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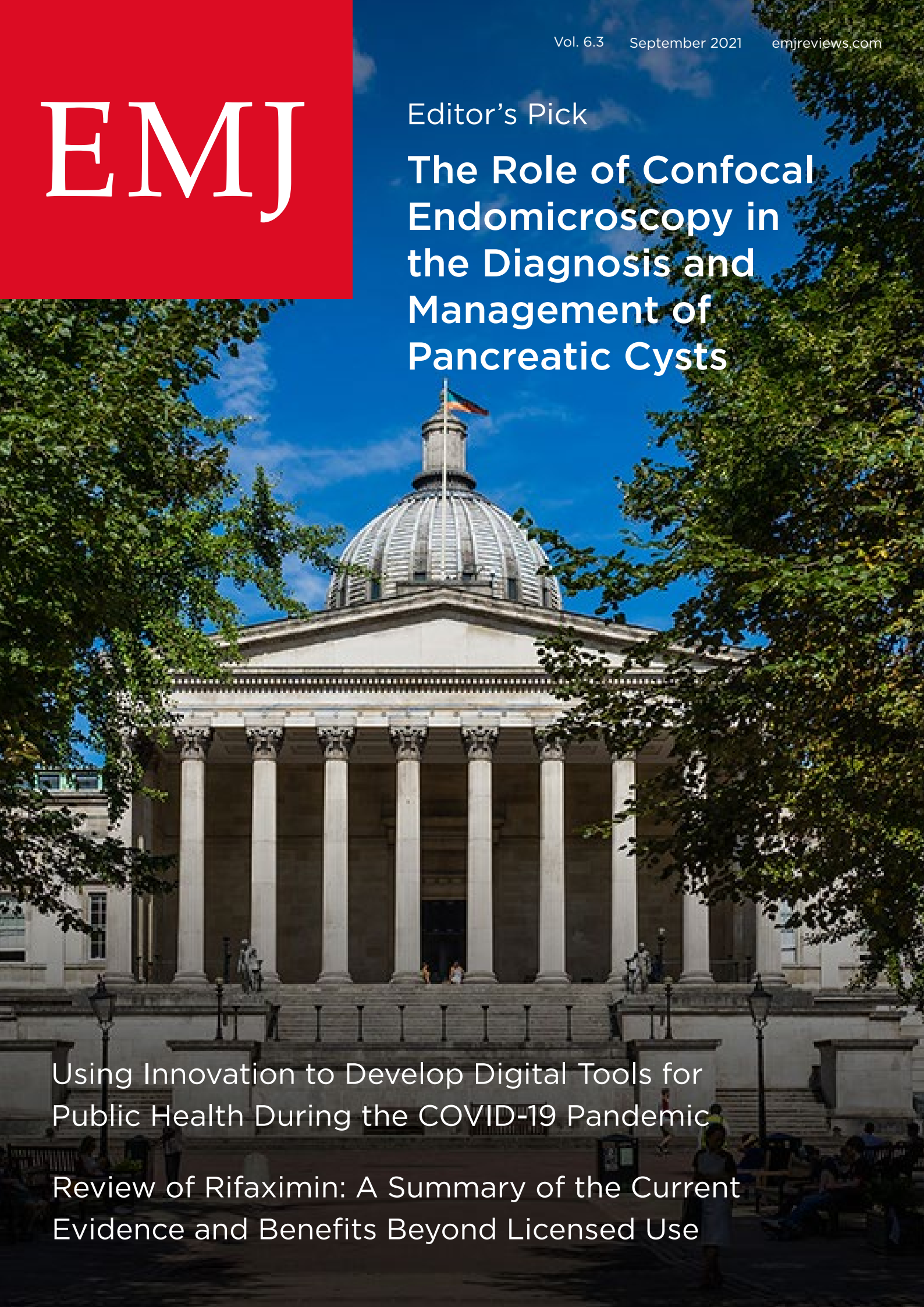
EMJ

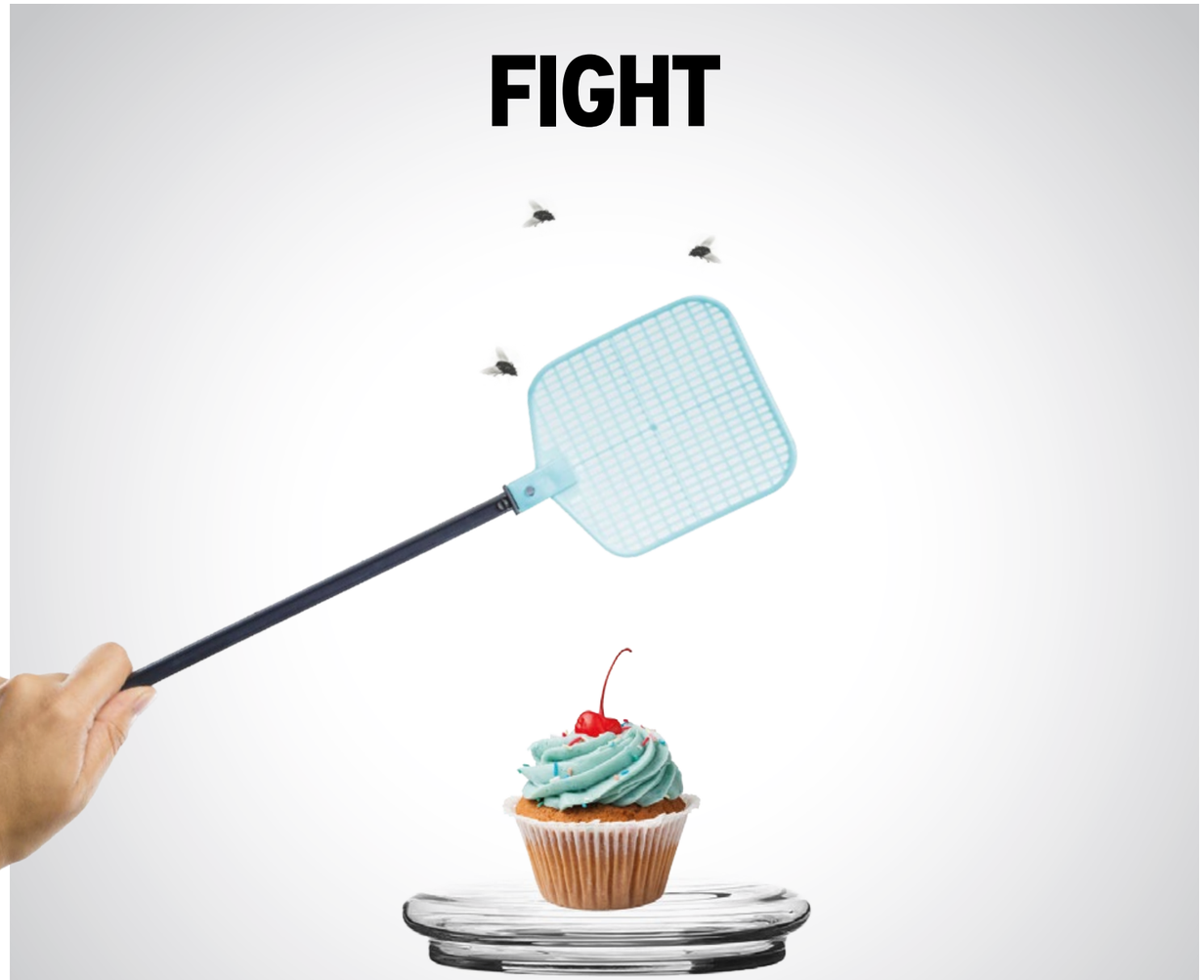
Editor's Pick

The Role of Confocal Endomicroscopy in the Diagnosis and Management of Pancreatic Cysts



Using Innovation to Develop Digital Tools for Public Health During the COVID-19 Pandemic

Review of Rifaximin: A Summary of the Current Evidence and Benefits Beyond Licensed Use



Abbreviated Prescribing Information for Kyntheum® 210mg solution for injection in prefilled syringe Please refer to the full Summary of Product Characteristics (SmPC) approved in your country before prescribing. ▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.**Indication:** Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy. **Active ingredient:** Each pre-filled syringe contains 210mg brodalumab in 1.5ml solution. 1ml solution contains 140mg brodalumab. **Dosage and administration:** Posology: Adults: The recommended dose is 210mg administered by subcutaneous injection at weeks 0, 1, and 2 followed by 210mg every 2 weeks. Consideration should be given to discontinuing treatment in patients who have shown no response after 12-16 weeks of treatment. Some patients with initial partial response may subsequently improve with continued treatment beyond 16 weeks. Each pre-filled syringe is for single use only. Elderly: No dose adjustment recommended. Hepatic and renal impairment: No dose recommendations can be made. Children and adolescents below the age of 18 years: Safety and efficacy of Kyntheum have not been established. Method of administration: Subcutaneous (SC) injection. Kyntheum should not be injected into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis. The pre-filled syringe must not be shaken. After proper training in SC injection technique, patients may self-inject Kyntheum when deemed appropriate by a physician. Patients should be instructed to inject the full amount of Kyntheum according to the instructions provided in the package leaflet. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. Active Crohn's disease. Clinically important active infections (e.g. active tuberculosis). **Precautions and warnings:** *Inflammatory bowel disease (including Crohn's disease and ulcerative colitis):* Cases of new or exacerbations of inflammatory bowel disease have been reported with IL-17 inhibitors. Therefore, Kyntheum is not recommended in patients with inflammatory bowel disease. If a patient develops signs and symptoms of inflammatory bowel disease, or experiences an exacerbation of pre-existing inflammatory bowel disease, Kyntheum should be discontinued and appropriate medical management should be initiated. *Suicidal ideation and behaviour:* Suicidal ideation and behaviour, including completed suicide, have been reported in patients treated with Kyntheum. The majority of patients with suicidal behaviour had a history of depression and/or suicidal ideation or behaviour. A causal association between treatment with Kyntheum and increased risk of suicidal ideation and behaviour has not been established. Carefully weigh the risk and benefit of treatment with Kyntheum for patients with a history of depression and/or suicidal ideation or behaviour, or patients who develop such symptoms. Patients, caregivers and families should be advised of the need to be alert for the emergence or worsening of depression, suicidal ideation, anxiety, or other mood changes, and they should contact their healthcare provider if such events occur. If a patient suffers from new or worsening symptoms of depression and/or suicidal ideation or behaviour is identified, it is recommended to discontinue treatment with Kyntheum. *Hypersensitivity reactions:* Rare cases of anaphylactic reactions have been reported in the post-marketing setting. In the event of an anaphylactic reaction, or any other serious allergic reaction, administration of Kyntheum should be discontinued and appropriate therapy initiated. *Infections:* Kyntheum may increase the risk of infections. Caution should be exercised when considering the use of Kyntheum in patients with a chronic infection or a history of recurrent infection. Patients should be instructed to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, they should be closely monitored and Kyntheum should not be administered until the infection resolves. Kyntheum should not be given to patients with active tuberculosis. Anti-tuberculosis therapy should be considered prior to initiation of Kyntheum in patients with latent tuberculosis. *Vaccinations:* It is recommended that patients be brought up-to-date with all immunisations in accordance with local immunisation guidelines prior to initiation of treatment with Kyntheum. Live vaccines should not be given concurrently with Kyntheum. The safety and efficacy of Kyntheum in combination with immunosuppressants, including biologics, or phototherapy have not been evaluated. **Drug interactions:** Live vaccines should not be given concurrently with Kyntheum. **Fertility, pregnancy and lactation:** *Women of childbearing potential:* Use an effective method of contraception during treatment and for at least 12 weeks after treatment. *Pregnancy:* There are no or limited amount of data from the use of brodalumab in pregnant women. As a precautionary measure, it is preferable to avoid the use of Kyntheum in pregnancy. Benefit risk for exposure of the infant to live vaccines following third trimester exposure to Kyntheum should be discussed with a physician. *Breast-feeding:* It is unknown whether brodalumab is excreted in human milk. A risk to the newborns/infants cannot be excluded. Whether to discontinue breastfeeding of discontinue Kyntheum therapy should be decided, taking into account the benefit of breast-feeding for the child and the benefit of therapy for the woman. *Fertility:* No data are available on the effect of brodalumab on human fertility. **Adverse reactions:** *Common (≥1/100 to <1/10):* Influenza, tinea infections (including tinea pedis, tinea versicolor, tinea cruris), headache, oropharyngeal pain, diarrhoea, nausea, arthralgia, myalgia, fatigue, injection site reactions (including injection site erythema, pain, pruritus, bruising, haemorrhage). *Uncommon (≥1/1,000 to <1/100):* Candida infections (including oral, genital and oesophageal infections), neutropenia, conjunctivitis. *Rare (≥1/10,000 to <1/1,000):* anaphylactic reaction. **See SmPC for a full list of adverse reactions. Precautions for storage:** Store in a refrigerator (2°C-8°C). Do not freeze. Keep the pre-filled syringe in the outer carton in order to protect from light. Kyntheum may be stored at room temperature (up to 25°C) once, in the outer carton, for a maximum single period of 14 days. Once Kyntheum has been removed from the refrigerator and has reached room temperature (up to 25°C) it must either be used within 14 days or discarded. **Marketing authorisation number and holder:** EU/1/16/1155/001, LEO Pharma A/S, Ballerup, Denmark. **Last revised:** July 2020

Reporting of Suspected Adverse Reactions
Adverse reactions should be reported according to local guidelines.

January 2021
MAT-40487

References:
1. Lebwohl M, et al. *N Engl J Med* 2015;373:1318–28. **2.** Kyntheum® (brodalumab) EU Summary of Product Characteristics. July 2020. Available from: https://www.ema.europa.eu/en/medicines/human/EPAR/kyntheum. Last Accessed: January 2021. **3.** Brembilla NC et al. *Front Immunol* 2018;9:1682. **4.** Pappu R et al. *Immunology* 2011;134:8–16. **5.** Baker KF and Isaacs JD. *Ann Rheum Dis* 2018;77:175–87.

PASI 100 at 12 weeks with Kyntheum®: 44% in AMAGINE-2 (n=612) and 37% in AMAGINE-3 (n=624) using NRI for missing data.[1]
IL, interleukin; NRI, non responder imputation; PASI, Psoriasis Area and Severity Index.

Kyntheum® (brodalumab) is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.[2] Kyntheum® is a fully human monoclonal antibody and the only biologic that selectively targets the IL-17 receptor subunit A.[2–5]

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IN THE FIGHT AGAINST
PSORIASIS
THINK RECEPTOR BLOCKADE

LEO

Contents

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Spencer Gore, CEO

Editorial Board

VIEW IN FULL ←

Aims and Scope

EMJ is an online only, peer-reviewed, open access general journal, targeted towards readers in the medical sciences. We aim to make all our articles accessible to readers from any medical discipline.

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

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

EMJ is published quarterly and comprises review articles, case reports, practice guides, theoretical discussions, and original research.

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EMJ 6.3

Welcome

Dear Readers,

It is my great pleasure to welcome you to the newest edition of *EMJ*, our multidisciplinary flagship journal. This journal brings together the latest scientific advancements from across a number of therapeutic areas of medical research. Readers will have the opportunity to read peer-reviewed articles, exclusive interviews, and research papers covering gastroenterology, hepatology, rheumatology, among other therapy areas.

Antibiotic resistance is a consistent and growing challenge faced by healthcare professionals and medical researchers. In their article, Nathwani et al. review the literature surrounding the promise of off-label use of rifaximin. Cirrhosis patients have a propensity for frequent hospitalisations often paired with frequent treatment with antibiotic therapy. These patients are, therefore, a demographic within which antibiotic resistance can develop easily and quickly. The authors discuss the current evidence surrounding the benefits of using rifaximin, beyond its current licensed use, to treat cirrhosis patients and potentially reducing their risk of developing antibiotic resistance.

An illuminating piece for those interested in hepatology is included in this issue. The article by Díaz et al. reviews the outcomes of patients with acute-on-chronic liver failure (ACLF), highlighting the role of organ transplantation by comparing patients before and after liver transplants. Through analysing the model for end-stage liver disease organ allocation system alongside patient outcomes, the authors explore the role of organ allocation, the clinical course of liver failure and the feasibility of liver transplantation in the sickest patients.

For the microbiologists in the audience, the article by Akbani and Bibi will be of interest. Through examining the case study of an adolescent male suffering from typhoid, Akbani and Bibi discuss how policy implementation can assist in preventing the spread of infectious disease. This is followed by an assessment of how controlling the spread of infections can reduce burdens on already pressured healthcare systems. This paper has real world significance with implications for both individual healthcare providers and the policy-makers as well as for the governing systems that control the provision of healthcare.

Finally, I would like to express my gratitude to the editorial board, expert authors, peer reviewers and interviewees for their fantastic contributions to this issue of *EMJ*. Publication of this journal relies on their dedicated efforts and commitment. All that remains is to thank you, the reader, for your continued support, as we continue to be the go-to place for healthcare professionals and hope you enjoy this flagship edition of the *EMJ*.

Spencer Gore

Chief Executive Officer, EMG-Health

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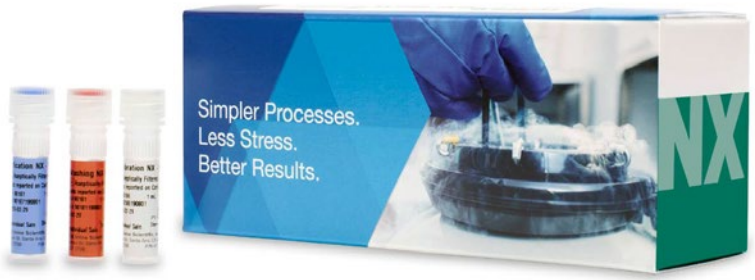

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Qualitative and quantitative composition: 1 pre-filled pen with 0.15 ml (0.20 ml; 0.25 ml; 0.30 ml; 0.35 ml; 0.40 ml; 0.45 ml; 0.50 ml; 0.55 ml; 0.60 ml) contains 7.5 mg (10 mg; 12.5 mg; 15 mg; 17.5 mg; 20 mg; 22.5 mg; 25 mg; 27.5 mg; 30 mg) methotrexate. *Excipients:* NaCl, NaOH, HCl, water for injections.

