levels, either subclinical or overt hypothyroidism, in the disease progression and mortality for patients with Stage 4 and 5 CKD.

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Prevalence of Carbapenem-Resistant *Enterobacteriaceae* and the Genes Responsible for Carbapenemase Production in a Tertiary Care Hospital in South India

Authors:	*Devesh N. Joshi,[1] Bhaskar Shenoy,[1] Bhavana MV,[2] Ranjeeta Adhikary,[2] Shivkumar Shamarao,[3] Archana Mahalingam[1] 1. Department of Pediatrics and Pediatric Infectious Diseases, Manipal Hospital, Bangalore, India 2. Department of Microbiology, Manipal Hospital, Bangalore, India 3. Department of Pediatric Intensive Care, Manipal Hospital, Bangalore, India *Correspondence to dr.deveshjoshi91@gmail.com

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Abstract

Introduction: Carbapenem resistance in Gram-negative bacilli (GNB) is a major concern in the management of resistant infections. The mechanism of carbapenem resistance is most commonly mediated by carbapenemases. The five most common genes (*NDM, KPC, VIM, OXA*, and *IMP*) are responsible for carbapenemase production. Knowledge of these genes is important for the management of the disease.

Objective: To estimate the prevalence of different genes responsible for carbapenemase production in GNB at a tertiary healthcare centre in South India.

Method: In this retrospective study, samples were collected over 16 months. Carbapenem-resistant GNB underwent to Xpert Carba-R assay (Cepheid, Sunnyvale, California, USA) for the detection of five important genes responsible for carbapenemase production: *NDM, KPC, VIM, OXA,* and *IMP*.

Results: Out of 184 carbapenem-resistant GNB, 20 samples were not included in this study. The rest of the 164 samples grew *Klebsiella pneumoniae* (152), *Escherichia coli* (10), and *Enterobacter* (2). *OXA-48* and *NDM* were the most common genes responsible, with 137 (84.5%) and 95 (58.6%), respectively. Among them, 70 (43.2%) showed the presence of both genes, and 1 (0.6%) showed the presence of *OXA-48*, *NDM*, and *VIM*. Individually, 66 (40.7%) of OXA-48, 24 (14.8%)

of NDM, and one (0.6%) of VIM. In this study, the authors did not find the presence of IMP or KPC genes.

Conclusion: As a result of limited options and the higher cost of antibiotics for carbapenem-resistant infections, knowledge of these genes helps in the selection and rational use of antibiotics reduces the cost of management and will prevent mortality and morbidity from these infections.

Key Points

1. To deal with multi-drug resistant bacteria, it is important to know the underlining mechanism of drug resistance. Molecular investigation is a new advancement in medical science and is useful in identifying this mechanism at a molecular level.

2. Carbapenemase production is the most important mechanism responsible for carbapenem-resistant *Enterobacteriaceae*. Knowing the prevalence of genes responsible for this carbapenemase production is very important for the selection of antibiotics.

3. Knowledge of the prevalence of genes responsible for carbapenemase in a particular region will help in antibiotic stewardship for the selection of empiric antibiotics when advance laboratory investigations are not available or while waiting for the reports.

INTRODUCTION

Carbapenem-resistant *Enterobacteriaceae* (CRE) is defined as *Enterobacteriaceae* that are resistant to the carbapenem group of antimicrobials. In the case where bacteria are intrinsically resistant to imipenem, the resistance to at least one carbapenem other than imipenem should be there to classify the organism as carbapenem-resistant.[1]

Resistance to carbapenems in Gram-negative bacteria, especially *Enterobacteriaceae*, is a major concerning emerging issue. There is a rising prevalence in the number of cases of CRE worldwide. In its publication 'Antibiotic Resistance Threats in the United States', the Centers for Disease Control and Prevention (CDC)[2] refers to CRE as an urgent threat that is claiming more than 1,000 deaths annually in the USA. Similarly in Europe, there are increasing reports of CRE, causing disseminated and hospital-acquired infections. The highest prevalence of CRE is observed in Mediterranean and Balkan countries. The prevalence in Greece and Italy is reported to be around 60% and 40%, respectively.[3,4] According to a study done in Asia, prevalence of CRE infection ranges from 0.6–0.9% of the total culture-positive infections.[5]

Although there are no uniform data available from India regarding CRE, published articles show the prevalence of carbapenem resistance among *Enterobacteriaceae* in India ranges from 18–31%. As most samples were collected from hospitalised patients in tertiary care centres, it may not represent the entire population.[6-10]

In order to act effectively, carbapenem molecules need to cross Gram-negative bacterial cell wall and reach intramembranous space with the help of the porin channels. There are three major mechanisms by which *Enterobacteriaceae* become resistant to carbapenem: enzyme production (carbapenemases), the formation of efflux pumps, and porin channel mutations. Of these, enzyme production is the main mechanism of resistance.[11] The porin channels can act as a filter and prevent antibiotics from reaching the site of action. The efflux pump removes the antibiotic molecule from the intramembranous space.[12] Unlike other mechanisms, carbapenemase-mediated resistance is usually transmitted by plasmids. They can easily be transferred from affected bacteria to unaffected ones. There lies the public health importance of carbapenemase-mediated resistance to carbapenems.[12]

Knowledge of different genes producing carbapenemase is important to be able to choose the appropriate antimicrobial.[13] Xpert Carba-R assay (Cepheid, Sunnyvale, California, USA) is a rapid, real-time PCR assay that is useful for identifying genes encoding for the carbapenemase along with bacterial isolates from various clinical specimens, and can be useful for managing patients with CRE. Among the carbapenemase encoding genes, *NDM*, *KPC*, *VIM*, *OXA*, and *IMP* are recognised as the most important carbapenemases because of their wide prevalence.[14]

The current study was undertaken to understand the prevalence of different genes responsible for the production of carbapenemases in the authors' setting.

Objectives

The objectives of this study were to estimate the prevalence of different genes responsible for carbapenemase production among *Enterobacteriaceae* in a tertiary healthcare setup in Bangalore, India, and to outline the treatment considerations for a patient with CRE infections where advance investigations are not possible.

METHODOLOGY

A retrospective chart review with convenient sampling completed between January 2020–April 2021. The study took place at a single centre, tertiary care, multi-specialty hospital in South India.

Inclusion criteria

Inclusion criteria includes all CRE being isolated during the study period and treating physicians requested for the molecular study (Xpert Carba-R) for the further management of the patient.

Exclusion criteria

Exclusion criteria includes carbapenem resistant Gram-negative bacteria other than *Enterobacteriaceae* and repeat samples from the same patient during the same hospitalisation period.

Data Collection

Data were extracted retrospectively from the Department of Microbiology between January 2020–April 2021, a period of 16 months. All CRE positive culture reports (from blood, urine, cerebrospinal fluid, swabs, and other body fluids) where the Xpert Carba-R assay was performed were included in the analysis. In the authors' laboratory, antibiotic testing is done by VITEK® 2 (bioMérieux, Marcy-l'Étoile, France) compact. *Enterobacteriaceae* that show resistance to carbapenems (defined by meropenem minimum inhibitory concentration: >8 mcg/mL)[15] were subjected to the Xpert Carba-R assay. The Xpert Carba-R assay is performed using the GeneXpert (Cepheid) platform. This is qualitative *in vitro* real-time PCR assay that detects five important genes producing carbapenemases, which include *IMP*, *KPC*, *NDM*, *OXA-48*, and *VIM*. This is an automated method wherein the samples from the culture plate are vortexed at high speed for 10 seconds in an elution reagent tube, which is later transferred into the specimen chamber of the Xpert Carba-R assay cartridge, as per the manufacturer's instructions. The result is interpreted by the machine and the run time is 47 minutes. One of the limitations of the Xpert Carba-R assay is that it is only able to detect four out of 10 variant genes (*blaOXA-48*, *blaOXA-162*, *blaOXA-163*, and *blaOXA-204*) of *OXA-48*.[16] This assay has high sensitivity and specificity (100% and 77%, respectively), with a positive predictive value and negative predictive value of 96% and 100%, respectively.[17]

RESULTS

A total of 50,144 patients were hospitalised during the study period. Among them, 9,424 (18.80%) had culture-proven infections. A total of 4,713 (50%) of the culture-proven infections were caused by *Enterobacteriaceae*. Among the total hospitalised patients, 2.55% had CRE infections. Among the total culture positive infections caused by *Enterobacteriaceae*, 27.18% were CRE.

Out of 1,281 CRE positive samples, 164 samples were analysed based on the inclusion and exclusion criteria. Out of these 164 samples, 64.0% were blood culture samples (105 out of 164); 12.2% (20 out of 164) were urine samples; 9.1% (15 out of 164) were tracheal aspiration; and purulent discharges constituted 6.1%

(10 out of 164), while the rest of the 14 samples were collected either from cerebrospinal fluid, wound swab, sputum, tissue samples, or other body fluids.

Klebsiella pneumoniae was the main *Enterobacteriaceae* isolated, constituting 92.64% (152 out of 164) of the organisms, while 10 samples (6.09%) grew *Escherichia coli*, and two samples (1.21%) grew *Enterobacter*.

