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Contact
inspirestudentjournal@gmail.com

Website
www.inspirestudentjournal.co.uk

Design
Cris Sutera
www.crissutera.co.uk

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INSPIRE provides a platform for students to experience research first hand, from taster days to funded Summer Studentship Research Projects. The ISHSRJ is a collaborative effort between the Universities of Bristol, Cardiff, Exeter and Plymouth. This issue continues to promote the work students have completed in effort to support INSPIRE's overall aim, to provide students with the opportunity to experience research and consider this in their chosen career path Moreover, the ISHSRJ provides students with the opportunity to experience the publication process first hand, as well as volunteer as a peer reviewer. This is an excellent way to discover new research and projects produced by students, whilst strengthening your CV. We strongly encourage all students reading this journal who feel inspired to engage in research to participate in what the INSPIRE scheme has to offer.

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FRONT COVER

Art by Sofia Rosca-Velea, University of Bristol. "Based on a small but striking moment with a memorable patient on a geriatric ward, this art piece explores the passing of time and the care we exert into keeping it at bay. The patient had just requested help with taking their watch off, and as three of us all scrambled to figure out the locking system – a very secure watch, compliments to the manufacturers! – it weighed on me that this might be the only bit of out-of-hospital identity the patient had left, and we were now removing it. I could tell the patient's morale lowered as they became quieter and made a comment that they could not deny their age any longer, even if before their conversation had been quick and witty and fun. When before they had been so in control of their own life – the watch was expensive, one they might have worked hard for – now they couldn't even take it off without help. The change in mood struck me a lot."

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Review

Challenging the "golden hour" of sepsis treatment – is it contributing to the over-administration of antibiotics?

Mehnaz Aabideen

Year 2, Medicine, Plymouth University Peninsula School of Medicine
Email: mehnazaabideen@gmail.com

Abstract

The first hour after recognising symptoms of sepsis in a patient is known as the "golden hour". Clinicians hold increased importance to this hour and believe that many therapeutic interventions will be most effective if administered within this time. One example is administering broad-spectrum antibiotics to septic patients to help eliminate the pathological cause of sepsis. However, antibiotic resistance still needs to be considered as part of antibiotic stewardship. It is important to balance the usefulness of the "golden hour" principle whilst considering the negative implications that overuse of antibiotics has on antibiotic resistance.

A literature search was conducted to explore this issue further. The key findings were that although antibiotics are paramount in sepsis treatment, administering them within one hour of sepsis diagnosis is not associated with an improvement in mortality. One could argue that giving broad-spectrum antibiotics is futile and will worsen antibiotic resistance. Other clinical interventions should be considered when trying to reduce the occurrence of antibiotic resistance, such as improved diagnosis of sepsis and de-escalation of antibiotic therapy.

Abbreviations

NEWS2 – National Early Warning Score 2
qSOFA – Quick Sequential Organ Failure Assessment
SOFA – Sequential Organ Failure Assessment

Introduction

Medical students, doctors and the general public hear the word sepsis and a sense of panic begins to set in. This increased vigilance is reflected in the hounding of emergency teams to administer antibiotics within the first hour of sepsis recognition, hailed as the "golden hour". However, the practicality of this protocol has been questioned in a landmark study conducted by Kumar et al[1] Is it worth administering antibiotics that could potentially save a septic patient's life, whilst running the risk of unnecessarily contributing to antibiotic resistance?

What is sepsis?

Sepsis is a life-threatening disorder that is characterised by a dysregulated immune response to infection and can lead to organ failure and eventually death.[2] Septic shock is a more advanced version of sepsis, whereby there are circulatory, cellular, or metabolic abnormalities.[3]

The diagnosis of sepsis is made based on symptoms that overlap with other non-infective pathologies. In addition, it takes a long time to determine the causative pathogen from blood cultures; this makes it harder to ascertain that the condition is sepsis in the acute stages of disease.[4] Some common symptoms are mottled or bluish skin; tachypnoea or hypotension.[5]

The exact incidence of sepsis is unknown – this is because there is a lack of an agreed definition for it. However, according to NHS England in 2015, sepsis was a contributory cause to 23,135 deaths. The exact contribution that sepsis plays in these deaths is currently unknown, as some of these patients had multiple comorbidities and frailty.[6] The UK Sepsis Trust shares that in 2017 there were 200,000 admissions to hospitals in England with one of the "definitely septic" diagnostic codes.[7]

Methods

Literature search

To investigate the issue of the "golden hour" further, a literature search was conducted primarily using PubMed, an online database.

Additionally, Google Scholar was used to search for further literature. The terms searched for included a combination of keywords from: "sepsis", "septic shock", "sepsis management", "antibiotic resistance", "antibiotic use", "sepsis six" and "golden hour of sepsis", using Boolean operators where appropriate to refine the search. Citation chaining was also used to find relevant articles.

Results

The initial search yielded 20 journal articles. After manually screening the abstracts for relevance to this literature review, eight were excluded as they were not specific to antibiotic administration or sepsis treatment in adults.

Discussion

How is sepsis managed clinically?

The Surviving Sepsis Campaign (SSC) is a collaborative initiative launched to reduce the risk of death from sepsis and septic shock worldwide, through developing and implementing protocols. These guidelines are evidence-based, which provides credibility for the widespread promulgation of said guidelines and is why the Campaign is commonly mentioned in the discourse surrounding sepsis. Participating in the Surviving Sepsis Campaign was associated with a 5.4% absolute survival rate for septic patients.[8]

One of the guidelines the Surviving Sepsis Campaign recommends is the Sepsis Six care bundle, commonly remembered by the 'BUFALO' acronym: bloods, urine, fluids, antibiotics, lactate, oxygen. In further detail, this involves taking two blood samples (to undergo microbiological culturing), monitoring urine output, starting the patient on fluids, administering intravenous antibiotics, measuring serum lactate and delivering high-flow oxygen.[9]

How are antibiotics used?

The general medical community acknowledge that one of the most important tenets of sepsis treatment is antibiotic administration. The common goal of antibiotic therapy is to have a drug concentration high enough to sufficiently kill as many bacteria as possible.[10] In an ideal world, this could be done by administering as many antibiotics as possible without any repercussions. However, one major threat to the value of these drugs is antibiotic resistance. Bacteria replication over time will naturally give rise to genetic mutations that cause it to become resistant to the antibiotics used to treat bacterial infections, and therefore making the antibiotic futile. This is becoming an increasingly worrying issue within healthcare as antibiotics are an essential part of treating serious infections. With the stagnation in antibiotic discovery someday antibiotics could be rendered useless if bacteria continue to develop resistance. This makes the debate surrounding the "golden hour" is so important.[11]

Deciding which antibiotics to start patients on in the acute setting may be difficult, as there is often a lack of more definitive blood culture data on the species and sensitivities of the infective micro-organisms. Sometimes clinicians get it wrong – studies have shown that 10-40% of the antibiotic regimens that are administered initially are inadequate or inappropriate.[12] The Surviving Sepsis Campaign recommends that the patient is started with broad-spectrum antibiotics intravenously, and then after the causative agent is determined, the therapy is to be de-escalated to be more targeted to the pathogen.[13]

During the initial stages of treatment, an antibiotic that targets a wide range of pathogens is needed. Piperacillin and Tazobactam are antibiotics that can be combined and used to treat gram-negative or Pseudomonas spp. bacterial infections, whereas Vancomycin can be used for gram-positive or Methicillin-resistant Staphylococcus aureus bacteria. Broad-spectrum carbapenems are also commonly used in sepsis treatment.[14] It may seem counter-intuitive to start a patient on antibiotics when you do not know what the bacteria causing the infection is. However, sepsis is a condition that is too unpredictable to wait for microbiological blood culture results as this can sometimes take several days.[15] During this time, the patient's health can potentially deteriorate and this could lead to death.

After considering both sides of the scale, it seems understandable that clinicians would rather take the risk of increased antibiotic resistance from administering broad-spectrum antibiotics, rather than the patient's deterioration and death.

Why is the timing of antibiotic administration important?

The timing of antibiotic administration is thought to be a major tenet of sepsis management since patients can rapidly deteriorate. There is common agreement that once sepsis is recognised, timely antibiotic administration will benefit the patient more and lead to better outcomes. However, the 60-minute time constraint of the "golden hour" is increasingly being called into question.[6]

Professor Mervyn Singer is very vocal about his discontent with 'timely' being misinterpreted as 'early'. In his letter to the Lancet, he highlights that a reason for inappropriate antibiotic administration is that clinicians will often administer antibiotics straight away, just for the sake of taking action against suspected sepsis. He argues that they do not realise that 'timely' means avoiding unnecessary delays, and not just administering them straight away.[16] Spiegel et al also address the one-hour time constraint in an editorial for the Annals of Emergency Medicine. They explain that although treatment with no delay is paramount in sepsis management, condensing the six treatment directives into a one-hour time limit may cause operational problems for emergency departments that are already struggling with three- and six-hour time limits previously used for sepsis treatment.[17] This may cause clinicians to be more rushed and could cause harm to patients.

The problem with misdiagnosing sepsis

A big issue with adhering to the golden hour protocol is that to meet the one-hour goal, clinicians in a rush may misdiagnose a patient with sepsis, and then start them on this treatment bundle. Essentially, the patient is being given high doses of broad-spectrum antibiotics for no clinical reason, which goes against a major dogma in antibiotic stewardship – broad-spectrum antibiotics should only be used when necessary due to the potential they have to increase antibiotic resistance.

A way to prevent this is by increasing the accuracy of sepsis diagnosis. SOFA (Sequential Organ Failure Assessment score) and qSOFA (quick SOFA) are two tools commonly used in determining prognosis in critical illness however, they are not recommended for sepsis identification. Instead, NEWS (National Early Warning Score) is more commonly used as it has better sensitivity and specificity compared to qSOFA, which only includes three of the seven NEWS2 criteria. In clinical practice it is recommended that if the patient has a qSOFA score above two, then the full SOFA score is obtained. However, this includes taking arterial blood gases, which is not routinely done in septic patients, and could jeopardise the small time window in sepsis management.[18] This further stresses the need for other measurements taken urgently such as serum lactate, in addition to NEWS2 to detect sepsis and diagnose it accurately.

Accurate diagnosis is important because many cases are diagnosed as sepsis but are not in reality. A retrospective cohort study looked at patients with acutely decompensated heart failure between 2015 and 2018 and found that sepsis was misdiagnosed in 25% of the patients.[19] This possibly taints the results yielded from the study, which puts the usefulness of the "golden hour" protocol into jeopardy. However, as 75% of the patients were accurately diagnosed, there needs to be a way to reduce misdiagnosis without eliminating the "golden hour" approach.

The evidence behind the "golden hour" protocol

A retrospective cohort study done by Kumar et al between 1989 and 2004 is the main piece of long-standing evidence used to back the "golden hour". This was the first landmark study done to examine the relationship between antibiotic administration and sepsis survival. The main finding was that patients who received antibiotics within the first hour of sepsis recognition had a 79.9% chance of survival. It was also found that with every additional hour, the chance of survival decreased by 7.6%.[1] Through critically appraising this study, a strength of it is that it is a large cohort study that used data from 14 ICUs and 10 hospitals in Canada and the USA. However, a weakness of this study is because of its retrospective design and the time span of 15 years, there is the potential for an absence of data on the confounding factors of this study, leading to confounding bias and diminish the quality of the study.

On the other hand, another study published in 2016 opposes the recommendations of the Surviving Sepsis Campaign. This is a systematic review and meta-analysis of 11 publications and sought to find evidence for the SSC guidelines.[20] In total, 11,017 patients' data was used. The results of this conflicted with those of the previous study and provided evidence against the Surviving Sepsis Campaign's recommendations. It was found that antibiotic administration within one hour of sepsis recognition in septic patients was not associated with an improvement in mortality.

A strength of this meta-analysis is that the selection process of the papers was very refined and ensured that only high-quality papers, all of which were multi-centre and had a large sample size, and closely related to the aim of the meta-analysis. Each study was scored, with eight being the highest, based on how sepsis was recognised, the study design, population sampling and data on the timing of antibiotics. The studies that yielded a score above four were included. However, a downside to this study is the potential for information bias. Some studies were not included in this meta-analysis due to a lack of response after contacting the author, therefore it is possible that not all potential data had been collected, which could alter the results.

No other studies have been done to directly compare the timing of antibiotic administration and sepsis survival. A randomised clinical trial comparing immediate and delayed antibiotic administration would be a very useful study to refer to, however this is difficult to organise and conduct due to ethical and patient safety concerns.[20] There is not enough data available to make a clear and direct claim.

De-escalation of antibiotic therapy

After the results of the blood cultures have been received, the emergency team will know the pathogen that is causing the patient's sepsis. Naturally, the antibiotic regimen could be adapted at this point to follow a more individualised approach. The antibiotic therapy can be changed from broad-spectrum antibiotics to a more narrow-spectrum antibiotic. This is called the de-escalation of antibiotic therapy. The main purpose of this is to prevent the unnecessary development of antibiotic resistance, which would happen if broad-spectrum antibiotics were used for the whole treatment plan.[21]

A meta-analysis of published studies sought to determine if de-escalation was a useful programme in septic patients – and the results support it to be. It was found that there is no difference in the length of hospital stay, and also there was significantly lower mortality in the de-escalation group when compared to the non-de-escalation group.[22] This forms the evidence that is backing the implementation of de-escalation protocols in hospitals. In the NHS, the "Start Smart then Focus" strategy is being implemented to back de-escalation of therapy after reviewing the regimen at 48–72 hours.[23]

Aside from data from academic studies, de-escalation as a programme ingrained into sepsis treatment is logical. We are in the age where antibiotics cannot be used freely – resistance plagues their massive potential, and we need to implement programmes to reduce it wherever possible. Antibiotic stewardship needs to underpin every single avenue of antibiotic therapy, including sepsis treatment. Switching to a narrow spectrum antibiotic as soon as the opportunity presents itself will help to reduce the unnecessary use of broad-spectrum antibiotics, which contribute to antibiotic resistance.

Conclusion

We can see that the current evidence for the "golden hour" of sepsis treatment is underwhelming. Setting a stringent time limit of one hour may be practically unfeasible and could inadvertently lead to the overtreatment of patients who are not septic. Antibiotic resistance will only continue to increase unless reasonable, logic-based programmes are implemented to combat it, for example de-escalation programmes and accurate sepsis diagnosis which is very important.

However, this does not mean that antibiotic administration is unimportant, in fact it is the cornerstone of sepsis treatment. Instead, this highlights the importance of evidence-based and operationally feasible guidelines. Nonetheless, the principle that the "golden hour" seeks to uphold is important. Timely antibiotic administration is paramount in such a time-dependent condition like sepsis. However, to back the stringent time limit of one hour, more studies need to be conducted.

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Mehnaz Aabideen

Hi! I am Mehnaz and I'm a second-year medical student studying at Peninsula Medical School, Plymouth University. My interest in medicine stems from my love of interacting with people of all different backgrounds. Writing has always been a way for me to delve deeper into topics that fascinate me, such as the protocols that surround sepsis management, and I really enjoy it! My passions outside medicine are reading, art and playing the piano. I am excited to be more involved in research and academic medicine as I continue my studies!

Review

The mechanistic action of tooth whitening products used in dentistry and their potential side effects

Yasmin Aziz
Year 5, Dentistry, Cardiff University
Email: yasminaziz32@gmail.com

Abstract

The popularity of tooth whitening is continuing to increase with images of white teeth becoming the norm on social media. However, the mechanistic action of tooth whitening products is not fully understood with several proposed theories as to what causes change in tooth shade. This review aimed to examine the mechanism by which tooth whitening products lead to whiter teeth. The adverse effects of tooth whitening products on the oral mucosa, dentition, and existing dental restorations are also reported.

This review found that whitening toothpastes modify tooth colour by using abrasive particles, optical agents, or chemical agents. The efficiency of abrasive particles is dependent on their hardness, shape, size, applied load and concentration. Optical agents such as Blue Covarine modify the visual perception of tooth colour by shifting the net colour towards white on the colour space model. Commercial toothpastes release less than 0.1% hydrogen peroxide, therefore do not produce significant tooth whitening. Hydrogen peroxide was thought to act through either the chromophore effect, interaction with the organic and inorganic tooth structure or via oxidisation of organic tooth tissue. Tooth whitening can also lead to sensitivity, damage to the oral mucosa and gingiva and potentially cause the release of harmful components from restorative materials.

This review highlights the importance of understanding the mechanism behind tooth whitening products and allows dental care practitioners to advise appropriate and safe methods to combat intrinsic and extrinsic staining.

Abbreviations

HAP - Hydroxyapatite
HGF - Human gingival fibroblasts
RDA - Relative dentine abrasivity
REA - Relative enamel abrasivity

Introduction

Dentistry has evolved from a profession primarily involved in the management and treatment of oral health and disease, to one that is increasingly involved in the provision of cosmetic procedures such as tooth whitening. This transition has been attributed to the popularity and societal acceptance of cosmetic interventions in order to enhance appearance.[1] The growing popularity of tooth whitening is reflected in the selection of whitening products available to patients and consumers.[2] Despite increased use, the underlying mechanism of tooth whitening is not well understood.[3] The review will further investigate the mechanism behind whitening agents and evaluate their potential side effects, ensuring the provision of safe whitening products with limited side effects on the dentition and oral tissues. Currently, the General Dental Council states that tooth whitening products that release between 0.1% and 6% hydrogen peroxide can only be sold to dental practitioners, with 6% being the maximum concentration dental practitioners can provide patients. These products cannot be used on patients younger than 18 years of age except for the purpose of treating or preventing disease.[4]

Tooth discolouration

Tooth discolouration can be categorised into two groups: intrinsic and extrinsic staining. Extrinsic stains occur in tooth surface deposits, particularly the dental pellicle or at the tooth surface due to chemical interactions.[2] Extrinsic stains are caused by smoking, chromogenic beverages and foods, and exposure to metallic salts.[5] Intrinsic staining results from changes in how light is scattered and absorbed by enamel and dentine. This can be attributed to genetic disorders, antibiotics, fluorosis, pulpal trauma, tooth resorption and ageing.[5,6,7]

It is imperative dentists understand the vast aetiologies of tooth discolouration as this may influence the whitening products and techniques required to manage discolouration.