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Therapeutic indications: Active rheumatoid arthritis in adult patients; polyarthritic forms of severe, active juvenile idiopathic arthritis, when the response to nonsteroidal anti-inflammatory drugs (NSAIDs) has been inadequate; severe psoriatic arthritis in adult patients; mild to moderate Crohn's disease either alone or in combination with corticosteroids in adult patients refractory or intolerant to thiopurines. *PEN additionally:* moderate to severe psoriasis in adult patients who are candidates for systemic therapy. *Syringe additionally:* severe recalcitrant disabling psoriasis, which is not adequately responsive to other forms of therapy such as phototherapy, PUVA and retinoids. **Posology and method of administration:** Should only be prescribed by physicians who are familiar with the various characteristics of the medicinal product and its mode of action. Patients must be educated to use the proper injection technique. The first injection of Metoject PEN should be performed under direct medical supervision. *Adults, rheumatoid arthritis:* The recommended initial dose is 7.5 mg of Metoject once weekly, administered subcutaneously. Depending on the individual activity of the disease and tolerability, the dose may be increased gradually by 2.5 mg per week. A weekly dose of 25 mg should in general not be exceeded. *Polyarthritic forms of juvenile idiopathic arthritis:* The recommended dose is 10-15 mg/m^2 body surface area (BSA)/once weekly, administered subcutaneously. In therapy-refractory cases the weekly dosage may be increased up to 20 mg/m^2 BSA/once weekly. Use in children < 3 years of age is not recommended as insufficient data on efficacy and safety is available for this population. *Psoriasis vulgaris, psoriatic arthritis:* Test dose of 5 – 10 mg should be administered parenterally, one week prior to therapy to detect idiosyncratic adverse reactions. The recommended initial dose is 7.5 mg of methotrexate once weekly, administered subcutaneously. The dose is to be increased gradually but should not, in general, exceed a weekly dose of 25 mg of methotrexate. *Crohn's disease:* Induction treatment: 25 mg/week administered subcutaneously. Response to treatment can be expected after approximately 8 -12 weeks. Maintenance treatment: 15 mg/week. *Elderly:* Dose reduction should be considered due to reduced liver and kidney function as well as lower folate reserves. If changing the oral to parenteral administration a reduction of dose may be required due to the variable bioavailability. **Contraindications:** Hypersensitivity to methotrexate or any of the excipients; severe liver impairment; alcohol abuse; severe renal impairment (creatinine clearance < 30 ml/min); pre-existing blood dyscrasias (bone marrow hypoplasia, leukopenia, thrombocytopenia, significant anaemia); serious, acute or chronic infections such as tuberculosis, HIV, other immunodeficiency syndromes; ulcers of the oral cavity and known active gastrointestinal ulcer disease; pregnancy, breastfeeding; concurrent vaccination with live vaccines. **Special warnings and precautions for use:** In the treatment of rheumatoid arthritis, juvenile idiopathic arthritis, psoriasis and psoriatic arthritis, and Crohn's disease, Metoject PEN (methotrexate) must only be used once a week. Dosage errors in the use can result in serious adverse reactions, including death. **Undesirable effects:** Most serious adverse reactions of methotrexate include bone marrow suppression, pulmonary toxicity, hepatotoxicity, renal toxicity, neurotoxicity, thromboembolic events, anaphylactic shock and Stevens-Johnson syndrome. Most frequently (very common) observed adverse reactions of methotrexate include gastrointestinal disorders e.g. stomatitis, dyspepsia, abdominal pain, nausea, loss of appetite and abnormal liver function tests e.g. increased ALAT, ASAT, bilirubin, alkaline phosphatase. Other frequently (common) occurring adverse reactions are leukopenia, anaemia, thrombopenia, headache, tiredness, drowsiness, pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia, oral ulcers, diarrhoea, exanthema, erythema and pruritus. *Effects:* Pharyngitis, infection (incl. reactivation of inactive chronic infection), sepsis, conjunctivitis. Lymphoma. Leukopenia, anaemia, thrombopenia, pancytopenia, agranulocytosis, severe courses of bone marrow depression, lymphoproliferative disorders, eosinophilia. Allergic reactions, anaphylactic shock, hypogammaglobulinaemia. Precipitation of diabetes mellitus. Depression, confusion, mood alterations. Headache, tiredness, drowsiness, dizziness, pain, muscular asthenia or paraesthesia/hypoaesthesia, changes in sense of taste (metallic taste), convulsions, meningism, acute aseptic meningitis, paralysis, encephalopathy/leukoencephalopathy. Visual disturbances, impaired vision, retinopathy. Pericarditis, pericardial effusion, pericardial tamponade. Hypotension, thromboembolic events. Pneumonia, interstitial alveolitis/pneumonitis often associated with eosinophilia. Symptoms indicating potentially severe lung injury (interstitial pneumonitis) are: dry, not productive cough, short of breath and fever, pulmonary fibrosis, Pneumocystis jirovecii pneumonia, shortness of breath and bronchial asthma, pleural effusion, epistaxis, pulmonary alveolar haemorrhage. Stomatitis, dyspepsia, nausea, loss of appetite, abdominal pain, oral ulcers, diarrhoea, gastrointestinal ulcers and bleeding, enteritis, vomiting, pancreatitis, gingivitis, haematemesis, haematorrhea, toxic megacolon. Abnormal liver function tests (increased ALAT, ASAT, alkaline phosphatase and bilirubin), cirrhosis, fibrosis and fatty degeneration of the liver, decrease in serum albumin, acute hepatitis, hepatic failure. Exanthema, erythema, pruritus, photosensitisation, loss of hair, increase in rheumatic nodules, skin ulcer, herpes zoster, vasculitis, herpetiform eruptions of the skin, urticarial, increased pigmentation, acne, petechiae, ecchymosis, allergic vasculitis, Stevens-Johnson syndrome, toxic epidermal necrolysis (Lyell's syndrome), increased pigmentary changes of the nails, acute paronychia, furunculosis, telangiectasia, skin exfoliation/ dermatitis exfoliative. Arthralgia, myalgia, osteoporosis, stress fracture, osteonecrosis of jaw (secondary to lymphoproliferative disorders). Inflammation and ulceration of the urinary bladder, renal impairment, disturbed micturition, renal failure, oliguria, anuria, electrolyte disturbances, proteinuria. Inflammation and ulceration of the vagina, loss of libido, impotence, gynaecomastia, oligospermia, impaired menstruation, vaginal discharge. Fever, wound-healing impairment, asthenia, injection site necrosis, oedema. Local damage (formation of sterile abscess, lipodystrophy) of injection site following intramuscular or subcutaneous administration. Subcutaneous application of methotrexate is locally well tolerated. Only mild local skin reactions (such as burning sensations, erythema, swelling, discolouration, pruritus, severe itching, pain) were observed, decreasing during therapy. **Overdose:** Calcium folinate is the specific antidote for neutralising the toxic undesirable effects of methotrexate. **Legal classification:** POM **Marketing authorisation holder:** medac GmbH, Theaterstr. 6, 22880 Wedel, Germany.

Date of revision of text: 06/2020 **(PEN);** 21.03.2021 **(syringe)**

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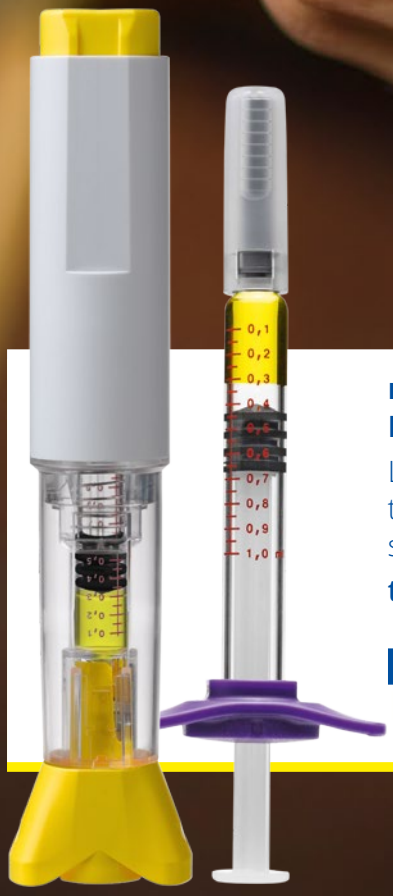

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Foreword

In this year's issue of the *EMJ*, you will find a number of very interesting, timely, and up-to-date articles from within the field of gastrointestinal diseases.

Portal hypertension (PH) is one of the main areas covered in this issue. Measurement of PH can still only be done invasively, which requires expertise and technical equipment. The growing demand for non-invasive parameters to evaluate PH in vast numbers of patients with non-alcoholic fatty liver disease is urgent and nicely addressed here.

In decompensated liver disease with ascites, prevention of spontaneous-bacterial peritonitis is of key importance for survival. Rifaximin, licensed for treatment of encephalopathy, is one of the potential future drugs of choice here. Even though not yet supported sufficiently by clinical study data, its promises and challenges are nicely reviewed.

If prevention fails in advanced cirrhotics, then acute-on-chronic liver failure often ensues. This grave condition would often require prioritised liver transplantation, but organ allocation systems are not yet equipped to meet the demand and clinical decision-making tools need to be improved in order to correctly assess urgency and futility.

Lysosomal storage diseases are rare but often overlooked, in particular when patients with the hallmarks of disease such as (hepato) splenomegaly are primarily submitted to hepatologists and not haematologists. Since diseases like Gaucher's disease can be treated very effectively, the main focus needs to shift to awareness and early detection, which is also reviewed in this issue.

Further important contributions are a report of an outbreak of multidrug resistant typhoid fever amongst younger patients in Pakistan and the very timely article on the use of innovation to develop digital tools for public health during the severe acute respiratory syndrome coronavirus 2 pandemic.

Markus Peck-Radosavljevic

Professor of Medicine, Chairman of the Department of Gastroenterology and Hepatology , Klinikum Klagenfurt am Wörthersee, Klagenfurt, Austria

Artificial Intelligence: The Piece of the Puzzle to Transform Inflammatory Bowel Disease Management?

This Amgen-sponsored symposium took place on 8th July 2021, as part of the virtual European Crohn's and Colitis Organisation (ECCO) 2021 congress

Speakers: Gionata Fiorino,[1] Edouard Louis,[2] Walter Reinisch[3]

1. Humanitas University and Humanitas Research Hospital, Milan, Italy
2. Liège University Hospital, Belgium
3. Medical University of Vienna, Austria

Disclosure: Fiorino has served as an advisory board member and consultant for MSD, Takeda, AbbVie, Janssen, Pfizer, Celltrion, Sandoz, AlfaSigma, Samsung, Amgen, Roche, Ferring, Mylan, and Galapagos. Louis has received fees for research grants from Takeda, Pfizer, and Janssen; educational grants from AbbVie, Takeda, and Janssen; speaker fees from AbbVie, Ferring, MSD, Dr Falk Pharma, Takeda, Janssen, Pfizer, and Celgene; has participated in advisory boards for AbbVie, Ferring, MSD, Takeda, Celgene, Janssen, Gilead-Galapagos, Arena, Pfizer, and Eli Lilly; and has acted as a consultant for AbbVie. Reinisch has served as a speaker for Abbott Laboratories, AbbVie, Aesca, Aptalis, Astellas, Centocor, Celltrion, Danone Austria, Elan, Dr Falk Pharma GmbH, Ferring, Immundiagnostik, Mitsubishi Tanabe Pharma Corporation, MSD, Otsuka, PDL, Pharmacosmos, PLS Education, Schering-Plough, Shire, Takeda, Therakos, Vifor, and Yakult; has served as a consultant for Abbott Laboratories, AbbVie, Aesca, Algernon, Amgen, AM Pharma, AMT, AOP Orphan, Arena Pharmaceuticals, Astellas, AstraZeneca, Avaxia, Roland Berger GmBH, Bioclinica, Biogen IDEC, Boehringer Ingelheim, Bristol Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Covance, Danone Austria, DSM, Elan, Eli Lilly, Ernest & Young, Dr Falk Pharma GmbH, Ferring, Galapagos, Gatehouse Bio, Inc., Genentech, Gilead, Grünenthal, ICON, Index Pharma, Inova, Intrinsic Imaging, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, LivaNova, Mallinckrodt, Medahead, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nash Pharmaceuticals, Nestlé, Nippon Kayaku, Novartis, Ocera, OMass, Otsuka, Parexel, PDL, Periconsulting, Pharmacosmos, Philip Morris Institute, Pfizer, Procter & Gamble, Prometheus, Protagonist, Provention, Quell Therapeutics, Robarts Clinical Trial, Sandoz, Schering-Plough, Second Genome, Seres Therapeutics, Setpointmedical, Sigmoid, Sublimity, Takeda, Therakos, Theravance, Tigenix, UCB, Vifor, Zealand, Zyngenia, and 4SC; has served as an advisory board member for Abbott Laboratories, AbbVie, Aesca, Amgen, AM Pharma, Astellas, AstraZeneca, Avaxia, Biogen IDEC, Boehringer Ingelheim, Bristol Myers Squibb, Cellerix, Chemocentryx, Celgene, Centocor, Celltrion, Danone Austria, DSM, Elan, Ferring, Galapagos, Genentech, Grünenthal, Inova, Janssen, Johnson & Johnson, Kyowa Hakko Kirin Pharma, Lipid Therapeutics, MedImmune, Millenium, Mitsubishi Tanabe Pharma Corporation, MSD, Nestlé, Novartis, Ocera, Otsuka, PDL, Pharmacosmos, Pfizer, Procter & Gamble, Prometheus, Sandoz, Schering-Plough, Second Genome, Setpointmedical, Takeda, Therakos, Tigenix, UCB, Zealand, Zyngenia, and 4SC; and has received research funding from Abbott Laboratories, AbbVie, Aesca, Centocor, Dr Falk Pharma GmbH, Immundiagnostik, Janssen, MSD, Sandoz, and Takeda.

Acknowledgements: Writing assistance was provided by Eve Blumson of Ascend, a division of Spirit Medical Communications Group, Manchester, UK Limited.

Disclaimer: This article was written by a medical writer and based only on the speaker presentations; the views and opinions expressed are not necessarily those of Amgen or the speakers. The speakers did not review this article.

Support: The symposium and the publication of this article were funded by Amgen.

Citation: EMJ. 2021;6[3]:13-20.

Meeting Summary

Artificial intelligence (AI) is a rapidly evolving field in medicine that has the potential to profoundly modify research and patient care. However, implementation of AI techniques is still in the early stages in inflammatory bowel disease (IBD) and the full potential of AI to guide disease management in IBD has yet to be realised.

Crohn's disease (CD) and ulcerative colitis (UC) are known to be progressive diseases. In eligible patients, early intervention with disease-modifying therapies can slow progression, prevent irreversible damage, and improve long-term patient outcomes. In order to facilitate early intervention, approaches to reduce referral times and allow for timely diagnosis of IBD are needed. Tools such as the Red Flags Index have been developed to aid identification of patients with CD, but AI-based referral and diagnosis tools are likely to emerge in the future.

Tools evaluated in IBD so far have employed AI methodologies to automate image analysis, and although useful for easing clinician workload, these tools are not likely to revolutionise patient care. In the future, AI could be used to analyse large, complex datasets to identify novel patterns and associations between patient and everyday variables and disease outcomes, allowing the prediction of disease course; ultimately, this may reduce the need for regular, invasive testing. Such an approach could lead to a new understanding of the disease, as well as improved patient management in IBD.

Personalised medicine has the potential to improve patient outcomes by tailoring disease management approaches to patient-specific factors; however, further research is needed before personalised medicine can achieve its full potential in IBD. Studies are underway to identify reliable predictors of disease course and treatment response in IBD to allow the development of personalised medicine approaches. Challenges around the implementation of personalised medicine clinical practice will also need to be addressed.

AI approaches have the potential to transform the management of IBD and facilitate a more individualised treatment approach, with the overall aim of improving patient outcomes.

Introduction

This symposium considered the role that AI may play in the future management of patients with IBD. Firstly, Gionata Fiorino highlighted the importance of early intervention and how AI approaches might be used to aid early diagnosis. Edouard Louis subsequently discussed the future role that AI might play in the treatment pathway, using examples from other therapy areas. Finally, Walter Reinisch considered how personalised medicine approaches may transform the management of IBD in the future.

Early Intervention: Fitting the Referral and Diagnosis Pieces Together

Diagnosis of patients with early-stage IBD, especially CD,[1] can be challenging due to non-specific symptoms and the lack of a single, non-invasive diagnostic test. As a result, patients with IBD currently experience considerable delays in referral and diagnosis. A survey of 4,670 patients by the European Federation of Crohn's and Ulcerative Colitis Associations (EFCCA)

revealed that although 70% of patients saw a specialist within 1 year of symptom onset, only 54% of patients received a final diagnosis of IBD in this time-frame.[2] In addition, 67% of patients needed to attend an emergency clinic more than once before receiving their final diagnosis.[2] Delayed referral and diagnosis is a major barrier to early intervention with disease-modifying therapies, particularly in CD, and can lead to disease complications and poor long-term patient outcomes.[1,3]

The 'Window of Opportunity' in Inflammatory Bowel Disease

CD is known to be a progressive disease: bowel damage measured using the Lémann index was significantly greater in patients with longer disease duration.[4] The benefit of treating patients with CD within a 'window of opportunity', before irreversible tissue damage occurs, is well documented. In a meta-analysis of 1,076 patients with CD treated with adalimumab, remission rates at 6 months and 1 year were significantly higher in patients with less than 1 year disease duration at baseline versus those with longer disease duration.[5] Increasing evidence in CD has shown that in eligible patients, early use of disease-modifying agents, such as biologics, slows disease progression, reduces tissue destruction, and leads to improved long-term outcomes, including prevention of hospitalisation and need for surgery.[3,6-8]

UC is also now considered to be a progressive disease,[3,9] and the concept of a 'window of opportunity' is emerging in UC. In a pooled analysis of patients with UC treated with infliximab in the ACT-1 and ACT-2 trials, early achievement of mucosal healing (at Week 8) was associated with improved outcomes after 1 year of treatment.[10,11] However, ACT-1 and ACT-2 did not specifically assess patients with early disease,[11] so further studies are needed to explicitly demonstrate the benefits of early intervention in patients with UC.

The Red Flags Index

Tools have been developed to try to reduce the time to diagnosis and facilitate early intervention in patients with IBD; one such tool is the Red Flags Index for CD.[1] This index includes eight items that are independently associated with a diagnosis of CD (Figure 1).[1] A prospective, observational study was performed to validate the Red Flags Index.[12] The Red Flags questionnaire was administered by general practitioners (GPs) to 112 patients with suspected CD; these patients were then referred to the nearest IBD centre to confirm or exclude CD diagnosis. Overall, 59% of patients completed the visit with the gastroenterologist and four patients were subsequently diagnosed with CD, with three classified as having early disease.

The index had a sensitivity of 50% and a specificity of 58%.[12] However, combining the Red Flags Index with measurement of faecal calprotectin significantly improved diagnostic

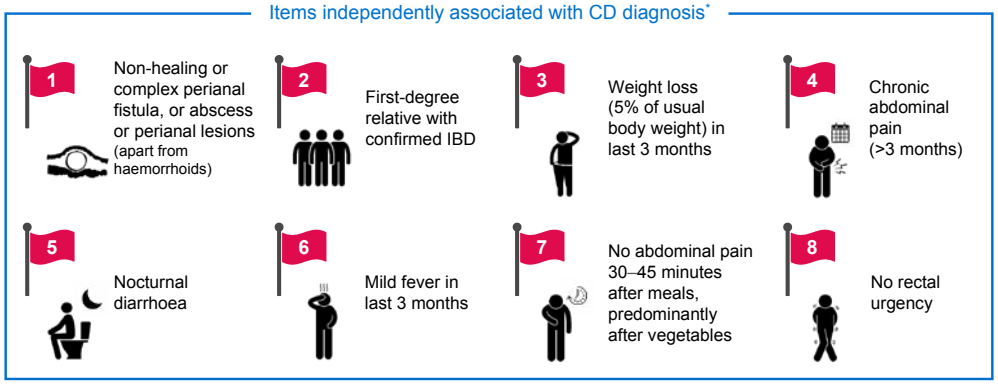

Figure 1: Red Flags Index for the diagnosis of Crohn's disease.[1]

*A Red Flags Index score of ≥8 was highly predictive of CD diagnosis.

CD: Crohn's disease; IBD: inflammatory bowel disease.

accuracy, giving a sensitivity of 100% and a specificity of 72%.[12] The results from this study demonstrate the value of combining clinical symptoms and biomarkers to aid in the early referral and diagnosis of CD.