The authors could identify the gene responsible for carbapenemase production in 162 samples by the Xpert Carba-R assay. However, two samples tested negative for all the identifiable genes (five genes) by the Xpert Carba-R assay, which could mean there were other enzyme coding genes or non-carbapenemase mechanisms responsible for the resistance.[11]

Among the CRE isolates, 40.7% (66 out of 162) showed the *OXA-48* gene alone, while 14.8% (24 out of 162) showed isolated *NDM* gene alone and 0.6% (1 out of 162) showed *VIM* gene as the inducer of resistance. A total of 43.2% (70 out of 162) of isolates showed the presence of a combination of both *OXA-48* and *NDM* genes, and 0.6% (one) organism showed the presence of *OXA 48*, *NDM*, and *VIM* in combination. Overall, the *OXA-48* gene was present in 84.5% (137 out of 162) isolates and *NDM* gene was the second common identified gene, having been found in 58.6% (95 out of 162) isolates. Notably, all the isolates were negative for *IMP* or *KPC* genes.

Table 1 shows the common resistance genes identified in each of the isolated organisms. The most common resistance gene carried by *Klebsiella* species, which was the authors' most common isolate, was a combination of *OXA-48* and *NDM*, followed by *OXA-48* alone and *NDM* alone. The most common resistance gene identified in *E. coli* species was the *NDM* gene in isolation, unlike the *Klebsiella* species.

Table 1: Carbapenem-resistant *Enterobacteriaceae* organisms and identified genes responsible for carbapenem resistance.

Organism	Number (n=164)	Percentage (%)	Gene identified (n=164)
K. pneumoniae	152	92.64	*OXA-48+NDM* (n=69)
			OXA-48 alone (n=64)
			NDM alone (n=17)
			VIM alone (n=1)
			OXA-48+NDM+VIM (n=1)
E. coli	10	6.09	*NDM* alone (n=6)
			OXA-48 alone (n=1)
			OXA-48+NDM (n=1)
			None (n=2)
Enterobacter	2	1.21	*OXA-48* (n=1)
			NDM (n=1)
Total	164	100.00	164

E. coli: Escherichia coli; K. pneumoniae: Klebsiella pneumoniae.

DISCUSSION

Early, rapid identification of the genes causing carbapenem resistance will help to choose appropriate antibiotics early in treating CRE infections. In this study, 162 out of 164 samples could identify the genes for carbapenemase production. The remaining two samples could have had other genes (other than the five that are identifiable by the Xpert Carba-R assay) or could have carbapenem resistance due to non-carbapenemase mediated mechanisms.

Among CRE isolates, although the *OXA-48* gene was the most prevalent gene in isolation (n=66 [40.7%]), which was followed by *NDM* (n=24 [14.8%]), the most common genetic mechanism causing carbapenem resistance was a combination of *OXA-48* plus *NDM*, as noted in 43.2% (70 out of 162) isolates.

In the authors' study, the most common CRE organism was *K. pneumoniae* (92.64% [152 out of 164]) followed by *E. coli* (6.09% [10 out of 164]]), and *Enterobacter* (1.21% [two out of 164]). Among the *Klebsiella* isolates, the most common mechanism of carbapenem resistance was found to be a combination of *OXA-48* and *NDM* (45.40% [69 out of 152]), followed by *OXA-48* alone (42.00%) and *NDM* alone (11.20%).

NDM alone (60% [6 out of 10]) was the most common mechanism recognised in *E. coli*, followed by *OXA-48* alone (10%) and combination of *OXA-48* plus *NDM-1* (10%).

In two of the isolates of *E. coli*, no gene could be identified. With one–one samples being positive for both *OXA-48* and *NDM*, both and were equally prevalent in the *Enterobacter* isolates.

In the study by Anandan et al.,[18] the predominant organisms were *K. pneumoniae* (n=88) and *E. coli* (n=32) out of the 120 CRE isolates from blood cultures. Conventional PCR identified an equal number of isolates showing *NDM* genes (40.0% [n=48]) and *OXA-48*-like genes (39.2% [n=47]). *E. coli* was the predominant *NDM* producing gene (62.5% [n=30]), followed by *K. pneumoniae* (37.5% [n=18]). *K. pneumoniae* was the predominant isolate testing positive for *OXA-48*-like gene (83% [n=39]), followed by *E. coli* (17% [n=8]). However, a total of 15 (12.5%) carbapenem-resistant isolates were found to be coproducers of *OXA-48* and *NDM*, unlike in the authors' study, where the combination mechanism was found to be most predominant.[18]

In the study by Sekar et al.,[19] 89 isolates were *E. coli* out of 177 isolates of CRE, and 88 isolates were the *Klebsiella* species. Among the *E. coli* isolates that tested positive for the carbapenemase genes, the predominant gene was *NDM* (12 out of 33), followed by *KPC* (9 out of 33) and *OXA-48* (6 out of 33). Among the *Klebsiella* species testing positive for the carbapenemase genes, 15 out of 32 were *NDM*, nine out of 32 were *OXA-48*, and three out of 32 were *KPC*, followed by two for *VIM*, two for *NDM* plus *OXA-48*, and one for *NDM* plus *KPC*.[19] These observations again highlight the differences in the pattern of resistance mechanisms compared to the authors' study.

Giri et al.[20] completed a similar study, where they collected samples from a tertiary care hospital in western Maharashtra, a state in India, and found that 90% (n=45) detected the presence of *NDM* gene, 60% (n=30) showed the presence of *OXA-48*, and 12% (n=6) showed *VIM* gene in 50 isolated CRE samples. Their findings were similar to the results presented in this article by the authors, with the most common mechanism of carbapenem resistance found to be due to the combination of *NDM* and *OXA-48* genes in 50% of the isolates, mostly associated with *K. pneumoniae* isolates.[20]

The study by Han et al.[21] identified the *KPC* gene as the most common mechanism of resistance among their CRE *Klebsiella* isolates, followed by the *NDM* and *OXA-48* genes; however, their *E. coli* isolates showed that *NDM* gene was predominant.

A multicentric study completed by Traczewski et al.[22] across the USA and Europe found that, out of 467 isolates, *Enterobacteriaceae* (predominantly *K. pneumoniae and E. coli)* are the most common isolates (343 out of 467). followed by *Pseudomonas aeruginosa* (80 out of 467), and *Acinetobacter baumannii* (44 out of 467). This study also showed that among 343 samples of CRE, 89 of them showed the presence of *OXA-48*, 83 *KPC*, 73 *NDM*, 51 *VIM*, and four *IMP-1*.[22]

There are three molecular major classes of β-lactamases produced by Gram-negative bacilli: Ambler Class A, Class B, and Class D (Table 2). In this, there is one more chromosome-encoded cephalosporinases (Class C or AmpC), which is produced by these bacteria that may possess slightly extended activity towards carbapenems, but it is not clinically much significant.[23]

Three major types of Class A carbapenemases include the nonmetallocarbapenemase class A/imipenemase, serratia marcescens enzyme, and *K. pneumoniae* carbapenemase enzymes. This class of enzymes hydrolyses a broad variety of β-lactams, which includes penicillins, cephalosporins, carbapenems, and aztreonam. But newer β-lactamases are showing effectiveness against them.[13,23]

Class B is a metallo β-lactamases (MBL), which have a broad spectrum of hydrolytic activity against all penicillins, cephalosporins, and carbapenems. Commonly available β-lactamase inhibitors (such as clavulanic acid, tazobactam, or sulbactam) are also ineffective against this class of β-lactamases. But monobactam and aztreonam are showing activity against them. The *NDM*, *VIM*, and *IMP* genes encode these enzymes.[13,23]

Class D β-lactamases are oxacillinases (OXAs); they include more than 200 enzymes, among them a few variants possessing some carbapenemase activity. This class of β-lactamases are not able to hydrolyse expanded-spectrum cephalosporins.[13,23]

When looking at the CRE isolates from the index and other studies (Table 3) *Klebsiella* and *E. coli* are seen as the predominant organisms implicated in these infections. Also, what is more striking is the finding that the *NDM* gene is predominant, either in isolation or in combination with *OXA-48*, as the mechanism of resistance in most isolates irrespective of the organism. The understanding of the local antibiogram along with the likely organism suspected to be causing the nosocomial infection is very vital in choosing the appropriate empirical antimicrobial whenever healthcare professionals are faced with such nosocomial infections (Table 2). The current standard antimicrobial sensitivity tests done in laboratories can identify isolates with carbapenem resistance but are unable to identify the mechanism of carbapenem resistance. Understanding of the mechanism of carbapenem resistance is vital in deciding the appropriate antimicrobial (Table 2). However, there is a lack of utilisation of these molecular testing methods when faced with CRE infections due to various reasons, like a lack of availability or of clear understanding of their utility and needs.