The removal of extrinsic stains

Extrinsic stains can be removed by dental prophylaxis and controlled by regular use of an effective whitening toothpaste.[8] Whitening toothpastes vary in formulations with a range of tooth-whitening technologies such as optical pigments and hydrogen peroxide.[9] Activated charcoal/carbon-based dentifrices also claim to cause tooth whitening. However, a recent review found insufficient clinical and laboratory data to verify the efficacy charcoal-based dentifrices.[10] The active ingredients in whitening toothpastes that modify tooth colour can be divided into three main groups: abrasives, optical agents and chemical agents.[11]

Abrasives

Abrasives are insoluble particles that become trapped between toothbrush bristles and the enamel surface. Abrasives are physically harder than stain particles allowing the abrasion of extrinsic stains from the tooth surface. Factors that affect the efficiency of abrasives include particle hardness, shape, size, applied load and concentration.[11]

Whilst abrasives can be efficient in removing stains, they also cause tooth wear. Studies have found that toothpastes with high relative dentine abrasivity (RDA) caused a statistically significant increase in mean dentine wear in comparison to toothpastes with a low RDA. However, these studies reported minimal abrasion to enamel and had low relative enamel abrasivity (REA).[12,13] Few studies in literature look specifically at the REA of toothpastes, this may be because enamel is harder than most abrasives in toothpastes (except for hydrated alumina, perlite and diamond powder). Therefore, most toothpastes have relatively low REA despite having high RDA.[14] Franzò et al[12] is an in-vitro study, therefore their results cannot be extrapolated in-vivo due to environmental differences such as the absence of saliva which can affect toothpaste concentration and pH, both factors known to affect the extent of dentine wear.[12,13] In contrast, Hooper et al[13] is an in-situ study which is able to replicate in-vivo conditions more accurately while retaining the sensitivity of laboratory analysis, therefore providing valid results regarding the effects of abrasives on dental wear.[15]

Excessive tooth wear can cause exposure of dentinal tubules resulting in dentine hypersensitivity.[16] However, Hooper et al[13] extrapolated mean enamel abrasion values to possible lifetime values and found that a lifetimes brushing would be equivalent to approximately 38µm of abrasion. This is clinically irrelevant as typically enamel thickness at the cervical margin is 130µm and is much thicker over the rest of the tooth.[13] Although, these predictions may vary greatly depending on the individual, their brushing habits and existing tooth wear.

Optical agents

Blue Covarine and other optical pigments found in whitening toothpastes mask the yellow appearance of dentine by depositing a semi-transparent blue layer on the pellicle-coated enamel surface. This modifies the visual perception of tooth colour as blue opposes yellow on the colour space model, as seen in **Figure 1**. This shifts the net colour towards white, resulting in the visually whiter teeth.[9,17,18] This may be ideal for patients with erosive tooth wear who have worn down their enamel. However, the colour space model suggests that Blue Covarine may not mask all stains unless they are on the yellow spectrum. Therefore, the nature of the stain is important to the efficacy of Blue Covarine as a tooth-whitening agent.

Joiner et al[17] found that 0.2% Blue Covarine treatment resulted in a significantly larger increase in mean vita shade change compared to water treatment. However, results vary as other studies have found no significant difference in mean vita shade change because of Blue Covarine treatment.[18,19] Further research is required to form a consensus on the whitening efficiency of Blue Covarine.

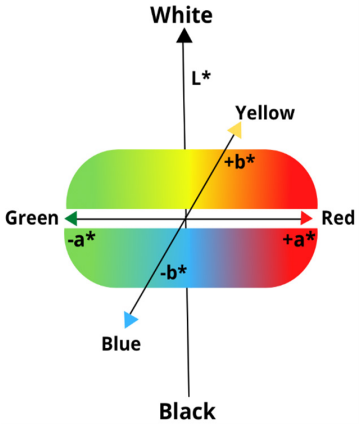

Figure 1. Colour space model Adapted from Joiner A, 2004[8], by Elsevier.

The removal of extrinsic and intrinsic stains

Chemical agents

Staining can be removed by bleaching, which is performed by oxidising agents like hydrogen peroxide, this is the main agent in most tooth-whitening products.[3,4] Hydrogen peroxide can be directly or indirectly applied in the form of sodium perborate or carbamide peroxide.[4] Oxidising agents are used in whitening toothpastes, whitening strips and gels, whitening rinses, tray-based tooth whiteners, and in-office whitening procedures.[3,20] Hydrogen peroxide is a highly unstable molecule that decomposes, giving rise to free radicals, reactive oxygen species and hydrogen peroxide anions.[21] The production of these reactive molecules is influenced by light, pH, temperature and interactions with transition metals.[22]

The penetration of chemical whitening agents has been investigated by Kwon et al[23] where it was observed that Rhodamine B dye readily penetrated through the enamel- dentin complex via the interprismatic spaces in enamel and along the dentinal tubules in dentine. They theorised that Rhodamine B and hydrogen peroxide may demonstrate similar patterns of penetration, as Rhodamine B has a low molecular weight (479gmol^{-1}) like that of hydrogen peroxide (34gmol^{-1}). However, as this study did not use hydrogen peroxide, it cannot provide conclusive evidence for the penetration pattern of hydrogen peroxide. Kwon et al[23] is an in-vitro study that utilised extracted teeth therefore the dentinal tubules were absent of fluid. It is suggested that outward fluid flow from the tubules may rinse them free of inwardly diffusing substances.[24] Therefore, the diffusion pattern observed by Kwon et al[23] may differ in vital teeth.

The interactions of chemical whitening agents

Chromophore theory

Whitening agents are thought to interact with intrinsically stained teeth according to the chromophore theory.[3] This would be the ideal mechanism of interaction as it only involves interaction of whitening agents with chromogens and preserves the tooth structure.

Tooth colour is determined by the combination of light reflected and scattered by semi-translucent enamel and the underlying dentine.[25] An object appearing white reflects all the colours of the visible light spectrum.[25] Chromogenic compounds like tannins, found in coffee, can have high molecular weights of up to 20,000g/mol.[26] These compounds absorb ambient visible light, decreasing the spectral reflectance of the tooth and resulting in the production of colour.[23] Hydrogen peroxide oxidises double bonds within

chromogenic compounds converting them into simpler molecules that are colourless and soluble.[27,28] As a result, tooth tissue may display reduced light absorption and increased light reflection which helping to explain the whitening action of peroxides. However, the chromophore theory is not fully supported as studies using spectroscopy have failed to detect chromogens or their breakdown products within the tooth structure.[3]

Interaction of organic compounds within dentine with peroxides

Another theory is that peroxides may interact with the tooth's organic compounds.[29,30] Kawamoto et al[29] proposed that the whitening effect was due to the breakdown of amino acids and amides that compose polypeptide chains in the organic dentine matrix. They added amino acids like proline and alanine which form core components of dentine proteins to 30% hydrogen peroxide and found proline was completely degraded. Similarly, Ubaldini et al[30] found that 25% hydrogen peroxide treatment caused a decrease in amides I, II, and III absorption bands analysed using spectroscopy. Therefore, protein degradation could alter the structure of the organic dentine matrix, changing how light is scattered and absorbed within the dentine layer which may affect tooth colour.[26]

Interaction of inorganic compounds with peroxides

Alternatively, tooth mineral may be the predominant factor affecting tooth colour while tooth organic content is mainly transparent.[31] Therefore, the effects of peroxides on the organic dentine matrix would have negligible effects on tooth colour. Eimar et al[32] found that tooth hue was associated with hydroxyapatite (HAP) crystal size. In addition, they found that tooth chroma was associated with enamel carbonization, and tooth lightness was affected by both HAP crystal size and carbonization. Eimar et al[31] used extracted teeth due to the impracticality of performing tests on teeth inside patients' mouths. Therefore, these results may not be extrapolated to vital teeth, as tooth colour has shown to differ in extracted teeth compared to vital teeth.[33]

Oxidation of organic tooth tissue

Oxidation of organic tooth tissue may also contribute to tooth whitening. Eimar et al[31] argues that tooth-whitening is not caused by deproteinisation of the organic matrix nor modification of the tooth's inorganic contents but may result due to oxidation of the transparent organic matrix into an opaque whiter material. In this study, 60 teeth were divided into four groups and treated with one of the following solutions: NaOH (deproteinising), EDTA (demineralising), hydrogen peroxide (oxidising agent) and distilled water (control). They found that immersion in both NaOH and peroxide resulted in lighter teeth, however the change in lightness caused by peroxide was much greater than that by NaOH.

Despite the proposed theories regarding the mechanistic action underlying bleaching agents, there is no conclusive evidence that supports any one of these theories. Therefore, further research into existing mechanisms is required to establish the true mechanism/s.
Side effects of chemical whitening agents

Chemical agents used in tooth-whitening have a range of side effects due to their oxidative nature. Local side effects include pulp sensitivity, cervical resorption, release of components from restorative materials, and alteration to the enamel surface.[34]

Tooth sensitivity

Tooth sensitivity is a common side effect of tooth-whitening. In a randomised, double-blind clinical trial, 172 people bleached their teeth for 14 days with 10% carbamide peroxide. 47% of people reported sensitivity during the procedure, and the average number of days of sensitivity experienced was 3.1.[35] Chemin et al[36] found a higher agent concentration resulted in greater sensitivity whereas, others have found that the incidence of sensitivity is the same whether 10% or 30% of hydrogen peroxide is used.[37] This suggests other factors may play a greater role in determining sensitivity such as bleaching time.[38] Failure of studies to show a difference between sensitivity and agent concentrations may be due to the strict selection of patients without a previous history of sensitivity.[39]

The mechanism behind bleaching sensitivity is not fully understood. However, it is thought that hydrogen peroxide and its by-products can diffuse down the dentinal tubules into the pulp, resulting in reversible pulpitis and tooth sensitivity.[5,40] Although, other studies hypothesise that sensitivity is due to direct activation of pulpal sensory afferents via TRPA1 ion channels which respond to oxidising compounds like peroxides.[41]

Oral mucosa and gingival effects

Oxidative stress can lead to genomic damage in oral mucosal cells.[42] Klaric et al[42] observed an increase in genotoxicity markers in oral mucosal cells following bleaching. Although the increase in genotoxicity markers was statistically significant, it was relatively small considering the high variability of markers at basal levels. As oral mucosal cells have a short lifespan, bleaching likely has negligible genotoxic and carcinogenic potential.[41] Furthermore, Goldberg et al[34] found that genotoxicity and carcinogenicity only occurs at concentrations that are never reached during dental procedures.

The effect of bleaching on human gingival fibroblasts (HGF) in-vitro has been examined by several studies. Tipton et al[43] found that hydrogen peroxide concentrations as low as 0.025- 0.05% killed off HGF. Another study found that the reduction in the number of HGF became significant at even lower concentrations of 0.0015% hydrogen peroxide.[44] This raises concern, as currently, over the counter whitening products contain hydrogen peroxide concentrations of 0.1%.[45] These products are used without the guidance of dental professionals, which may result in improper use and harm to the gingiva. Although, it is thought that enzymes in the oral environment may be able to destroy hydrogen peroxide, thereby, protecting oral tissues from cytotoxicity.[44]

Effects on restorations

Khamverdi et al[46] found carbamide peroxide concentrations of 16% caused a significant increase in the release of mercury and silver from amalgam restorations. Released mercury may be absorbed by oral, respiratory, and gastro-intestinal mucosa, increasing the risk of toxic systemic side-effects.[46] However, it is suggested that the dental biofilm may reduce the release of mercury from dental amalgam in-vivo, reducing the risk of potential amalgam toxicity.[47]

Conclusion

There are numerous whitening products and methods that alter tooth colour. The mechanism behind whitening agents used in dentifrices such as abrasives and optical dyes, is well established. However, the mechanism responsible for peroxide tooth-whitening is a complex phenomenon. Extensive research is required to establish how hydrogen peroxide oxidises the transparent organic contents of the tooth into an opaque whiter material. Further research is also needed to disprove other proposed mechanisms by which bleaching results in whiter teeth. However, for this to occur there are limitations that need to be addressed, such as the inability of current instrumental methods to detect the presence of chromophores within the tooth. The side effects of whitening agents are typically minimal/ temporary when used according to the manufacturer's guidelines. Due to the lack of literature regarding the in-vivo effects of hydrogen peroxide, its effects within the oral cavity are not yet fully established.

In summary, dentists should be able to give patient-specific advice regarding tooth-whitening, taking into consideration the type of staining, dietary habits, previous restorations and any oral or systemic

conditions a patient may have. This is likely to minimise the potential side effects of agents and optimise tooth-whitening.

Contribution statement

The author has made substantial contributions to the conception or design of the work, drafted the work, and gave final approval of the version to be included in Inspire.

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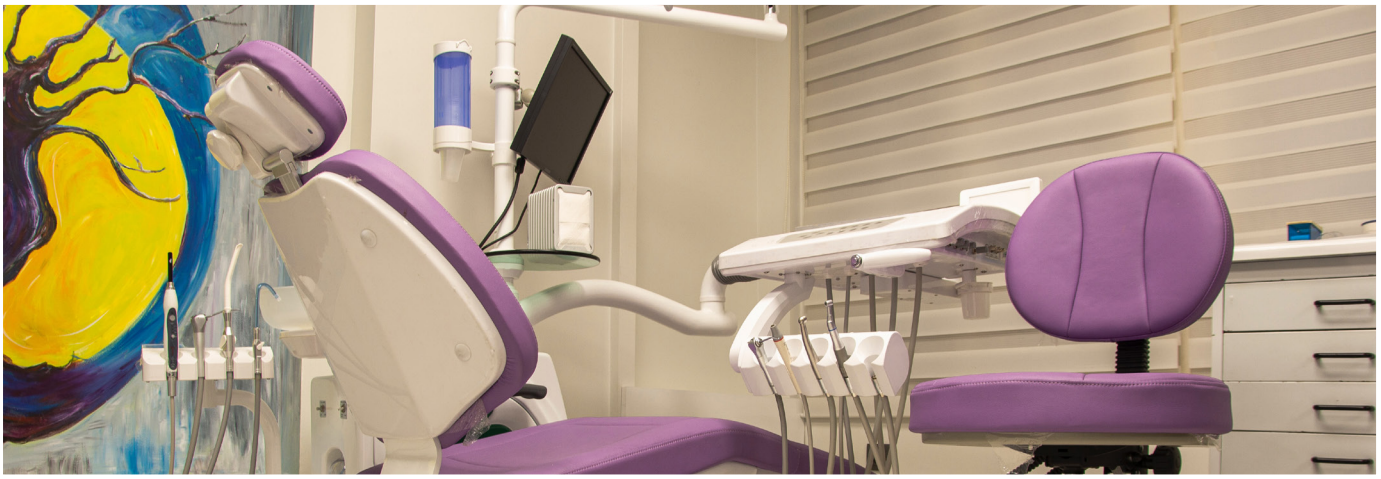
Yasmin Aziz

I recently graduated from Cardiff University and will be completing my dental foundation training in Sussex. My special interests include restorative dentistry and oral surgery. Dentistry has progressed from a profession solely responsible for treating disease to one that is increasing concerned about aesthetics. As a result of this shift, I have become interested in the range of tooth whitening technologies available and the mechanism by which they whiten teeth. I am also interested in the influence of artificial intelligence on the field of oral maxillofacial radiology and its potential future uses in healthcare.

Review

Ergonomic interventions to prevent work-related musculoskeletal disorders and pain among dental professionals

Mohammad Khalfan
Year 2, Bachelor of Dental Surgery (BDS), University of Glasgow
Email: 2508013k@student.gla.ac.uk



Abbreviations

CC1 - Conventional chair with back rest
CC2 - Conventional chair without back rest
ICC - Intraclass correlation coefficients
DASH - Disabilities of the Arm, Shoulder and Hand
Df - Degrees of freedom
MSDs - Musculoskeletal disorders
MSK - Musculoskeletal
PAC - Posture Assessment Criteria
PICO - Population, Intervention, Comparator, Outcome
RCTs - Randomised controlled trials
RULA - Rapid Upper Limb Assessment
SSC - Salli saddle chair
Vs - Versus

Background Musculoskeletal disorders (MSDs) and pain at work are among the most common occupational disorders worldwide. Such disorders are caused by a variety of factors. However, in dentistry, MSDs are primarily caused by treatment delivery methods such as awkward posturing and working for prolonged hours. The purpose of this literature review is to establish available ergonomic interventions for dental professionals and their role in reducing MSDs.

Search methods Electronic databases (PubMed and Google Scholar) were searched for relevant records to the question of interest. The last search was carried out on 7 June 2022.

Eligibility criteria Randomised controlled trials (RCTs), intervention or evaluation studies and cohort studies published in English and after January 2005 to date were eligible for inclusion.

Conclusion Ergonomic interventions, particularly magnification loupes, Salli Saddle Chair with magnification, ergonomic education and training courses and light dental instruments with wide diameter are effective in improving MSDs symptoms (neck, shoulder and lower back) and working posture. Such interventions should be implemented at early stages of the undergraduate curriculum to prevent MSDs development later in life.

Introduction

Dentistry is a physically demanding profession whereby high levels of clinical training is paramount. Cumulative exposure to such training places undesirable stress on various body regions, affecting one's productivity and therefore increasing the risk of developing work-related musculoskeletal disorders (MSDs) and pain. MSDs are injuries to the musculoskeletal (MSK) system occurring due to singular or repetitive trauma, severely affecting one's daily life. They can manifest in the upper limbs (forearm and wrist), postural muscles (neck, shoulders, upper and lower back) and lower extremities (hips, thighs, knees and ankles). Untreated MSDs can potentially develop into degenerative and inflammatory processes such as tendonitis and carpal tunnel syndrome.[1]

Dentistry carries a concerningly high prevalence for MSDs worldwide. In the US, approximately 46% to 71% of dental students report body pain with the percentage rising by school year. Due to physical differences and gender-specific physiological factors, female dental professionals are more likely to develop MSDs than male counterparts.[2] There are several factors underlying the high rate of MSDs among those practising dentistry. The primary reasoning is that the oral cavity is a constrained working area that is challenging to access and navigate. This would force dental professionals to maintain static body postures, where body positions are maintained

for more than four seconds. It is considered uncomfortable as it involves flexion of the head and neck to the front and side, together with inclination and rotation of the trunk towards the patient. This can be painful when performing dental treatments that may require working for prolonged periods such as root canal treatments and restoring a cavity. Other factors contributing to the development of MSDs include the usage of vibrating tools and the high exposure to repetitive shoulder and hand movements.[3] This would explain why MSDs account for 29.5% of the reasoning for premature retirement.[4]

Emerging evidence illustrates that ergonomic interventions such as ergonomic dental chairs and instruments play a fundamental role throughout a professional's life. Since the physical burden associated with dentistry tends to accumulate from the preclinical years, early and effective implementation of these interventions may lower MSDs rate, potentially reducing early retirement rates.[3-5] This review aims to establish available ergonomic interventions for dental professionals and their role in reducing MSDs.

Methods

Eligibility criteria

The study's eligibility criteria were developed using the Population, Intervention, Comparator, Outcome (PICO) framework (**Table 1**). The review process included randomised controlled trials (RCTs), intervention or evaluation studies, and cohort studies that were available with full texts and published after January 2005. Case reports, descriptive cross-sectional studies, and non-English studies were excluded from the review process.

Table 1. Eligibility Criteria for the study selection per PICO framework.

PICO	Study Inclusion Criteria
Population (P)	Dental professionals such as dentists, dental students, dental assistants, dental laboratory assistants, dental hygienists, dental hygiene students, dental technicians and dental surgeons.
Intervention (I)	Ergonomic design options such as dental chair or lighting, dental loupes, dental instruments, and prismatic spectacles. Only interventions carried out for a minimum of three days were included in the study.
Comparator (C)	All relevant control groups, even those representing both the control and intervention groups (own controls).
Outcome (O)	Associated with symptoms of MSDs (neck, shoulder and lower back pain) or working posture, which is likely to be related to MSDs.