In the future, AI approaches may further improve the efficiency of referral and diagnostic tools in IBD. AI could be used to automate the analysis of electronic health records to identify patients who may fit the criteria for a diagnosis of CD using the Red Flags Index. Similarly, AI could be used to identify items in electronic health records associated with a later diagnosis of UC, allowing development of a Red Flags Index specifically for UC. Further refinement of the Red Flags Index could also be carried out using AI, to identify the minimum inputs needed for accurate diagnosis.

What Can Artificial Intelligence Bring to the Patient Management Puzzle?

AI is a rapidly evolving field in healthcare, which has the potential to profoundly modify research and patient care;[13] AI techniques have been used with success in many areas of medicine. One recent example is drug repurposing for the treatment of COVID-19. An AI algorithm was used to search a large repository of medical information to identify approved drugs that might block the severe acute respiratory syndrome coronavirus-2 viral infection process.[14] The algorithm predicted that baricitinib, a JAK inhibitor, may reduce the ability of the virus to infect cells in the lungs.[14] In a subsequent clinical study, baricitinib combined with remdesivir, an antiviral agent, was found to be superior to remdesivir alone in reducing recovery time among hospitalised patients with COVID-19.[15]

AI approaches are also being used in IBD, although the use of AI in IBD is not as advanced as in other fields of medicine (Figure 2). Research has progressed from initial exploratory proof-of-concept studies, through to the development of time-saving AI-based tools, such as algorithms capable of automated image analysis. Algorithms to help guide clinical decisions are beginning to be investigated; however, the overall goal of AI, which is to help facilitate a fully personalised treatment approach to improve patient outcomes, has still not been reached.

Artificial Intelligence in Image Analysis in Inflammatory Bowel Disease

To date, AI techniques in gastroenterology have mostly been used to aid analysis of images generated during endoscopy procedures. A feasibility study showed that a deep-learning algorithm could be used to detect and localise colonic polyps in real-time with an accuracy of 96.4%.[16] This system could be used to improve the adenoma detection rate for the prevention of colorectal cancer.[16] In CD, AI has also been used to help automate the analysis of capsule endoscopy imaging. Capsule endoscopy is

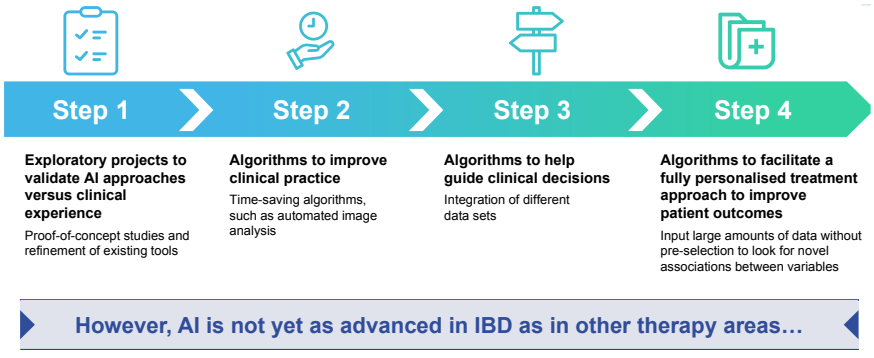

Figure 2: The evolution of AI in inflammatory bowel disease.

AI: artificial intelligence; IBD: inflammatory bowel disease.

a valuable tool for the diagnosis of CD, but analysis is tedious and requires the clinician to manually identify several views of the same lesion from a large amount of video footage, which can be difficult. A machine-learning algorithm was able to automatically identify images of the same lesion with an accuracy of 88%, thus reducing burden for the clinician.[17] A deep-learning algorithm has also been used in UC to evaluate inflammation severity in colonoscopy images.[18] This algorithm was able to differentiate colonoscopy images of varying Mayo endoscopic scores with a high degree of accuracy, and could act as a companion tool during endoscopy.[18] These time-saving AI algorithms will improve clinical practice; however, they will not revolutionise patient care and only scratch the surface of what AI is capable of. So, what should be the aim of AI in IBD?

Future Use of Artificial Intelligence in Inflammatory Bowel Disease

The potential for AI in IBD extends much further than automation of image analysis. In the future, AI could be used to analyse vast amounts of unselected data on patient variables and disease outcomes to identify complex patterns and associations that are beyond the scope of the human brain. Such an approach could lead to a new understanding of disease and improved patient management in IBD. For example, could AI be used to help find novel associations between everyday patient variables and disease outcomes in IBD? AI could be used to integrate a broad range of patient data collected during everyday life, such as blood pressure, sleep cycles, and physical activity levels, to predict disease evolution in real time. Tools based on these analyses could help to avoid the need for regular invasive testing.

Metabolomic analysis is another area where AI is likely to play a role in the future. Metabolomics is the analysis of small molecular metabolites in biological samples such as urine, stool, blood, and tissue biopsies. Due to the complexity of the data, AI techniques such as machine-learning are often used for data interpretation.[19] Metabolomics has already been used to provide insights into IBD pathogenesis,[19] and the potential exists for metabolomics to allow enhanced patient stratification for clinical management. Could metabolomic analysis of stool samples be used to diagnose IBD or predict relapse in the future?

There are many steps in the patient journey where AI could be employed to improve the management of IBD, but pressing unmet needs are currently reducing referral times and prediction of response or relapse to a given therapy. Identification of early markers of disease (pre-Red Flags) could aid a person to self-refer to a GP and other variables measured in everyday life could signal a GP to refer the patient to a gastroenterologist. Once diagnosis is confirmed, AI could be used to predict response to treatment prior to initiation of a given therapy or monitor a patient once therapy has commenced for markers that may predict relapse of disease, facilitating a fully personalised treatment approach. The era of personalised medicine is about to dawn in IBD, and AI techniques could allow its full potential to be realised.

The Coming-of-Age of Personalised Medicine in the Inflammatory Bowel Disease Clinic

Personalised medicine is the tailoring of disease management approaches based on patient-specific factors to help improve patient outcomes. Factors assessed can include genetics, epigenetics, and the microbiome, as well as clinical and lifestyle factors.[20] Personalised medicine is of particular value in multiple-hit diseases such as IBD, where patients can be highly heterogenous due to the complex interplay between genetic and environmental factors that drives the pathogenesis of the disease.[20,21] Long-term disease management can be difficult in IBD and there is a need for personalised medicine to transform disease management by allowing selection of the most effective therapy for each individual patient (Figure 3). However, implementation of personalised medicine remains a challenge in IBD, as reliable predictors of disease course and treatment response are lacking.

In IBD, some aspects of disease management in routine clinical care are already governed in part by personalised medicine. Patient and disease characteristics are already used to guide clinical decision-making,[22] and biomarkers of inflammation, such as faecal calprotectin and C-reactive protein, can be used to predict the course of the disease[23,24] and monitor treatment response.[22] Therapeutic drug monitoring can also be used to guide dose adjustments and optimise outcomes.[25]

Clinical Decision Support Tools

Clinical decision support tools based on commonly collected clinical data on patient and disease characteristics are in development for IBD to help predict response to biologic therapies.[26,27] A clinical decision support tool was developed to identify factors associated with clinical, steroid-free, and durable remission following treatment with vedolizumab in patients with CD included in the GEMINI 2 trial.[26] Multivariable logistic regression was used to identify variables associated with remission, including no prior bowel surgery, no prior anti-TNF exposure, and no prior fistulising disease, as well as baseline albumin and C-reactive protein levels. In the final prediction model, a points system was developed to give a weighting to each variable. This final model was then validated in an independent cohort of patients treated with vedolizumab (the VICTORY cohort). A cut-off

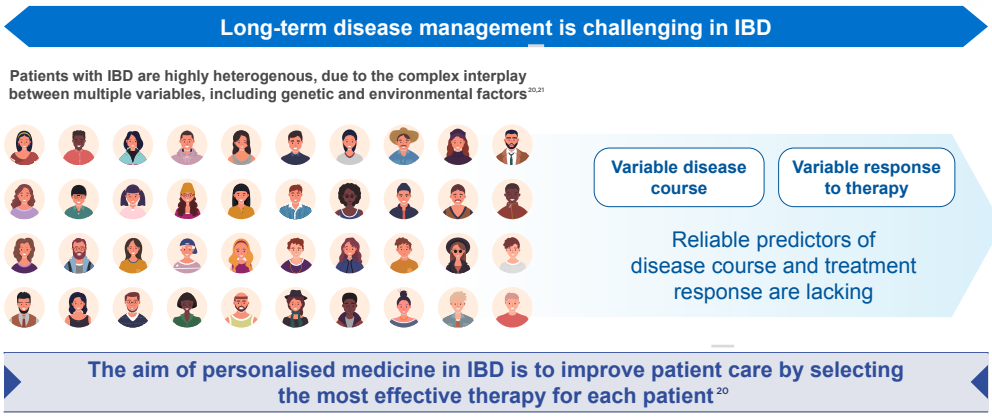

Figure 3: The need for personalised medicine in inflammatory bowel disease.[20,21]

IBD: inflammatory bowel disease.

value of 13 points identified patients in clinical remission after vedolizumab with 92% sensitivity; patients in steroid-free remission with 94% sensitivity; and patients with mucosal healing with 98% sensitivity.[26] Multivariable logistic regression was also used in a separate study to develop a matrix-based tool to predict primary non-response to infliximab in patients with CD. Three simple clinical factors were included in the final predictive model: age at first use of infliximab, BMI, and previous surgery. The model demonstrated good accuracy, with an area under the receiver operating characteristic curve of 0.8 (95% confidence interval: 0.67–0.93).[27] In the future, AI techniques could be used to integrate further variables predictive of response and improve the accuracy and clinical applicability of these tools.

Biomarkers of Prognosis and Response

Despite these advances, further research is needed before personalised medicine can achieve its full potential in IBD. Prognosis at diagnosis and prediction of response to targeted treatments are key stages in the IBD treatment pathway where advances in personalised medicine could help to improve patient outcomes. Studies are currently being carried out to investigate the potential for omic datasets, including genomics, the microbiome, and cellular composition data, to inform personalised medicine approaches and improve patient stratification.

Genomic risk scores developed using genome-wide single nucleotide polymorphism data could play a future role in disease prognosis. In a study

from the International IBD Genetics Consortium, which included >68,000 patients with IBD and 29,000 healthy controls, genomic risk scores were predicted based on single nucleotide polymorphisms. The genomic risk score was found to be associated with disease severity in patients with CD.[28] Patients with higher predicted genomic risk scores had clinical characteristics typically associated with a more severe disease course, including requirement for bowel resection ($p<0.03$), younger age at onset ($p<0.005$), and ileal disease location ($p<0.003$).[28] Analysis of the gut microbiome also offers potential for identification of predictive biomarkers for disease progression. In one study, complex associations were identified between multi-omic components of the gut microbiome and host that may influence disease activity in IBD.[29]

Biomarkers of treatment response are also being investigated in IBD. Novel markers of anti-TNF response have been studied in two single-cell analysis studies. In the first study, analysis of inflamed tissue from patients with CD allowed identification of a unique cellular module, consisting of IgG plasma cells, inflammatory mononuclear phagocytes, activated T cells, and stromal cells, that was significantly associated with anti-TNF response.[30] In the second study, analysis of colon tissue from patients with UC revealed that inflammatory cell signatures from pre-treatment samples may be associated with future anti-TNF response.[31] While a range of potential biomarkers of response have been identified in preliminary studies in IBD, none have yet been validated for use in the clinic. Appropriately powered studies are required to validate potential biomarkers of response.

Challenges Surrounding the Implementation of Personalised Medicine in Inflammatory Bowel Disease

In addition to the lack of validated predictive biomarkers, there are several other challenges surrounding the optimisation and implementation of personalised medicine tools in IBD. Research is needed to further optimise diagnostic criteria before personalised medicine and AI approaches can be used to aid diagnosis. In addition, personalised medicine will require the development of definitions of response that are rooted in the biology of the disease, rather than in patient-reported symptoms. Consensus opinions are also needed on reproducible patient characteristics that can be used to inform personalised medicine approaches, as well as the most appropriate time to assess treatment response.

Personalised Medicine in Other Therapy Areas

Despite similar challenges, personalised medicine approaches have been implemented successfully in other therapy areas including oncology, where a companion diagnostic test to predict response to a targeted therapy has been developed in non-small cell lung cancer. The KEYNOTE-001 study identified a clear link between the efficacy of pembrolizumab, a monoclonal antibody that targets the programmed cell death protein (PD-1), and tumour expression of the PD-1 ligand (PD-L1). Based on these data, pembrolizumab is only indicated in patients who have a tumour that expresses PD-L1 above a specific level, as determined by the companion diagnostic assay.[32] Another example is in rheumatoid arthritis, in which an exploratory study has used machine learning to develop a biomarker panel to predict non-response to anti-TNF.[33] Development of a similar tool in IBD would be extremely useful for the advancement of personalised medicine.

Concluding Remarks

AI techniques are emerging in IBD, but further study is needed to allow these tools to reach their full potential in the management of disease. Initial data in IBD have shown that AI-based tools can be used to ease clinician workload by analysing images or cumbersome datasets. However, AI also has the potential to improve patient outcomes by facilitating early referral and diagnosis, as well as predicting prognosis and response to treatment. The era of personalised medicine is only just dawning in IBD. Clinical decision support tools are in development and novel biomarkers of treatment response have been identified, but these findings need to be validated before they can be used in the clinic to improve patient outcomes. AI techniques may help to accelerate the search for appropriate personalised medicine tools in the future, but standardisation of various parameters in disease management is needed before the era of personalised medicine in IBD can truly begin.

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Pragmatism and Smoking Cessation: The Role of Harm Reduction in Creating Healthier Smoke-Free Societies

Interviewees: Krzysztof Filipiak,[1] Nadjib Bouayed[2]

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Interview Summary

Despite the extensive body of evidence demonstrating the risks of tobacco, many people continue to smoke. Medical science has not yet found a 'cure' for this. Instead, healthcare professionals (HCPs) have access to a range of strategies, including pharmacological and psychological interventions, to help support smoking cessation. Yet giving up is not easy and not everyone succeeds. The reasons why are as varied as they are complex, ranging from physical addiction to an emotional dependence on the habit. Barriers include a lack of adequate support from smoking cessation services or HCPs, withdrawal symptoms, and psychosocial factors such as the challenges of adapting to behaviour change.

For those people who are unable or unwilling to quit, harm reduction strategies can help reduce the risks associated with smoking, from cardiovascular disease to cancer. While the evidence base is still relatively immature, some studies have shown that products such as e-cigarettes and heated tobacco systems can deliver the addictive nicotine with significantly fewer toxicants and carcinogens than cigarettes.

In this interview, Krzysztof Filipiak, past President of the Polish Society of Hypertension (PTNT) and former Deputy Rector Magnificus and Dean for Science at the Medical University of Warsaw, Poland, and Nadjib Bouayed, President of the Algerian Association of Vascular Surgery of the University Hospital of Oran, Algeria, share their views on the pragmatic approach. They explain how finding the best intervention for each patient is of utmost importance and why harm reduction strategies have a place in smoking cessation services. They also review the current literature on products such as heat-not-burn (HnB) systems and identify gaps in the evidence base.

TOXINS AND CARCINOGENS

Smoking is a major public health issue contributing to 8 million global deaths every year.[1] Yet, while people smoke because they are addicted to nicotine, it is not the nicotine that kills them: it is the substances that are generated during tobacco combustion. According to a report from the Royal College of Physicians' (RCP) Tobacco Advisory Group, most of the harm caused by smoking arises not from nicotine but from other components of tobacco smoke.[2]

Cigarette smoke contains thousands of chemicals including at least 70 carcinogens. When someone lights a cigarette, the tobacco combusts releasing toxicants that cross the alveolar barrier and enter the bloodstream. Filipiak explained that these chemicals elicit systemic oxidative stress and inflammatory responses that can lead to abnormal lipid profiles and pro-coagulation, while also affecting normal endothelial functions.[3]

This can result in a plethora of serious health problems including myocardial infarction, stroke, atherosclerosis, diabetes, lung and chronic obstructive pulmonary diseases, eye disease, and rheumatoid arthritis.[4] Filipiak explained that together with older age, male sex, diabetes, arterial hypertension, and elevated serum cholesterol levels, smoking is one of the most important risks for cardiovascular disease. It also has the potential to cause cancer almost anywhere in the body, from the mouth and throat to the lungs, stomach, liver, kidneys, and cervix.[5]

Smoking can also have a significant impact on quality of life, explained Bouayed: "When someone is addicted to cigarettes, his appetite decreases. His complexion becomes dull, his voice becomes hoarse, and his taste and smell are altered. His teeth turn yellow-ish and crumble, and he runs out of breath on exertion due to bronchial obstruction. For all these reasons his quality of life slowly but surely decreases."

The consequences of tobacco smoking, the professors pointed out, do not stop at the individual. "Historically, we have been focused on active smoking, but we now know that passive smoking is also very important. We now know that those who spend time with a smoker can also become victims of smoking," said Filipiak. In fact, of the 8 million deaths linked to smoking around the world every year, 1.2 million are the result of non-smokers being exposed to second-hand smoke.[1]

The impact on healthcare systems, where cardiovascular disease and cancer are the main causes of mortality and morbidity, is also significant, said both professors. Data have shown that smoking-related diseases are responsible for 1.5–6.8% of national health system expenditures."[6]

MOUNTING EVIDENCE

None of this is news. The evidence on the dangers of smoking has been mounting for decades and has informed a wide range of public health strategies designed to discourage and dissuade people from the habit. Advertising and sponsorship bans, restrictions on smoking indoors, and wide-spread education programmes have all raised awareness of the dangers.

Yet, while there has been a drop in the number of smokers in recent years (e.g., in England, the proportion of the adult population who smoked fell from 19.8% in 2011 to 14.4% in 2018[7]), it remains a significant health problem. "We have adopted changes in smokers' habits, we have created special places for them to smoke, banned smoking in public places, schools, hospitals, and restaurants, but it did not change a lot," said Filipiak.

Some people, he went on, even continued to smoke after a cardiac event such as acute coronary syndrome, a percutaneous coronary intervention, or coronary artery bypass graft surgery. Bouayed agreed: "In my daily practice as a vascular surgeon treating serious tobacco-related illnesses, I spend my day advising people to quit. Despite all the suffering and surgery they undergo, only around 10% stop smoking: the rest continue."

PHYSICAL AND EMOTIONAL ADDICTION

Asked why people continued to smoke despite the huge volume of evidence demonstrating its harms, Bouayed said there was a multitude of factors, both physical and psychological. "When

a smoker wants to stop, deprived of his dose he becomes anxious, irritable, sleepless, and he increases in weight." These physical withdrawal symptoms, which may also include dizziness, depression, frustration, impatience, and headaches, can be extremely uncomfortable,[8] and some people will start using tobacco again to ease them, he added.

Others will give up for a period, after an acute cardiac event perhaps, and then relapse, said Bouayed, pointing to the emotional element of the struggle. "The smoker experiences great pleasure when smoking, and he does not want to quit this pleasure. He thinks that when he is confronted by a social or professional problem, a cigarette is the only thing that can help him."

The difficulty lies, then, in there being no single barrier to successful cessation; rather, there are a variety of interconnected structural, individual, and psychosocial factors.