Table 2: Different carbapenemases and response to antibiotics.[12,13,23,24]

Carbapenemases/ drug	Ceftazidime/ avibactam	Meropenem/ vaborbactam	Imipenem-cilastatin-relebactam	Cefiderocol
Class A (e.g., *KPC*)	Yes	Yes	Yes	Yes
Class B (e.g., *NDM, VIM,* and *IMP*)	No*	No	No	Yes
Class C (e.g., *OXA*)	Yes	No	No	Yes

*Broad spectrum of hydrolytic activity including all penicillins, cephalosporines, and carbapenems will not work with exception of monobactam aztreonam.[24,25]

Table 3: A comparison between different studies.

Study	Index study (N=164)		Anandan et al. (Christian Medical College [CMC] Vellore, India [N=120])[18]		Sekar et al. (Government Thiruvarur Medical College [GTC], India [N=177])[19]	
Most common organism and common gene responsible for carbapenem resistance	*K. pneumoniae* (n=152)	*OXA-48* (n=64)	*K. pneumoniae* (n=88)	*OXA-48* (n=39)	*E. coli* (n=89)	*NDM* (n=12)
		NDM (n=17)				
		OXA-48+NDM (n=69)		*NDM* (n=18)		*KPC* (n=9)
		OXA-48+NDM+VIM (n=1)				*OXA-48* (n=6)
Second most common organism and common gene responsible for carbapenem resistance	*E. coli* (n=10)	*OXA-48* (n=1)	*E. coli* (n=32)	*NDM* (n=30)	*K. pneumoniae* (n=88)	*NDM* (n=15)
		NDM (n=6)		*OXA-48* (n=8)		*OXA-48* (n=9)
		OXA-48+NDM (n=1)				*KPC* (n=3)

Study	Giri et al. (Maharashtra, India [N=50])[20]		Han et al. (China [N=935])[21]		Traczewski et al. (USA and UK [N=485])[22]	
Most common organism and common gene responsible for carbapenem resistance	*E. coli* (n=22)	*NDM* (n=6)	*K. pneumoniae* (n=709)	*KPC* (n=456)	*Enterobacteriaceae* (mainly *K. pneumoniae* and *E. coli* [n=343])	*OXA-48* (n=89)
		OXA-48 (n=2)				*KPC* (n=83)
		NDM+OXA-48 (n=10)		*NDM* (n=150)		*NDM* (n=73)
Second most common organism and common gene responsible for carbapenem resistance	*K. pneumoniae* (n=20)	*NDM* (n=5)	*E. coli* (n=149)	*NDM* (n=143)		*VIM* (n=53)
		OXA-48 (n=1)				
		zNDM+OXA-48 (n=14)		*KPC* (n=4)		*IMP* (n=4)

E. coli: Escherichia coli; K. pneumoniae: Klebsiella pneumoniae.

The authors' study could be used as some form of guidance in understanding the challenges and also in making the right choices when it comes to treating CRE infections. The *NDM* gene, being the predominant mechanism arming the CRE organisms, means that it becomes difficult to treat them adequately with the current available antimicrobial armamentarium. The ceftazidime avibactam combination is the only new antimicrobial combination currently available in the authors' setting. This combination thankfully works for the *OXA-48* strains. However, in the presence of the *NDM* mechanism of resistance, what is needed is the combination of aztreonam avibactam.[24,25] In the absence of this combination in the market currently, the authors are forced to use the combination of ceftazidime avibactam plus aztreonam to tackle these nosocomial infections. What seems to be the way forward is for the authors to have the combination of aztreonam avibactam available, which will help them to spare the ceftazidime avibactam combination to treat *OXA-48* infections alone. The concern is the emergence of resistance and, above all, what is more important is to realise the ever increasing means of resistant infections and working committedly towards various preventive measures that aim to limit such infections, and also the emergence of the resistance mechanism.

LIMITATIONS

The authors believe that the current study from their centre, being a single centre study, may not be representative of the prevalence of CRE infections and the mechanisms of resistance in these infections in every centre in this part of the globe. Hence, a multicentre study in a larger scale, across various parts of the country, is the need of the hour.

The current molecular testing employed in their lab (Xpert Carba-R) can identify limited mechanisms of carbapenem resistance. Two of their isolates testing negative for all known mechanisms suggest the possibility of other unidentifiable mechanisms that is outside the scope of the Xpert Caba-R assay. Availability of more advanced molecular testing, with a broader panel of genetic testing possibilities, will be able to identify those mechanisms, and may help the authors to understand and prepare them to tackle these organisms better.

Finally, this was a molecular study, but there were no Clinical and Laboratory Standards Institute (CLSI) guidelines available for the newer β-lactam/β-lactamase inhibitors combination antibiotic sensitivity pattern of the bacteria.

CONCLUSION

Appropriate molecular testing to identify the mechanism of resistance in CRE infections is important for understanding the epidemiology of these infections and plan the appropriate antimicrobial therapy.

Availability of cost-effective molecular testing facilities and improving awareness of the importance of testing are needed in order to tackle CRE infections more effectively.

KPC gene mechanism does not seem to be the prevalent mechanism of resistance among the authors' CRE isolates at the time the study was undertaken. However, the authors may need to periodically look into the available data annually to recognise and change their antimicrobial prescription practice.

Moving forward, a properly planned multicentric study with adequate representative samples will be able to give a clearer understanding of the prevailing mechanisms of CRE resistance in India, and is the need of the hour.

Above all, every healthcare setup needs to have a written infection control policy and mechanisms in place to make sure there is the appropriate implementation of the same in order to prevent these life-threatening infections from affecting patient outcomes in the era where technological advancements have given us the opportunity to treat complex disease processes effectively.

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From CoNFLict to Confidence: Solving a Diagnostic Dilemma Using Neurofilament Light – A Case Report

Authors: *P.M. Loveland,[1,2] D. Eratne,[1,3-5] S. Holper,[1,2,6] N. Yassi,[1,2,6] R. Watson,[1,2]

1. Population Health and Immunity Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia
2. Department of Medicine, The Royal Melbourne Hospital, University of Melbourne, Parkville, Australia
3. Neuropsychiatry, The Royal Melbourne Hospital, University of Melbourne, Parkville, Australia
4. Department of Psychiatry & Melbourne Neuropsychiatry Centre, University of Melbourne, Parkville, Australia
5. National Dementia Diagnostics Laboratory, The Florey Institute of Neuroscience and Mental Health, Parkville, Australia
6. Department of Neurology, Melbourne Brain Centre at The Royal Melbourne Hospital, University of Melbourne, Parkville, Australia

*Correspondence to Loveland.p@wehi.edu.au

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Abstract

Distinguishing neurodegenerative from primary psychiatric conditions is often challenging for clinicians, particularly when assessing older people presenting with neuropsychiatric symptoms. Measurement of fluid biomarkers of neurodegeneration is an emerging approach offering improved diagnostic accuracy. This report explores the use of emerging fluid biomarkers to address diagnostic challenges, framed around a case where the diagnosis of delirium with dementia was revised based on biomarker analysis, enabling treatment of a primary mood disorder with disabling psychiatric symptoms.

Key Points

1. Overlap in the clinical presentations for psychiatric conditions, delirium related to underlying dementia, and early behavioural variant frontotemporal dementia create diagnostic challenges, particularly for older adults. Misdiagnosis may lead to inappropriate treatment and related complications.

2. This case report demonstrates how the measurement of neurodegeneration-associated fluid biomarkers can markedly improve the accuracy and timeliness of diagnosis for patients presenting with neuropsychiatric symptoms and diagnostic uncertainty.

3. Clinical studies measuring cerebrospinal fluid and blood neurofilament light levels demonstrate its power to distinguish between primary psychiatric and neurodegenerative conditions; therefore, neurofilament light is a promising candidate for translation to clinicians' diagnostic 'toolkits' in the near future.

INTRODUCTION

Measurement of fluid biomarkers of neurodegeneration is an emerging approach offering improved diagnostic accuracy of neuropsychiatric conditions, particularly for atypical presentations. This article reports a case where the diagnosis of delirium with dementia was revised based on biomarker analysis, enabling treatment of a primary mood disorder with resolution of recurrent disabling psychiatric symptoms.

CASE DESCRIPTION

A 75-year-old male was admitted to a tertiary Australian hospital's acute medical unit with 3 weeks of progressive agitation and paranoia. This was on a background of multiple similar admissions for hyperactive delirium and behavioural variant frontotemporal dementia (bvFTD) clinically diagnosed 2 years prior. Other medical history included ischaemic heart disease, atrial fibrillation, hypertension, and dyslipidaemia. They had no psychiatric history.

Extensive delirium work-up, including blood and urine analysis, neuroimaging (MRI), electroencephalography, and cerebrospinal fluid (CSF) analysis for infective or autoimmune conditions, failed to reveal a precipitant. Despite care in a specialised delirium management ward for over a week, and treatment with intramuscular haloperidol, they remained agitated, disinhibited, and paranoid. Psychiatric evaluation deemed a primary psychiatric disorder to be unlikely, given the consistency of this presentation with previous delirium episodes.