MSDs = Musculoskeletal disorders, PICO = Population, Intervention, Comparator, Outcome.

Literature search strategy

A literature search was conducted to find relevant literature related to ergonomic interventions and MSDs. Electronic databases and hand searches for articles were performed in the following databases: PubMed and Google Scholar. The last search was carried out on 7 June 2022. The search terms for the intervention of interest consisted of: "Dental professionals/personnel", "Ergonomics", "Ergonomic interventions", "(primary) Prevention", "Musculoskeletal pain", "Musculoskeletal disorders". These terms were used in various combinations, together with adjuncts of "or" as well as "and". These terms identified papers relevant to this review's scope. Additional papers were detected by reviewing the bibliographic lists of the original papers.

Selection of studies

Relevant papers found were imported into referencing software Endnote X9. The title and abstract of relevant papers were screened for relevance, and if deemed suitable, the full texts were retrieved and analysed. Those reports which met the eligibility criteria of the present review were selected. The literature search identified eleven papers in total.

Ergonomic dental chair

Dental professionals often adopt awkward postures to deliver dental treatments for prolonged periods of time. Dable et al (2014) compared the working posture of dental students in three different seats including the Salli Saddle Chair (SSC), conventional chair with back rest (CC1) and conventional chair without back rest (CC2) with and without using magnification while performing similar dental procedures. The magnification system used consisted of double lens with detachable light source to create better visibility from a distance. Postures were evaluated using the Rapid Upper Limb Assessment (RULA) (**Appendix 1**). After three months of training, all three groups were taken for assessment. RULA scores were significantly lower for those who used SSC with magnification as opposed to those using conventional chairs without magnification (CC1 and CC2) (1.57 ± 0.50 vs 7.03 ± 0.49 and 7.01 ± 0.45, $P < 0.01$). As a result, students who previously had a mild form of MSK pain reported to experience little to no MSK pain after using SSC compared to CC1 and CC2. In comparing SSC with or without magnification, use of magnification is not beneficial to students who habitually bend at work.[6]

Hallaj et al (2016) evaluated the role of installing arm support (extension) in dental chairs on MSD symptoms. Participants were required to complete a questionnaire which involved answering demographic questions about their age, gender, years of experience, daily hours of exercise and hours of working per day. This feedback questionnaire was split into two parts (i.e. before and after use). Based on the collected data, a customer satisfaction analysis was performed. The body postures of participants were calculated using the RULA scores, which averaged around 3.14, by which the combined bending and twisting of the back decreased by 13.8%. A sharp decline in the wrist's excessive bending up and down and pressure on the neck and shoulder was observed during dental work at 41.4% and 79.3%, respectively.[7] The findings of this study reflect that the arm support installation has improved dentists' body posture significantly, which can be further improved by adjusting the patient positioning and dental chair to support the dentist's neck when carrying out dental procedures.

Magnification loupes

Modern technologies such as magnification loupes have been proposed as a preventive intervention for MSDs in Dentistry. Magnification loupes are optical magnifying devices used in clinical practice and educational settings, mostly to magnify the visual field (teeth and gingiva).[3] Hayes et al (2014) conducted a study to assess the impacts of magnification loupes on health-related outcomes (working posture and symptoms of MSDs) among dental professionals. This was achieved through calculating the Disabilities of the arm, shoulder and hand (DASH) scores (**Appendix 1**). At baseline, DASH scores were lower among participants in the control group (dental hygiene students) compared to the intervention group (dental hygienists) (4.99 ± 6.25 vs 8.56 ± 9.64). However, six months after wearing magnification loupes, the DASH scores for the intervention group declined significantly to be lower than that for the control group (5.17 ± 5.29 vs 7.84 ± 8.73, $P < 0.05$).[8] Despite being statistically significant, improvements in DASH scores were negligible showing that wearing loupes may have little to no impact on improving MSDs and working posture. This may have occurred because DASH scores are designed to detect higher level of pain and disability and thus may not accurately measure lower levels of

pain.[9-10] The findings of this paper limited the ability to conclude whether magnification loupes have a direct effect on reducing symptoms of MSDs or not.

Maillet et al (2008) assessed the efficiency of magnification loupes in improving working posture during the provision of dental treatments (hand scaling) by calculating the Posture Assessment Criteria (PAC). The study found that students who received magnification loupes achieved higher ergonomic scores compared to students who did not (6.4 ± 2.61vs 10.8 ± 4.24, df = 34, $p < 0.000001$). In turn, wearing magnification loupes has enhanced the working postures significantly ($p < 0.001$), simultaneously increasing the quality of their dental work.[11] The findings of this early study were supported by another study which also depicted that magnification loupes positively impacted the working posture of dental professionals.[6]

Two studies investigated the impacts of wearing prismatic spectacles on health-related outcomes. Prismatic spectacles are a specific type of magnification loupes. These include a prism between the lenses, which reflects and magnifies without reducing field of view. Lindegård et al (2012) found that using prismatic spectacles improved working posture and MSDs symptoms, in which 80% of participants reported an improvement in the quality of their work. This could be explained by the reduced neck flexion offered by the prismatic spectacles when comparing both the control group and the intervention group (3.6◦ vs 8.7◦, $p < 0.01$ and 3.3◦ vs 8.2◦, $p < 0.05$). Furthermore, while a reduction of four units in the head and neck exertion inclinometer was noted among the intervention group, only two units' reduction was identified in the control group.[12] Lindegård et al (2016) found similar results. This was the case as those who used prismatic spectacles reported decreased MSD symptoms and also achieved significant improvements in clinical diagnoses ($p < 0.05$), self-reported pain ($p < 0.05$), perceived exertion ($p < 0.01$) and self-work ability ($p < 0.05$) as compared to those who did not use prismatic spectacles.[13] This might mean that prismatic spectacles can facilitate dental work by allowing professionals to maintain a more upright position with less neck bending, which can be paramount when conducting vision-demanding tasks such as root canal treatments. Overall, the findings of these reports may indicate to that an early introduction of the magnification loupes especially during undergraduate dental training, may improve working posture, quality of the dental work, and potentially lower premature retirements associated with MSDs. However, since reports underpinning the role of prismatic spectacles in lowering MSDs symptoms are limited and have a short follow-up period, high quality studies to assess the long-term effects are warranted.

Ergonomic dental instruments

Rempel et al (2012) compared the impacts of two different dental instruments, a lightweight dental Instrument with a wide diameter (Instrument I) vs a heavy dental Instrument with narrow diameters (Instrument II), on MSD prevalence in dental professionals. Pain scores were adjusted for potential confounding factors (age and occupation). It was found that the improvements in adjusted pain scores for instrument I were greater than Instrument II for the shoulder region ($P < 0.05$).[5] This may mean that using light-dental instruments with wide diameters can be a feasible and cost-effective intervention to prevent upper-extremity MSDs, making them more suitable for subgingival professional mechanical plaque removal (PMRP). The authors also noted a reduction in nocturnal disturbance due to finger numbness in those using light-dental instruments with wide diameters compared to heavy-weight dental instruments with narrow diameters.

Ergonomic education and training courses

Farrokhnia et al (2018) evaluated the impacts of incorporating educational interventions in dental professionals who suffer from MSDs. Prior to initiating the intervention, approximately 87% of participants reported MSDs in at least one region of the body. During the follow-up period, there was a decline in reports of MSD symptoms. Fewer participants reported pain in the neck (10.97 ± 20.44 vs. 7.91 ± 17.01, $p < 0.01$), left shoulder (5.80 ± 17.21 vs. 2.95 ± 9.33, $p < 0.01$) and right shoulder (8.85 ± 19.76 vs. 5.24 ± 13.51, $p < 0.01$), amongst other regions of the body, thereby dropping the rate of MSDs to 81%. Although this was associated with improved working posture, which is likely to further reduce MSDs over the long term, the reported confidence intervals are wide. This could be explained by using a relatively small sample size (n=84) which consisted mainly of males. The representativeness of the sample is affected, since it was solely collected from Tehran via convenient sampling. Other factors that may underlie variability in the findings can include: a) males experiencing greater pain in the neck than females; b) pain in the neck worsened with age; c) inconsistencies in the number of breaks between treatments; and d) inconsistencies in the number of regular weekly exercises.[14] Therefore, a high-quality prospective cohort study is warranted to provide a more accurate estimate of the role of ergonomic educational courses in improving MSDs prevalence among dental professionals.

Dehghan et al (2016) conducted a randomised controlled trial (RCT) to evaluate the effectiveness of a multifaceted ergonomic programme. There was a reduction in MSD reports especially in shoulder pain [44% vs 80% ($p < 0.05$)] and neck pain [62% vs 84% ($p < 0.01$)] among those who received the programme at three-and six months post-intervention. The authors also found declined reports of MSD symptoms for all body regions as opposed to participants in the control group who only reported less pain in the back.[15] In another study, there were improvements in MSD symptoms by 49% among those who received training in ergonomics for three months, albeit 17% of students reported opposing effects. During the follow-up, 25% of students reported having improved dynamic working posture. Post-intervention, 87.7% of participants reported adjusting their daily habits.[16] Conclusively, ergonomic education positively led to fewer MSD reports, with improved working posture and quality of dental work. The overall outcomes of both studies would encourage the early implementation of ergonomic education within the dental undergraduate curricula.

Limitations

Several limitations exist in this review and its included studies. First, all studies included involved small sample sizes followed up over a short period, which limited the ability to evaluate the role of ergonomic interventions on MSDs in the long term. Second, six studies had no actual control groups and hence own controls were used and monitored between baseline and follow-up. Hence, these studies were relying mostly on self-reported questionnaires which therefore may have introduced response and recall bias in the outcome results.[5-7,11,14,16] Third, a common surveying method of pain is RULA scores.[6-7] Reports have found that RULA tends to overestimate the ergonomic risk of low-level MSDs.[20-21] Fourth, this review had no geographical restrictions, which limited the ability to compare interventions due to variations in environmental factors and workload associated with dentistry worldwide. However, this did not affect recommendations from being withdrawn based on the findings of the included studies.

Conclusion

In summary, routine dental procedures often require awkward posturing, the use of vibrating instruments for prolonged periods, and repetitive hand and shoulder movements. These are likely to be associated with MSK pain, potentially MSDs. The findings of this paper suggest that ergonomic interventions, especially magnification loupes, SSC with magnification, ergonomic education and training courses, and light dental instruments with wide diameters can effectively reduce neck, shoulder and lower back pain and possibly improve working posture. Effective institutional

implementation of such interventions, particularly at the early stages of the undergraduate curriculum, is likely to reduce MSD development later in life, and thus reduce premature retirement rates. Given that all studies included in this review involved small sample sizes monitored over a relatively short time frame, larger longitudinal studies are required to assess the long-term effects of the ergonomic interventions discussed among dental professionals. Cost-effectiveness analysis studies are also required to justify the routine use of these interventions in dentistry.

Appendix 1

Score interpretation and Reliability of Outcome Measures.

Measure	Description	Score interpretations	ICC*
RULA[17-19]	A survey method developed for investigating ergonomics of workplaces to report work-related upper limb disorders. It incorporates three scoring tables and diagrams depicting various body postures to evaluate not only exposure to risk factors associated with working posture, but also other important factors that are likely to vary between individuals, including operator's pace and apt movements	Potential scores range from 1 to 7, with 1-2 points indicating negligible risk and hence no action required; 3-4 points indicating low risk and hence change may be needed; 5-6 points indicating medium risk and hence further investigation and change should occur soon; ≥6 points indicate very high risk, requiring immediate change. A higher overall score indicates a greater risk of exposure	0.53
DASH[9-10]	A self-report questionnaire that consists of 30 questions that assesses symptoms in the arm, shoulder and hand. Responses are scored one to five on a Likert-type scale based on the participants' ability to perform specific activities.	Potential Scores range from 0 (no disability) to 100 (most severe disability). While a specific score cannot determine the exact level of disability (mild, moderate or severe) or whether an individual is able or not to work objectively, recent reports estimate that a score of 0-29 is the point where upper-limb disorders are no longer an issue. A higher overall score suggests a greater risk of exposure.	0.96

**Reliability expressed as intraclass correlation coefficients (ICC). RULA = Rapid upper limb assessment, DASH = Disabilities of the Arm, Shoulder and Hand*

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Mohammad Khalfan

Hi! I am Mohammad. I was born and raised in Kuwait. Currently, I'm a second-year dental student at the University of Glasgow. I have a keen interest in medical research. Outside of academia, my other interests include volunteering and photography.

Review

Why do allergies occur?

Rasheed Shehadeh

Year 2, Medicine, Cardiff University
Email: ShehadehR@cardiff.ac.uk

Abstract

What are allergies and why do they occur? The science underpinning allergies is complex, as are the theories attempting to explain its causes. In this review, I explore the interaction between our decreasing vitamin D levels, our increased cleanliness, and the decreased biodiversity of the human microbiota in destabilising our immunoregulatory systems. These factors are linked to recent lifestyle changes, which helps demystify the increasing rates of atopy in the West. Importantly, I have also illustrated the molecular sequence of events during an allergic reaction and why some allergies are more common than others.

Abbreviations

APC – Antigen Presenting Cell
IgE – Immunoglobulin E
IID – Infectious intestinal diseases
MHC – Major Histocompatibility Complex
OF – Old Friends
Tregs – Regulatory T cells

Introduction and rationale

An allergy is a complex immunoregulatory response occurring after an atopic individual, someone who is predisposed to react in the following way, produces elevated amounts of Immunoglobulin E (IgE) against a typically harmless substance. This is classed as a hypersensitivity type 1 reaction.[1]

Allergies are increasingly common with a staggering 44% of British adults now suffering from at least one allergy, rising by 2 million between 2008 and 2009 alone.[2] Intriguingly, the cases of allergies are specifically increasing in Western countries[3] as the prevalence of food allergies in preschool children is now as high as 10% in Western countries, but remains just 2% in China.[4]

A growing uncertainty as to why allergies occur and why their numbers are rising means that demystifying allergies is increasingly crucial to the world's health and economy.

Main findings

How does an allergic reaction arise?

The first time an atopic individual is exposed to an allergen, the specific allergen protein binds to dendritic cells, which are Antigen-Presenting Cells (APC)[1] which will then hydrolyse the allergen and display them on their MHC II (major histocompatibility complex) surface proteins. A naive CD4+ T-Helper cell binds to this and is activated, it therefore stimulates a strong Th-2 response[3] which will secrete interleukins IL-4 and IL-13 to stimulate B cells. Consequently, the B cells will proliferate and produce antibody-secreting cells, which will produce IgE, and memory cells, explaining why allergies remain for years.[1]

Some of this IgE will bind to the allergen to form an antigen-antibody complex to aid detection and phagocytosis via opsonisation.[3] However, most of the IgE will bind to Fc receptors on Mast Cells, subsequently releasing histamine from cytoplasmic granules to produce the characteristic symptoms of allergic reactions.[1] However, these symptoms will not be noticeable until the individual is re-exposed to the allergen.[3] This process is called sensitisation.[1]

When this atopic individual is then re-exposed to the allergen, the allergen binds directly to the IgE on the mast cells and causes a cross-link of receptors, meaning that both antigen-linking features of an antibody bind to the antigen and so the antibody is now linking two antigens.[3] Consequently, the mast cells degranulate and release a large volume of histamine and other chemicals.[1] Histamine causes vasodilation of blood vessels and renders the capillaries more permeable to white blood cells to allow them to engage with the allergen in the infected tissue, enhancing inflammation.[3] Other symptoms include mild irritations, redness and rhinorrhoea due to excessive mucus production.[1]

The interleukin IL-5 initiates and maintains the inflammation built up by eosinophil white blood cells and releases prostaglandins E1 and E2 to liberate an inhibitor of histamine release, maintaining inflammation.[2] However, this histamine release can also lead to a narrowing of the bronchioles in the lungs – anaphylaxis – which could result in heart failure or even death.[1] The severity of the symptoms depends on the genetic makeup of the individual and the quantity of the allergen consumed.

What can cause an allergic reaction?

A wide range of allergens could cause this allergic reaction explored above. We know of 400 proteins from 170 different foods that act as allergens.[3] Having said this, recent research has found that eight foods (the "Big 8") account for 90% of all food allergies consisting of: milk, eggs, fish, crustacean, shellfish, tree nuts, peanuts, wheat and soybeans.[4] The high prevalence of these eight allergens is often conflated to our large level of consumption of these foods or the structure of the proteins.

Additionally, due to the similarity between the molecular structure of these allergens, 48% of atopic individuals have more than one allergy.[5] This is called cross reactivity. Furthermore, most allergies are due to aeroallergens such as pollens or spores[6] leading to allergic rhinitis (hay fever) affecting around one in every five people in the UK.[8]

Why do allergies occur and why are they now more prevalent?

Answering these questions has given birth to many different theories.

One interesting connection is that our decreasing levels of vitamin D could be detrimental to the immune system and has increased the levels of asthma.[7] An early correction of vitamin D deficiency might maintain a healthy microbial ecology and allergen tolerance, decreasing the risk of food allergies in children.[8] In the US, vitamin D insufficiency has almost doubled in a span of 10 years,[9] while the percentage of atopic individuals is approaching 50% globally.[10] A low level of vitamin D at age six was also associated with increased allergies and asthma at age 14 in one study from Australia.[8] In addition to this, a study involving 616 Costa Rican children with asthma aged 6–14 years, found that 28% of the children had insufficient vitamin D levels.[11]

Most importantly, vitamin D has immunomodulatory effects on allergen-induced inflammatory pathways[12] by acting on the VDR (vitamin D receptor) expressed on a variety of fundamental immune cells, including T cells and B cells.[13] Many of these cells, such as activated macrophages and dendritic cells, are capable of synthesising biologically active vitamin D. This mechanism, called extrarenal expression of CP27B, enables immune cells to quickly increase the local concentration of vitamin D, which is potentially needed to shape adaptive immune responses.[14] A clinical study involving mild allergic asthmatics who underwent an allergen challenge showed a significant increase in vitamin D receptor binding protein (VDBP) but not 24 hours after the allergen challenge. This strongly suggests a role for vitamin D mediated immune responses during the immediate allergic reaction.[15]

The main significance of vitamin D is its ability to inhibit both Th1- and Th2-type responses by having potent antiproliferative effects on CD4+ T cells, suppressing both the production of IL-4 and IL-13 which prevents B cells from being stimulated.[16] Moreover, Regulatory T cells (Tregs) are T-helper cells that play an important role in maintaining immune homeostasis in response to allergen exposure by suppressing Th2 mediated inflammation.[17] Vitamin D can induce antigen specific IL-10–producing Tregs.[17]

This all illustrates the importance of vitamin D in the immune system which could corroborate the claim that it is our decreasing vitamin D levels increasing the number of atopic individuals, as an allergy is just a malfunction of the immune system. Moreover, it also explains that the specifically large increase in allergies in the West could be due to the increased time spent indoors in these wealthy nations and the naturally colder and less sunny climate.[34,35]

However, this theory does not explain why Finland has a higher rate of allergic individuals than the neighbouring Karelian region, despite both regions having the same level of sun exposure.[18] Therefore, it can be concluded that our decreasing vitamin D levels might only be somewhat related to our increasing number of allergies.