SUPPORTING CESSATION

There is no one-size-fits-all approach to providing smoking cessation support, but Filipiak said more HCPs should follow the European Society of Cardiology's (ESC) 'Five As' rule:[9]

1. Ask: systematically enquire about smoking status at every opportunity.
2. Advise: unequivocally urge all smokers to quit.
3. Assess: determine the person's degree of addiction and readiness to quit.
4. Assist: agree on a smoking cessation strategy including setting a quit date, behavioural counselling, and any pharmacological support.
5. Arrange: schedule a follow-up appointment to discuss progress and offer any additional support that might be necessary.

Scientific societies and medical experts recommend a stepwise approach to supporting smoking cessation.[9,10] It starts with education on the harms of smoking before moving on to pharmacological treatment with cytisine, varenicline, or bupropion if this proves ineffective. Nicotine replacement therapies, which might include nicotine gum, lozenges, patches, nasal sprays, and inhalers, may also be needed at this stage. Second-line therapies might include a combined preparation of bupropion and naltrexone.

Filipiak emphasised that people should be offered comprehensive medical and psychological counselling via a smoking cessation clinic at every step of this pathway. Psychological interventions with proven efficacy include individual counselling, group therapy, and programmes specifically aimed at groups such as pregnant women, young people, or people living with health conditions such as chronic obstructive pulmonary disease.

People need expert and specialist advice, said Bouayed. "Weaning is not easy. It is necessary to support addicts in their quest for abstinence," he added.

HARM REDUCTION

Despite the evidence to support this approach, it is important to remember that it will not work for everyone. Some people will continue to smoke despite the efforts of HCPs, smoking cessation services, and pharmacological assistance. This raises the question of harm reduction strategies.

While complete smoking cessation is always preferable, Bouayed and Filipiak said there was a role for pragmatic harm reduction strategies for those who were unable or unwilling to quit.

The concept of harm reduction is not unique to smoking cessation. Examples from the substance misuse sector include needle exchanges and providing safer injection facilities for people who inject drugs to protect them from blood-borne viruses, overdose prevention programmes, and opioid substitution treatment.[11] The objective of such policies is to mitigate the risks associated with the behaviour and thus reduce hospitalisations and deaths, explained Bouayed.

In the tobacco arena, harm reduction strategies usually centre on substituting cigarettes with less harmful products and are intended for adults who would otherwise continue to smoke.[12] Substitutes might include e-cigarettes, which work by heating a nicotine-containing liquid to produce a vapour, or HnB products, which heat,

rather than burn, tobacco to create an aerosol that contains nicotine and tobacco flavour, but with significantly fewer toxicants than cigarette smoke.[13]

THE EVIDENCE FOR HARM REDUCTION PRODUCTS

Such strategies do not eliminate risk, but the evidence, while still relatively immature, suggests that they may be able to reduce it.

A consensus study from the USA National Academies of Science, Engineering, and Medicine, published in 2018,[13] stated that there was conclusive evidence to show that e-cigarettes increase airborne concentrations of particulate matter and nicotine in indoor environments, when compared with background levels. In addition, most e-cigarette products "contain and emit numerous potentially toxic substances," which may include acetaldehyde, acrolein, and formaldehyde, the authors said.[13]

An independent report by Public Health England (PHE) said the long-term impact of nicotine delivered by e-cigarettes on lung tissue is not yet known, and that the evidence does not yet demonstrate how addictive the devices are, when compared to tobacco cigarettes.[14] However, the report also estimated the overall risk of harm associated with e-cigarettes to be less than 5% of that from smoking tobacco, and the risk of cancer at less than 1% of that of smoking tobacco.[14] It also said that, compared to cigarette smoke, heated tobacco products were "likely to expose users and bystanders to lower levels of particulate matter and fewer harmful and potentially harmful compounds." The extent of that reduction, it went on, varied between studies, which were few in number at the time of publication.[13] "The limited evidence on environmental emissions from use of heated tobacco products suggests that harmful exposure from heated tobacco products is higher than from e-cigarettes, but further evidence is needed to be able to compare products," said the report.[14]

It is worth noting that there are also data to suggest that harm reduction products are often used by smokers as smoking cessation or reduction aids. PHE's vaping evidence update, which was published earlier this year, for example, found that >50,000 people who would otherwise have continued to smoke stopped with the help of an e-cigarette product in 2017. It also said that cessation strategies that included vaping products had some of the highest success rates, of between 60% and 74% in 2019 and 2020.[15]

The ESC smoking prevention guidelines, published in 2016, say that e-cigarettes are probably less harmful than traditional tobacco cigarettes as they deliver the addictive nicotine without the majority of harmful chemicals coming from the combustion process.[9]

According to the guidelines, some studies and real-world data have indicated that e-cigarettes are "moderately effective" as smoking cessation and harm reduction aids.[16-18] Interestingly, they found that changes in behaviour, rather than in nicotine delivery, was a significant contributing factor to this outcome. The document went on to say that there were many unanswered questions about e-cigarette safety, on their efficacy in terms of harm reduction and smoking cessation, and their impact on public health.[9] "Although no safety issues have been observed in the short-term (2 years), determining the long-term health effects of e-cigarettes (and in particular dual use with cigarettes) will require more research," said the authors.[9]

Heated tobacco products were not included in the scope of the recommendations as the scientific evidence base was immature at the time of publication. Since then, however, evaluation has demonstrated that the aerosol created by HnB systems does not contain carbon-based nanoparticles and that, when compared to burned tobacco, levels of cardiovascular toxicants are reduced by an average of approximately 90%. A German Federal Institute for Risk Assessment (BfR) analysis of a commercially available HnB product, for example, concluded that the system delivered a comparable amount of nicotine to a cigarette, but with approximately 80–90% fewer aldehydes and 97–99% fewer volatile organic compounds. The authors concluded that levels of major carcinogens were markedly reduced in the HnB product emissions when compared to those of conventional tobacco cigarettes.[19]

Outlining the available evidence, Filipiak said cardiovascular benefits had been observed with heated tobacco products when compared to

cigarette smoke. "The adhesion of monocytic cells to human coronary arterial endothelial cells *in vitro* is significantly lower following exposure to the aerosol than after exposure to reference cigarette smoke.[18] There are also some data to show that switching to heated tobacco halted the progression of cigarette smoke-induced atherosclerotic changes *in vivo,*"[20] he said.

Another paper, which was an independent randomised, cross-over study, compared the effects of HnB devices, e-cigarettes, and traditional cigarettes on oxidative stress, antioxidant reserve, platelet activation, flow-mediated dilation, blood pressure, and satisfaction scores. In all, 20 participants used all three products, with an inter-cycle wash-out period of one week. Single use of all the products led to an adverse impact on oxidative stress, antioxidant reserve, platelet function, flow-mediated dilation, and blood pressure. "A hierarchy of effects was apparent for some measures, with HnB and e-cigarette less impactful than traditional cigarette on some dimensions of oxidative stress, antioxidant reserve, platelet function, and blood pressure," said the authors. "In addition, HnB had less acute effects on soluble Nox2-derived peptide, 8-iso-PGF2α-III, and vitamin E, and appeared more satisfying and capable of decreasing desire for continuing smoking than e-cigarette."[20]

The reduced exposure to harmful and potentially harmful constituents may have a positive impact on smokers' health. This was demonstrated during a six-month, USA-based clinical study involving 984 adult smokers. It analysed a range of measures of biological responses that are known to be negatively affected by smoking and positively affected by cessation. These clinical endpoints, all of which are associated with smoking-related disease, were linked to lipid metabolism, endothelial function, inflammation, oxygen delivery, oxidative stress, lung function, platelet function, and carcinogenesis. After switching from smoking to an HnB product for six months, all biomarkers showed favourable changes in the same direction as that with smoking cessation, and smokers who predominantly used HnB showed improved biological effects relative to those who continued smoking, with similar nicotine levels in both groups, said the authors.[21]

GROWING THE EVIDENCE BASE

Taking all the available evidence into account, Filipiak said he believed that switching from cigarettes to HnB devices had the potential to reduce the risk of smoking-related diseases when compared with continued smoking. There is still, however, a limited number of clinical studies investigating the effect of heated tobacco products on cardiovascular diseases.

Filipiak explained that his team was planning a study to help to fill the gap. "It will be a locally initiated research programme on how switching from cigarettes to heated tobacco affects cardiovascular biomarkers of potential harm in patients with stable coronary artery disease," he said. "We would like to assess how switching will affect biomarkers associated with atherosclerosis and coronary artery disease or its equivalent: atherosclerosis in other vascular beds such as carotid artery disease, atherosclerotic aorta, peripheral arterial disease. We are looking forward to learning more about heated tobacco products and their possible role in smoking cessation."

PRAGMATISM UNTIL CESSATION

Summing up, Bouayed said nicotine addiction is a huge problem that requires a systemic solution.

"It is absolutely necessary to have strategies to reduce the risks of smoking. When we see the great suffering of patients who have lung cancer, stroke, or critical ischaemia of the limbs, we cannot remain insensitive and do nothing," he said. "The most effective way to avoid becoming addicted to smoking is to never start. Young people must, therefore, be informed and educated from school on the harmful effects of tobacco and its huge consequences. I believe that every effort should be made to ensure that people never start smoking."

In the meantime, the professors agreed, HCPs should do whatever they can to help all smokers, including those who use products that could potentially reduce the risks, to stop completely. However, they also need to accept that this is not always possible.

When someone is either unwilling or unable to quit, harm reduction strategies are an effective,

pragmatic approach to cutting the risks for the individual, their communities, and healthcare systems. There is a growing body of scientific evidence to suggest that HnB products, which heat tobacco and deliver nicotine via an aerosol, significantly reduce exposure to harmful toxicants and carcinogens. They could, then, play an important role in future harm reduction strategies.

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Embedding State-of-the-Art of Cardiac Fibrosis Imaging into Standard Practice

Interviewees: Antonio Berruezo,[1] Francis E. Marchlinski[2]

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Interview Summary

The 12-lead ECG has long played the leading role in identifying the region of the heart responsible for tachycardia to aid in the diagnosis of cardiac arrhythmias and the planning of ablation procedures. However, the approach is not without its limitations.

ECG often struggles to give an accurate picture of where ablation should be targeted, has poor spatial resolution, and low sensitivity in terms of determining the extent of damaged myocardium. For many years, electrophysiologists have combined the ECG with invasive catheter electroanatomic mapping to obtain a more detailed picture of the location of arrhythmia. In recent years, physicians have combined these tools with non-invasive MRI and CT imaging, which provide black and white DICOM cardiac images, in a bid to gain a better understanding of the underlying anatomy, pathology, and fibrosis. This will ultimately enable more accurate pre-procedure planning.

Now, advanced imaging solutions promise to take this complementary approach to the next level. By providing teams with a colour-mapped 3D image of all the fibrotic abnormalities within the heart, this new paradigm has the potential to cut complications, boost patient outcomes, and make workflows more efficient.

Despite the growing body of evidence for the advantages of this complementary approach and its inclusion in the 2019 Expert Consensus Statement on Catheter Ablation of Ventricular Arrhythmias, adoption has been slow. Radiologists and electrophysiologists cite concerns around patient safety, a lack of training, and organisational hurdles as barriers.

In this article, EMJ spoke to two pioneers of state-of-the-art cardiac fibrosis imaging: Francis E. Marchlinski, Perelman Center for Advanced Medicine, Philadelphia, Pennsylvania, USA, and Antonio Berruezo, Teknon Medical Center, University of Barcelona, Spain. They explain how the limitations of the traditional approaches are contributing to an unmet need in the field of diagnosing and treating cardiac arrhythmias, the challenges and benefits of incorporating advanced imaging into electrophysiology workflows, and how using advanced 3D cardiac imaging can improve outcomes in arrhythmia treatment.

EVOLUTION OF FIBROSIS DETECTION

Combining ECG with imaging techniques allows for safer, more targeted arrhythmia interventions, while also delivering more efficient workflows. Despite growing evidence for this complementary approach, such as its inclusion in 2019 Expert Consensus Statement on Catheter Ablation of Ventricular Arrhythmias,[1] it has not yet been widely adopted into standard practice.

Explaining the current state of play, Berruezo and Marchlinski said that ECG was, and would remain, the gold standard for detecting the approximate source of various arrhythmias. However, it does have several limitations, both pre- and intra-procedurally.

Marchlinski said: "Our experience with thousands of patients has allowed us to develop a robust way of looking at 12 ECG leads and determining where the arrhythmia originates. But there are limitations, especially as you get more diseased hearts, the ECG becomes less accurate, particularly for arrhythmias due to large circuits, where the ECG does not tell you exactly where to ablate."

He described the ECG as "a starting point for regionalisation," and explained that combining it with cardiac imaging provided a complementary picture to increase precision. Over the years, we have recognised that the reason people develop arrhythmias is typically because of abnormal anatomy. Definition of that abnormal anatomy, with a variety of imaging techniques, helps us to focus our attention on the regions of interest for more detailed, focused electrical recordings once we start mapping with catheters," he said.

Echocardiogram was once the standard imaging technique in this scenario, noted Berruezo. "However, it has low sensitivity in identifying fibrosis, especially when the volume of fibrotic tissue is low, and when it is only affecting the sub-endocardium," he said. It is also challenging to identify hypokinesia on echocardiogram. As such, MRI has emerged as the modality of choice for fibrosis identification, revealed Berruezo, explaining that it was able to detect areas of fibrotic tissue, as well as wall thinning.

Now, advanced image processing software, which replaces black and white DICOM images with a full-colour, 3D reconstruction of the anatomy, promises to take cardiac imaging to the next level.

Marchlinski described the advances, which "give you a surgeon's view of the heart," as "really exciting." "At [my institution], we have been using 2D imaging for a while," he said. "The next step for us is [the implementation of] very sophisticated techniques where you can use reconstructed 3D images and get well-defined areas of normal and abnormal anatomy and integrate them into our mapping systems. It gives you a roadmap for where the anatomic abnormalities are, and where to focus your electrical recordings. It's been breathtaking in terms of the information that can now be gleaned."

Explaining the process, Berruezo said the acquired images are processed with Automatic Detection of Arrhythmic Substrate (ADAS 3D) software (ADAS3D Medical SL, Barcelona, Spain), and merged into the navigation system.

"We use them to form the pre-procedure plan, and then start the procedure. The first step is the reconstruction of an anatomic structure, usually the aortic arch, with the mapping catheter for electroanatomic map, and image integration. The next step is navigation, without the need for fluoroscopy, and mapping directed to the scar identified by the images. Different mapping manoeuvres can characterise the critical scar components as identified by the images," he said.

The technique has an extremely important role to play in pre-procedure planning, he stated, explaining that electronic anatomic mapping (EAM), despite being the most widely used method for ventricular tachycardia (VT) substrate identification and targeting ablations, was sometimes imprecise when used alone. "Even when using multi-electrode mapping catheters, EAM is less sensitive to identifying the VT substrate, especially if this is located deep in the left ventricle wall or the epicardium. The scarring is obscured, in some cases, by the far-field effect of the surrounding tissue," he said. "With these imaging techniques, you can see the VT substrate before you even begin the procedure."

A 3D visualisation of the full extent of the scarring, including its distribution, core, and border zone across segments, can improve the accuracy and reduce the duration of mapping (Figure 1).

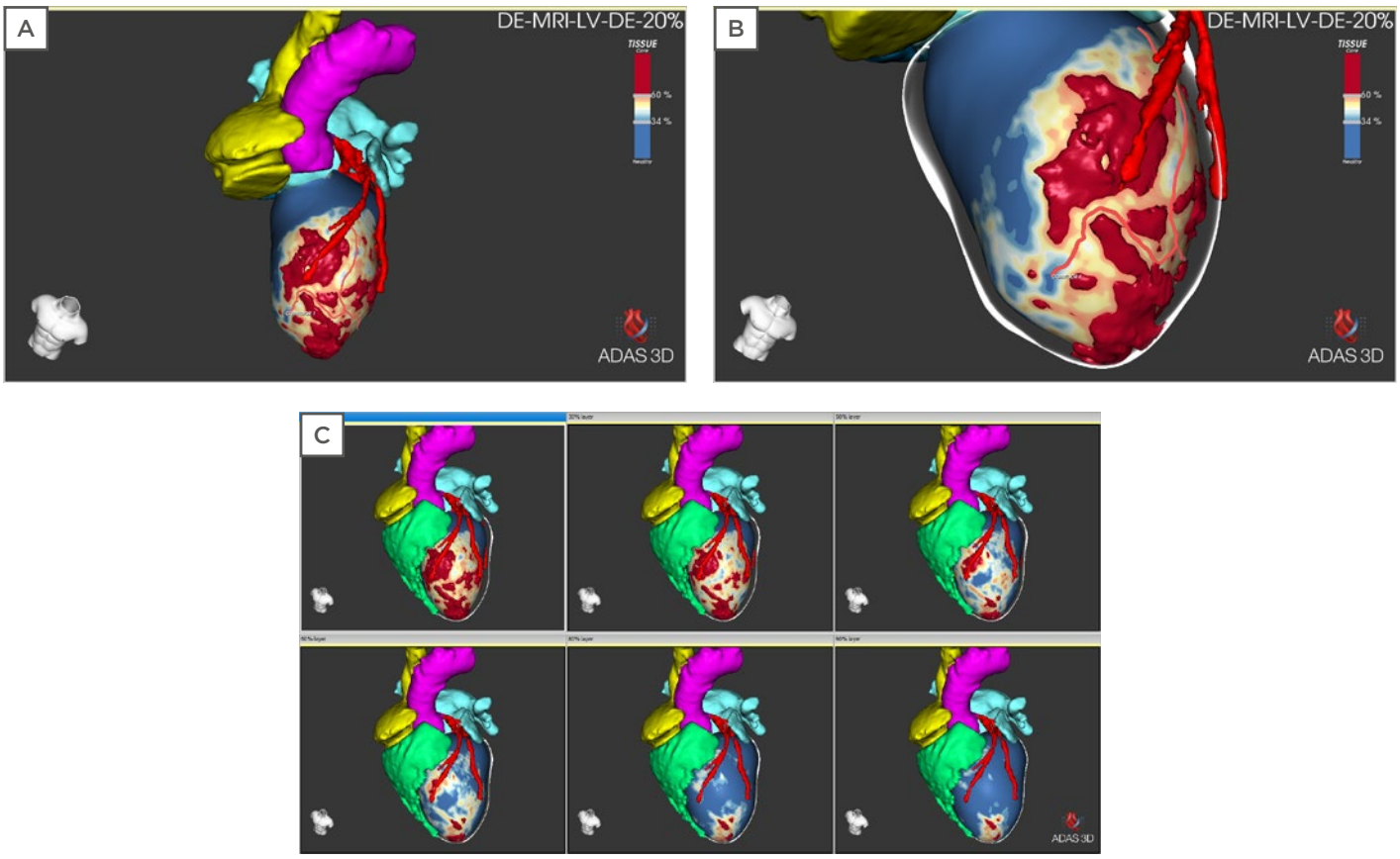

Figure 1: 3D visualisation of extent of scarring.