However, careful review of previous admissions, and assessments from interceding outpatient Memory Clinic appointments, revealed three similar episodes lasting 3–6 weeks over the preceding 2 years, with complete symptom resolution between episodes. Objective cognitive assessments, repeated between episodes and during the current admission, were stable (Montreal Cognitive Assessment [MoCA] score: 25/30). Outpatient neuropsychological evaluation also demonstrated stable cognitive performance within the normal range, inconsistent with dementia.

Ongoing diagnostic uncertainty prompted further CSF analysis. Biomarker assay results for Alzheimer's disease[1] (amyloid β1–42 and phosphorylated tau) and general neurodegeneration (neurofilament light [NfL] and total tau) are given in Table 1. While amyloid β1-42 levels were decreased, total tau and phosphorylated tau levels were normal. Absence of marked NfL elevation, despite 2 years of severe neuropsychiatric symptoms, argued strongly against underlying neurodegenerative pathology such as bvFTD. In light of this, reassessment of the patient's mental state and review of their clinical trajectory by the acute hospital Old Age Psychiatry consultation service resulted in a revised diagnosis of bipolar affective disorder. This facilitated referral to an inpatient psychiatric hospital, where treatment with lithium and quetiapine achieved long-term remission, sustained for 3 years.

DISCUSSION

For patients presenting with neuropsychiatric symptoms, particularly in cases of diagnostic uncertainty as described here, addition of fluid biomarker measurement to the diagnostic toolkit can markedly improve the accuracy and timeliness of diagnosis.

Table 1: Biomarker assay results for Alzheimer's disease.

CSF protein	Result (pg/mL)	Normal reference (pg/mL)/interpretation
T-tau	259	<304 (60–70 years); <379 (>70 years)
P-tau	57	<59 (60–70 years); <74 (>70 years)
Aβ1-42	355	>656 (>60 years)*
NfL	682	Not elevated for >70 years†

CSF biomarker results profile was not consistent with neurodegeneration or Alzheimer's disease-related pathology.

*An isolated reduced Aβ1–42 can be a non-specific finding in in many neurodegenerative and non-neurodegenerative conditions and may normalise after acute episodes. Therefore, in the absence of abnormalities in t-tau and p-tau, low Aβ1–42 was not considered to be suggestive of an Alzheimer's disease-related pathology.

†Age-normative ranges for NfL remain to be validated for routine clinical use. This result was compared against a contemporaneous research population involving patients with psychiatric and neurodegenerative disorders, for which the same analytical technique was employed.[2] The optimal research cut-off for distinguishing neurodegenerative from primary psychiatric and non-neurodegenerative disorders in people aged >70 years was 970 pg/mL (from this research study cohort).

Note: NfL concentrations were measured in duplicate using a commercial ELISA (NF-Light™ [UmanDiagnostics, Umeå, Sweden]), according to the manufacturer's protocol.

Aβ1–42: amyloid β1–42; CSF: cerebrospinal fluid; NfL: neurofilament light; p-tau: phosphorylated tau; t-tau: total tau.

Distinguishing early bvFTD, delirium related to underlying dementia, and psychiatric conditions from one another can be especially challenging due to symptom overlap.[3] Misdiagnosis may lead to inappropriate treatment and significant complications, including repeated hospitalisation and antipsychotic administration, as demonstrated by this case. Particularly in older adults, treatment of presumed hyperactive delirium in the context of dementia with antipsychotics carries a risk of significant mortality and morbidity; therefore, rigorous interrogation of atypical presentations is imperative.[4,5] Objective disease markers are needed to improve diagnostic accuracy in clinical scenarios such as these.

NfL appears particularly promising as a candidate for clinical application in the near future. Clinical studies using CSF NfL levels demonstrate its power to distinguish between primary psychiatric and neurodegenerative conditions, with a recent study showing high discriminatory accuracy (area under the curve: 0.94; sensitivity: 92%; specificity: 87%).[2,6] Given the logistical challenges inherent in CSF sampling, advances allowing reliable measurement of NfL in blood significantly improve the feasibility of rapid translation to the clinic.[7] Concordance between CSF and blood NfL levels has been established across a range of neurodegenerative conditions, with subsequent blood-only studies supporting NfL as a useful tool for the discrimination of neurodegenerative and psychiatric diagnoses.[8,9]

CONCLUSION

Clinicians should be optimistic about the much-needed diagnostic clarity that NfL measurement, in CSF or blood, may offer their patients suffering from neuropsychiatric symptoms.

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Pulmonary Tuberculosis Presenting as Acute Respiratory Failure and Unilateral Complete Lung Collapse: Two Case Reports With Review of Literature

Authors: Deependra Kumar Rai, *Vatsal Bhushan Gupta, Priya Sharma, Ameet Harish

Department of Pulmonary Medicine, All India Institute of Medical Sciences (AIIMS), Patna, India
*Correspondence to vatsalgupta.gkp@gmail.com

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Abstract

Massive haemoptysis, which can result in abrupt respiratory failure, is a potentially fatal consequence of pulmonary tuberculosis. Radiologically, it can present as a complete collapse of one lung due to endobronchial clot formation. Here, the authors report two cases, one of whom was a female who was pregnant and near term, who presented with massive haemoptysis followed by severe respiratory distress. Fibre optic bronchoscopy was performed in both cases, and clots were retrieved. One of the patients required intubation and invasive mechanical ventilation. The procedure was technically difficult because of the acute hypoxaemia, necessitating a team of pulmonologists and anaesthetists. Bronchoalveolar lavage enabled the authors to clinch the diagnosis. Post-procedure, both patients showed rapid clinical and radiological improvement. In resource-limited settings where rigid bronchoscopy is not available, fibre optic bronchoscopy can be performed for clot retrieval, as it can be a life-saving procedure for the patient.

Key Points

1. Massive haemoptysis with unilateral complete lung collapse and rapid respiratory failure are life-threatening complications of pulmonary tuberculosis. In order to clear the airways, this necessitates immediate hospitalisation and blood clot extraction.

2. Fibre optic bronchoscopy with saline lavage and forceps extraction can be used to enable clot removal in a piecemeal manner in resource-constrained areas when rigid bronchoscopy facilities are not accessible.

3. A suction catheter can be inserted over a paediatric fibre optic bronchoscope and progressed to the location of the obstruction. After this, bronchoscope should be removed and a direct connection made between the suction catheter and suction port. This enables removal of a large blood clot.

INTRODUCTION

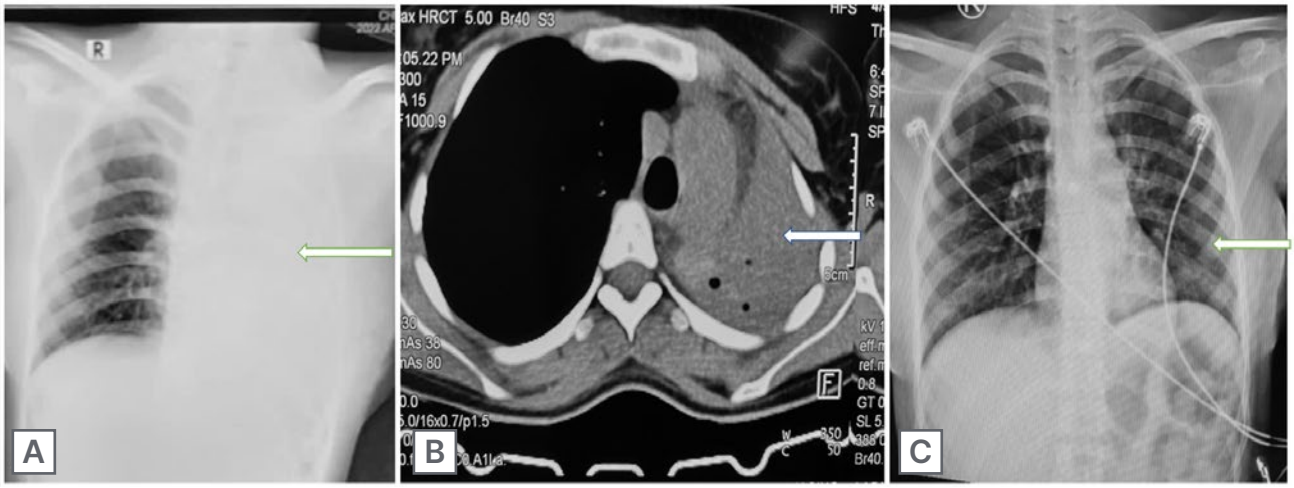
Any haemoptysis exceeding 100 mL/hr, causing abnormal gas exchange/airway obstruction or leading to haemodynamic instability is defined as life-threatening or massive haemoptysis.[1] Few case reports have described blood clot formation secondary to massive haemoptysis leading to airway obstruction.[2] Here, the authors report two cases who presented within a span of 1 month, where massive haemoptysis lead to acute respiratory failure. On radiology, there was unilateral complete lung collapse. Flexible bronchoscopy was used in both instances to remove the clots. Pulmonary tuberculosis (PTB) was the underlying aetiology in both cases.