One of the more major theories is called the "Hygiene Hypothesis," which proposes that our reduced exposure to microbes due to our increased levels of hygiene and cleanliness has been detrimental to the immune system and has led to this hypersensitivity. These microbes and pathogens would have been important in balancing and developing the immune system.[3]

This theory was not directly based on observations of the immune system but more on relationships between data. This theory was thought to have explained why children who went to day-care had lower instances of allergies than those children who did not attend such a scheme[6] and the fact that farmers' children who drank unpasteurised milk had lower instances of allergies than those who drank pasteurised milk also corroborates the theory.[6] An inverse association between atopy and family size is also explained by this theory as an increased family size would mean increased levels of contact with other individuals, increasing virus exposure and so supposedly reducing atopy because of a more developed and balanced immune system.[19]

The "Hygiene Hypothesis" attempts to explain the European positive correlation between gross national product and incidence of asthma.[20]

However, this theory has led to many dangerous ideas being held by the public such as that we should wash our hands sometimes, but not others. This would increase our rate of infections and the subsequent deaths and reduction in public well-being is a far larger problem than allergies. For example: a recent study has shown that there are 17 million cases a year of food and non-foodborne infectious intestinal diseases (IID) in the United Kingdom, with an annual cost of £1.5 billion to cover resource and welfare losses.[21] Despite hospitals in developed countries adhering to strict hygiene protocols, 7% of inpatients contract an infection.[22] Considering most of these viral infections cannot be treated by antibiotics, preventative methods based on hygiene are crucial. Effective hygiene practices must therefore not be abandoned.

Moreover, the link between infectious diseases and allergies remains controversial as studies carried out in Denmark, UK and Finland reaffirm that allergies are not prevented by childhood infections.[23] Furthermore, it could seem implausible to conflate the major increase in asthma prevalence from the 1960s to the significant changes in sanitation in the 1920s.[24] Reducing our "excessive" hygiene will therefore not necessarily reduce atopy, exacerbating the danger brought by increasing our exposure to infections.

Although scientists agree on some of the fundamentals of the Hygiene Hypothesis, the name of the theory has been considered to be a dangerous misnomer which could potentially suggest the misinformed public to adopt less hygienic practises. The name "Microbial Deprivation Hypothesis" has been suggested as a reform. Avoiding the term 'hygiene' would help focus attention on determining the true impact of microbes on atopic diseases, while minimising the risks of discouraging good hygiene practice.

Furthermore, there has been a consensus among scientists and immune biologists that there are in fact principles within the Hygiene Hypothesis narrative itself that need reform. This has given birth to the "Old Friend Mechanism" theory, first proposed by Professor Graham

A.W. Rook in 2003,[25] which blames the increase in atopy on our less diverse microbiome, which arose from changes in our lifestyle.

The human gut is the natural niche for more than 1014 bacteria of more than 1000 different species,[26] this microbiome is essential in immuno-regulation.[26]

The Hygiene Hypothesis suggested that childhood viral infections are fundamental to the development of the immune system but advancements in evolutionary sciences have proven this as improbable.[25] It is unlikely crowd infections persisted in small hunter-gatherer circles as they either induced immunity or killed the entire group.[27] The Old Friends Mechanism theory proposes that the vital microbial exposures necessary for the development of the immune system are not these colds or other childhood infections, but rather microbes already present during primate evolution when the human immune system was evolving. These microbes are referred to as the "Old Friends" (OF).

OF microbes include species in all environments and the non-harmful microbes transmitted between humans.[25] The species constituting the human OF have varied through time, for example prior to contemporary medical developments it included helminths and hepatitis as these infections survived within hunter-gatherer groups and hence had to be tolerated.[25]

Crucially, these OF exposures interact with the immunoregulatory systems that avoid overreactions, which is the underlying cause of allergies.[28] The diversity of microbial exposure is fundamental for two main reasons. Firstly, a wide variety of organisms would be tolerated by infants if they are exposed to a wide variety of nom-harmful bacteria during these crucial years where immunoregulatory systems are being established. Secondly, increasing the variety of bacteria that one is exposed to establishes memory lymphocytes to recognise novel pathogens.[29]

It is agreed that the most vital times for OF exposure are during pregnancy, delivery and the early stages infancy.[29] However, the nature of these stages in our lives are drastically changing, which changes our microbial exposure and so leads to the reduction of the biodiversity of the human microbiome which could therefore lead to the now imbalanced immune system being hypersensitive to certain substances.

For example, Caesareans have increased in prevalence since 1950 and now account for 25% of UK births[30] and a 2008 review showed that a Caesarean section is linked to an increased risk of atopy.[31] Even breastfeeding compared to bottle feeding has a large influence on gut microbiome.[32]

In addition to this, Finnish research concluded that people living in rural spaces had a more biodiverse skin microbiota and a reduced rate of atopy.[33] However, about 82% of people in England now live in urban areas,[34] which decreases the biodiversity of the microbiota, possibly explaining the sharp rise in allergies. This is exacerbated by the fact that about 50% of people spend less than one hour a day outdoors, according to a survey across the US and Europe with a sample size of nearly 17,000 adults.[35]

Furthermore, our diet can influence the health and diversity of our microbiota.[36] It has been reported that a diverse diet which is high in fibre and polysaccharides, which are digested by the microbiota,[37] is the most effective in maintaining the health of our microbiota.[37] Whereas a diet that lacks in fibre can eliminate crucial microbes.[38] Although researchers at the University of Otago in New Zealand say people should be eating a minimum of 25g of fibre per day, fewer than one in 10 adults eats 30g of fibre daily in the UK.[39] This has led to the unfortunate fact that people living in developed countries have a less diverse microbiota than hunter-gatherers[40] which could have led to the large number of atopic individuals in these countries.

Another lifestyle alteration which has reduced the biodiversity of the human microbiome could have been the increase in prescribed antibiotics after their development in the 1950s, aligning with the increase in allergies since the 1970s.[41] According to recent studies, antibiotics, especially macrolides, can enhance the risk of asthma in children by inducing long-term effects on the microbiota.[42] This notion was supported by a 2014 review of over 50 studies.[42]

Our vitamin D intake, as explored previously, is also connected to the OF mechanism theory as it has recently been shown that the composition of the gut microbiome can be altered by vitamin D exposure.[43]

However, it could be argued that all these trends could also be explained using the Hygiene Hypothesis as both the Hygiene Hypothesis and Old Friend mechanism theories could be seen to be arguing based on the same principle. Both the reducing level of exposure to microbes and infectious diseases, proposed by the Hygiene Hypothesis, and the reducing biodiversity of the human microbiome from reducing microbial exposure, proposed by OF theory, are causative of the same problem and could be seen as synonymous as both appear to intertwine.

However, further analysis of the validity of the Hygiene Hypothesis claim magnifies the subtle difference between the two theories and exemplifies the higher credibility of the OF mechanism theory.

It appears invalid to claim that our decreased exposure to infectious diseases could have increased the atopy rate, possibly by causing the decline in the biodiversity of the microbiome, as the simple premise that "we are too clean" is invalid. It has been proven that implementing regular anti-bacterial cleaning habits in Western homes has no long-term effects on the levels of microbes[10] as they are replaced by dust and air.[44] Excessive cleanliness therefore does not facilitate a completely sterile home.

The most important point is that since the 1800s, the microbial content of our homes has significantly changed. Cleanliness practices are not solely to blame for this, the adjustment from rural surroundings in the 1800s to our modern indoor-dominated life has played a huge role.[25] This means that we now interact with a totally different and less diverse mix of microbes. It is this change that is most likely the cause of the increase in atopy, rather than our increased cleanliness and reduced infections.

There are also other factors that argue against the role of hygiene in increasing atopy. Hygiene is insignificant in causing microbiome disruption compared to our changed diet and the increase in antibiotic use.[25] Additionally, exposure to the natural environment facilitates the interaction, via the airways, with the microbes found in house dust. Hygienic practices are unlikely to be responsible for the reduced inputs from this key source.

Despite the Old Friends mechanism being a preferable theory over the Hygiene Hypothesis, the reduced focus on easily improvable factors such as hygiene and cleanliness does mean that acting based on the Old Friends mechanism is less feasible.

Allergies and their increase are most likely explained by the increasingly profound reduction of the biodiversity of the human microbiome due to changes to our daily lives (as proposed by the OF mechanism theory) and, to a limited extent, our excessive cleanliness (as proposed by the Hygiene Hypothesis). Additionally, our decreasing vitamin D levels could contribute to these changes to our human microbiome, all causing this malfunction of the immune system.

Conclusions and recommendations

We now understand that allergies are most likely to be explained by a genetic tendency interacting with our less biodiverse microbiome,

which is because of many factors. These factors include our reduced interaction with nature and possibly our reduced exposure to pathogens or our decreased levels of vitamin D, to cause the immune system to "malfunction" and treat what is harmless as if it were harmful. Based upon this crucial understanding, we can approach solving atopy by attempting to increase our microbial exposure by altering our diets or even conducting microbiota transplants in C-section infants.

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Rasheed Shehadeh

Hi, my name is Rasheed Shehadeh and I am a 2nd year medical student at Cardiff University. I am particularly interested in neurology and immunology. My hobbies include going to the gym and playing basketball.

Review

Novel target-specific imaging techniques for better detection and quantification of vulnerable plaque and plaque progression

Man Zhou
Year 3, Medicine MBBS, GKT School of Medical Education, King's College London
Email: man.zhou@kcl.ac.uk

Abstract

Atherosclerosis remains a leading cause of cardiovascular disease.[1] Current imaging techniques including invasive coronary angiography (ICA) and coronary computed tomography angiography (CCTA) are limited in evaluating the morphological changes of atheroma. They only provide visual assessment of luminal stenosis. Flow-limiting stenosis seen from ICA or CCTA often does not translate into causing myocardial infarction (MI). As a result, considering new imaging techniques that can provide information on plaque characterisation and assess the content and degree of stability of these rupture-prone plaques to prevent thrombotic events, is crucial. Thus, novel magnetic resonance imaging (MRI) and positron emission tomography (PET) imaging techniques need to be explored. Imaging target agents bind to specific atherosclerotic biomarkers in vivo, providing non-invasive visualisation and quantification of plaque content with high signal amplification. This review provides an overview of the pathology of atherosclerosis, different plaque biomarkers and its target agents, as well as potential clinical applications.

Abbreviations

ACS - acute coronary syndrome
CAD - coronary artery disease
CCTA - coronary computed tomography angiography
ICA - invasive coronary angiography
LDL - low-density lipoproteins
MI - myocardial infarction
MRI - magnetic resonance imaging
PET - positron emission tomography
SMC - smooth muscle cells

Introduction

Atherosclerosis remains a leading cause of cardiovascular disease and results in 50% of all deaths in Western society.[1,2] Even with generally good health, people aged 40 and above have about a 50% increased likelihood of developing severe atherosclerosis, with this risk increasing with age.[3] Untreated atherosclerosis could lead to major complications such as ischaemic heart disease, coronary artery disease (CAD) and ischaemic stroke.[2] Plaque burden measures the percentage plaque area over the external elastic membrane of the arterial wall.[4,5] As a result, assessing plaque burden, its progression and evaluation of response to treatment are of growing importance.[4,5] The gold standard for diagnosing CAD is currently using invasive coronary angiography (ICA).[6] ICA involves intracoronary injection of radio-opaque dye to opacify the lumen and outline any occlusion with X-ray imaging. However, the invasive nature of this technique makes screening or further investigations a huge challenge in large patient populations.[3]

Recent developments in coronary computed tomography angiography (CCTA) have allowed for rapid, non-invasive and accurate imaging in patients with suspected coronary heart disease without severe disease such as patients presenting with atypical symptoms or moderate risk of disease. Results are detailed enough for doctors to make decisions that are 95-99% accurate in patients.[7] However, diagnostic accuracy is reduced in vessels with significantly high microcalcification due to poorer spatial resolution compared to ICA, thus limiting application of CCTA in this important patient group.[8] Moreover, prolonged exposure to ionising radiation can lead to malignancy.[9]

More importantly, visual assessment of luminal stenosis using ICA and CCTA correlates poorly with haemodynamic significance.[6] Significant CAD is defined by more than 70% stenosis in a major coronary vessel as diagnosed by ICA or CCTA.[10] The majority of plaques causing MI do not cause flow-limiting stenosis on ICA and up to 1/3 of ruptured plaques demonstrate less than 75% stenosis. Current imaging techniques, ICA and CCTA, focus on the lumen instead of the vessel wall providing only indirect detection of atherosclerosis. They fail to consider degree of plaque stability or other plaque characteristics associated with risk of rupture.[11] Hence, patients with

more vulnerable plaque and therefore at higher risk of stenosis, fail to be identified for treatment. Since these plaques are easily missed on angiography, insights into better imaging techniques that might enhance prediction of MI are surfacing. As a result, there is a need for more novel imaging modalities to target detection of atherosclerosis. This essay will explore current state-of-the-art molecular imaging approaches for the detection of atherosclerosis and discuss the need for these imaging techniques.

Pathology of atherosclerosis

Atherosclerosis can be characterised as a chronic inflammatory disease due to hardening or thickening of arteries due to plaque accumulation in the intima of an artery.[12] Hyperlipidaemia, hyperglycaemia, hypertension, tobacco smoke, obesity and sedentary lifestyle are important risk factors of the disease.[13] Excessive accumulation of low-density lipoproteins (LDL) due to these risk factors result in LDL oxidation. The oxidised LDLs are phagocytosed by macrophages known as foam cells.[14] Oxidative stress coupled with risk factors leads to endothelial dysfunction thereby resulting in endothelial permeability, cytokine expression, leukocyte adhesion and platelet aggregation.[15,16] Foam cells adhere and migrate into arterial intima through endothelial dysfunction and accumulate within the intima forming yellow fatty streaks.[13] Inflammation may promote the growth of plaques and trigger plaque rupture and thrombosis.[17]

Atheroma formation occurs when altered smooth muscle cells (SMC) and myofibroblasts, migrate from media to intima and synthesise collagen. The fibrous cap composes of collagen fibres, SMC, macrophages and T cells. As LDLs continue to accumulate under the fibrous cap within the arterial wall, a lipid-core is formed. These foam cells undergo apoptosis or necroptosis and increased oxidative stress, resulting in the formation of a necrotic core within the plaque.[18] As the plaque grows due to the proliferation of fibrous tissue, the bulge within the artery increases, reducing blood and oxygen supply to cardiac muscle.[13] Stenosis of coronary artery causes ischaemia of cardiac muscle and results in death of cardiac tissue, responsible for perfusion of the body, leading to MI.

There are two types of plaques (**Figure 1**): stable versus vulnerable. The major difference between these are that stable plaque is characterised by thick fibrous cap with poor-lipid core while vulnerable plaque has a rich-lipid core with thin fibrous cap prone to rupture causing thrombosis.[19] If rupture occurs in a coronary artery, downstream ischaemia and MI results. Other changes in vulnerable plaques include remodelling, microcalcification and angiogenesis.[10]

The composition of a vulnerable plaque (**Figure 1**) is characterised by low elastin and collagen, and high tropoelastin, albumin, intraplaque fibrin and microcalcification content.

Elastin is produced primarily by SMC. It is formed by polymerisation of tropoelastin monomers. However, there is increased expression of this extracellular matrix protein in the media during plaque development, making elastin a potential biomarker for atherosclerosis. Pathological stimuli are responsible for triggering elastogenesis and recruitment of proinflammatory cells in atherosclerosis, leading to a remarkable rise in elastin content during plaque progression. However, more recent studies show that ineffective elastogenesis and elastolysis favour the accumulation of tropoelastin rather than cross-linked elastin in atherosclerotic plaques. This reduces elasticity of the vessel, increasing risk of stenosis.[21]

During atherosclerosis, endothelial permeability is increased due to the damaged endothelial glycocalyx which albumin, the most abundant plasma protein in plaques, is bound within. During plaque development, there is increased albumin infiltration into the intima and deposition in the adventitia.[22]

Fibrin is a major constituent of thrombi formed following plaque rupture. Fibrin molecules bind to form long fibrin threads that trap platelets which hardens to form a blood clot.[23] Fibrin accumulation can also take place within the atherosclerotic lesions, contributing to their growth.[24] The necrotic core of advanced plaques can also accumulate fibrin.[25] Hence, fibrin is an important coagulant that is present throughout plaque development.

Microcalcification represents an active stage of intimal calcification associated with inflammation and contributes to mechanical instability of plaques.[26,27] Vascular SMCs have the potential to undergo osteoblastic differentiation and generate calcified deposits. Plaque rupture seems to correlate positively with the amount of microcalcifications and negatively with macrocalcifications.[26]

Imaging of atherosclerosis and its biomarkers

MRI

Molecular MRI is especially suited for imaging and detection of atherosclerosis as it can evaluate relatively thin arterial vessel walls. MRI takes advantage of the high prevalence of hydrogen in the body to produce images. After being excited by radiofrequency pulses from the MRI scanner, the time taken (T) for the hydrogen proton to recover back to equilibrium and subsequently the rate of relaxivity (R) is measured by the scanner. As different tissues differ in their amount of H atoms, tissues containing higher fat content recover faster. Gadolinium(Gd)-based contrast agent binds to tissue and decreases T1 relaxation, enhancing the signal and creating a brighter image.[4]

Molecular MRI is a non-invasive technique that allows for the visualisation of biological markers in vivo.[4] MRI provides excellent soft-tissue contrast and is able to achieve higher spatial resolution, compared to other modalities.[4] MRI also provides direct visualisation of thrombi, allowing for more rapid and reliable diagnosis and, ultimately, significantly improving the clinical outcome of thrombotic disease.[28] In the next part of this review, four of such biomarkers of atherosclerosis and their imaging techniques are expanded upon.