A) 3D volume of the core scar is shown on the 20% layer (endocardial). Core scar is red, border zone is green-yellow, healthy tissue is blue. **B)** ADAS 3D left ventricular image highlighting a corridor of border zone tissue in the 20% layer. The centre line of the border zone is illustrated with the solid red line. **C)** ADAS 3D left ventricular image of 20% (endocardial top left), 30%, 50%, 60%, 80%, and 90% (epicardial bottom right) layers. Adjacent coronaries from CT are shown in red, right ventricle (green), left atrium (cyan/light blue), aorta (pink).

ADAS: Automatic Detection of Arrhythmic Substrate (ADAS 3D) software (ADAS3D Medical SL, Barcelona, Spain).

Marchlinski said: "Planning is important, and we have always used imaging to get us there. This incredibly detailed 3D imaging gives us the location of the intramural scar, areas of epicardial scar, and the incredible ability to characterise, in three dimensions, the nature of the scar, where there are gaps, or lack of continuity, as well as what we refer to as non-ischaemic scar, patches of scar and other areas responsible for arrhythmias that may not have been identified with just coronary angiography or looking at the ECG."

OUTCOME BOOSTING COMBINATION

Marchlinski was keen to point out this was a complementary approach, and that both physiology and advanced imaging had something to bring to the table when diagnosing and treating arrhythmias. It is the combined pictures of electrical readings and imaging that provides the detailed information on the arrhythmia circuit that clinicians need.

"Electrical recordings are very valuable. We always say electrograms never lie." He added that imaging "works hand in glove with the electrical information." This is particularly true when investigating intramural areas that cannot directly be registered with electrical information; when attempting to capture information from the opposite side of the heart, such as the epicardium; and when access is complicated. "It is not that each is perfect. When you use them together, your procedures are faster, and you focus your electrical readings in a more appropriate way. You apply the energy more safely."

The results, Berruezo and Marchlinski agreed, were higher clinical value, higher efficacy, and improved workflows. If imaging could reduce the need to induce VT during an ablation procedure, it would make treating patients who become haemodynamically unstable easier, explained Berruezo. "This not only leads to better outcomes and fewer complications during ablation, but also decreases early mortality."[2]

In addition, the approach can reduce the time it takes to perform an ablation from more than 4 hours in some centres to just 30 minutes, he said. "Imaging permits us to transform complex ablation into an easier, safer, faster, and more reproducible procedure that can be performed during a stable sinus rhythm in the majority of cases," commented Berruezo.

CHALLENGES

Devices and MRI

There is a strong body of evidence to support the use of 3D imaging in the detection and treatment of arrhythmias. For example, in a recent meta-analysis of image-guided versus conventional VT ablation, VT-free survival was observed in 82% (interquartile range [IQR]: 74–90%) of those receiving image-guided ablation compared with 59% (IQR: 54–64%) of those receiving conventional mapping ($p<0.001$) during a 35-month mean follow-up period. There was an overall survival rate of 94% (IQR: 90–98%) in the image-guided cohort versus 82% (IQR: 76–88%) in those patients treated conventionally ($p<0.001$).[3]

In addition, the 2019 Expert Consensus Statement on Catheter Ablation of Ventricular Arrhythmias recommends using this technique adjunctively to guide VT ablation procedures and describes it as both accurate and non-invasive.[1]

However, there is still some resistance in terms of introducing it into standard workflows. One of the main barriers, said Marchlinski, is perceived safety issues. "In some radiology departments, there is still some concern related to the safety of imaging people with implantable electronic devices (IED), worries that it might create heating and damage the technology or the site where the leads contact with the heart."

However, the data, and clinical experience, demonstrate otherwise, said Marchlinski, whose centre has been routinely imaging patients, including those with devices, "for some years."

In 2016, Dandamudi et al.[4] published a review of outcomes experienced by 58 people with IEDs who underwent cardiac or thoracic MRI. The study found no clinically significant changes in atrial and ventricular sensing, impedance, or threshold measurements. There were no episodes of device mode changes, arrhythmias, therapies delivered, electrical reset, or battery depletion.

Another observational study of 139 patients concluded that the risk of MRI in people with abandoned leads was low.[5]

"We know we can do this safely. Treatment protocols are approved by institutional review boards, and patients are counselled on the low potential for risk and monitored carefully. Devices are also checked post-procedurally to make sure there have been no adverse effects," said Marchlinski.

Berruezo said his department scans all patients before they receive an implantable cardioverter-defibrillator (ICD) to obtain a reference point, a pathway that reflects the consensus guidelines.[1]

As Dandamudi et al.[4] concluded: "When a comprehensive IED magnetic resonance safety protocol is followed, the risk of performing 1.5T magnetic resonance studies with the device in the magnet isocenter, including in patients who are pacemaker dependent, is low."

Another commonly cited barrier to adoption is concerns around the noise artefact that can occur when imaging people with devices or leads. Again, Marchlinski said, this unease was unnecessary, explaining that wide-band sequences could largely deal with the problem.

Berruezo said it was also worth noting that inferior myocardial infarctions are less affected by artefacts. The same is true of ICDs implanted on the right, and "probably" subcutaneous ICDs. Manoeuvres, such as displacing the ICD to an upper position, can also be helpful in reducing noise.

"The fear that has been associated with using MRI in people with devices should be forgotten. It should be embraced as a standard because it adds value. It has been tried and tested for

years and there are plenty of publications and documents from the evidence-based literature to support this becoming the new standard of care," said Marchlinski.

Organisational Barriers

Even those convinced of the benefits of advanced imaging in the detection and treatment of arrhythmias experience organisational barriers in terms of bringing the technology into standard practice. Overcoming logistical challenges is essential, and success relies on cross-specialty collaboration, particularly between electrophysiology (EP) labs and radiology departments.

"Everybody is using imaging now, so everybody has to stand in line," said Marchlinski. "If you are going to start using it, you need to have a workflow, both in EP and radiology, that will facilitate that. It is critical these workflow issues are addressed." For this to happen, both departments need to understand and embrace the role of advanced imaging, and follow standardised protocols that guarantee image quality. "We have been very lucky at Penn. We have some great colleagues who have been at the forefront of this. They have pushed to make it happen, and were willing to add patients to the schedule. But it does take co-operation, otherwise the roadblocks are cumbersome," he said.

There are also training needs on both sides of the coin (3D image acquisition and processing), said Berruezo. He explained that while most MRI machines will have 3D capability, not all radiologists were accustomed to using the method. Fortunately, he went on, it would take "fewer than a dozen cases" to bring radiologists up to standard of 3D MRI imaging acquisition.

Electrophysiologists also need to become familiar with the use of advanced 3D imaging. "The software we use, ADAS 3D, is available, and has CE [Conformitè Europëenne] approval and FDA [U.S. Food and Drug Administration] clearance," said Berruezo. Image processing can be done by anyone in the EP lab, including physicians, technicians, or engineers, all of whom will be able to quickly scale the short learning curve, he added, explaining the time per procedure was typically 15–20 minutes, and tends to shorten with adoption.

Another hurdle is securing approval for additional costs associated with 3D image acquisition and advanced processing software. "If you begin to use the software, the initial costs will affect your early revenue, therefore you have to approach your supply chain committees of your hospitals and say what value it provides. You have to show them evidence-based literature, and hopefully your own experience with preliminary data, that shows that this does work, this does enhance efficacy, and there is some reduction in the duration of procedures, so your costs related to procedural time is reduced," said Marchlinski. Crucially, improving outcomes results in added value, particularly for the patient, making the investment worthwhile, he added.

Berruezo agreed, adding that the 2019 consensus document meant hospitals "should understand they should acquire" the imaging solution, which he described as inexpensive. "It is now a Class IIa recommendation to use imaging to pre-plan the ablation procedure, and it is also a Class IIa recommendation to use it inter-procedurally to improve outcomes,"[1] he said. "This is something that will help physicians to improve outcomes, so there is an obligation to do it."

NO GOING BACK

Both Berruezo and Marchlinski routinely scan patients before implanting an electronic device, and both say they would never go back. "We love imaging," said Marchlinski, "the more information the better."

Asked his advice to his colleagues around the world, Berruezo said the sooner they start using advanced 3D imaging the better. "After they have done a few cases, they will never again do VT ablation without imaging, if it is available."

Imaging is not going anywhere. If anything, it will only get more advanced and provide more opportunities, said the two experts. Berruezo stated: "We are at the era of 'virtual dissection'. 3D anatomy and the possibility to see the structure of the heart and the substrate for VTs in 3D is providing a new way to learn. I'm sure we have only just begun to learn the possibilities of applying this technology to new ways of performing VT ablation."

Marchlinski agreed, saying that "a lot of smart people" were making "a lot of smart correlations"

based on 3D image data. "In the future, I think there will be real-time advanced 3D imaging. I think we will be ablating patients inside the MRI magnets so we can watch lesion formation. There will be real time imaging where we will get ongoing images, while we are applying the energy, and changing the anatomy."

The potential use of advanced imaging to guide focused radiotherapy ablation in patients who are not stable enough, due to the complexity of disease or access issues, for example, to undergo electrophysiology, is another area of growing interest. Marchlinski said: "If we use imaging appropriately, and as we define and confirm the reliability of these imaging signature patterns for identifying circuitry of ventricular arrhythmias, you can see where this type of data will serve some patients as standalone information to help guide ablative therapy when you are using external beam radiation to try to target and eliminate arrhythmias." He described it as an "important, non-invasive strategy" that was currently being explored.

It is time, they both agreed, for EP and radiology colleagues to embrace advanced 3D imaging. "It is a valuable tool, and it's recommended in the guidelines," said Marchlinski, advising people to take advantage of imaging to help guide ablation when they can. "From the very simplest pieces of information, when there's intramural data, or intramural abnormalities, or epicardial abnormalities, to now more sophisticated, detailed definition on a 3D basis with this very sophisticated 3D reconstruction software. When you combine that anatomic information with the electrophysiology, it makes sense that you are going to get the best outcomes. That's been in all the preliminary experience, and that's been in the observational data."

Berruezo agreed: "It is highly precise, permits ablation to be very directed at target sites, and provides accurate revelations with very small needs in terms of procedure duration and risk of complications." It is all about, he added, improving patient outcomes.

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Perspectives of the Methofill® (Methotrexate) Pre-filled Injector Device: Insights from a Rheumatology Nurse Consultant and Results from a Real Life Patient Experience Survey

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INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, progressive, inflammatory joint disease characterised by symmetrical inflammation of the peripheral joints and associated with cartilage and bone damage and substantial disability.[1] This disease impacts significantly on occupational and daily activities, and is associated with increased mortality.[2-5] RA is the most common autoimmune inflammatory arthritis, affecting approximately 1% of the population.[6] A wide range of point and period prevalence of RA is reported in the literature, with average results of 51 in 10,000 and 56 in 10,000, respectively.[7]

Methotrexate (MTX) is one of the mainstays of treatment for active RA.[8,9] MTX administered as a subcutaneous injection may overcome the limitations of oral MTX.[9] However, needle phobia, patient treatment misconceptions, incorrect drug administration, and dexterity problems can reduce patient adherence to subcutaneous drug treatments.[10]

For this article, the EMJ conducted an interview on 12th May 2021 with Nurse Consultant Kate Hunt from Surrey, England, who has a wealth of experience and expertise in managing patients with active RA, to gain her perspective on the impact of active RA on adult patients and the benefits and challenges of self-injection MTX treatments for these patients. The results of a survey[11] conducted to gain insight into patients' experiences and perceptions of self-injection MTX treatment were also discussed.

METHOFILL® (METHOTREXATE) SELF-INJECT PATIENT SURVEY

This was a cross-sectional, self-reported survey conducted between April 2019 and May 2020 on behalf of Accord-UK Ltd in partnership with Day Lewis Pharmacy to gather real-life

experience from 63 adults with active RA, psoriasis vulgaris, psoriatic arthritis, or Crohn's disease using the Methofill® pre-filled injector device (Methofill SelfDose).[11] The survey questionnaire captured anonymous data on experience of self-injecting MTX and perceptions of Methofill SelfDose (ease of grip, ease of use, preference, confidence, and satisfaction).[11]

IMPACT OF RHEUMATOID ARTHRITIS ON THE PATIENT

Hunt explained that the most frustrating aspects of active RA for patients include a lack of symptom patterns, and variable pain intensity and joint location, meaning that every day is different. Consequently, active RA may have a significant impact on quality of life: patients may need to adapt their life according to their symptoms, daily activities could be affected, and life might have to be planned, rather than spontaneous.

Joint discomfort is a key characteristic of active RA, and patients rarely achieve complete remission, Hunt claimed. Another important factor in active RA is fatigue, which Hunt considered is mostly joint-pain related and is sub-optimally managed.

Hunt observed that the huge psychological impact of a chronic disease such as active RA is increasingly being recognised, although psychological support services are limited by cost. She referred to the online information and support available for patients with active RA (e.g., National Rheumatoid Arthritis Society [NRAS],[12] Versus Arthritis,[13] NHS [UK National Health Service][14]) as a positive improvement in active RA management; however, the ideal situation would be to have psychologists working alongside RA nurses to provide optimum care.

PATIENTS' CONCERNS ABOUT TREATMENT FOR RHEUMATOID ARTHRITIS

The main concern patients with active RA have about treatment, Hunt remarked, is that MTX is a cytotoxic drug, and they fear it will give them cancer. Patients also worry about adapting to taking long-term treatment, potential side effects (including hepatic and renal effects and nausea) and monitoring (liver function tests).

Hunt outlined how a motivational, persuasive approach by healthcare professionals encourages patients to adhere to treatment and open up about their concerns. She described patients with active RA as proactive and receptive to new treatment options.

TREATMENT ADHERENCE IN ACTIVE PATIENTS WITH RHEUMATOID ARTHRITIS

Treatment adherence is not specifically measured in the adult patients with active RA in Hunt's care, but she defined adherence as reasonable. Hunt indicated the reasons for non-adherence are complex and relate to fear of side effects, perception of benefit versus side effects, comorbidities, concomitant medications, and the patient's core beliefs about long-term treatment.[15]

Hunt summarised how, in her experience, non-adherence leads to disease progression, joint pain, seizing up/reduced mobility, and decreased quality of life.[16,17] Non-adherent patients are offered extra information and training on their current treatment or are given an alternative treatment. For example, patients non-adherent to oral MTX (e.g., because of nausea, lack of efficacy) can be prescribed subcutaneous MTX.[18] Hunt described MTX as the 'baseline drug' on which she aims to keep as many patients as possible "the long-term safety data around MTX is favourable."[19-21]

KEY PATIENT NEEDS IN RHEUMATOID ARTHRITIS TREATMENT

Hunt has considerable experience of self-injection devices in patients with active RA and listed the key patient needs as a device that is simple to use, includes education (e.g., injection guides,[22] nurse demonstration of technique using a dummy device, videos, online information), has individual support during the first injection, and diary or calendar reminders for administering treatment. Uptake of self-injection devices in her experience is good, as the devices are "designed around the

patient." Hunt identified easy to hold and easy and simple to use as crucial device-related factors, with the selection of which "patient-orientated" device is given to patients often depending on availability and cost.

MAIN CHALLENGES AND CONCERNS PATIENTS HAVE WHEN SELF-INJECTING METHOTREXATE

Hunt disclosed how patients who are new to self-injecting MTX worry about handling needles, and whether they will be able to use the device on days when their hands are particularly painful; psychological effects and barriers to accepting long-term treatment are also common.

The needle is hidden within the device in most designs, which reduces patient stress surrounding needle handling. Hunt acknowledged that many patients find these devices easy to operate, even on days when their hands are exceptionally sore, as they are "designed so well," and commented that as the treatment is effective, "bad days" with debilitating pain might be less common. She specified that patients find self-injection easy once the technique has been demonstrated to them. Psychological difficulties are addressed with motivational guidance, training, and support. A total of 81% (46/57) of patients in the survey[11] currently self-injecting MTX stated that they had no concerns or fears about self-injecting MTX (data on file: UK-03028), which indicates patients are generally less apprehensive once they are familiar with their treatment.

BENEFITS OF SELF-INJECTING METHOTREXATE TREATMENTS

Hunt noted the possible benefits of self-injecting MTX treatments for adult patients with active RA as potentially higher dose administration (and potentially increased efficacy) and fewer gastrointestinal side effects (e.g., nausea) than oral treatment,[23-25] and delay or avoidance of administration of biologics.

METHOFILL SELFDOSE INJECTION DEVICE IS EASY TO GRIP

Hunt described the Methofill SelfDose injection device as bulkier than other MTX injection devices; therefore, patients with age- and/or disease-related poorer hand grip can hold the device without having to squeeze tight. She pointed out that the large handle on the device enables patients to use the base of their hand rather than their thumb to administer the injection.[22] Hunt stated this is important for patients with overlapping active RA and osteoarthritis, as the latter particularly affects the thumbs and could make thumb activation of the device difficult.

Hunt commented that her patients "were able to hold the device without much grip at all." The survey[11] results support this observation: 75% (43/57) of patients strongly agreed/agreed that Methofill SelfDose was easy to grip while injecting (Figure 1; data on file: UK-01931).

METHOFILL SELFDOSE INJECTION DEVICE IS EASY TO USE

Hunt is responsible for a large cohort of adult patients with active RA who use Methofill SelfDose, most of whom find it easy to use, have confidence in their device, and are treatment adherent (Hunt estimated that only approximately two of her >150 patients on Methofill SelfDose have switched back to their original device). In line with this, the survey[11] showed that 75% (43/57) of patients strongly agreed/agreed that Methofill SelfDose was easy to use (Figure 2; data on file: UK-01943) and 89% (51/57) of patients strongly agreed/agreed that they were confident to inject Methofill SelfDose at home (Figure 3; data on file: UK-01944).

PATIENTS ARE OPEN TO SWITCHING TO THE METHOFILL SELFDOSE INJECTION DEVICE

According to Hunt, patients with active RA are used to having their treatments changed and are amenable to switching devices provided they are informed beforehand and are reassured it is the same drug, just in a different device. Patients are supported through the switch to Methofill SelfDose with education and training.