CASE REPORT 1

A 19-year-old female presented to the emergency room with complaints of dyspnoea, cough with expectoration for 1 week, and chest pain for 2 days. They had a history of massive haemoptysis 7 days before. Blood was bright red, measuring approximately 300–400 mL. The patient received numerous injections from a local doctor in order to achieve haemostasis. They had no history of any other skin or mucosal bleed, and no comorbidities. There was no history of prior antitubercular treatment or contact with patients with tuberculosis. On examination, they were dyspnoeic maintaining a saturation of peripheral O_2 (SpO_2) of 95% with a non-rebreathing face mask at 15 L/min, respiratory rate of 28 /min, pulse rate of 124 /min, and blood pressure (BP) of 108/62 mmHg. PaO_2/FiO_2 ratio was 76 (FiO_2 approximately 100%). Chest X-ray showed opaque haemithorax with an ipsilateral mediastinal shift (Figure 1A). On high-resolution CT (HRCT) there was collapsed left lung with an abrupt cut-off of the left mainstem bronchus (Figure 1B).

The patient was admitted to the intensive care unit in an isolated cubicle and kept on a high flow nasal cannula at 60 L/min. A fluid bolus of 800 mL (20 mL/kg) was given over 30 minutes. Mean BP was below 65 mmHg; thus, dopamine (the first line inotrope of choice in the author's institution for when central venous access is not available) infusion was started at 5 µg/kg/min to prevent hypovolemic shock and renal hypoperfusion. A quick bedside check video bronchoscopy revealed blood clots obstructing the entire left mainstem bronchus. The procedure was abandoned due to significant desaturation. Haemoglobin was 13.2 g/dL. No blood transfusion was required. Total leukocyte count, platelet count, and liver and kidney function tests were within normal limit. The next day, the patient was shifted to the operating theatre and electively intubated. Due to non-availability of rigid bronchoscopy, which is the ideal procedure here, a video bronchoscopy was done via an endotracheal tube of size 8 mm. Clots were retrieved with biopsy forceps of size 2.4 mm and foreign body forceps. However, a few large clots could not be extracted with forceps or suctioned via bronchoscope working channel. Hence, the authors employed a paediatric fibre optic scope over which a flexible 18 French suction catheter was positioned. The left mainstem bronchus was reached with the bronchoscope and suction catheter, which were then removed, leaving the catheter in place and being advanced further. The catheter was connected to the suction channel and a large blood clot was removed. Remaining clots were suctioned subsequently and patency was achieved in all the lobes. Bronchoalveolar lavage (BAL) was collected for further testing. The patient was extubated on the table and kept on facemask at 4 L/min. There was resolution of lung collapse on chest X-ray (Figure 1C). The next day, the patient had a SpO_2 of 97% on room air and a BP of 120/72 mmHg.

Figure 1: Radiological findings in case 1.



1A) Chest X-ray showing opaque hemithorax with ipsilateral mediastinal shift (white arrow).
1B) HRCT showing collapse of left lung with abrupt cut off of left mainstem bronchus (white arrow).
1C) Chest X-ray post procedure showing resolution of lung collapse (white arrow).

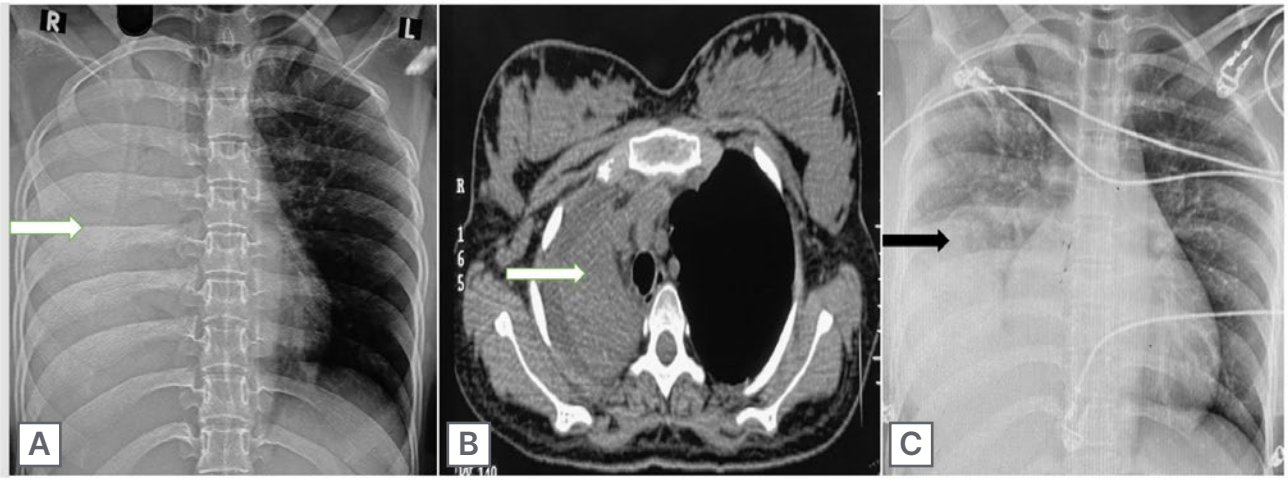
HRCT: high-resolution CT.

Mycobacterium tuberculosis was detected on BAL GeneXpert (Cepheid, Synnyvale, California, USA). The patient was initiated on anti-tubercular treatment (ATT) based on their weight band, and is under follow-up.

CASE REPORT 2

A 21-year-old female, 37 weeks pregnant, presented to the emergency room with complaints of dyspnoea, cough, and chest pain for the past 6 days. They had a history of massive haemoptysis 6 days prior. Due to concerns about haemoptysis reoccurring, their scheduled normal vaginal delivery was cancelled, and they instead had a lower segment Caesarean section under spinal anaesthesia at a private hospital. The haemoptysis was bright red and approximately 500 mL. There was no history of fever, loss of appetite, or weight loss, and no comorbidities or prior respiratory illness. Post-lower segment Caesarean section, the patient became symptomatic and hypoxic. They were managed with O_2 and other supportive care at a private hospital. The neonate was healthy. At presentation, the patient was severely dyspnoeic with a SpO_2 of 60% at room air and 92–98% with non-rebreathing face mask at 15 L/min. They had tachycardia, tachypnoea, and their BP was 100/70 mmHg. They were admitted to the intensive care unit in an isolated cubicle. Chest X-ray showed opaque right hemithorax (Figure 2A). On HRCT there was collapse consolidation of right lung parenchyma with ipsilateral mediastinal shift and minimal right-sided pleural effusion. (Figure 2B). A short bedside check fibre optic bronchoscopy revealed complete occlusion of the right mainstem bronchus by blood clots. The patient was shifted to the bronchoscopy suite, and video bronchoscopy was performed under minimal sedation with 1 mg of intravenous midazolam without intubation and invasive mechanical ventilation. Blood clots were removed with saline lavage, biopsy forceps of size 2.4 mm, and foreign body forceps. The procedure took approximately 2 hours, and patency of the entire right lung airways was achieved. Patient saturation improved gradually during the procedure. BAL was taken from the right lower lobe. Within the next 24 hours, all vitals were stable. Chest X-ray showed marked radiological clearing (Figure 2C). BAL for acid-fast bacilli was 1+ and GeneXpert detected mycobacterium tuberculosis (TB), which was rifampicin sensitive. Bacterial and fungal cultures were sterile. ATT was started in accordance with the patient's weight band, and the patient is under follow-up.

Figure 2: Radiological findings in case 2.



2A) Chest X-ray showing complete collapse consolidation of right lung (white arrow).
2B) HRCT showing complete collapse consolidation of right lung parenchyma with ipsilateral mediastinal shift and minimal right sided pleural effusion (white arrow).
2C) Chest X-ray showing significant radiological improvement post procedure (black arrow).

HRCT: high-resolution CT.

DISCUSSION

India is a country with a high burden of TB. The World Health Organization (WHO) TB statistics for India for 2021 give an estimated incidence figure of 2.59 million cases, 188 cases per 100,000 population.[3] A cough lasting for more than 2 weeks, chest pain, haemoptysis, weakness or fatigue, weight loss, lack of appetite, chills, fever, and night sweats are the common symptoms associated with PTB. Sputum microscopy, culture test, as well as the newer molecular tests such as GeneXpert and Truenat are helpful in diagnosis.[3] TB was found in 79.2% of patients with haemoptysis, according to an Indian study.[4] The majority of patients with a diagnosis of TB have a good outcome. This is mainly because of effective treatment. Without treatment mortality rate for tuberculosis is more than 50%.[5] According to the Global TB report, response to ATT was 85% among new and relapsed cases of PTB in India, when treated with the standard four drug regimen.[6]

Several disorders have been described where an endobronchial blood clot can lead to airway obstruction. A few benign conditions include PTB, bronchiectasis, vasculitis, invasive fungal infections, bleeding disorders, post-tracheotomy, and trauma during suctioning. Malignant diseases include bronchogenic carcinoma, carcinoid tumours, metastatic pulmonary nodules, and other similar diseases. A history of mild or massive haemoptysis may be found before an endobronchial blood clot formation in most cases; however, respiratory failure is seen in approximately 30% of patients without a previous history of haemoptysis.[2]

PTB presenting as massive haemoptysis followed by clot formation could be a life-threatening complication, as it can lead to respiratory failure. Active PTB is a hypercoagulable state as these patients show low haemoglobin, elevated total leukocyte count, platelet count, plasma fibrinogen, factor VIII, plasminogen activator inhibitor 1, and decreased antithrombin III and protein C levels. Etamsylate is commonly administered to control bleeding. It works by increasing capillary vascular resistance and platelet adhesiveness.[7] In pregnancy there is an elevation of factors VII, VIII, and X, as well as fibrinogen, and von Willebrand factor, leading to a marked increase in procoagulant activity, which is maximal around the term. Prothrombin

Table 1: Case reports of complete lung collapse in pregnancy with pulmonary tuberculosis as the underlying aetiology.