Elastin and tropoelastin

Makowski et al demonstrated the successful use of Gd-labelled elastin-specific MR contrast agent (Gd-ESMA) for the quantification of plaque burden using a mouse model (**Figure 2**). The high spatial resolution achieved through the amplified signal provided by Gd-ESMA allows for accurate evaluation of plaque burden, characterisation, progression and regression.[4] More currently, Phinikaridou et al used Gd-labelled tropoelastin-specific MR contrast agent (Gd-TESMA) for tropoelastin imaging of atherosclerosis in animals (**Figures 3 and 4**). The probe was able to distinguish between cross-linked elastin and tropoelastin. It provided favourable pharmacokinetics, increased R1 relaxation rate with disease progression. It also shows the effectiveness of treatment from disease regression as well as differentiate between stable and vulnerable plaques with a high level of specificity and sensitivity.[12]

Albumin

Phinikaridou et al also demonstrated gadofosveset as an albumin-binding MRI contrast agent. It is taken up through damaged endothelium and used as a surrogate marker to quantify vascular permeability and identify rupture-prone atherosclerotic plaque and its progression through a rabbit model (n=10). MRI is able to quantify both morphological and functional changes of the arterial wall which not only may be used to detect plaque progression but also unstable atherosclerotic plaques.[29]

Comparison between MR imaging of stable and rupture prone plaques at 3 and 12 weeks of high fat diet shows increased endothelial permeability in rupture prone plaque and increased vessel thickening caused by plaque formation from 3 to 12 weeks in both plaques. Corresponding R1 relaxation maps depicts higher R1 in rupture-prone compared to stable plaque at 12 week (R1; 2.30±0.5 versus 1.86±0.3 s^{-1}; $P<0.001$), suggesting higher endothelial permeability to gadofosveset.[29]

PET

PET scan uses an injected radioactive tracer for non-invasive, sensitive and relatively rapid imaging. However, due to its low spatial resolution and lack of anatomical information, it is compensated by hybrid imaging with MRI or CT.[30]

Microcalcification

PET/CT molecular imaging uses ^{18}Fluorine-Sodium Fluoride (^{18}F-NaF) radioactive contrast agent (**Figure 5**) to potentially detect clinically significant high-risk nascent microcalcification and active unstable atherosclerosis.[27,31] ^{18}F-NaF has a likely capacity to detect high-risk plaques indicating its possible role in identifying vulnerable plaques and in predicting MI. The basis for ^{18}F-NaF uptake in atherosclerosis is assumed to be analogous to its accumulation in areas of bone remodelling. Since macrocalcifications have a relatively small surface-to-volume ratio, the radioactivity signal detected is proportionally smaller than microcalcifications, with a larger surface-to-volume ratio, allowing for distinction and detection of mainly microcalcifications.[31]

Macrophages

^{18}Fluorine-fluorodeoxyglucose (^{18}F-FDG) is another PET tracer detected by PET/CT (**Figure 6**) that is taken up by macrophages and has shown to be a robust surrogate of plaque activity and composition. In many preclinical and clinical studies, regions of high macrophage density are associated with increased FDG uptake in plaques.[32] During atherogenesis, the necrotic core formed within the atheroma due to hypoxia causes an increase in demand for glucose uptake. As ^{18}F-FDG is a glucose analogue, it will preferentially accumulate in macrophages. Thus, as ^{18}F-FDG uptake increases, its accumulation is readily detected and quantifiable. It can be used as a sensitive measure of metabolic activity, especially in vulnerable plaque with high concentration of proinflammatory macrophages which result in high metabolic activity. It is evidenced that higher FDG uptake in plaque is associated with higher risk of recurrent cerebrovascular event. Through FDG-PET imaging, the systemic nature of atherosclerosis has also been explored. FDG uptake is closely associated with the neighbouring tissues supplied by the artery, suggesting a systemic increase in expression of inflammation rather than a localised phenomenon.[11]

Discussion

Possible clinical application

Atherosclerosis remains a predominant trigger of many cardiovascular diseases such as CAD and acute coronary syndrome (ACS). Hence, MRI imaging of atherosclerosis is key to not only aid in detection and monitoring, but also quantify the change in plaque burden through morphology and anatomical structures over time. This is especially helpful in assessing disease progression and the usefulness of therapeutics. MRI imaging of specific biomarkers shows a significantly higher enhancement of signal intensity compared to other modalities. MRI imaging also provides better contrast-to-noise ratio (CNR) allowing for clearer and more accurate imaging. The prompt clearance of contrast agent from blood pool also prevents toxicity build-up. MRI imaging can also be used to identify inflammatory burden within plaque. Moreover, MRI imaging is non-invasive and does not require radiation exposure, which in the long term may cause cellular damage and malignancy.

Furthermore, several target specific contrast agents have been approved for clinical use (e.g. gadofosveset) and new agents (e.g. ESMA, TESMA) show promising results in several animal studies with hopes for future clinical usage.[25] In some cases, patients with CAD may present with symptoms of chest pain without diagnostic ECG changes. Therefore, early detection of fibrin-rich thrombus may prove to be useful in both diagnosis and early treatment. Monitoring of thrombolysis is another potential application.[33]

Limitations

An obstacle for clinical application of target specific MR contrast agents is the low sensitivity of MRI (microM) in comparison to PET (nM). Consequently, for decent signal detection, relatively high local concentration (~50microM) is required. Thus, for small molecular weight MR contrast agents, imaging is limited to high abundance biological target agents. A nanoparticle has been developed to reduce the injected dose to around 0.1 mmol/kg or lower due to its increased relaxivity upon binding. Moreover, more recent MR contrast agents prefer to use DOTA in lieu of DTPA chelates due to its markedly better stability to reduce safety concerns regarding toxicity.[25] The use of hybrid modalities such as PET/MR are being explored to overcome this. PET, though unable to provide anatomical information or high spatial resolution, has a higher sensitivity than MRI, hence lowering the injection dosage. However, low specificity of the PET tracer and high cost serve as major limitations and the use of cardiovascular PET/MRI is still in its budding stages of development.[34]

Moreover, many of these studies use animals and have small sample sizes. This may not truly reflect the human atherosclerosis pathology. Although there are some ex vivo human studies, this may not be representative of human atherosclerotic pathology. Therefore, more in vivo animal and human studies in larger sample sizes need to be undertaken to establish the translational potential of MRI imaging.[21]

Extensive preclinical evaluation is another potential hurdle in the shift of MRI of atherosclerosis from a preclinical to clinical level. Thorough assessment of drug safety through toxicity studies are required. Convincing production partners to manufacture, upscaling production and commercialising the contrast agents for clinical use also presents as an arduous process.

Vulnerable plaque versus vulnerable patient

Only a small proportion of these identified rupture-prone plaques result in clinically adverse events. As a result, all rupture-prone plaques with high risk of thrombotic complication and rapid progression should be considered as vulnerable plaques. Therefore, to support a more personalised medical approach, it may be more appropriate to use the term "vulnerable patient" in the assessment and identification of patients at high likelihood of developing adverse clinical events in the near future. One such assessment is CT calcium scoring. It can be used as a surrogate of the total coronary atherosclerotic plaque burden and enhance risk prediction in vulnerable patients. Despite recent technological enhancements, personalised risk prediction remains limited in identification and prevention of adverse clinical events.[10]

Conclusion

MRI imaging of specific biomarkers offers a potentially powerful strategy in personalised preventive and diagnostic medicine for atherosclerosis. Future developments in MR technique such as combining several biomarkers for better detection could be explored. Theranostic approaches, which provide diagnosis and treatment simultaneously, can also be looked into to provide more efficient and tailored therapy.

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Man Zhou

Man Zhou is a 3rd year international medical student from Singapore, currently studying at King's College London. She is part of the committee in Surgical Society and Women In Medicine societies of her university, as well as

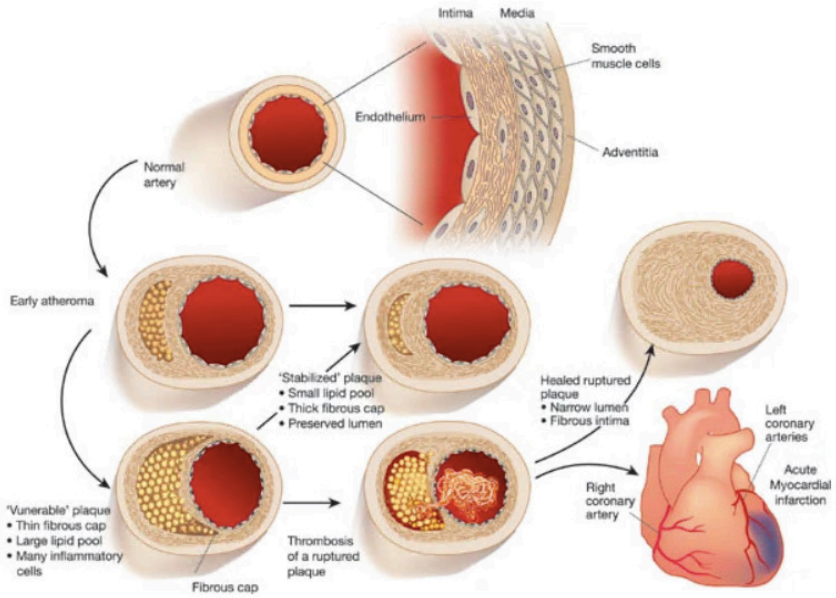


Figure 1. Illustration of plaque progression and rupture in a coronary artery: it also shows how the ruptured plaque could heal and result in subclinical events or proceed to lead to a myocardial infarction of the heart. Reprinted from Libby (2002),[20] by Nature.

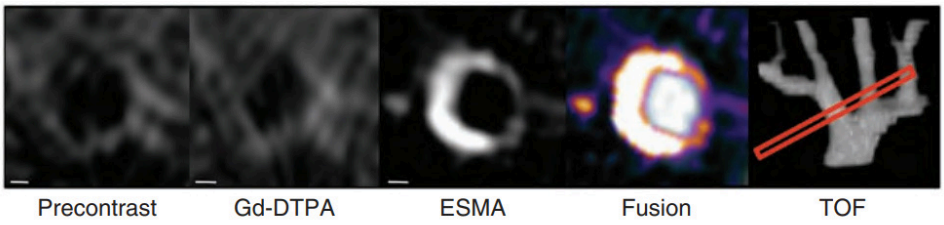


Figure 2. Cross sectional imaging of the brachiocephalic artery (BCA) in a male Apoe-/- mouse after consuming a high fat diet for 12 weeks: The time-of-flight (TOF) angiogram of the BCA visualises path and flow within the vessel. Fusion of high-resolution DE-MRI and TOF provides spatial information of luminal anatomy and contrast uptake. Reprinted from Makowski et al (2011)[4], by Nature Medicine.

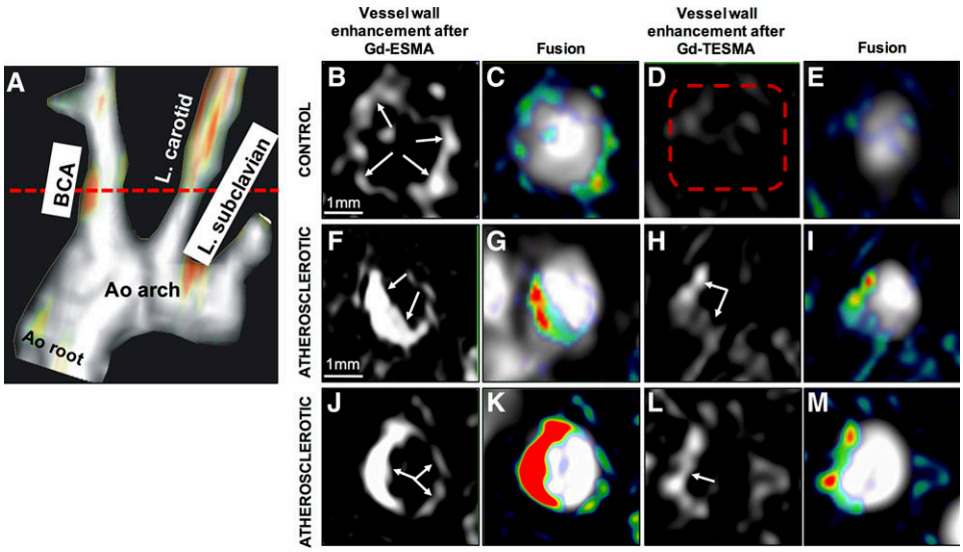
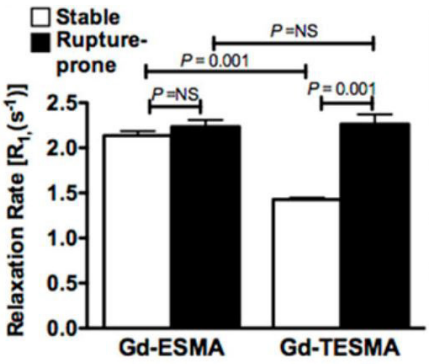


Figure 3. In vivo MR comparison of BCA vessel wall enhancement using Gd-ESMA and Gd-TESMA in ApoE-/- mice: there is a lack of uptake of Gd-TESMA in control **(D, E)** compared to Gd-ESMA **(B, C)** suggesting that there is an absence of tropoelastin accumulation in normal mice. **(F-M)** MRI images of 2 diseased mice show signal amplification with both Gd-TESMA and Gd-ESMA due to the presence of tropoelastin and cross-linked elastin respectively. Reprinted from Phinikaridou et al (2018)[21], by Circulation: Cardiovascular Imaging.



	$R_{1\ Gd\text{-}ESMA} \geq 2.2\ s^{-1}$ and % (CI)	$R_{1\ Gd\text{-}TESMA} \geq 1.65\ s^{-1}$ and % (CI)
Sensitivity	67.8 (48.6-83.3)	84.4 (67.2-97.7)
Specificity	66.7 (53.3-78.3)	92.3 (82.9-97.5)
PPV	51.2 (40.5-61.8)	84.4 (69.7-92.7)
NPV	80.0 (69.9-87.3)	92.3 (84.2-96.4)

Figure 4. Quantification of brachiocephalic vessel wall: Markedly higher R1 in vulnerable plaque compared to stable plaque on after administration of Gd-TESMA. Reprinted from Phinikaridou et al (2018)[21], by Circulation: Cardiovascular Imaging.

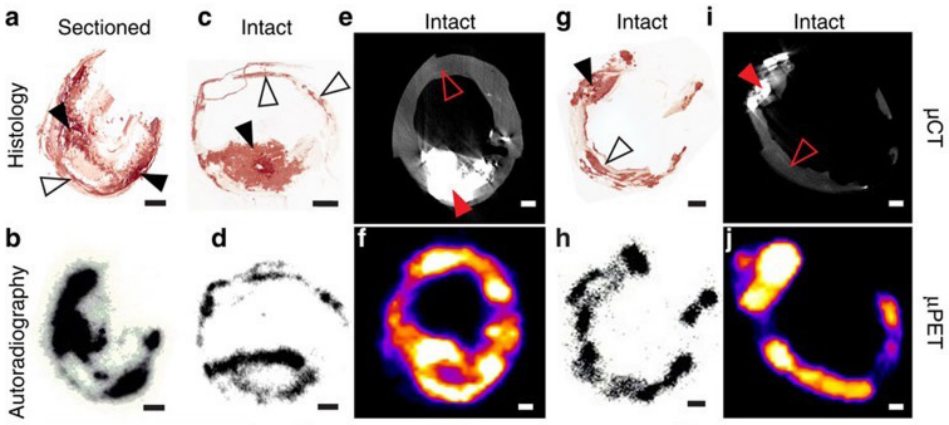


Figure 5. Pet/CT scans of micro- and macrocalcification compared to histology and autoradiology: (a,b) When the carotid artery is sectioned before incubating in ^{18}F-NaF, ^{18}F-NaF binds to both microcalcification (white arrowheads) and macrocalcification (black arrowheads) surfaces. **(c,d)** However, when the order is reversed such that the carotid is incubated fist and then sectioned, ^{18}F-NaF binds to all microcalcifications (white arrowheads) but only surface level of macrocalcifications (black arrowheads). **(e,f)** ^{18}F-NaF binds only to the surface level of macrocalcifications in a μPET/μCT. **(g,i)** A μCT scan on its own is unable to detect microcalcifications as seen in Alizarin Red histology due to low sensitivity. **(h,j)** However, ^{18}F-NaF μPET scan is able to match autoradiography signal and detect microcalcifications. Reprinted from Irkle et al (2015)[31], Nature Communications.

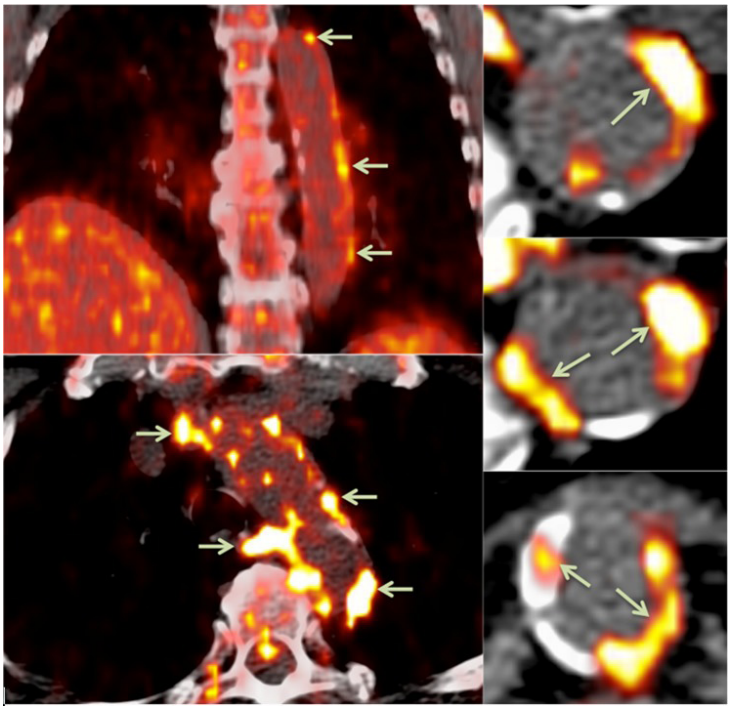


Figure 6. FDG-PET/CT indicating regions with focal radiotracer uptake in the descending aorta vessel wall (arrows). Reprinted from Evan, Tarkin, Chowdhury, Rudd (2016)[11], Current Atherosclerosis Reports.

Research

A dental volunteering project in the indigenous communities of Bocas del Toro, Panama: lessons learned.

Liam Fletcher
Year 5, Dentistry, University of Bristol
Email: oj18783@bristol.ac.uk

Abstract

Background
Panama recognises seven indigenous populations that make up 12% of its population. The Ngäbe population comprises 60% of the indigenous peoples who mainly reside in Bocas Del Toro. Our knowledge of the oral health status of indigenous populations around the globe is lacking. This study aimed to bring awareness of the current oral health status of the Ngäbe population and the wider indigenous populations globally.

Methods
A descriptive cross-sectional study design was used integrating ethnographic research methods. Data for this study were obtained during a three-week volunteering position facilitated by Floating Doctors. Clinical data was extracted from electronic records and observations of dietary habits and oral hygiene (OH) practices took place between 25 July and 12 August 2022. A 'complete observer' method of participant observation was used.

Results
In total, 184 patients were seen between the dates specified. 104 patients presented with pain, 65 presented for a check-up and 15 presented for other reasons. 81.4% of those attending had evidence of caries. At least 50% of patients that presented had unrestorable caries. The teeth most commonly involved were the mandibular first permanent molars. Our observations highlighted a large consumption of high-sugar soft drinks, a lack of effective OH and the absence of fluoride interventions as being the main causative factors in the clinical observations made.