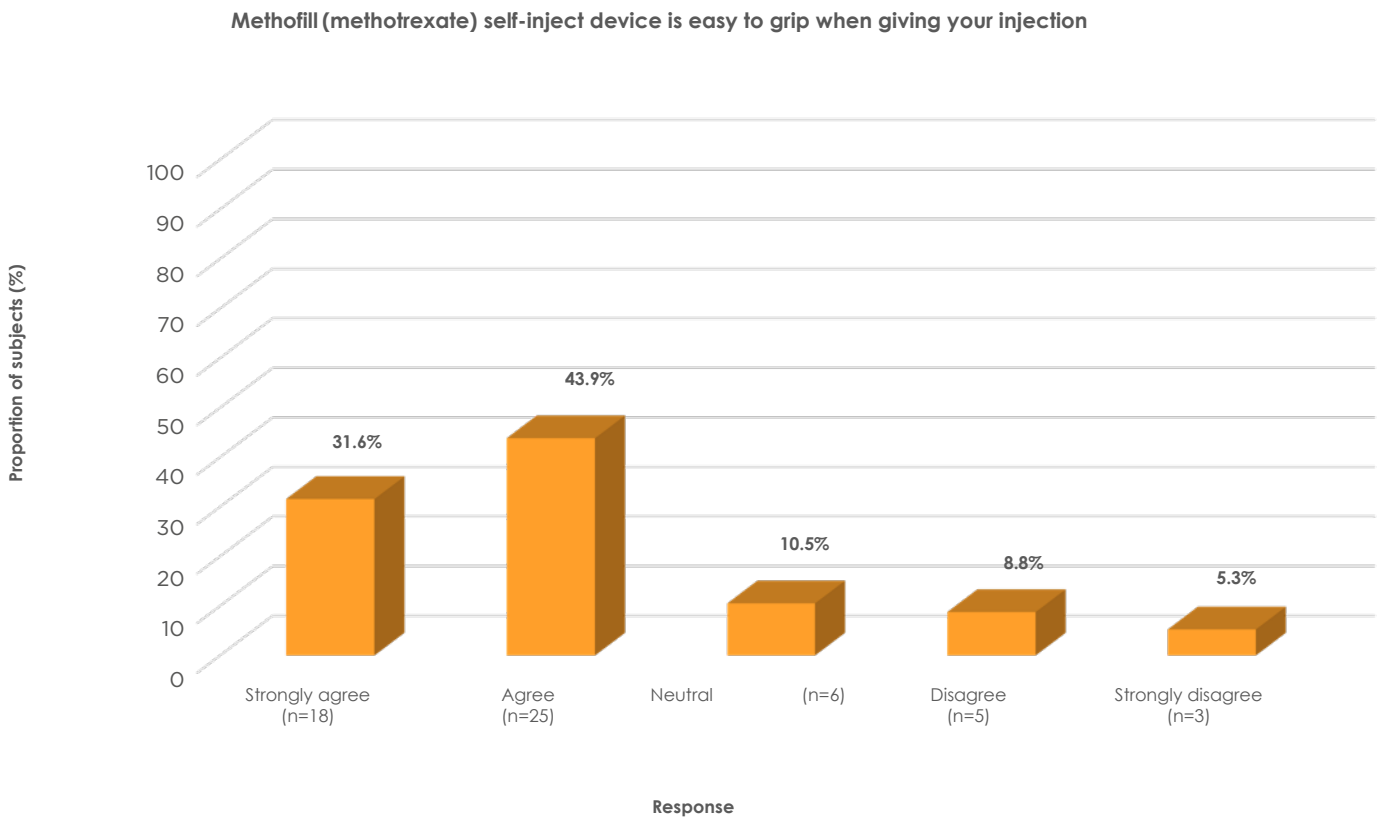

Figure 1: Patients' view on ease of grip of the Methofill® self-inject device.

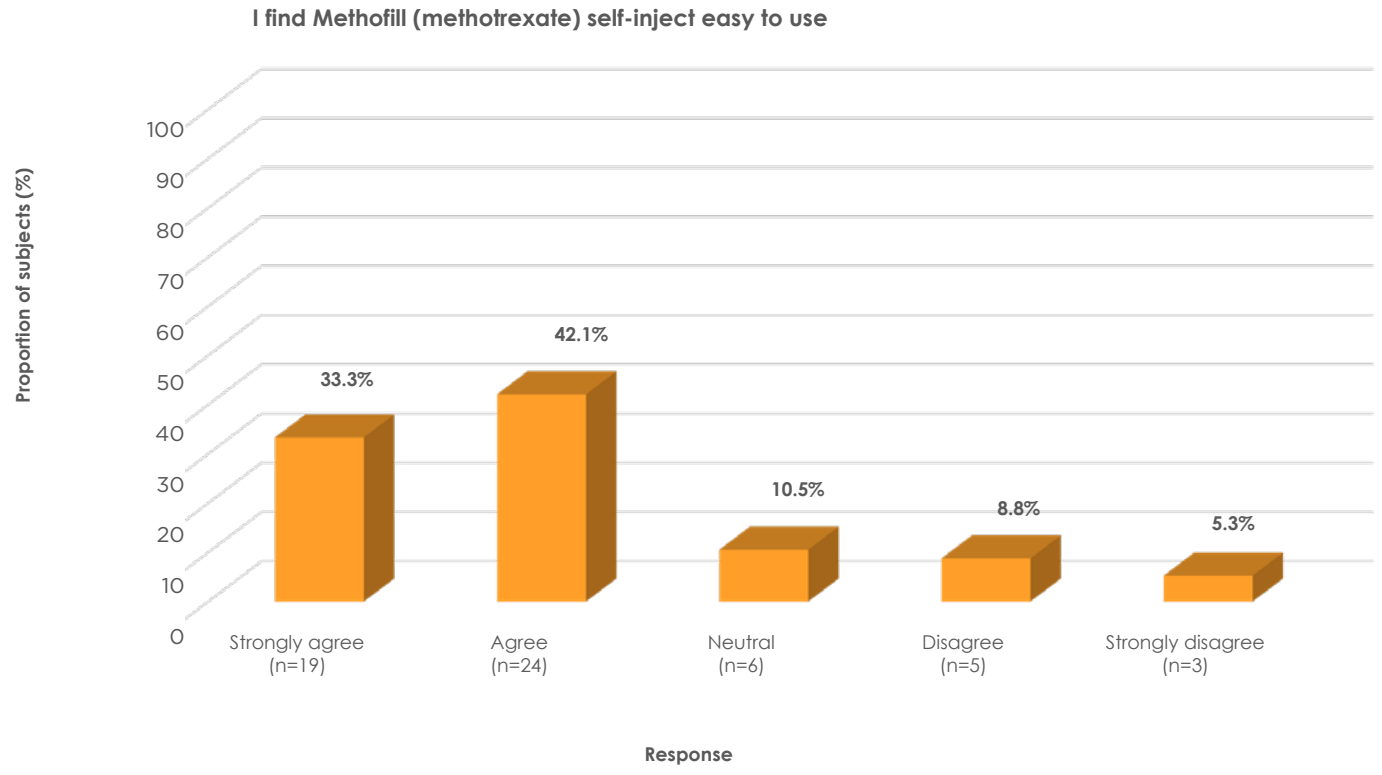

Figure 2: Patients' view on ease of use of Methofill® self-inject device.

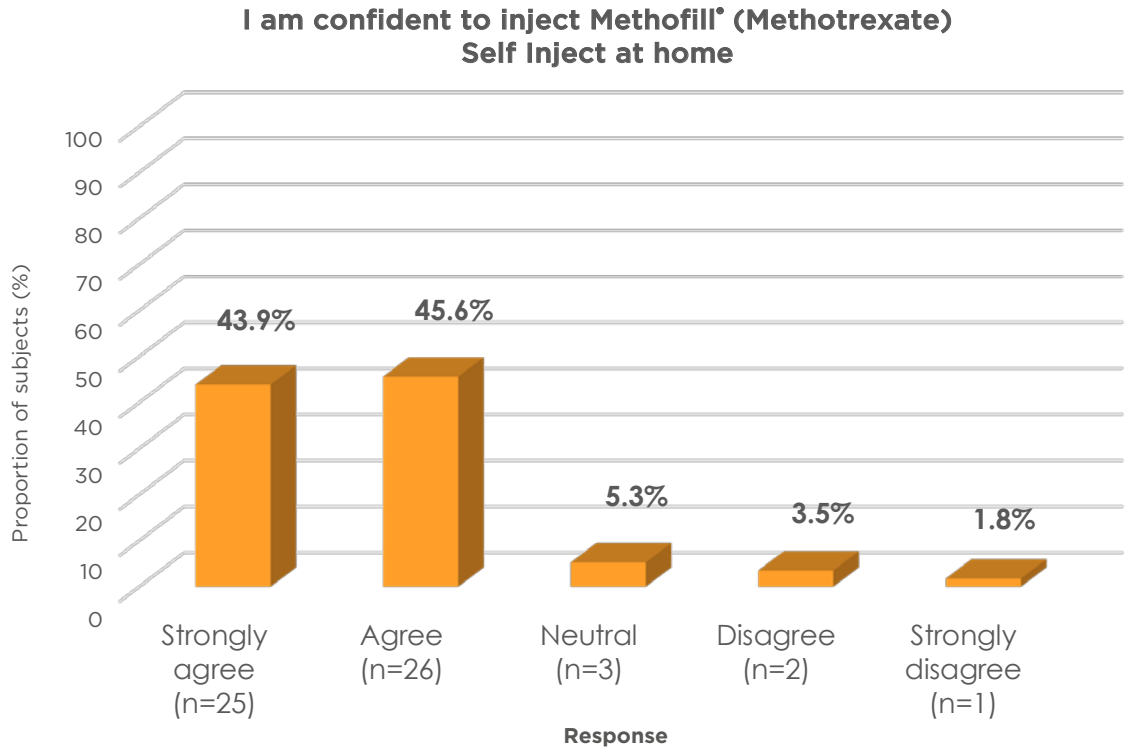

Figure 3: Confidence to inject Methofill® (Methotrexate) Self Inject at home.

Hunt clarified how patients who may not perceive a problem with their current self-injection device are advised of the positive features of Methofill SelfDose, such as easy to grip, easy to use, and hand rather than thumb activation.

Of those who expressed a preference in the survey[11] 47% (20/43) of patients preferred Methofill SelfDose to their previous injection device (data on file: UK-01946). In Hunt's experience, patients do not tend to express a preference for one device over another; however, good uptake of and adherence with Methofill SelfDose reflect acceptance of this device.

CONCLUSION

Hunt concluded that Methofill SelfDose benefits patients with active RA by helping to improve disease control and quality of life and is an effective way of giving the baseline drug, MTX, with ease and simplicity of use, enabling confidence in the device and good adherence. She reiterated that the design of Methofill SelfDose enables patients with poorer hand grip to hold the device without difficulty and administer the injection effectively with the base of their hands. In keeping with the 68% (41/60) of patients in the survey[11] who were 'satisfied' (score of ≥7 on a scale of 1–10) with the Methofill SelfDose for administering their injections (data on file: UK-01945), Hunt judged the majority of patients in her care were satisfied with Methofill SelfDose.

Although there were limitations to the survey (small, anonymous patient cohort with unknown training and experience of Methofill SelfDose; no direct head-to-head comparison with other devices; no significant understanding of patient experience or perspective on previously used devices), the results concur with the insights from Hunt, indicating that Methofill SelfDose could be a positive tool to improve patient confidence, therapy adherence, and treatment outcomes in RA.

Biography

Nurse Consultant Kate Hunt

Kingston Hospital, NHS Foundation Trust

Hunt is currently a rheumatology nurse consultant at Kingston Hospital NHS Foundation Trust.

Hunt has been working in rheumatology for the over 25 years, having completed both a BSc in Health Studies at Surrey University, UK and an MSc in Rheumatology Nursing at Keele University, UK. She has been a non-medical prescriber for over 10 years.

Nurse Hunt's role is very clinically based, focusing on managing patients' long term conditions of inflammatory arthritis. Hunt also chairs the Hospital Nurses Specialist Group (NSG) and is an active member of the drugs and therapeutic group.

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UK-03046 - DATE OF PREP SEPTEMBER 2021

The Role of Confocal Endomicroscopy in the Diagnosis and Management of Pancreatic Cysts

EDITOR'S PICK

The contribution of the role of endoscopic ultrasound-guided confocal endomicroscopy via needle puncture of pancreatic cysts to evaluate their benign or malignant potential more reliably is of potential high importance for both accurate diagnosis of malignancy, leading to timely surgery. Or, otherwise, definitive confirmation of the benign nature of such a pancreatic lesion, saving the patient from anxiety about progression and costly long-term follow-up. Even though this will not be applicable for broad-range usage, it will be a very helpful additional tool in highly specialised centres.

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Abstract

Pancreatic cystic lesions are an increasingly common clinical finding. Current diagnostic techniques cannot reliably differentiate patients with high-risk lesions requiring surgical resection from those that can be safely surveyed or discharged. As a result, some patients may undergo unnecessary surgery with associated morbidity while others enter long-term surveillance with associated healthcare costs. Needle-based confocal laser endomicroscopy enables real time microscopic examination of the epithelial lining of a cyst wall at the time of a standard endoscopic ultrasound examination. The procedure is associated with low rates of adverse events, especially when the probe is loaded into the fine-needle aspiration needle before the procedure and examination times are limited. Needle-based confocal laser endomicroscopy has consistently been shown to have better diagnostic accuracy than cytology, which is often paucicellular and non-diagnostic in pancreatic cystic lesions. Studies have shown that diagnostic accuracy in needle-based confocal laser endomicroscopy is 84–95% in mucinous lesions and 39–99% in serous lesions. However, this technology is expensive and its place in diagnostic algorithms remains uncertain. Despite this, health economic analyses in certain health systems have been favourable, largely because of its potential to be able to discharge patients with benign lesions, such as serous cystic neoplasms, from long-term surveillance. Widespread adoption of this technology is unlikely but it has the potential to have an important role in indeterminate pancreatic cystic lesions .

INTRODUCTION

Pancreatic cystic lesions (PCLs) are an increasingly common finding. They are present in 1.2–2.6% of patients undergoing abdominal CT,[1,2] up to 13.5% of patients undergoing an abdominal MRI,[3] and up to 45.0% of asymptomatic individuals undergoing magnetic resonance cholangiopancreatography.[4] PCLs have a broad differential diagnosis, including benign lesions such as serous cystic neoplasms (SCNs) and pseudocysts, as well as premalignant lesions such as mucinous cystic neoplasms (MCNs) and intraductal papillary mucinous neoplasms (IPMNs).[5] In accordance with international and European guidance, patients with PCLs that are thought to be malignant or at high-risk of malignant transformation are referred for immediate surgical resection. Patients with low-risk but premalignant cysts are recommended to undergo long-term surveillance.[6,7]

However, current diagnostic tools are imperfect and cannot always differentiate between high- and low-risk cysts. As a result, approximately one-fifth of patients with completely benign disease undergo unnecessary pancreatic resections annually.[8] In addition, differentiating premalignant cysts from all other cysts continues to be challenging. As a result, relatively few patients are discharged from follow-up and growing numbers of patients are entering surveillance. This is anxiety-provoking for patients and costly for healthcare systems.

Consequently, there has been an interest in developing novel diagnostic tools that improve the pre-operative assessment of PCL, such as through the needle biopsy forceps,[9,10] molecular fluid markers,[11] and needle-based confocal laser endomicroscopy (nCLE; Figure 1). This review will focus on the utility of nCLE to differentiate pancreatic cyst subtypes and accurately detect malignant lesions. It will also examine the safety profile of this novel technology and l earning curve.

METHODS

PubMed, EMBASE, and the Cochrane Library were reviewed for studies published in the English language up to 1st July 2020. Medical Subject Headings (MeSH) terms were decided by a consensus of the authors and were "confocal endomicroscopy AND pancreatic neoplasms", and were restricted to the title, abstract, and keywords. Articles that described the use of nCLE in solid pancreatic lesions were excluded. Any study with fewer than three patients was excluded.

All references were screened for potentially relevant studies not identified in the initial literature search. The following seven variables were extracted for each report when available: number of patients, type of cyst, sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy. The outcomes of 17 papers are presented in the review (Figure 2).

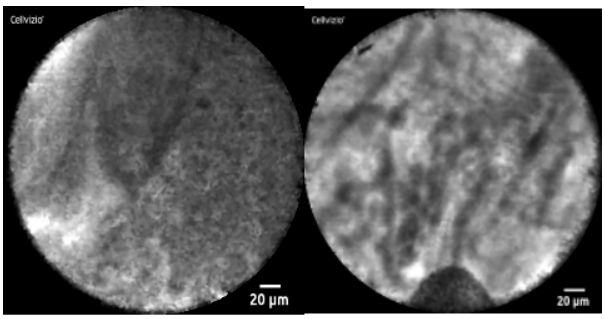

Figure 1: Needle-based confocal laser endomicroscopy pancreatic cyst images.

A) Needle-based confocal laser endomicroscopy image of a superficial vascular network, which is indicative of a serous cystic neoplasm. B) Needle-based confocal laser endomicroscopy image of papillary projections consistent with an intraductal papillary mucinous neoplasm.

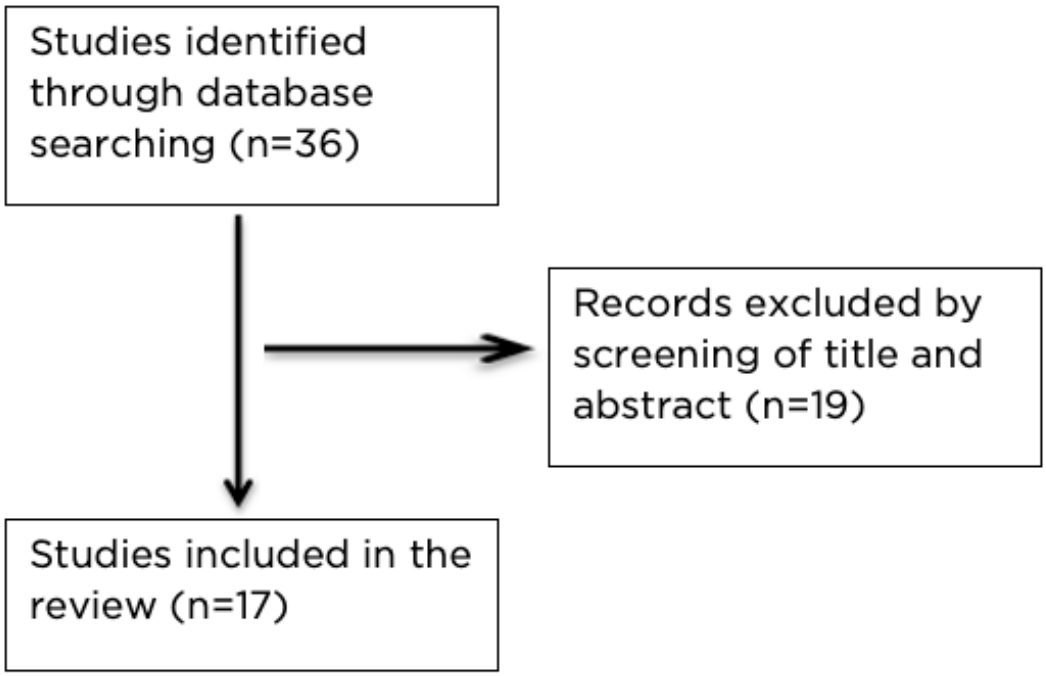

Figure 2: Review schema.

Due to the significant heterogeneity in the studies, a pooled analysis (or a meta-analysis) was not performed.

Procedure

Confocal laser endomicroscopy is a novel diagnostic device that can provide real time optical histology. nCLE creates an equivalent pathological image via the transmission of a low-power laser, which be focused on the epithelium of the cyst wall.

The AQ-Flex miniprobe (Cellvizio; Mauna Kea Technologies, Paris, France) can be passed down a 19-gauge fine-needle aspiration (FNA) needle during an endoscopic ultrasound (EUS) examination. The reflected fluorescent light is returned to the operating system, via the probe, to form an image.

To perform an EUS-nCLE examination, the AQ-Flex probe is loaded into a 19-gauge FNA needle. The PCL is then identified and 2.5 ml of 10% fluorescein is administered intravenously. Once the cyst is punctured under EUS control, the probe is then advanced until the tip protrudes 2 mm beyond the needle's bevel and the device is locked at this level. Unlocking the probe allows it to be retracted into the needle, which is used during cyst puncture. To begin scanning, the needle and probe are advanced until in contact with the cyst wall. Pictures and short sequences of video are then recorded for no more than 10 minutes in most cases. The probe can then be removed from the needle and cyst fluid aspiration performed for amylase, carcinoembryonic antigen, cytology, and other assays as required. Antibiotic prophylaxis is recommended for all EUS-nCLE cases.