Author/ Year	Age	Duration of pregnancy	Clinical features	Radiology	Diagnosis	Management
Singhal et al. (2008)[3]	20	36 weeks	Cough with haemoptysis, fever, loss of appetite	Complete left lung collapse	Sputum AFB positive	Clot retrieval via rigid bronchoscope
Masukume et al. (2013)[8]	33	18 weeks	Haemoptysis, breathlessness	Complete left lung collapse with pleural effusion	Sputum AFB positive	Conservative management

AFB: acid-fast bacilli.

fragments and thrombin–antithrombin complexes are increased. Protein S activity is significantly reduced along with activated protein C resistance. As a result, overall fibrinolytic activity is impaired during pregnancy.[8,9] Bleeding in the authors' case could be the result of one or more of the above factors. Table 1 gives the description of the two cases in which PTB in pregnancy caused severe haemoptysis and the development of endobronchial clots that resulted in total lung collapse, which to the best of the authors' knowledge are the only two cases published in literature.

Initial management of endobronchial clot includes evaluation by fibre optic bronchoscopy, followed by saline lavage and suctioning. If unsuccessful, this is followed by extraction with the help of biopsy forceps, either en bloc or in piecemeal fashion. Rigid bronchoscopy is the preferred technique for suctioning and forceps extraction of blood clots. It enables effective tamponade of the bleeding airway preventing the contralateral lung from getting affected. Recently, techniques for the dissolution of blood clots with the help of topical thrombolytics, such as streptokinase, urokinase, and tissue plasminogen activator have also been described.[7,10,11] Cryotherapy via flexible bronchoscopy can also be used for clot removal.[12,13]

CONCLUSION

Massive haemoptysis secondary to pulmonary tuberculosis can lead to complete lung collapse and acute respiratory failure. Use of fibre optic bronchoscopy for clot removal is a time-consuming process, as they have to be removed in piecemeal fashion. However, this can be a life-saving procedure for patients in centres where advanced bronchoscopic techniques like cryoextraction and rigid bronchoscopy are not available.

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Cutaneous Squamous Cell Carcinoma of the Hand Presenting as Clinical Perineural Invasion

Authors:	*Sera Sarsam,[1] Shyamalar Gunatheesan,[2] Nigel Mann[3] 1. Austin Health, Heidelberg, Victoria, Australia 2. ODE Dermatology, Fitzroy, Victoria, Australia 3. Department of Plastics and Reconstructive Surgery, The Northern Hospital, Melbourne, Victoria, Australia *Correspondence to sera.sarsam@live.com

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Abstract

Cutaneous squamous cell carcinoma of the hand with clinical perineural invasion is uncommon. This article describes a case of a 70-year-old female who presented with a small painful nodule on the dorsum of the left hand with minor skin surface changes who underwent excisional biopsy. A deep long subcutaneous cord was palpable extending proximally from the nodule. Intraoperative findings showed a tumour growing 2.5 cm along the dorsal cutaneous nerve of the hand, and histopathological examination revealed a primary well-differentiated squamous cell carcinoma with perineural invasion. This case highlights the importance of considering malignancy as a differential diagnosis when dealing with atypical lesions.

Key Points

1. Cutaneous squamous cell carcinoma of the hand with clinical perineural invasion is uncommon. Early detection and treatment of this malignant disease is vital to preserving the function of the hand, and hence quality of life.

2. This article describes a rare case of cutaneous squamous cell carcinoma of the hand presenting as a tender dermal nodule on the dorsum of the hand, with palpable extensive neural spread along an adjacent cutaneous nerve. It also discusses the different presentations of cutaneous squamous cell carcinoma, and the risk of perineural invasion and its implication.

3. Clinicians should be aware of the different possible presentations of cutaneous squamous cell carcinoma of the hand, and should have a high index of suspicion when dealing with atypical lesions of the hand.

INTRODUCTION

Cutaneous squamous cell carcinoma (SCC) contributes to 20% of non-melanoma skin cancers and early diagnosis is vital to reducing the risk of local and distant metastasis.[1] Perineural invasion (PNI) is a well-established, high-risk feature in cutaneous SCC and is defined as the invasion of the space surrounding the nerve.[2] Cutaneous SCC with PNI may present with neurological symptoms, including sensory changes, paraesthesia, pain, or paralysis.[3] This article reports an atypical case of cutaneous SCC presenting as a tender dermal nodule on the dorsum of the hand, with palpable extensive neural spread along an adjacent cutaneous nerve.

CASE DESCRIPTION

A 70-year-old White female was referred by a dermatologist with a 6-month history of a painful and slow-growing nodule on the dorsum of their left hand. The patient had seen their general practitioner 2 months earlier, who performed an ultrasound scan of the lesion showing a hypoechoic structure that could be characterised as a neuroma. A shave biopsy of the skin overlying the nodule had been done; it was not sufficient to diagnose the nature of the lesion, showing only solar keratosis. The patient's past medical history included previous surgical excision of a left medial forearm SCC and a chest wall basal cell carcinoma. They had Fitzpatrick skin Type II with no significant history of sun exposure.

Physical examination revealed a tender 12 mm subcutaneous nodule on the dorsum of the left hand, associated with sensory loss in the fourth web space. There was no axillary lymphadenopathy. Based on the examination findings, the differential diagnoses included a neural lesion, glomus tumour and malignancy. The patient underwent excisional biopsy with flap repair surgery. The operative findings at surgery revealed a visible neural tumour growing along the dorsal cutaneous nerve over a distance of 2.5 cm (Figure 1) that was resected to the depth of bare extensor tendon. Histopathological examination demonstrated a primary well differentiated SCC involving the deep and transverse margins, with perineural invasion and probable complete intraneural obliteration by the SCC (Figure 2). A further wide excision of the lesion was considered; however, to avoid potential compromise of the extensor apparatus, the patient was referred for radiotherapy.

At the 1-month follow up appointment, prior to radiotherapy, the patient noticed a small lump growing adjacent to the surgical site, with a punch biopsy revealing recurrence of the SCC. The patient then underwent wide local excision of the entire wound and large split skin graft repair. Histopathology confirmed no residual SCC, and the further excised segment of nerve showed no tumour proximally or distally. No post-operative radiotherapy was felt indicated at this stage due to adequate surgical clearance.

At follow-up, the graft healed well, and the hand returned to full normal function. There were no signs of local recurrence and no lymphadenopathy of the axilla at the 12-month interval. The patient will continue follow-up with their dermatologist for ongoing surveillance.

DISCUSSION AND CONCLUSION

Cutaneous SCC is the most common malignancy of the hand, and typically presents on its dorsal surface.[4] One study has reported that cutaneous SCC affecting the hand bears a higher recurrence rate when compared to other body sites.[5] Atypical presentations for hand SCCs have been previously reported in the literature. Both Fisher et al.[6] and O'Sullivan et al.[7] have reported cutaneous SCC of the hand presenting as a chronic wound infection on both the right index and left ring finger, which failed to respond to treatment in a 33-year-old and 43-year-old

male, respectively. In both cases, histopathology showed well differentiated cutaneous SCC with no PNI reported. In addition, cutaneous SCC of the hand has been reported to disguise as an infected epidermal cyst.[8]

Cutaneous SCC with PNI is considered a high-risk skin cancer with a poorer prognosis. Leibovitch et al.[2] has reported the incidence of PNI in cutaneous SCC to be 4.7% in primary lesions. The presence of PNI is associated with increased recurrence rate and increased lymph node metastasis rate.[3,9] Furthermore, SCC with PNI have a 3-year disease-specific survival rate of 64% compared with 91% for SCC without PNI.[10] There are certain tumour characteristics that increase the risk of PNI; these include tumour size greater than 2 cm, SCC in the head and neck region, male gender, recurrent disease, and immunosuppression.[2,3]

Cutaneous SCC with PNI can present with neurological symptoms with no obvious skin lesion resulting in misdiagnosis and delay in treatment. A case has been reported in a 75-year-old male who initially presented with nasal blockage, right-sided face pain, and right eye ptosis was misdiagnosed as sinus infection and Bell's palsy. After multiple investigations, including MRI, histopathological confirmation was taken from a scaly skin patch on the right cheek, which showed a moderately differentiated cutaneous SCC with PNI.[11]

The location of the tumour in this case was unusual for cutaneous SCC presenting as clinical PNI; such lesions are commonly found in the head and neck region.[2] Most cases described in the literature involved the trigeminal nerve, followed by the facial nerve.[3] The authors are

Figure 1: Intraoperative photograph of the tumour growing along the dorsal cutaneous nerve of the hand (yellow arrows), and macroscopically normal dorsal cutaneous nerve (blue arrows).