Conclusion
The current oral health status of the Ngäbe population is that of a reflection of the social and geographical barriers faced by these people. The burden of oral disease is attributed to dental caries. More complex issues such as social inequalities and environmental hazards play a significant role in the oral health of these communities. These findings likely reflect that of the wider indigenous population. It is important for us as a global society to reflect on these issues and their causes if we wish to improve the oral health outcomes of those within indigenous populations.

Abbreviations

N - number
OH - oral hygiene

Introduction

Panama recognises seven indigenous populations that make up 12% of its population.[1] The Ngäbe population comprises 60% of the indigenous peoples who mainly reside in western provinces including Bocas Del Toro.[2] These indigenous populations have faced many challenges in recent decades, notably their struggle to obtain the legal rights to ancestry territories.[1] Additionally, there are high degrees of social segregation, with indigenous populations possessing a low socio-economic status.[3] Rudimentary educational infrastructure leading to literacy rates that are substantially lower compared to the national average is also an issue.[4] These factors undoubtedly create disparities in the quality of health education and healthcare accessibility within these communities, especially

considering their geographical barriers (**Figure 1**). These barriers make access to oral health education and dental care extremely difficult.

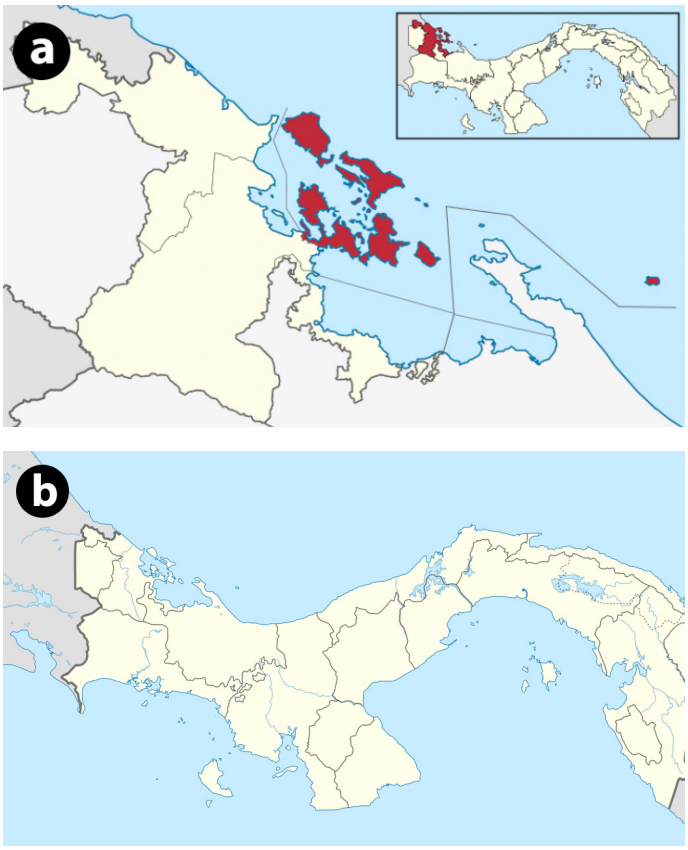


Figure 1. (A) Shows the location of Bocas Del Toro highlighted in red. Multiple islands that form an Archipelago. Image by Alexrk - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=6909551 **(B) Shows the location of Bocas del Toro on the northwest of Panama.**[5] Image by By Milenioscuro - Own work, CC BY-SA 3.0, https://commons.wikimedia.org/w/index.php?curid=24654195

Perhaps the most widely known cultural practices relating to the oral health of indigenous people is the art of dental modification. The practice of drilling, chipping and shaping teeth into triangles for aesthetic purposes dates back thousands of years.[6] However, little is known regarding the burden of oral disease in such communities. National health surveys are routinely used to investigate the oral health of a population. However, owing to the factors already highlighted, it is unlikely these surveys reflect the oral health of indigenous populations. Additionally, having consulted the literature databases, studies investigating the oral health status of indigenous communities globally are scarce and there are no studies pertaining to the Ngäbe population specifically. Accordingly, our knowledge of the oral health status of this community and the wider indigenous population around the globe is lacking. A United Nations report highlighted that poor access to healthcare in indigenous populations is a common theme and so it can be expected that the oral health status of the Ngäbe population may reflect that of indigenous populations globally.[7] Therefore, this study aimed to bring awareness of the current oral health status of the Ngäbe population residing in Bocas Del Toro, Panama, in addition to investigating the dietary habits and Oral Hygiene (OH) practices within this population. As social, cultural, and behavioural factors are likely to be comparable between indigenous populations across the globe, this study will provide an insight into the oral health landscape of such communities.

Methods

A descriptive cross-sectional study design was used integrating ethnographic research methods to obtain data relating to the cultural determinants of oral health. The study population was the Ngäbe people who reside in Bocas Del Toro, Panama. Data for this study were obtained during a three-week volunteering position facilitated by the organisation Floating Doctors. This is a non-profit organisation permanently based in Bocas Del Toro that provide medical, dental and veterinary care to the indigenous people residing in this province. This organisation covers a total of 27 communities of which care is provided at three-monthly intervals. Due to the structure of care provision, only six communities were visited by the study author (N=7000). The decision of which communities were visited on a given week was decided by the organisation's timetable at the time of visiting.

Ethnographic research methods

It was decided that a 'complete observer' method of participant observation was to be used owing to ethical considerations and time constraints. This method meant that no effort was made to obtain data on the dietary habits and OH practices above and beyond the natural dental history taken at the point of care. This also meant that the participants of the study did not know they were being observed. Observations of dietary habits and OH practices took place between 25 July and 12 August 2022 and included any observation relating to these determinants of oral health whilst the author was present within the community. A note journal was used to record this data and entries were made as soon as possible following an observation. Where observations were made on clinic, the author recorded this at the next available convenience. This process meant that all data was recorded within four hours following initial observation. Data regarding OH practices were mainly taken from clinical histories owing to the time at which these events would take place.

Clinical data collection

Dental clinics were held remotely within the community and at a base clinic on Isla Cristobal. Electronic record keeping was the responsibility of the dental coordinator who was not involved in care provision. Data was recorded by the dental coordinator upon patient presentation, following initial examination and following treatment completion. This meant all relevant data was recorded on the electronic database contemporaneously. Clinical data input between 25 July – 12 August 2022 was extracted from the electronic records to be used in this study. From these records, data was sought for age, gender, presenting complaint, examination findings and treatment carried out. Microsoft Excel was used to synthesise and tabulate the data.

Ethics

In line with the ethical principles for ethnographic research, efforts were made to ensure that this study protected the autonomy, wellbeing, safety, privacy and dignity of participants. Clinical data was only extracted from those who willingly presented to the clinic and consented to treatment, maintaining the autonomy of patients. The data extracted from the records and used in this study contained no patient identifiable data. Qualitative data pertaining to our outcomes was derived either from that of the natural medical and dental history taken at the point of care or observations made by the researcher within the field. Where patients did not express information about our outcomes, no effort was made to probe for this. Therefore, no information was purposefully extracted from the patient for use within this study. Additionally, a 'chance observation' style was adopted, meaning the observer made no effort to place themself in locations they were not naturally needing to be in. In this way, the privacy and dignity of participants was maintained.

Results

Dietary observations

Like all indigenous populations, the Ngäbe people rely on food derived from their immediate environment. This largely consists of beans, lentils, plantains, meats and fresh fruit. Therefore, individuals largely consume a balanced diet. Confectionary such as sweets and chocolate were not sighted often in the majority of communities.

The exception to this being a small convenience store within the more developed community Pueblo Nuevo (**Figure 2**). As expected, children in this community were often seen with this confectionary. In contrast, all communities had several stores selling sugary drinks such as Coca Cola. It was noted that in these stores there are no sugar free options and a bottle of Coca Cola costed less than a bottle of water. On multiple occasions, children as young as two were seen drinking juices from a carton for prolonged periods of time. Empty soda and juice bottles were observed frequently within the communities as well as in school classrooms, confirming their high intake of sugary drinks.

Figure 2. Shows an example of a convenience store selling sodas and confectionary.

Oral hygiene observations

Evidence regarding OH practices was limited. It was noted that several patients mentioned they had never brushed their teeth. Evidence of fluoride use was scarce. Empty toothpaste tubes were identified in only two communities (**Figure 3**). It was encouraging to see a mother brushing her daughter's teeth in one community; however, this was the only direct observation of OH practices.

Figure 3. Shows one of the only pieces of evidence of fluoride use within the communities visited (bottom right). The image also shows a large number of empty soda bottles.

Clinical observations

In total, 184 patients were seen between the dates specified. 104 patients presented with pain, 65 presented for a check-up and 15 presented for other reasons including cavities, discoloured teeth, and aesthetic concerns (**Figure 4**). Of those presenting with pain, all were found to have caries. Of the 84 patients presenting for a check-up or reasons unrelated to pain, 49 were found to have dental caries. This meant that 81.4% of those attending had evidence of caries. It was observed that the vast majority of these presentations were extensive and beyond the point of restorability. Indeed, 78 extractions were completed, of which nine were deciduous teeth and 69 were permanent teeth. Only teeth that were deemed to be clinically unrestorable were extracted. This meant that at least 50% of patients that presented had unrestorable caries. The teeth most commonly involved were the mandibular first permanent molars in those in the mixed or permanent dentition. However, for those in the deciduous dentition the majority of teeth, including the anterior teeth, were affected. Of the 184 patients seen, 124 were adults and 60 were children or adolescents (**Figure 5**). Unfortunately, gender could not be matched with the presenting case and so it was not possible to determine the proportions of males or females attending. However, it was observed that the vast majority of presentations were adult or adolescent females and children. When adult or adolescent males presented, they often had severe caries at multiple sites accompanied by pain or abscesses.

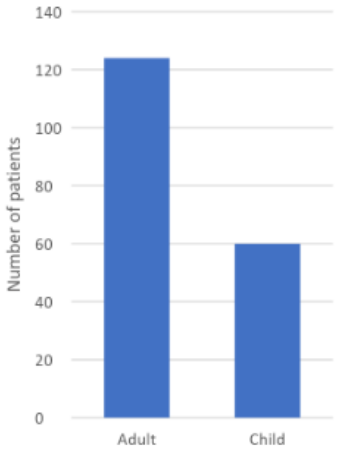


Figure 5: Shows the number of adult and child patients who attended the dental clinic.

Moreover, although not recorded, almost all patients had dental plaque-induced gingivitis. The prevalence of periodontitis was observed to be low. This is shown by the fact that only one patient's presenting complaint was related periodontal issues. Very few patients presented with signs of tooth wear.

Discussion

The aim of this study was to gain an awareness of the current OH practices and dietary habits of the Ngäbe community and whether these factors were reflected within their oral health. Given the similarities of indigenous communities across the world, these results may offer an insight into the oral health of indigenous communities on a wider scale. An ethnographic approach was taken to identify these practices whilst within the communities. Regarding dietary factors, it is clear than the main sugar source is from sodas and fruit juices. This is not an uncommon issue within remote indigenous communities all across the world. A study conducted jointly by the Public Health Advocacy Institute of Western Australia and Diabetes Western Australia highlighted the accessibility and availability of soft drinks within the indigenous communities of Australia.[8] This accessibility is owed to the sponsorship and community grants given to soda companies to promote their products even in the most remote locations. Recently an advertising campaign by Coca Cola has been heavily criticised promoting the consumption of their product in indigenous communities. This is one example highlighting the negligence and lack of responsibility of large soft drink manufactures.[8,9] Moreover, they discovered that residents of these communities often feel safer drinking soft drinks compared to water sourced from their environment.[8] As such, the issue of increasing soda consumption may be a more complex issue than once thought, with people relying on sodas as a source of safe hydration. Additionally, soft drinks were in some areas easier to obtain than fresh water from the local environment. This trend was somewhat reflected in our observations, with bottled water being more expensive and thus deemed more of a commodity than soft drinks. As opposed to the sales and marketing of soft drinks within these communities, education on the general and dental health consequences of high sugar sodas is non-existent. Our observations did not identify one piece of evidence relating to the harm sodas can cause to the dentition or general health, notably in the school environment. In fact, it was observed that the only dental education

that the communities received was from the Floating Doctors Dental Team which reinforced OH and dietary advice at every three-month visit. It is not surprising therefore that in addition to extremely high caries rates, the prevalence of type 2 diabetes is very high. Uniting both oral health and general health in the provision of health education would be key to combat the issue of sugar consumption in indigenous communities. This study confirms the need for increased education and awareness within the remote communities that have such access to soft drinks. Educational projects not only need to target young adults, but also parents who are unaware of the consequences of giving their children large quantities of sugary drinks and sodas. However, the issue of high soda consumption may be more integrated within the culture of remote indigenous populations more than we first thought. Systemic issues such as poor access to fresh water needs to be addressed alongside educational resources in order to see an impact of educational interventions.

Moreover, very little data was observed regarding the OH practices of this population. However, based on several dental histories, the general impression the author got was that OH measures were at best suboptimal and at worst non-existent. Indeed, several patients reported never to have brushed their teeth. This was evidenced by the poor oral hygiene witnessed by volunteers. Despite this, it was pleasing to see the level of engagement by the children of these communities when delivering oral hygiene instruction. It was disappointing to see such a lack of fluoride measures, notably toothpaste, being used within these communities given its ease of implementation. The implementation of fluoride interventions would go a long way in reducing the dental caries burden experienced by this population. However, access to fluoride products such as toothpaste may be the biggest barrier in achieving this given their remote location. Furthermore, OH education was scarce within each community, and so there is a desperate need for the provision of education relating to oral hygiene. Despite the good will of overseas dental volunteering projects, a lack of trust and communication between those delivering oral health education and indigenous people can reduce the effectiveness of such interventions.[3] Therefore, providing the knowledge and resources to education providers within the environment, such as schoolteachers, may be a more effective intervention. However, several studies have shown that educational interventions, as well as fluoride interventions, have only had a minimal impact on caries prevalence in indigenous communities.[10,11,12,13] The main factor in this poor success being the perpetuating social and cultural inequalities experienced by indigenous people.[10,12,13] As such, addressing these factors on an international level must be a priority if we wish to see substantial improvements in the oral health outcomes of indigenous communities.

The majority of patients presenting to the dental clinic were symptomatic driven. As such, the rates of caries within the treated sample of patients may not reflect the true burden of caries within the Ngäbe population. However, that is not to say the data collected does not highlight the severity of the disease experienced by these individuals, as although only 50% of patients had unrestorable caries, many young patients with unrestorable, asymptomatic teeth did not receive an extraction. The vast majority of such patients would fit the diagnosis of rampant caries. Therefore, the severity of caries that presented to us is likely to be greater than that reflected in our clinical data. Interesting, the upper permanent molars were often spared from dental caries. This pattern fits with our dietary observations as fluids are likely to sit at the bottom of the mouth and bath the lower mandibular molars. Moreover, there were very few issues related to periodontal disease. This is surprising considering the observed prevalence of diabetes within this population. Given the link between periodontitis and diabetes,[14] these results were unexpected. An explanation for this could be that few patients were seen over the age of 40 and so the cohort of the population likely to possess this disease did not present to us. Additionally, not one patient reported a history of alcohol or tobacco consumption, which may contribute to the very low rates of periodontal pathology. Despite the observed intake of sodas, tooth wear rates were very low. However, it is likely that this was overlooked by the author owing to the volume of caries presented. Conclusively, the oral disease burden most likely lies with dental caries within indigenous communities at present.

Only 65 patients presented for a dental check-up, which is a very small proportion of the total population who had access to our clinic. Additionally, it was observed that a large proportion of these patients were children of whom attended with parents with a chief complaint. It was generally observed that patients were accepting, and sometimes eager, to extract the tooth in question. This was the case even if the tooth could be saved at a dental clinic, which is not surprising considering the time and financial implications of this journey. Therefore, it can be inferred that the importance of maintaining oral health may not come high on the priority list for many people within the Ngäbe community. Factors influencing the perceived importance of oral health in indigenous communities may include the perceived severity of dental pain, barriers to access such as transport and finances, the social and aesthetic impacts of poor oral health, and the level of oral health education.[15] This study confirms such conclusions with the majority of visits being symptomatically driven and many patients expressing their inability to attend our dental clinic at base owing to transport and financial issues. The social impacts of poor oral health were also observed, with parents often bringing their children to our clinic complaining of the unsightly appearance of their heavily carious teeth. Knowing these factors is important if we aim to increase the perceived importance indigenous populations place on their oral health as it facilitates oral health education that aligns with the beliefs and values of indigenous people.

The clinical data presented largely reflects the paediatric and female individuals within this population. Male patients were rarely treated due to work commitments. It could be assumed that owing to the labour-intensive nature of their occupation, their need for energy and rehydration is greater, and their intake of sodas may reflect this. This would fit the trend seen as the male patients that did present did so with gross caries. This highlights the importance of considering the wider social factors that may influence whether patients are able to attend remote dental clinics offered by dental volunteering projects in order to maximise the number of people that benefit from such projects.

Importance of this study

There are approximately 476 million indigenous people making up 6% of the global population yet represent 19% of those living in poverty.[16] Poor health outcomes are inextricably linked to poverty due to issues such as poor health literacy and limited access to healthcare provision. This study highlights the systemic issues faced by indigenous communities in the context of oral health. It is vitally important that we are aware of the oral health inequalities we still face globally so that we strive to bridge these gaps, especially in an era where the field of dentistry is becoming ever more expensive and unattainable. The lessons learned in this study shows a stark reality of how, despite the best efforts from non-profit organisations, dental volunteering projects are likely going to assume the role of 'damage controller' with respect to oral health. Social inequalities in a wider context and better access to sustained preventative care needs to be addressed at a local, and international level, if we want to see any improvement in the oral health status of our indigenous communities.

Strengths and limitations

A strength of this study was that observations were made contemporaneously by the author, meaning no observations were omitted. Additionally, having a dental coordinator whose role was to collect clinical data meant that this data was accurate and made at the point of care. The nature of the volunteering project meant that

the author was fully immersed within the culture of this community, allowing for rich experiences that has led to a full understanding of this community in the context of oral health.

Limitations of this study include that there was only one observer. This meant that ethnographic data relied on one person being in the correct place and thus led to very fewer observations, particularly for oral hygiene practices. Additionally, without additional observers, the impressions portrayed within this study reflects that of only one individual. As such, bias cannot be excluded. Another limitation was the three-week duration of this study. More time would have allowed greater observations and thus a better insight into the determinants of oral health within the Ngäbe population.

Conclusion

The current oral health status of the Ngäbe population of Bocas del Toro, Panama, is that of a reflection of the social and geographical barriers faced by these people. The burden of oral disease is strikingly high and attributed largely to dental caries. A high intake of high-sugar beverages, the absence of self-sustaining dental education and lack of access to fluoride interventions and dental care are just some of the factors responsible. More complex issues such as social inequalities and environmental hazards also play a significant role. These findings are likely to reflect that of the wider indigenous population globally given they face the same social determinants of health. It is important for us as a global society to reflect on these issues and their causes if we wish to improve the oral health outcomes of those within indigenous populations.