RESULTS

Safety and Efficacy

The first EUS-nCLE study in PCL used a prototype miniprobe. Procedures were undertaken in four centres in the USA. Eighteen patients were included: 16 patients with a PCL and two with a solid pancreatic mass. nCLE images were obtained in 94.4% but technical challenges were encountered in 33.3% and post-procedural pancreatitis occurred in 11.1%. The authors concluded that nCLE was a feasible technique to obtain additional clinically relevant information about the cyst. The rate of pancreatitis was higher than expected and therefore the authors recommended modifications such as limiting

imaging time and not moving the probe along the cyst wall but instead imaging distinct points on the wall.[12]

Defining and Differentiating Cyst Subtypes

The INSPECT trial explored the diagnostic potential of this technology in PCL. This multi-centre study included 66 patients and was conducted over two stages. In the first part of the study, images were compared to final histology and reviewed by a panel of experts that included a gastrointestinal pathologist. The group recognised that the presence of epithelial villous structures could identify pancreatic cystic neoplasms, which included mucinous cystadenomas, IPMNs, and pancreatic adenocarcinoma. In the second part of the study, the presence of epithelial villous structures had a sensitivity, specificity, positive predictive value, and negative predictive value of 59%, 100%, 100%, and 50%, respectively.[13]

The DETECT study redefined epithelial villous structures and papillary projections as indicative of mucinous PCL. The study combined cystoscopy using a through-the-needle fibre-optic probe (SpyGlass [Boston Scientific, Marlborough, Massachusetts, USA]) followed by nCLE in a series of 30 patients. The procedure was technically successful in 97%, with one probe exchange failure. The sensitivity of cystoscopy and nCLE was 71% and 77%, respectively, but increased to 93% when the two techniques were combined.[14]

Giovannini et al.[15] defined the nCLE definitions for individual PCL subtypes in an endoscopic atlas published in 2014. These definitions were further refined and validated in a number of subsequent studies (Table 1).

The CONTACT studies compared nCLE videos to corresponding histopathological pictures. This pilot study defined a SCN by the presence of a superficial vascular network (Figure 1), which correlated to a dense and subepithelial capillary vascularisation, as seen on pathology. In the second part of the study, 66 images from 31 patients were shown to a group of experts. They found the definition to have an accuracy of 87%, sensitivity of 69%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 82%.[19]

In the CONTACT 1 study, published by this group the following year, new nCLE criteria were described for MCNs, pseudocysts, and pancreatic neuroendocrine tumours. Mucinous lesions were differentiated, with an IPMN being defined by the presence of papillary projections (Figure 1) whereas MCNs were identified by a thick grey line. Bright uniform particles in clusters (likely representing macrophages) against the dark background were indicative of a pseudocyst. Furthermore, black neoplastic cells in clusters with white fibres were suggestive of a cystic neuroendocrine tumour. In a retrospective validation study, these criteria had a diagnostic specificity of >90% for mucinous cysts and 100% for non-mucinous cysts.[20]

Kadayifci et al.[21] explored the diagnostic utility of nCLE in mucinous cysts. They visualised typical features of mucinous cysts in eight out of 12 (66%) cases. The superficial vascular network was observed in two out of three patients with a SCN. Sensitivity, specificity, and diagnostic accuracy of epithelial structures in detecting a mucinous cyst were 66%, 100%, and 80%, respectively.

In the CONTACT 2 trial, 202 patients were recruited. Of these individuals, 78 had PCLs with a pathology-based diagnosis (53 premalignant and 25 benign PCLs). nCLE was conclusive in 71 of the 78 cases (91%). The sensitivity and specificity of nCLE for the diagnosis of SCN, mucinous PCL, and premalignant PCL were all ≥95% (confidence interval: 85–100%). In mucinous lesions, the area under the receiver operating characteristic curve was significantly better for nCLE than for carcinoembryonic antigen of >192 ng/mL (0.98 versus 0.81; $p<0.01$) or EUS morphology (0.98 versus 0.82; $p<0.05$).[17]

Krishna et al. compared *in vivo* and *ex vivo* images to final pathology in 10 patients to further define nCLE subtype features. Final definitions were similar to those proposed by the CONTACT group.[15,17,21] The main difference in definitions was that SCN was defined by the presence of a fern-like pattern on nCLE. In this study, *in vivo* and *ex vivo* nCLE correlated with surgical histopathology in all cases.[22] These definitions were validated in 49 patients, 26 with a pathology diagnosis. The sensitivity, specificity, and accuracy for diagnosing mucinous PCL were 94%, 82%, and 89%, respectively.[23]

Table 1: Clinical effectiveness of needle-based confocal laser endomicroscopy in identifying common mucinous and serous pancreatic cystic lesions.

Study	Diagnostic aim	Cases (n)	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic accuracy of nCLE (%)	Diagnostic yield of cytology (%)
Mucinous PCL								
Konda VJ et al.,[13] 2013 INSPECT	Neoplastic cystic lesions (IPMN, MCN, or cancer)	66	59	100	100	50	71	26
Nakai Y et al.,[14] 2015 DETECT	Mucinous cystic lesions	30	80	100	100	80	89	3
Krishna SG et al.,[16] 2017	Mucinous cystic lesions	29	95	94	NR	NR	95	NR
Napoleon B et al.,[17] 2019 CONTACT	Mucinous cystic lesions	206 (78 in subgroup)*	95	100	100	94	97	NR
Keane MG et al.,[18] 2019 CONCYST	IPMN	56	90	NR	96	NR	87	66
Serous PCL								
Napoleon B et al.,[17] 2019	SCN	71 (subgroup)*	95	100	100	98	99	NR
CONTACT								
Keane MG et al.,[18] 2019 CONCYST	SCN	56	56	NR	55.6	NR	39	66
Krishna SG et al.,[16] 2017	SCN	29	99	98	NR	NR	98	NR
Napoleon B et al.,[19] 2015 CONTACT	SCN	31	69	100	100	82	87	36

*Subgroup of those patients with a conclusive needle-based confocal laser endomicroscopy diagnosis were compared with final diagnosis.

IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm; nCLE: needle-based confocal laser endomicroscopy; NPV: negative predictive value; NR: not reported; PCL: pancreatic cystic lesions; PPV: positive predictive value; SCN: serous cystic neoplasm.

In a subsequent study by the same group, which included 29 patients, sensitivity, specificity, and accuracy for the diagnosis of mucinous PCL improved further to 95%, 94%, and 95%, respectively.[16] Recently, the same authors conducted a larger prospective study of 144 patients undergoing nCLE of a PCL. Sensitivity, specificity, and diagnostic accuracy for a mucinous lesion were 98%, 94%, and 97%, respectively. nCLE was found to be more accurate in classifying mucinous and non-mucinous cysts compared with current clinical care ($p<0.001$).[24]

The authors' group recently published the UK multi-centre experience of using nCLE in indeterminate PCL. The CONCYST trial showed EUS-nCLE had a superior diagnostic accuracy to cytology (76.8% versus 71.0%) but this did not reach clinical significance. More variation was seen in the diagnostic accuracy of individual PCL subtypes than had been recognised previously. The sensitivity of SCN was only 55.6% but was 90.0% for IPMN and 100.0% for pancreatic ductal adenocarcinoma.[18]

Recently, groups have also explored combining the use of nCLE with microforceps biopsy during the same EUS session. The diagnostic yield for each modality was 34.1%, 75.0%, and 84.1% for cytology, microforceps biopsy, and nCLE, respectively. When cytology, microforceps biopsy, and nCLE were combined, the diagnostic yield increased to 93.2% and led to a change in management in 52.3% of cases. NCLE led to a discontinuation in surveillance in 31.8% ($p<0.05$) and an additional 10.7% referred for surgery who otherwise would have been surveyed.[25]

Adverse Events

The rate of associated adverse events, particularly acute pancreatitis, following EUS-nCLE has been a concern. In the first pilot study by Konda et al.[12] of EUS-nCLE using a prototype probe, technical challenges were encountered in 33.3% and post-procedural pancreatitis occurred in 13.0% of patients with PCL. Cystic lesions appeared to be more susceptible to pancreatitis than solid masses.[12] In the DETECT study, which used the AQ-Flex probe, rates of post-procedure pancreatitis of 7% were reported. This higher rate was attributed to the insertion of the cytascope in addition to the nCLE probe.[14] In more recent, larger non-feasibility studies, rates of adverse events have fallen considerably and are similar to EUS FNA, with rates of pancreatitis 0.0–3.5%.[16-19,21] This has largely been brought about by modifications to the technique, including pre-loading the probe into the FNA needle and limiting procedural time to less than 10 minutes.[12]

Detecting Dysplasia and Prognostic Subtypes of Intraductal Papillary Mucinous Neoplasms

Histologically, IPMNs are classified by type (gastric, intestinal, pancreatobiliary, or oncocytic) and level of dysplasia (low- or high-grade dysplasia or presence of invasive cancer). These details provide important prognostic information, which is usually only available after surgical resection. Recently, some groups have proposed that this information can be obtained by nCLE. In one study, four patients with different subtypes of IPMN were examined. EUS-nCLE showed characteristic finger-like projections with inner vascular core in all cases. Although the image patterns of the papillae for the gastric, intestinal, and pancreatobiliary subtypes were similar, in the oncocytic subtype, the papillae were thick and demonstrated a fine scale-like or honeycomb pattern, which correlated with pathology.[26]

A recent study also explored the feasibility of differentiating levels of dysplasia using nCLE. Cytology in cystic lesions is only diagnostic in approximately one-third of cases, even in high volume tertiary referral centres.[8,27] In a recent study, which conducted a post hoc analysis of patients who had nCLE in resected IPMN, increased papillary epithelial width and darkness were found to have a sensitivity of 90% and 91%, respectively, for detecting high-grade dysplasia or adenocarcinoma.[24] However, it is known that there is heterogeneity in the level of dysplasia within the epithelium of an IPMN.[28] Potentially, an area of high-grade dysplasia could therefore be missed during an nCLE examination because there is an area of the cyst that is inaccessible and therefore not imaged (e.g., behind the needle). However, these initial findings offer a potentially promising way of differentiating low-risk lesions, which could be surveyed in order to avoid surgical resection. These findings will need to be validated in larger studies before being employed more widely in clinical practice.

Intraobserver Agreement

Intraobserver agreement (IOA) between endosonographers has provided heterogeneous results in EUS-nCLE. IOA was first explored in the CONTACT studies. IOA was reasonable,with κ=0.72[20] and for SCN κ=0.77.[19] In a further study by Karia et al.,[29] de-identified nCLE video clips were reviewed by six endosonographers at five institutions. The k statistics were low for individual imaging features, with a mean accuracy of only 46% (range: 20–67%). The low accuracy rates were attributed to poor image quality and the effect of the endoscopist individual learning curve. IOA and intraobserver reliability (IOR) have also been assessed for differentiating mucinous from non-mucinous cysts and were found to be κ=0.67 and κ=0.78, respectively.[23]

Recently, IOA and IOR was assessed in six endosonographers (each of whom had performed nCLE >30 times). They were asked to review the nCLE images of PCLs from 29 patients. The overall sensitivity, specificity, and accuracy for the diagnosis of mucinous PCL were 95%, 94%, and 95%, respectively. IOA and IOR were also considerably higher, being κ=0.81 and κ=0.86, respectively, supporting that there is a learning curve to image interpretation in nCLE.[17]

Cost-Effectiveness

nCLE is an expensive technology, with high initial outlay costs for the laser scanning units, as well as ongoing probe costs per procedure, which are over and above the cost of an EUS examination. However, as described above, the device has potential to improve the reliability of confidently differentiating benign cysts such as SCN. This information can allow patients to be discharged from long-term surveillance and reduce the number of patients undergoing unnecessary operations. Thus, there is clear potential for healthcare cost savings. The members of the CONTACT study group conducted a retrospective health economic analysis for 209 nCLE cases conducted in France. They found nCLE over EUS FNA alone led to substantial changes in management for 28% of patients ($p<0.001$), with a reduction in clinical costs of 13% in the public sector and 14% in the private sector.[30]

DISCUSSION

The international consensus guidelines on the management of IPMN recommend that an EUS is performed in all suspected IPMNs with worrisome features or cysts greater than 2 cm, and when surveillance is advocated.[31] Similarly, the American College of Gastroenterology (ACG) and European consensus guidelines recommended performing an EUS when findings are expected to change clinical management.[7,32] Although EUS can provide useful clinical information to influence the management of PCL, its utility is often limited by the ability to get sufficient fluid for analysis, the sensitivity of cytology for detecting dysplasia, and by current biomarkers (e.g., carcinoembryonic antigen) for accurately detecting mucinous lesions.[27] nCLE allows real time imaging of the cyst wall and additional clinical information during the EUS examination. Therefore, it is an attractive emerging technology.

Multiple prospective studies have now described the utility of nCLE in indeterminate PCLs and in those PCLs with worrisome features. nCLE findings in cyst subtypes have been carefully correlated with pathological findings to provide accepted definitions.[15] These definitions have then been validated in a number of multi-centre studies. The presence of a superficial vascular network or fern-like pattern is indicative of a SCN; papillary projections are suggestive of an IPMN; a dark band is representative of a MCN; bright particles are characteristic of a pseudocyst; and dark areas are typical of malignancy. The most recent large multi-centre studies have shown that these criteria have a sensitivity of >95% for detecting serous or mucinous lesions.[16,17] However, there are some situations where nCLE has been found to be less effective, for example, when the epithelial lining has been denuded, which can occur as the cyst enlarges. In SCN, the presence of a superficial vascular network is indicative; however, in an oligocystic SCN, it may not be present.[33] In an IPMN, it is known that the presence of inflammatory changes and dysplasia can be variable along the cyst wall. In addition, it is only possible to examine the adjacent wall of an IPMN with the probe, which could be a source of diagnostic discrepancies. Early studies have also demonstrated the potential of nCLE in detecting pathological subtypes of IPMN and

levels of dysplasia. These findings are promising but require validation in larger studies.[24,26]

Rates of pancreatitis following nCLE are 0–13%.[14,19,26,34] Rates of adverse events have fallen substantially from the early nCLE studies (Table 1) and there appears to be a number of factors associated with increased rates of pancreatitis. The early nCLE studies backloaded the probe, which has the potential for more movement within the cyst. Therefore, this is no longer recommended. The DETECT study required longer needle access time because the procedure was combined with SpyGlass™ (Boston Scientific, Marlborough, Massachusetts, USA), cystoscopy, which prolongs the procedure and leads to a higher rate of post-procedural pancreatitis.[14] Overall, any prolonged procedure time over 10 minutes or additional manipulation of the cyst should be avoided.[14,26] Some of the adverse events are also potentially due to puncturing the cyst with a 19-gauge needle. In theory, if a probe compatible with a 22-gauge needle was available, this could make it easier to image cysts in the head of the pancreas and uncinate and potentially result in fewer adverse events; however, studies to formally evaluate safety and efficacy would be needed for verification.

Little is known about the learning curve in nCLE in PCL. There are two main aspects to the learning curve: the procedure and subsequent image interpretation. The technical aspects of the procedure are similar to an EUS FNA for experienced endosonographers; however, obtaining high-quality nCLE images and interpreting them takes more experience and training.[16] The manufacturer provides online learning modules to support an endosonographer's image interpretation training on how to differentiate cyst subtypes, as well as offer in-room support with the device. Further studies are required to better define learning curves in this technique in order to inform future training programmes.

There has also been a growing interest in ways to improve nCLE interpretation and make it more straightforward for the endoscopist, such as through combining the technology with fluoroscopically-labelled markers and antibodies. In a study in Crohn's disease, labelled antibodies were administered topically in 25 patients, leading to the detection of intestinal membrane-bound TNF+ immune cells during confocal laser endomicroscopy. High numbers of membrane-bound TNF+ correlated with subsequent response to anti-TNF therapy and mucosal healing, demonstrating the potential for tailoring medical therapies.[35] In the pancreas, the utility of this application has been demonstrated in swine. After injection of labelled antibodies against epidermal growth factor receptor and survivin into the pancreas with an EUS FNA needle, expression could be successfully detected with nCLE and could differentiate ductal from acinar cells. nCLE findings were confirmed on subsequent histology.[36]

CONCLUSION

EUS-nCLE is a promising technique, with improved diagnostic accuracy when compared to cytology and existing cyst fluid biomarkers. Recent studies have also demonstrated the potential of the technology to detect dysplasia, as well as cyst subtype, with reasonable accuracy. Overall, rates of associated adverse events are low. The technology is relatively expensive but may be cost effective in certain healthcare settings. Further work is needed to determine its place in diagnostic algorithms for PCL.

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Using Innovation to Develop Digital Tools for Public Health During the COVID-19 Pandemic

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Abstract

Introduction: Technology has played a key role in enabling public health to respond to the COVID-19 pandemic at a pace and scale never seen before. The Digital Health and Care Innovation Centre (DHI) assisted with development of two new digital services to enable testing and contact tracing at scale using innovative methods.

Methods: The DHI employed a design innovation approach by bringing all relevant stakeholders together to co-design new technology services to identify the 'preferred future'. Workshops were used to identify the preferred solutions. The innovative methods for development of digital health tools included adopting an iterative approach, addressing the situational requirements posed by COVID-19, and democratising technology for purposes of pandemic control.

Results: A National Notification Service (NNS) for automation of delivery and feedback (if results messages were viewed) was developed and adopted by five of the 14 health boards in Scotland, processing over 7 million results since inception.

The Simple Tracing Tools (STT) is an open-platform web-based app that is designed for data entry by contact tracing teams. STT was adopted by all local health protection teams and informed development of the national case management system.

Discussion: The Cynefin framework can be used to understand the design innovation process when facing the challenges of designing digital tools during a pandemic. There are significant opportunities for public health to engage with digital health to transform the pandemic response and derive benefit for tackling future population health challenges.

INTRODUCTION

This paper describes a case study of the co-design and development of two new COVID-19 digital services to support the Scottish Government's Test and Protect strategy.

All aspects of health services have adapted in response to the COVID-19 pandemic. Public health is at the forefront of the COVID-19 response and is no exception in embracing innovative ways of working. Technology has played a vital role in enabling public health services to manage clusters of COVID-19 as the scale and intensity of the pandemic threatened to overwhelm normal practice.[1] Examples of innovative practice include developing novel digital technology to abet symptom checking,[2] contact tracing,[3] and quarantine compliance.[4] In Scotland, public health has relied on 'legacy technology' and manual processes to carry out outbreak control. Expertise was not lacking, but the scale of the pandemic meant the service was under-resourced and unable to increase the workforce rapidly to respond. The digital infrastructure in public health required transformation to facilitate an increase in testing and contact tracing capacity.

The Digital Health and Care Innovation Centre (DHI) is one of the Scottish Government's innovation centres funded by the Scottish Funding Council, working with NHS Scotland's Health Boards and Scotland's local authorities. They have a remit to improve Scotland's health using digital technology and encouraging economic growth for Scotland.[5] Public Health Scotland (PHS) engaged with the DHI to develop new digital tools and services that would support local Health Boards and national agencies to identify and manage outbreaks of COVID-19.