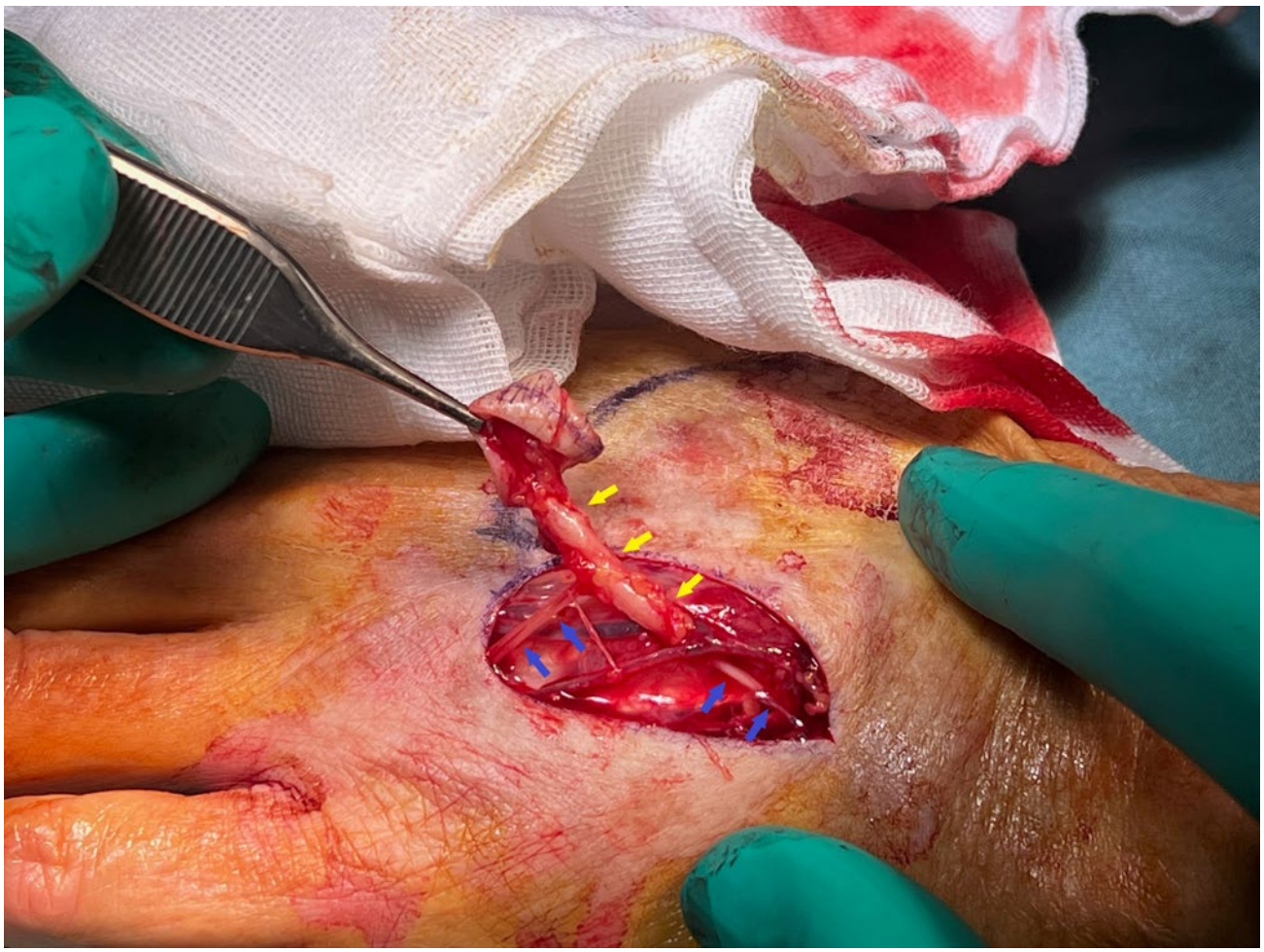
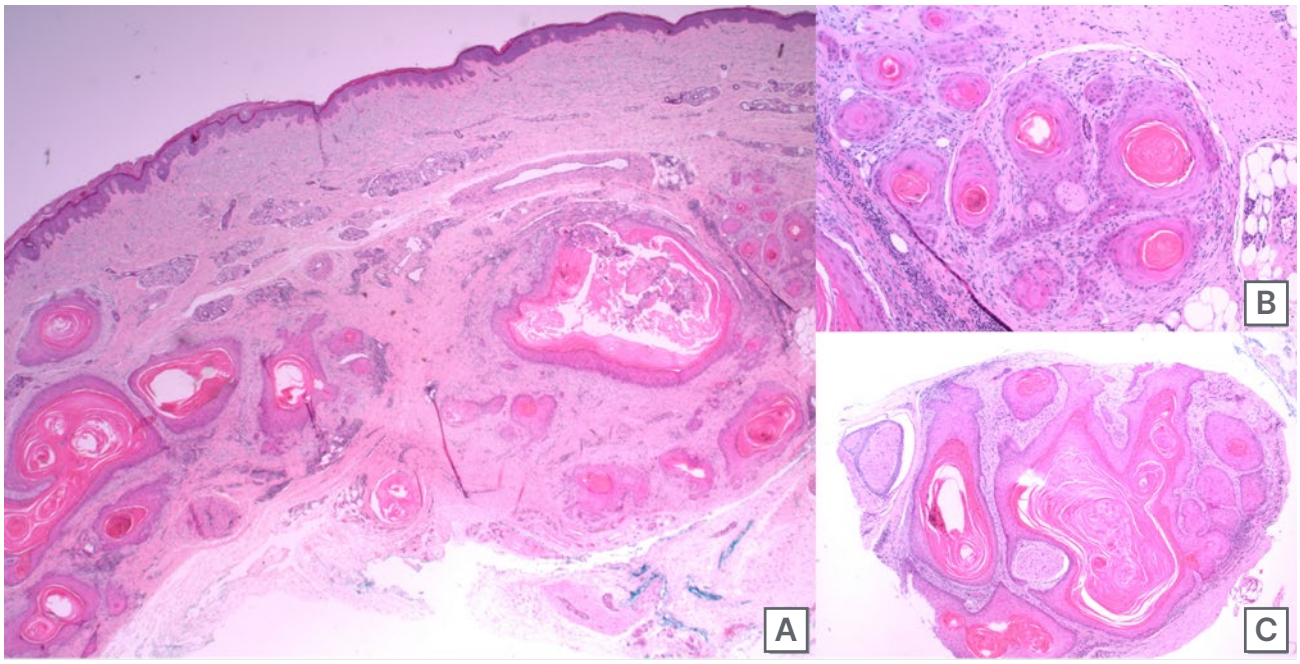


Figure 2: Histopathologic photographs of the left dorsal hand nodule using a haematoxylin and eosin stain.



A) 2x: excisional skin biopsy showing SCC infiltrating through full thickness skin.
B) 10x: photograph at high magnification showing 0.1mm diameter nerve in centre surrounded by SCC.
C) 4x: photograph of the detached subcutaneous nerve (top left and centre left) showing complete intraneural obliteration by SCC.

SCC: squamous cell carcinoma.

not aware of any previously reported case of cutaneous SCC of the hand presenting with neural dysfunction related to PNI. Karia et al.[3] have demonstrated that the presence of clinical PNI increases the risk of local recurrence of cutaneous SCC compared to those with incidental PNI, as well as increasing the risk of death. Therefore, SCC of the hand with clinical PNI is considered high-risk skin cancer, and ongoing surveillance is recommended.

In conclusion, cutaneous SCC with clinical PNI of the hand is uncommon. In this case, the initial shave biopsy was inadequate to exclude a diagnosis of cutaneous malignancy and the lack of apparent cutaneous lesion may have been misleading. Notably, the cutaneous SCC was growing along the dorsal cutaneous nerve of the hand forming a subcutaneous cord. Early diagnosis was essential to achieve a positive outcome for the patient. Clinicians should be aware of the different possible presentations of cutaneous SCC of the hand and should have a high index of suspicion, especially when assessing a patient with a nodule associated with neurological symptoms.

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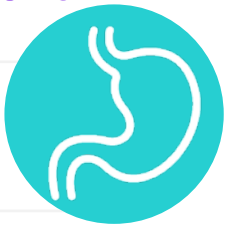
Severe, Refractory Anaemia Associated with *Helicobacter Pylori* Infection Managed With *L. Reuteri* DSMZ17648 (Probiotic) and Haeme Iron Supplements: A Case Report



Authors:	*A. Hinduja Aarti Clinic, Navi Mumbai, Maharashtra, India *Correspondence to dranand01@gmail.com

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Abstract

Helicobacter pylori infection can be observed with increased frequency in patients with iron deficiency anaemia (IDA), especially in resistant cases. This case report describes a case of resistant IDA that responded to probiotic (*Lactobacillus reuteri* DSMZ17648) and oral haeme iron polypeptide supplementation, highlighting that oral probiotic supplement trial may be considered before antibiotic therapy for *H. pylori* treatment in a patient with IDA.