Acknowledgements
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Liam Fletcher

My name is Liam and I am a final year dental student at the University of Bristol. This summer we travelled to Panama, Bocas Del Toro, to volunteer with the organisation Floating Doctors. Not only was this an incredible experience, but we also got to see the full extent to how healthcare project's function and the difficulties faced both at an organisation level and at a patient level. We were very grateful to the wonderfully kind indigenous populations who entrusted us to carry out their dental treatment. I hope this article provides a glimpse of what it's like to volunteer abroad but also the wider issues that we face if we wish to provide effective programmes in the future.

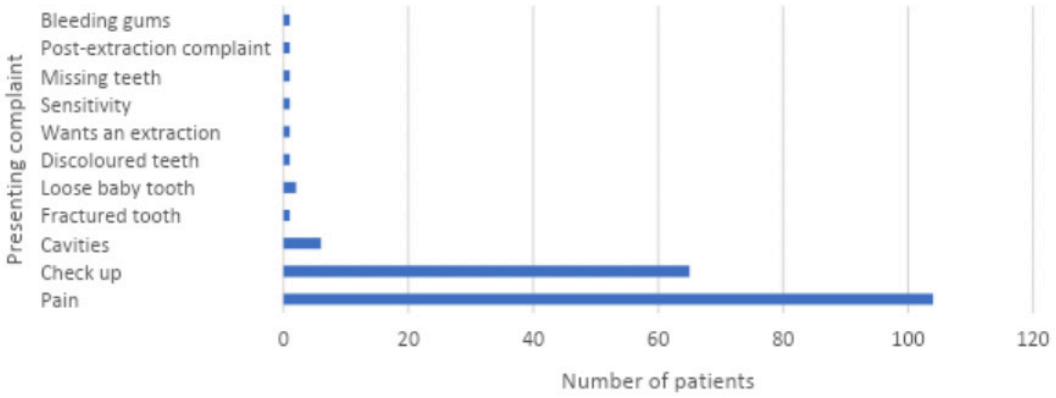


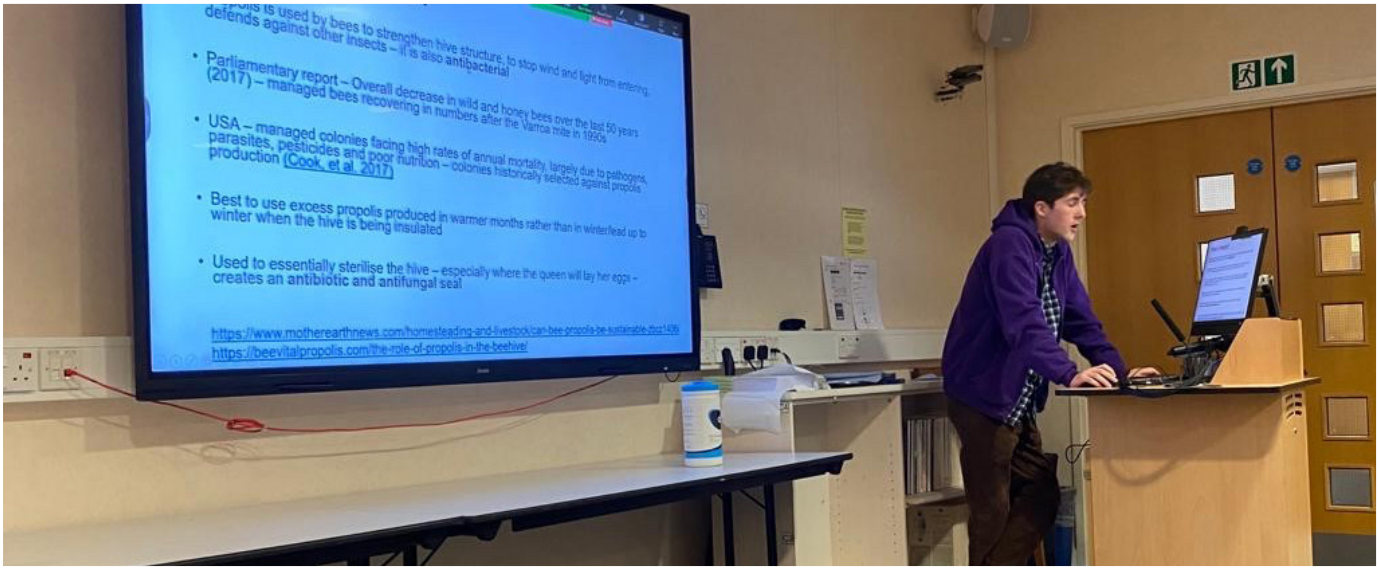
Figure 4: Shows the number of patients presenting with varying chief complaints.

Conference Report

One Health Showcase report

Tomas Nicholas

Dentistry, University of Plymouth
Email: tomas.nicholas@students.plymouth.ac.uk



On 10 November 2022, the One Health Showcase took place at the University of Bristol. The event had a focus on the intersection between human health, animal health and environmental health, creating an interdisciplinary framework. Funded by the INSPIRE scheme between the universities of Plymouth, Exeter, Bristol and Cardiff, it was both online and in-person, to allow for networking but also access to the event where travel was not possible.

There was a total of five speakers from a range of backgrounds, including medicine, dentistry and veterinary science. The variety of talks given showed how the concept of One Health can be applied to multiple disciplines and can be taken into consideration in the work carried out by both clinicians and researchers. This event provided a great platform for the One Health message to be delivered and allowed students to understand the multitude of ways it can be applied and woven within their disciplines.

The first talk was given by the author of 'Tickets for the Ark' Rebecca Nesbit (see interview on page 34). An overview of some of the issues to be considered with conservation was given, which provoked some interesting thoughts about where and how efforts should be focused. How we decide on what species to focus on conserving and how we go about this is something I had never previously thought about. This is an ever-important topic today, where global warming, trophy hunting and the ethics of how we treat animals is discussed a lot more openly. The intersection of how conservation efforts and its commercialisation can impact humans with a potential for both a negative and positive impact on local communities was interesting, due to the differing socio-economic landscapes where conservation efforts are happening.

Following this were the student talks, with the first presented by Virginija Vikelyte, a fourth-year medical student at the University of Exeter presenting 'Living with Environmental Change' where the talk focused on antibiotic (colistin) resistance due to aquacultural dissemination.

The second presentation was by Jessica Williams, also a fourth-year medical student at the University of Exeter, who discussed bacteriophages and their potential place in finding a solution to antimicrobial resistance (AMR). This talk particularly focused on their use in chronic suppurative lung disease. Both talks had a common theme of AMR, which is often described as a "silent pandemic" with an increasing sense of urgency surrounding this, and very topical with antibiotic resistance week starting soon after the showcase.[1] After these talks, it opened up a discussion surrounding antimicrobial use, such as in the meat industry, where animals are often fed antibiotics as part of their diet to prevent infections occurring within the populations to ensure no loss of product, with this having the potential to drive antibiotic resistance, predicted to kill 10 million people a year by 2050.[2,3]

The third student talk was presented by myself, an intercalating dental student at the University of Plymouth. The talk was titled 'The sustainability of bee propolis and the effects of propolis mouthwash on markers of oral health' which took into consideration the preservation of the oral microbiome, oral health and the ecological impact of using products derived from animal sources. This talk also had themes of AMR and considered the environmental impacts of using products derived from animal sources, particularly in this case how it may influence bee survival and populations.

The final presentation was a veterinary focused talk by Jamil Dowling, a veterinary medicine student at the University of Bristol who shared his experience of conservation work abroad. This gave a great overview of what conservation work actually involves, bringing to life some of the other aspects of the event, and I think it was great that this introduced further discussions of how to get involved with similar projects and research.

The evening finished with some food, drinks and an opportunity to socialise and network. It was an excellent to discuss further thoughts evoked by the talks, especially as the three groups of medical, dental and veterinary clinicians do not get the opportunity to share ideas with each other regularly. I think this is incredibly important that these discussions start with students in these fields, as they will be shaping the future of clinical practice and research.

I found a common theme between the medical and dental students was the apparent lack of awareness of One Health in comparison to veterinary students, which we thought should change and be integrated into more curriculums. A topic brought up that I though was interesting was the use of single use plastics, which are convenient and aid infection control, but ultimately has a negative impact upon the planet that we live in and should be taken seriously. From my own experience, I feel as though consumption of single use plastics is excessive in dentistry and more efforts should be made to reduce this usage.

Thank you to Sofia Croppi and all others involved in the organisation of this wonderful event.

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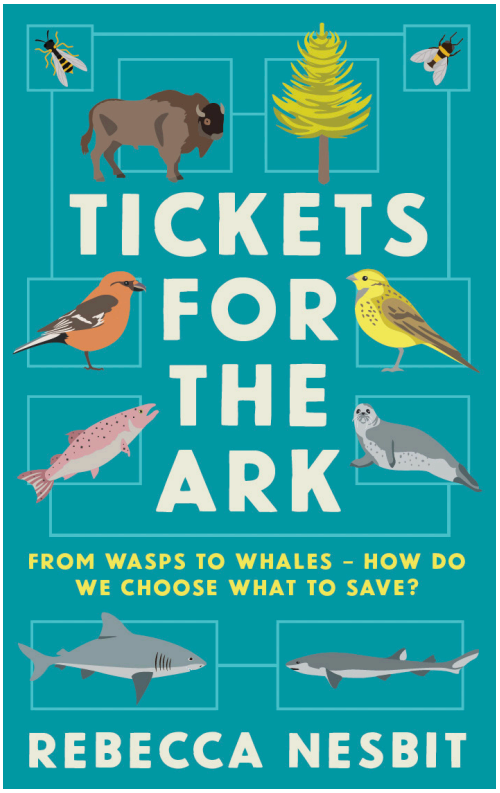
Interview

Ecologist Dr Rebecca Nesbit



Tell us about yourself and your academic background; how you became an ecologist.

I've been interested in nature and the environment ever since I was a small child, and my family encouraged it. As a teenager I spent time volunteering on nature reserves, including residential placements on islands, which was an amazing experience. It revealed how dedicated and knowledgeable ecologists can be. I then went to Durham University to study Biology. It was valuable to have a broad degree, although it was the ecology modules that interested me the most.

Why did you choose butterfly migration for your PhD and what was the most interesting thing you saw/discovered?

There was a great element of chance in this. As a nature reserve volunteer I was introduced to moth trapping, and was amazed to discover that some of the moths were migrants – I had no idea that insects crossed continents. It meant that when I saw an advert for a PhD studentship studying migration I was very keen to apply. Part of this work was using data collected by entomological radars, which showed that butterflies migrate at high altitudes - some are flying hundreds of metres above our heads!

Are you still engaged in research and what is your focus?

I don't do any research of my own, but I'm in touch with lots of former colleagues and am always keen to see what they are working on.

The subtitle of your book asks 'how do we choose what to save?' – in an ideal world, which endangered animal/plant would be top of your list to save and why?

I keep changing my mind, but today I'm trying to choose between any of the three orangutan species and the African savanna elephant. Orangutans because all species are critically endangered, so there's a real risk we could lose them all, and I hate the thought of a world without these fascinating, intelligent creatures. The elephants I'm likewise choosing because of their intelligence and cultural value, but also because of the important role they play in ecosystems.

What do you think is the biggest challenge facing the natural world today and is it beatable?

Climate change. I don't think it's beatable, in that this isn't a problem that will go away. However, nature has an amazing power to adapt, and I think we will see species moving and evolving. I also believe that efforts to tackle climate change will be successful. I don't think they will be as successful as we might hope – targets will no doubt be missed. But that doesn't mean the effort is wasted. Every reduction to the level of warming is extremely valuable and will reduce the human and animal suffering that climate change can bring.

What advice can you offer students who want to make their practice or research environmentally friendly?

Each situation will require different actions, but often we know what these actions are yet still face barriers to doing them. I would say acknowledge those barriers and think about whether you can overcome them. This is partly about being bold and not taking the path of least resistance. If you want to go to a conference or field site by train not plane, argue your case. If you see disposable plastic being used unnecessarily, challenge this and try to think of alternatives. And at every stage, think about whether you can justify the work you're doing. Did you need that many replicates? Is each part of your experiment likely to give useful data? Are you asking an important question? There's no point in using resources unless they are likely to produce valuable results. Likewise, your time is too precious not to use it wisely.

You have also done a lot of media outreach including TEDx, Radio 4 and Newsround. What tips do you have for the successful communication of scientific and sometimes difficult subjects?

1. Practise. You can seek out opportunities, including asking the university communications team whether they need volunteers for anything.

2. Listen. This will give you an insight into whether you are being understood. Also, you may be surprised what you learn – treat science communication as a chance to engage rather than educate.

3. Tell stories. We take the life of a scientist for granted, but your experiences may be alien to others. It can be helpful to share stories of your life alongside your results.

As an artist/fiction writer, how important do you feel creativity/ the creative process is to other fact-based subjects like science?

Science can be very creative, in the way we solve problems and think of alternative ways to explain what we observe. I think exploring creativity in other areas supports these skills. There are also specific benefits depending on your artform – I find drawing helps me observe the world, and writing for a wide audience makes my scientific writing easier to understand. If I had a musical talent, maybe I'd be better at identifying bird sounds. And sometimes it's just helpful to have a hobby – if you have multiple interests, it can be easier to weather the storm when one is going wrong.

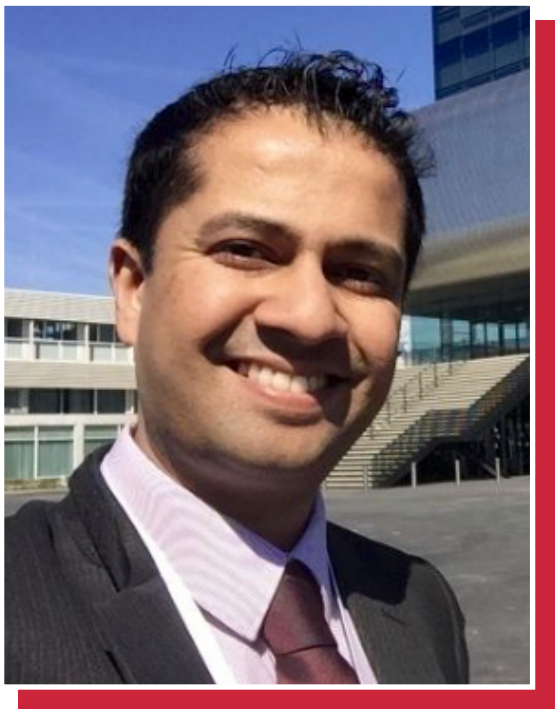
More info:
www.rebeccanesbit.com
Twitter @RebeccaNesbit

Rebecca's book *Tickets for the ark: from wasps to whales – how do we know what to save?* was published in February 2022 and is available in bookshops and online.

Photo credit: Alexander Mahmoud

Interview

Consultant paediatric neurologist Dr Dipak Ram



Introduction

I'm Dr Dipak Ram and I am a consultant paediatric neurologist at Royal Manchester Children's Hospital. I am also the Royal College of Paediatrics and Child Health (RCPCH) National Training Advisor for paediatric neurology training. That involves overseeing the paediatric neurology training across the whole of the UK as well as recruiting new trainees into paediatric neurology posts across the country. This role also involves supporting the trainees currently in posts across the country and helping them transition to become consultants. Another role I have is the British Paediatric Neurology Association (BPNA) chair of the Cerebrovascular Interest Group and this involves chairing a group of clinicians and health professionals interested in paediatric neurovascular disorders and stroke and helping to improve the services across the UK.

What does a typical week as a paediatric neurologist involve?

Most paediatric neurologists will have a slightly niche job plan based on their area of expertise. I am predominantly a clinician so I am patient facing most of the time and I have on-call weeks where I am on site in Royal Manchester Children's Hospital and seeing patients which come through the door with various paediatric neurological conditions as well as emergencies. The referrals could come from the general paediatrics team, A&E, paediatric intensive care, neonatal intensive care, other specialties within the hospital, or district general hospitals. This is really exciting and interesting because I see a whole breadth of paediatric neurology conditions and keep learning on the job and coming across conditions which I've never seen before - so really fascinating work!

The on-call weeks are busy but full of learning as I mentioned, so it's always really rewarding. On non on-call weeks, the roles could be different for each paediatric neurologist but my role would be to do outpatient clinics which could be in Royal Manchester Children's Hospital or outreach clinics in District General hospitals where we sit with the local paediatricians and see cases together. This helps with the education of general/community paediatricians too. Other things during a typical week would be involvement in research. I am part of some clinical trials and do work for this as an investigator. Other roles part of my routine work include delivery of specialised services because paediatric neurology is really complex and there are so many subspecialties within paediatric neurology. I do some work with specialised services in demyelination/multiple sclerosis in children, Batten disease, metachromatic leukodystrophy, as well as the inherited white matter disease service in the UK. These specialised services are delivered as part of a multidisciplinary team to try and improve services for patients with these rare conditions across the UK.

There are a lot of opportunities for teaching and education for junior doctors and medical students, which I'm involved with as part of my role as a consultant. As you can imagine, the week is filled with lots of interesting and different cases and it's that variety which is what keeps me going.

What qualities make a good paediatric neurologist?

I think clear communication skills are really important because we deal with really complex patients and, sometimes, this involves breaking bad news to patients about rare diseases or neurodegenerative conditions. It is important to have very clear communication skills and also to be aware of how to build a rapport with patients and families. Another important quality is teamworking within an MDT, which I think is really integral because delivery of paediatric neurology services is always by a team. It is really important to be a team player and work well within an MDT. A lot of our work is delivered together with other health professionals. For example; specialist nursing staff, dietitians, occupational therapists, physiotherapists, speech and language therapists, community paediatricians, geneticists and trainees are frequently part of our MDT meetings. All of these people and many others are involved in MDT working and it's very important for paediatric neurologists to work well within the team, but to also have leadership skills so that you that we can make sure that we make a robust MDT decision with a patient-centred approach.

When did you decide to become a paediatric neurologist?

When I was doing an SHO rotation in paediatric neurology, I completely fell in love with the specialty! It was so unique and interesting, and I realised that my consultant was still learning on the job despite being a paediatric neurologist for over 20 years. I remember being told that paediatric neurology is an ongoing and continuous learning experience and I thought to myself: this is exactly what I want to do! Every patient is completely unique despite them having the same condition and I think that's what makes neurology fascinating. When I did my SHO job, I remember there being many subspecialties within paediatric neurology, which intrigued me. For example: epilepsy, neuromuscular, neurovascular, movement disorders, neurogenetics and acquired brain injury. All these different areas were so exciting and there were so many innovations and new things happening in different areas. I was really interested to see how these advances were going to play out in the future. That's when I decided I definitely

wanted to be a paediatric neurologist and I applied for a training post thereafter.

How do you achieve a good work life balance?

I think this is really important! I'm a strong advocate for good work life balance. I think it is important to make sure that you have things to do outside work and not get too drawn into work, because that's always easy when there are so many exciting things going on. I find it easy to think about life outside work separately, so I keep busy by playing tennis and the usual things: music, movies and having time to socialise with friends and family. Part of achieving a good work life balance is having a good team to work with, so making sure that you have colleagues who can cover you whilst you are on annual leave so that you don't get drawn into work when you are on leave. I think that this is such an important thing and it's definitely achievable as a consultant paediatric neurologist, as long as you ensure that you are efficient with your work and make sure that you have colleagues who work well with you within the team.

Why should someone consider a career in paediatric neurology?

As I mentioned above, there are so many exciting things happening in paediatric neurology and I think the learning always continues. There are so many subspecialties within paediatric neurology itself, such as epilepsy, which then subspecialises further to the epilepsy surgery service, ketogenic diet service, and vagal nerve stimulator service for example. The same applies to other subspecialties, for example neuromuscular, cerebrovascular, movement disorder and other areas. I think if someone considers a career in paediatric neurology, they have so many options within paediatric neurology to subspecialise in. The other big reason to do paediatric neurology is that there are so many opportunities for research. If you're research orientated, there are so many things going on in paediatric neurology and there are many academic paediatric neurologists across the country who are happy to support trainees to blossom into academicians in the future.

In your career, what are some of the most impressive advances in medicine that you have seen?

Paediatric neurology has come a long, long way and we have seen many impressive advances over the past couple of decades or so. One of the most impressive advances has been in neuromuscular medicine where we now have treatment options for spinal muscular atrophy type 1 (SMA1), which was previously an incurable condition. In the past, without treatment, children with SMA1 would unfortunately die within the first year of their life. At present, we are using disease modifying treatment to try and modify the condition, which is really revolutionary. Initially, we started using Nusinersen, which is an antisense oligonucleotide, which is given via lumbar puncture at set intervals, which demonstrated good outcomes when affected patients received this treatment early. This completely modified a disease where children in the past would never be able to sit and have difficulties with breathing and passed away within their first year of life. Now, they are able to stand and walk, which is revolutionary! Following on from that, there has recently been Zolgensma which is a gene therapy being used to treat SMA too. This is a one-off intravenous gene therapy which is given to modify the condition and these children again have had really good outcome. Another revolutionary treatment recently has been Libmeldy, which is a gene therapy used for metachromatic leukodystrophy (MLD). This is a condition which was previously fatal and children with the classical form of late infantile MLD would normally pass away in the first 10 years of their life. Now, there is stem cell gene therapy available for this condition and again, this has modified the condition where these children are no longer rapidly deteriorating and instead, remaining very stable in general. As you can see, there are so many exciting advances and really impressive things going on in paediatric neurology!

What advice would you give medical students considering a career in paediatric neurology?

We really welcome medical students to consider doing tasters in paediatric neurology, because that would give you a good opportunity to see all the exciting things which are happening and also have an overview of what a life as a paediatric consultant neurologist is like. The other thing to do is to think about presenting at a conference. The BPNA conference runs every year in January and it would be good for you to speak to someone in your local paediatric neurology unit so that you can have an oral or poster presentation at the conference. The local team would be very happy to support you with all the research areas going on across the country. There is a recruitment champion in each paediatric neurology centre and there are trainees supporting this as well as consultants. Information for this can be obtained on the BPNA website.

What were the biggest struggles you faced in your first year as a doctor?

I think naturally, as you can imagine, the first year as a doctor is very much a 'rabbits in the headlights' feeling and I remember still feeling and thinking 'Can I really do this?'. After finishing five years of medical school, I realised that the biggest struggle you actually face is yourself! My take on it is that medicine is a lifelong learning process, so make sure you have a good support network inside and outside of work. Inevitably, everyone is going to have struggles as a doctor, but as long as you have good supervisors and a good support network outside of work, then I think the struggles that actually happen are a lot less than you can imagine them to be!

I am very happy to answer any questions. Feel free to email me at dipak.ram@mft.nhs.uk

Senior medical writer Dr David Buist

What led you to getting involved in medical writing?

After finishing my PhD, I stayed on in the lab for few months but it soon became clear to me that I needed to find something else. I greatly enjoyed writing my PhD thesis and helping to review the dissertation of a master's student I was supervising, so I contacted a former colleague from the lab who had started working as a medical writer a couple of years previously. Until that point, he was the only person I knew who was working in medical communications (or "med comms"), despite it being a career that was often touted as a good alternative to lab work for those who enjoyed writing. He encouraged me to apply, and I haven't looked back!

Could you sum up what is medical writing? e.g. why might someone engage you on their project and what is your typical day like?

Med comms is a very broad field but the majority of the work we do at my company is writing manuscripts that are published in academic journals, as well as writing abstracts, posters, and oral presentations for congresses. Most of our clients are pharmaceutical companies, but we also work for non-pharma clients, such as companies who develop diagnostic assays. There is a variety of reasons that pharmaceutical companies work with medical writing agencies. Firstly (and most obviously), we are experts at communicating information clearly and concisely, whereas a lot of people generating data and/or treating patients are not. Secondly, most projects involve collating and implementing feedback received from multiple authors and other key stakeholders—in some cases this can be over 30 people across four or five drafts—so it is very logistically complex and excessively laborious for our clients to manage themselves.

It is difficult to give an idea of a typical day because there is normally quite a lot of variety. At the moment I am working on three manuscripts that are all at different stages of development. I am also working on a large PowerPoint slide deck, redrawing figures and making sure that all of the information is appropriately referenced. I normally have at least one meeting a day; this morning it was a meeting with our clients to discuss a manuscript that we will be starting to write soon. This is a very collaborative industry and most days I have quite a bit of back-and-forth with colleagues to discuss the status of various projects.

What skills do you need to be a medical writer?

You obviously need to be good at writing, but you also need to have an eye for detail and to be able to pull out the most important bits of information from data that you receive. We often talk about the importance of "the editorial eye". This is the ability to spot things that don't look quite right that most people would not notice—misaligned text boxes on a PowerPoint slide, different fonts or font sizes being used within the same document, noticing the one number in a table that has two decimal places when every other number is reported to only one decimal place, etc. It really helps to be nerdy about the rules of language, and to be interested in learning about things like the difference between hyphens, en-dashes, em-dashes, and minus signs (- – — –, in that order), and knowing how to use them correctly. This is one of the few careers where being pedantic is a real positive and won't have you labelled as a bore!

What are the challenges of medical writing in itself?

Med comms is a very fast-paced industry, and we are constantly working to very tight deadlines. For the most part, the clients we work with are great, but every so often you come across one who can be very difficult to deal with and doesn't seem to like anything you do for them. It can be a bit disheartening to work with such people but fortunately they really are very rare!

What is the most rewarding aspect of your job?

I am pretty nerdy about both science and language, so I really enjoy the challenge of trying to work out the clearest and most succinct way to convey a certain message. I also like working as part of a team, where we are all dependent on each other to do our best work. Pretty much all the projects we have involve writing about cutting-edge scientific research and clinical trial data, and it is exciting to work so closely with the people doing this work, some of whom are world-renowned experts.

Would you say that medical writing would be suitable for a medical/dental/veterinary student interested in a non-clinical career?

Medical writing is definitely something that these people should consider. I know that we have writers who have come straight to us after finishing a medical degree. I don't personally know of anyone who has come from a dental or veterinary background, but that doesn't mean they don't exist—I just haven't met them yet! Most people who start as medical writers have a PhD, although I know of some people who "only" have a master's degree. I think the key academic experiences that would qualify you for a medical writer position are having exposure to some level of research and writing that are beyond what you would expect from a typical three-year undergraduate degree.

I should also note that within med comms, there are not just writers, but also the client services team. These people do not do any writing but, as the name suggests, they are the main point of contact between the agency and the clients, and are mostly responsible for managing the timelines and financial aspects of projects. There is less requirement for people in client services roles to have a strong scientific background, although most have at least an undergraduate degree in some branch of science. Similarly, while it is important for members of a client services team to be able to put together a well-

written email, there is less requirement for them to be very strong writers, so this could be a good option for people who want to stay close to science but not too close!

What advice would you give to someone pursuing a career in medical writing?

The number one piece of advice I can give is to use the resources available at www.firstmedcommsjob.com and www.medcommsnetworking.com. Med comms is a very secretive world and it is extremely hard to find out anything useful about it, a lot of which is due to the highly confidential nature of the scientific data we write about. When I was first investigating med comms as a career, I went to a networking day organised by MedComms Networking. It was a really useful way to get a much greater level of insight into the industry than what is available online.

When it comes to actually applying for a job, I would recommend making sure that your cover letter and/or CV focus on transferable skills that would be useful for med comms, for example, mention your dissertation/thesis and any other writing you've done, including blogs or writing for a student publication. Also, list any presentations you've done at university level, which can include posters and orals presented to either internal or external audiences. It doesn't matter how small or insignificant you think it is, it is all valid experience. And finally, it almost goes without saying, but you need to be extremely careful that your cover letter and CV do not contain any typos or formatting errors—if they do, you will almost certainly fall at the first hurdle!

Senior Editors, Winter 2022

Anoushka Agarwal

University of Bristol

Hi, my name is Anoushka Agarwal, and I am a third-year veterinary student. Alongside my passion towards the veterinary profession, I took a keen interest in working as an editor with the INSPIRE Student Journal earlier this summer. For me, this paves way for the increased dissemination of veterinary-related knowledge across readers and creates opportunities for collaboration across various medical domains that work cohesively to add to an ever-expanding body of knowledge.

Ernestine Ago

University of Exeter

Hi everyone, I'm Ernestine a fifth-year medical student at the University of Exeter. Having graduated with a bachelor's degree in Medical Science, I've always had a keen interest in research. Over my time in medical school, I have been involved in the INSPIRE program in various ways, taking part in the summer research scheme in my first year and then been a peer reviewer in my third year. I have really enjoyed my time taking part in the INSPIRE program and have loved the opportunity to be a senior editor. I especially enjoyed taking part in the behind the scenes work that makes the journal possible, particularly encouraging student involvement in research and helping build links between researchers and students. I believe that research is an important aspect of medical education and from my experience taking part in various research projects, I know there is a vast amount of learning and experience to be had through taking part in research as a medical student. INSPIRE's place as a journal for students by students is something that I feel is important and I'm glad I've had the opportunity to be involved.

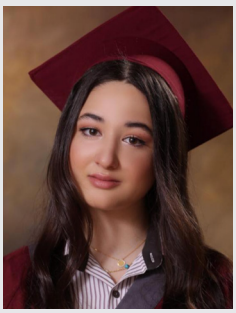
Humaira Ahmed

University of Plymouth

Hi, my name is Humaira Ahmed. I am a third-year medical student, and a BSc (Hons) Biomedical Science graduate. I have a passion for medical microbiology having completed a research placement and thesis in hospital infection control research. Infection control is a huge part of clinical practice within a hospital which is closely associated with my aspiration to pursue a career in medicine. I am currently interested in neuropsychiatry and surgery. Recently, I published a collaborative paper with Dr Tina Joshi and Adventist Health Hospital, California, USA. This paper investigated the isolation of Clostridiodes difficile bacteria from single-use hospital gowns.

As a senior editor for the INSPIRE journal, I hope to encourage others to get involved in medical research. This student journal provides amazing opportunities that I would advise others to get involved with.

Zaina Aloul



Cardiff University

Hi everyone, I'm Zaina, a fourth-year medical student at Cardiff University. I'm thrilled to be part of this year's INSPIRE Student Journal editorial team, to work along my colleagues to publish a Autumn and Winter 2022 issue. I first got involved with academic research by being a peer reviewer for INSPIRE in 2021. After peer reviewing numerous papers written by students on a variety of medical topics, I become fond of academic research and writing. My interests are surgery, cardiology neurology, and genetics! Outside of medicine, I enjoy going on outdoor hikes, and hope to complete the three peak mountain challenges before I graduate. I look forward to reading your papers and helping you publish your research!

Elizabeth Brennan

University of Bristol

I am a third-year medical student at the University of Bristol. I have thoroughly enjoyed being a part of the INSPIRE team as a senior editor. It has allowed me to explore my interest in research and develop greater insight into the field. I have learnt how a journal is run, the importance of timely and effective communication within a team and the roles and responsibilities of an editor. I am particularly interested in global health, surgery and human factors application in medicine.

Joshua Erhabor

University of Exeter

Hi, my name is Joshua Erabor, and I am a final year medical student with an interest in research education. My time with INSPIRE has been amazing so far and I've learnt so much about the publication process! I enjoy neurosurgery and hope to specialise in that field.

Frances Andrea Eslabra

University of Exeter

Hi, my name is Frances Eslabra. I have just finished my fourth year studying medicine at Exeter University and am now intercalating in a masters in Health Data Science. I am particularly interested in how data analysis can inform clinical decision making and improve patient outcomes for the future — it's such an exciting field with so much potential! I aspire to become a surgeon someday, with my preferred field being neurosurgery, but I also really enjoy learning about plastics and orthopaedics. Being an editor for the INSPIRE journal is such a rewarding experience, with my favourite part being reading all the original articles my peers have submitted.

Senior Editors, Winter 2022

Liam Fletcher

University of Bristol

Hi! My name is Liam and I'm a fifth-year dental student at Bristol. My first exposure to research was during a Nuffield placement I undertook where I got to work with leading academics investigating the role of ALCAM in the HGF signalling pathway in breast and prostate cancers. Since then, my passion for research has grown, leading to my role as editor of this year's INSPIRE Journal. INSPIRE is such a good initiative that gives students the platform to engage in research, the publication process and more and I am very excited to be a part of it this year. My interests lie on the interface of where medicine meets dentistry, and I look forward to reading the work fellow students submit! My interests outside of my BDS include running, football and, currently, Wordle!

Genevieve Lawrence

Cardiff University

Hi! I'm Genevieve and I am currently in my final year of medicine at Cardiff University, having intercalated in Emergency, Prehospital and Immediate Care last year. My intercalated research project was centred on medication safety incidents in the Emergency Department and how they arise. It's exciting to see how research has led to changes in how we practice medicine, even within the short time we have been at university, and this one of the main reasons why I wanted to join INSPIRE!

I'm particularly interested in research in the acute medical setting, such as emergency and prehospital medicine, anaesthesia, and acute medicine. Through INSPIRE, I hope to learn about a wide range of topics in medicine, dentistry and veterinary medicine from the students that are passionate about them. Outside of medicine I love to make pasta, learn languages and go to dance classes. I'm looking forward to seeing the submissions and this year's editions!

Tomas Nicholas

University of Plymouth

Hi, my name is Tomas, and I am an intercalating dental student at the University of Plymouth. I have had a long-standing interest in research, especially relating to oral/systemic links.
This recently led me to undertake a research studentship investigating the effects of a novel mouthwash on microcirculation. I also have an interest in medical/dental education, previously acting as the academic secretary for my dental society where I delivered revision sessions!
I hope other students feel encouraged by the journal, especially dental students, to get more involved and familiar with research, academic writing and the peer reviewing process. Outside of academics, I enjoy spending my time by the sea, listening to electronic music, and exploring Devon and Cornwall with my friends.

Medha Raketla

Cardiff University

Hello, I'm Medha and I'm a second-year medical student at Cardiff University. My initial experiences with research involved writing literature reviews and gaining insight into laboratory research through INSPIRE's taster days. I am very keen to widen access to research experiences for undergraduates, and I believe INSPIRE provides multiple such opportunities. Being involved at INSPIRE has led me to realise the importance of clinical research in medicine, and I hope through my role as member of the editorial board I can convey the appeal of research to other like-minded students! Outside of academics, I enjoy running and writing :)

Sofia Rosca-Velea

University of Bristol

Hi! I'm Sofia and I am a second-year medical student at Bristol and have had the pleasure of being an Associate Editor at INSPIRE for the past year. I won 'the EPQ with the longest title' award with: "A Comparison Between Exon Skipping and Utrophin Upregulation for the Treatment of Duchenne Muscular Dystrophy" – the project also being my first introduction to research in the medical sector. I loved it, and particularly loved the joy of writing research so that it can be enjoyed by everyone. One of the core principles of INSPIRE is that the journal is by students, for students, and I feel very privileged to be involved for that reason. Knowledge should be selflessly shared. Art, medicine, and the art of medicine are also very important to me, so look out for the art feature in the journal!

Victoria Vincent

University of Plymouth

Hi! My name is Vicky and I'm a fourth-year medical student at Plymouth. Research and quality improvement is so important to allow for the progression of healthcare services. I first got involved with INSPIRE when I submitted a paper on the management of rhegmatogenous retinal detachment. This gave me a flavour for research, but also allowed me to gain an interest on how we could improve the current healthcare setting. I am now extremely passionate about quality improvement, carrying out several audits. My current interests in medicine include maxillofacial surgery and orthopaedics. I am very excited to read the submissions to the upcoming journals and encourage everyone to partake in the submission and publication process.

Advisory board, Winter 2022

Sam Deutsch,
Cardiff University

Rajeev Ravi,
University of Plymouth

Yusuf Sarwar,
University of Exeter

Natasha Singhal,
University of Plymouth

Virginija Vilkelyte,
University of Exeter

List of referees, Winter 2022

Moyowa Arenyeka
University of Plymouth

Deborah Inyang
King's College London

Kyriakos Keklikoglou
University of Bristol

Courtney Jeannette Lendon
University of Exeter

Jordan Mistry
University of Plymouth

Mimi Mostefai
University of Exeter

Naomi Nadkarni
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Eleanor Orum
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Michael Sinka
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Li Yun Soh
University of Bristol

Becky Wall
University of Glasgow

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University of Bristol

www.bristol.ac.uk/medical-school/study/undergraduate/inspire
www.bristol.ac.uk/vet-school/research/inspire

Bristol Medical School Co-Leads: Dr Anu Goenka, Clinical Lecturer in Paediatric Infectious Diseases and Immunology; Dr Becky Foster, Senior Lecturer in Clinical Sciences.
Bristol Veterinary School Lead: Professor Linda Wooldridge, Chair in Translational Immunology
Bristol Dental School Lead: Mr Mark Gormley, Consultant Senior Lecturer

Cardiff University

www.cures.cardiff.ac.uk/inspire

Cardiff School of Medicine Co-Leads: Dr William Davies, Senior Lecturer (Basic Science), Dr Emma Tallantyre, Clinical Reader
Cardiff School of Dentistry Lead: Dr Heather Lundbeck, Clinical Lecturer in Paediatric Dentistry

University of Exeter

www.medicine.exeter.ac.uk/study/ug/medicine/researchopportunities

Lead: Dr Joanna Tarr, Senior Lecturer, Faculty of Health and Life Science

University of Plymouth Peninsula School of Medicine and Dentistry

www.plymouth.ac.uk/about-us/university-structure/faculties/health/inspire

Leads: David Parkinson, Professor of Neuroscience;
Vehid Salih, Associate Professor in Oral & Dental Health Research

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