Key Points

1. This case report addresses the iron deficiency anaemia (IDA), a global health problem occurring primarily due to nutritional deficiency, and resistant IDA due to the presence of *Helicobacter pylori* infection.

2. The authors' case report highlights that screening for *H. pylori* is recommended in refractory IDA, and this treatment approach should also include probiotics and iron supplements.

3. The remission of IDA in patients using a unique strain of probiotic (*Lactobacillus reuteri* DSMZ17648) before using antibiotics shows a novel approach to using probiotics before antibiotics, especially in patients with antibiotic resistance or hypersensitivity.

INTRODUCTION

Iron deficiency anaemia (IDA) is a global health problem affecting both developing and developed countries, particularly in Asia.[1] Nutritional deficiency, menstrual blood loss, and chronic gastrointestinal blood loss are the common causes of IDA.[2] Association between *Helicobacter pylori* infection and IDA has been known for the past three decades.[3] *H. pylori* infection affects over 4.4 billion individuals, and its prevalence varies from 18.9–70.1%.[4] Besides gastric disease, *H. pylori* is associated with extra-gastric diseases. Though the exact mechanism remains unclear, a few postulated causes could be gastric and intestinal inflammation; erosions and ulcers leading to chronic occult blood loss; iron malabsorption from alteration of gastric acidity; atrophic gastritis; reduction in ascorbic acid in gastric secretions; and alteration in iron metabolism due to increased hepcidin level and decreased haeme oxygenase-1 levels.[3,5] IDA is observed in *H. pylori* infection irrespective of the presence or absence of peptic-ulcer disease.[6] The American College of Gastroenterology (ACG) guidelines suggest testing for *H. pylori* infection in patients with unexplained IDA despite an appropriate evaluation.[7] Most patients with *H. pylori* respond to the initial combination treatment of a proton pump inhibitor, clarithromycin, amoxicillin, and metronidazole.[7] However, a significant failure rate for eradication therapy has been reported due to poor compliance and antimicrobial resistance. This has led to the increased role of probiotics species along with standard iron therapy. Prominent probiotic strains, such as *Saccharomyces boulardii* and *Lactobacillus johnsonii* La1, reduce the *H. pylori* bacterial load.[8] With this background, in this paper the author reports on the case of an adult female with severe IDA associated with *H. Pylori* infection, who had significant improvements with the use of probiotic strain *Lactobacillus reuteri* DSMZ17648.

CASE DESCRIPTION

A 38-year-old female visited the Aarti Clinic, Navi Mumbai, India, with complaints of extreme fatigue, dyspnoea on exertion, and palpitations. They also had constipation and bloating after meals. Their relevant medical and menstruation history were normal. On examination, the patient had severe pallor, tachycardia, and hypotension. Systemic examination revealed no significant abnormalities. Their haemoglobin (Hb) was 6.8 g/dL, with a microcytic hypochromic picture. In other indices, haematocrit was 26.9%, mean corpuscular volume was 66.6 fL, and mean corpuscular haemoglobin was 16.8 pg. Platelets and total leukocyte counts were normal. There were no thyroid hormone abnormalities. The patient's Hb electrophoresis was also normal. They had been experiencing these complaints for the last 3 months.

For severe anaemia, the patient was treated with oral and intravenous iron at different centres, but the haematology picture did not change significantly. Based on their non-specific abdominal symptoms, their stool was examined for routine and opportunistic pathogens, which were normal. Stool test for *H. pylori* antigen was positive. The author's centre counselled the patient, and advised upper gastrointestinal (GI) endoscopy, but the patient refused to undergo any invasive procedure.

Based on clinical presentation and antibody report (the patient had a history of allergic reactions to multiple antibiotics, and was very afraid of consuming antibiotics), they were started with *L. reuteri* DSMZ17648 probiotic twice a day for 1 month, accompanied by supplementation of oral iron as haeme iron polypeptide administered twice a day, along with an iron-rich diet. At 1 month follow-up, the patients' Hb had increased to 11.1 g/dL, their haematocrit was normal, and they had stable haematological indices. They had complete relief from their fatigue and abdominal symptoms. The probiotic was continued once a day for another

month while the iron supplement was continued for another 3 months once a day. At 3 month follow-up, Hb had increased to 13.5 g/dL with improvement in microscopic features. The patient was completely symptom-free at the end of 3 months, and there was no recurrence of anaemia at 3 month follow-up.

DISCUSSION

Moderate to severe IDA that does not respond to corrective measures with iron supplementation warrants further investigation. *H. pylori* infection has been identified to be a cause of IDA. However, it may not be suspected in routine anaemia evaluations. Such a situation is a diagnostic and treatment challenge for the treating physician.

In refractory IDA, a full gastroenterology workup with upper and lower GI endoscopies is necessary to establish the IDA cause, and thereby plan and optimise specific treatment success. Multiple studies have established the higher prevalence of *H. pylori* infection in patients with refractory IDA.[6,9,10] In this case, severe anaemia was observed that did not respond to oral or iron supplementation. Given the substantial presence of *H. pylori* infection in the Indian subcontinent, the patient was evaluated for this infection, which turned out to be present. Studies have established that 14 days of triple therapy for *H. pylori*, along with iron supplements, is effective in improving Hb concentration, haematological indices, and anaemic symptoms.[10,11] However, antibiotic treatment may often lead to GI side effects and cause alterations in the gut microbiome. The use of probiotics along with triple-therapy of *H. pylori* has been shown to reduce the GI upset and improve the microbial environment.[12]

The use of probiotic strains, especially *S. boulardii, L. reuteri,* and *Lactobacillus rhamnosus GG,* is effective in *H. pylori* eradication, and reduces the antibiotic-associated GI adverse effects.[8] The *L. reuteri* DSMZ17648 strain that was used is a highly specific and antagonist to *H. pylori*. This strain co-aggregates *H. pylori*, and probably masks the bacterial surface structures, thereby interfering with its motility and impairing ability to bind with gastric mucosa. Also, this probiotic strain may compete with *H. pylori* for binding with specific strains. Thus, *H. pylori* is cleared from the stomach. This probiotic strain does not interfere with other commensal intestinal flora.[13] An Indian study[14] reported a significantly improved rate of *H. pylori* eradication rate of 86.6%, reduced intensity of GI symptoms, and also treatment-related side effects with the addition of *L. reuteri* DSMZ17648 to standard triple drug therapy.[14]

In addition, the author's centre used haeme iron polypeptide for iron supplementation because conventional oral iron (non-haeme) supplementation is associated with poor compliance, GI side effects, and suboptimal GI absorption of iron.[15] Haeme iron polypeptide is a new generation of oral iron therapy that lacks any dietary or drug interactions, and can be taken irrespective of mealtimes, and co-administered with other medications.[16] Compared to conventional oral irons, haeme iron polypeptide has seven times greater bioavailability and negligible side effects, and is postulated to be absorbed by dual mechanisms.[17,18] Gastrointestinal absorption of haeme iron is far less affected by dietary constituents such as polyphenolic tannins, phytates, and soy and dairy products (calcium).[15,16,19] This could have also supplement in the improvement of IDA.

In this case, the underlying cause of IDA was *H. pylori* infection. *H. pylori* can cause anaemia by several different mechanisms, especially by blood loss and iron malabsorption. The remission of IDA in a patient with probiotic treatment even before the use of antibiotics shows a novel approach to using probiotics before antibiotics, especially in patients with antibiotic resistance or hypersensitivity.

In this report, a major limitation was the patient's unwillingness to undergo upper GI endoscopy. This would have revealed bleeding lesions in the GI tract, or other GI disorders causing IDA, which could not be ruled out. However, even in the absence of ulcerative GI disease, IDA can occur.[6] The author's clinic did not find occult bleeding in the stool examination. The use of probiotics in this case was a very considerate decision that added to the treatment success without an aggressive standard antibiotic regimen. The probiotic preparations administered contained *L. reuteri* DSMZ17648, which is known to be effective.

CONCLUSION

This case highlights that screening of *H. pylori* should be undertaken in patients with refractory IDA. It is emphasised that the root cause should be identified in all cases of anaemia, especially the resistant ones, and it is important to understand that merely replacing iron may not help in restoring IDA conditions. *H. pylori* might not always be presented with classical symptoms of reflux, acidity, and abdominal pain. However, constipation and bloating are lesser common presentations that need attention.

Apart from the standard regimen, the use of probiotics should be recommended as a supportive treatment option. A trial of probiotics even before prescribing antibiotics can help improve symptoms, and also assist in reducing the resistance. The author emphasises that the use of an oral iron supplement with lesser gastric intolerance can ensure a good level of compliance. Therefore, it is important to rule out *H. pylori* infection, especially in moderate to severe anaemia, in the Indian context. A trial of probiotics before *H. pylori* antibiotic therapy can be helpful for patient management.

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