Contact Tracing in Scotland

Contact tracing is a well-recognised practice in public health that identifies individuals who may have been exposed to an infectious disease and providing them with advice to limit spread of the disease. In the case of COVID-19 in Scotland, that advice was to self-isolate for 10 days.[6] Contact tracing in Scotland is led by the local health board Health Protection teams, with support from the national agency, PHS, if there are cross-border or international issues. National guidance and policies are adapted by boards to suit local practice and the available resources, with the result that contact tracing is similar from a strategic perspective across Scotland but may differ operationally with different data recording systems in place. Disease vector control often requires requesting or enforcing individuals to remove themselves from elements of society to protect others, while not necessarily benefiting themselves directly.[7] This has borne the authoritative stance of Health Protection for certain actions such as tracing and quarantine; however, COVID-19 has illuminated the role of active participation by the citizen.[8] Moving the citizen towards a central role in public health services is a paradigm shift from traditional health protection models, which adopts a more directive, service-led approach.

Aim

The DHI, in partnership with PHS and the National Health Service (NHS) National Services Scotland (NSS), were tasked with using their experience in innovation and digital health to develop digital services to assist the Scottish Government's Test and Protect strategy.[9] Here, the authors describe the development process of two services that were co-designed over ten weeks between March 2020 and May 2020, using innovative methods:

1. The National Notification Service (NNS) is a service that automates the delivery of test results for COVID-19 across Scotland.
2. The Simple Tracing Tools (STT) is a web-based service to enable large numbers of individuals to carry out contact tracing at a local and national scale.

This paper will describe the new services and outline the process and innovation methods used by the DHI, both in the design-led approach and the technological approach.

The Challenge

Two aspects of the 'test, trace, isolate, support' strategy[10] were identified by public health specialists that could benefit from digital development in the immediate- to short-term: test result management and contact tracing. As contact tracing is usually initiated on a positive test result confirming a case, services were developed as separate but interdependent digital tools.

The DHI formed a core team consisting of the DHI's Chief Technology Officer, a Design Researcher, a Public Health Innovation Fellow, and Public Health Specialist at PHS. This team organised and facilitated co-design workshops, analysed workshop outcomes, identified the expert participants required, and progressed the development of the tools through to the point of handover to NSS.

METHODS

The DHI held a series of 29 workshops over 92 days between 9th March (first workshop) and 8th June (final delivery) to co-design and deliver the two new services. This work began with an initial face-to-face design workshop held at Health Protection Scotland (HPS), the national health protection organisation, on 9th March 2020. Participants at the workshops included public health experts, e-health leads, laboratory leads, and industry partners. The DHI and HPS invited the participants and some invitees elected to invite others whom they thought relevant. The DHI arranged this workshop at short notice in response to the developing COVID-19 situation in Scotland. After the initial workshop (the only face-to-face contact for this work), all following workshops and meetings were held using an online, virtual whiteboard to visualise concepts and online meeting services to facilitate conversation. The visual output from the analysis of each workshop was shared as widely as possible between workshops to help communicate new learning across a wide range of stakeholders (Figures 1 and 2). Workshops followed a participatory design approach. The DHI prepared visual scaffolding before each workshop to facilitate discussion between disparate stakeholders and ensure key challenges were addressed. Scaffolding highlighted the citizen as the centre of the service.

Participatory design was a useful methodology to support meaningful contributions from a wide range of participants, including public health experts, novice contact tracers, e-health leads, occupational health leads, sexual health leads, software developers, and information and clinical governance leads. Time pressures dictated that the partnership was not able to involve citizens in the co-design of these systems.

Workshops could be single discipline, or multidisciplinary across the fields, dependent on the questions and challenges unearthed. The DHI design researcher facilitated the workshops. The topics of each workshop would depend on the immediate requirements to inform progress, and included, in order:

1. Which services are needed?
2. Service design model
3. Prioritisation of features
4. Iterative design of prototypes
5. Future of service
6. Governance required to continue development

Topics were revisited with different experts and reiterated during the development of the two services. An iterative series of workshops informed the ongoing design. The software development team could also pose questions back to relevant experts to inform development through these workshops. To the best of the authors' knowledge, national public health services have not been co-designed by participants from across the health and technology professions. Specifically, not in response to a national pandemic.

Service Needs Identified

Participants co-produced the requirements for the services after agreeing on the services needed. Note that development started while the design of the services was still happening due to the speed at which the services needed to be delivered (Figure 3). For the citizen, the services needed to be accessible, respect privacy, acceptable, easy to use, improve the experience of the service, and promote self-management. For public health, the services needed to be effective, evidence-based, safe and secure, rapid, adaptable, reliable, not widen inequalities, and promote self-management.

The Design Approach

The DHI employs a design innovation approach, bringing relevant stakeholders together through participatory, design-led workshops to co-design new technology services.[11]

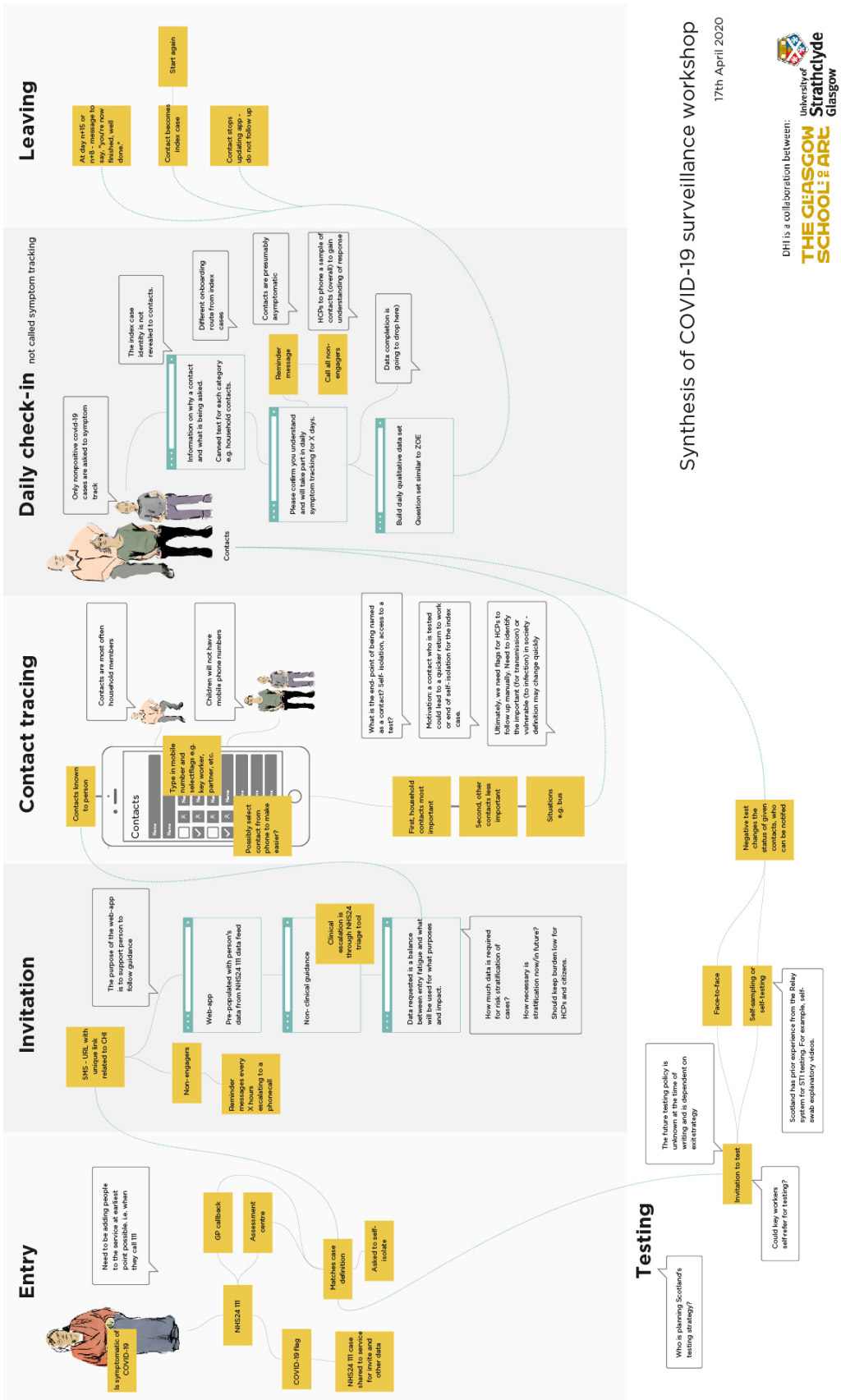

Figure 1: Possible future patient journey of 'testing, tracing, and isolating' developed during a remote co-design workshop when some aspects of what would become the Scottish Government's 'test, trace, isolate, support' approach were unknown.

The figure is indicative of the types of visual communication produced by participants during workshops.

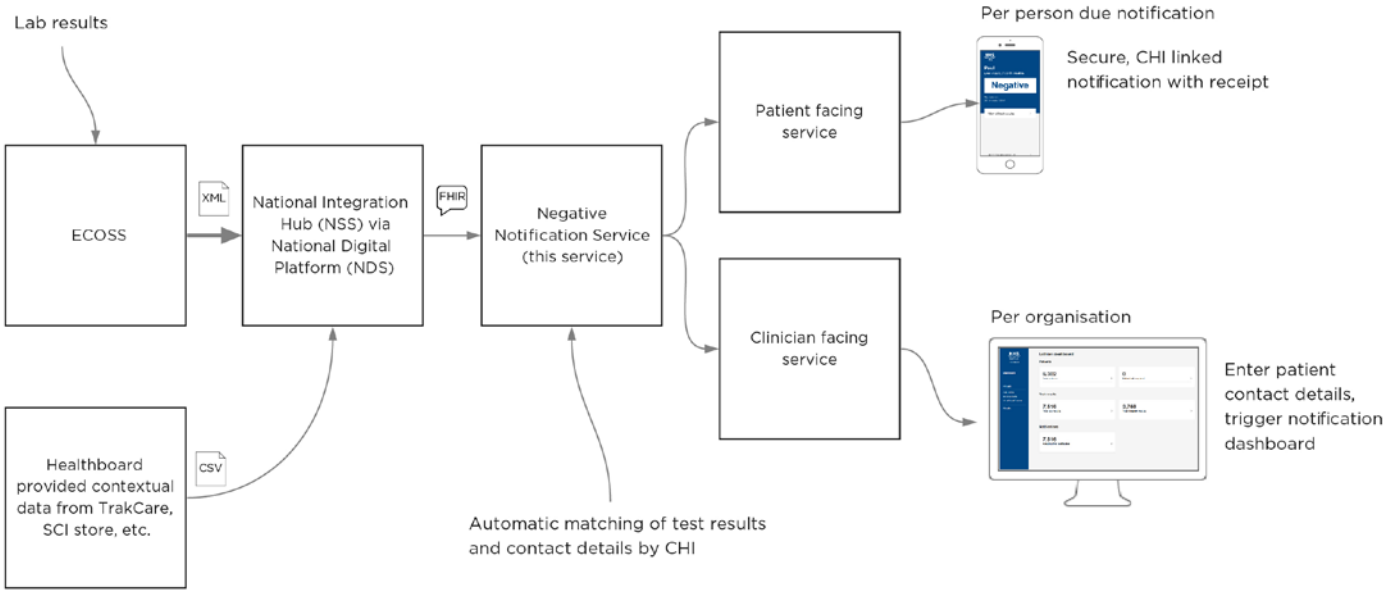

Figure 2: A co-designed, simplified diagram of data flow for the National Notification Service. Note that the Negative Notification Service became the National Notification Service during the project.

CHI: Community Health Index; CSV: comma-separated values; ECOSS: Electronic Communication of Surveillance in Scotland; FHIR: Fast Healthcare Interoperability Resources; NDS: NES Digital Service; NSS: Negative Notification Service; SCI: Scottish Care Information; XML: eXtensible mark-up language.

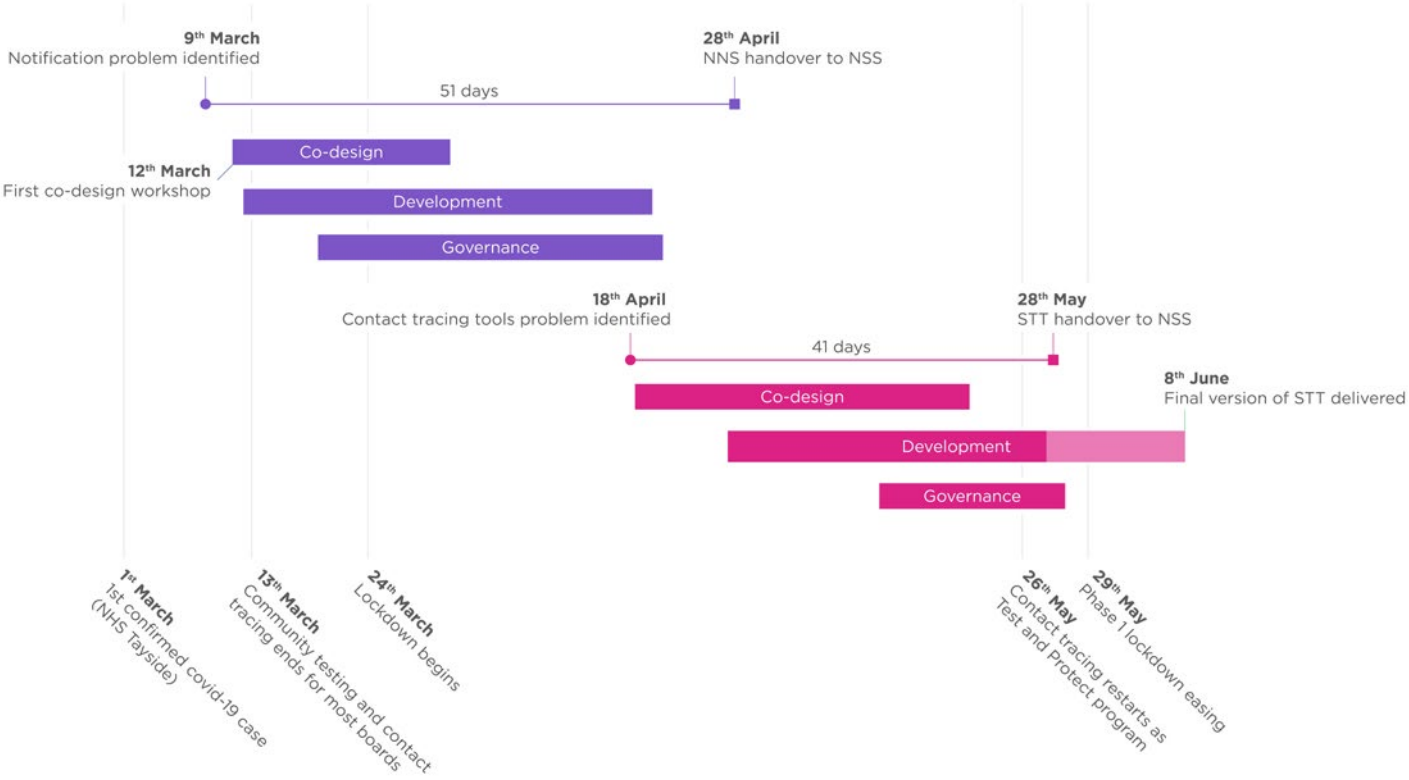

Figure 3: Showing the project timeline alongside significant pandemic dates.

NNS: National Notification Service; NSS: National Services Scotland; STT: Simple Tracing Tools.

Table 1: Summary of features of Simple Tracing Tools and National Notification Service and relevance to service.

	Patient story	Service story
SMS to inform patient result available.	I want to be able to receive my result in a format that is fast and convenient.	I want to be able to automate results to ensure rapid dissemination.
Unique URL to view a test result.	I want to be the only person who can see my result.	I want to ensure the correct individual receives the result.
Feedback to service if result viewed.	I want to know the service has followed up my result.	I want to know if the individual has viewed their result as further action may be required.
Restrict notification for some patient cohorts, e.g., care home residents.	I do not want to be sent my test result multiple times.	I do not want vulnerable patients or families to receive results via SMS inappropriately.

SMS: short message service; URL: uniform resource locator.

Ideally, digital services should meaningfully involve those that will use the service (e.g., healthcare staff) and those that will be subject to the future service (e.g., Scotland's citizens) in the design. In this way, those people's lived experience should be reflected in the delivered services and mistakes due to assumptions, or unknown problems and opportunities, should be minimised. The DHI call such a solution the 'preferred future', a future service that accounts for constraints but is the most preferable according to the appropriate people. As already noted, citizens were not included in this co-design due to limited time. Ideally, those subject to the new service would be meaningfully included in the design of it. Analysis was done during workshops by consent (not by the authors in isolation) and followed an 'analysis-on-the-wall' approach.[12] That is, participants agreed upon what they had proposed through consensus and diagrams summarising and communicating the decisions were produced on the fly during workshops or were prepared for the next workshop. For example, a mostly empty version of Figure 1 was used for the initial discussion of the 'test, trace, isolate, support' strategy (before it was named TTIS). The diagram in Figure 1 was built during the workshop by participants (with facilitation) and only minor adjustments (e.g., spelling mistakes, alignment) were made before dissemination to stakeholders. This is true of Figure 2, which was also built using an online collaborative whiteboard during the workshops, by the participants, with facilitation.

Identifying the Preferred Solution

During the development process, the partnership posed the question: "What if we put the citizen at the centre of pandemic control and enabled them to self-manage testing and contact tracing?"

Through participatory design workshops, the DHI considered the imminent potential future where every citizen is engaged in pandemic control. The DHI and partners developed digital tools in an innovative and agile way, while accepting some answers or solutions were not readily available. Through open exploration, they could consider and progress the potential options (an approach sometimes termed negative capability[13] in design research). Due to the conditions of the pandemic and changing landscape of policy, guidelines, and services, knowledge of both the virus and the system aiming to control the virus was in constant evolution. Additionally, the scale of the pandemic could only be estimated from modelling, and so best- and worst-case scenarios were anticipated.

The Technological Approach

A vital part of any innovation methodology is to foster the environment for creativity and change. The DHI does this through a Demonstration and Simulation Environment (DSE).[14,15] A

significant challenge faced by innovators when implementing a novel digital technology within the NHS is overcoming the perceived risks of change. The DSE is a 'safe space' that enables clinicians, patients, and technologists to work together to redesign their underlying service delivery models with digital tools developed in tandem. The DSE produces simulated services that show how future, preferred services would be made without the constraints of existing health and care system constraints.

This collaborative 'de-risking' model focuses on the principles to 'learn by doing' and 'show not tell'. For COVID-19, the clinical users were part of developing the tools through concept co-design, into a simulated environment and then into real use as part of their live systems. Rapid iteration of features was possible to inform agile releases and collaboration with partners to develop the anticipated future state of a more extensive technical infrastructure and case management system. In this approach, Public Health agencies could develop their preferred possible contact tracing service. In this instance the services began as simulated services before being commissioned for deployment.

RESULTS

Through the design innovation processes, the DHI identified two significant aspects of pandemic control that would be improved through the co-design and adoption of novel digital tools in Scotland. Through collaborative workshops with relevant organisations, these two digital tools were co-designed, developed, and implemented within 10 weeks from conception to enable automated test notification and contact tracing at scale, as shown in Figure 3.

Operational and Situational Technology Requirements Related to the COVID-19 Pandemic

A solution that required minimal data integration was desirable. At the first workshop, the participants identified a single national source of results of COVID-19, using Electronic Communication of Surveillance in Scotland (ECOSS). At later workshops, the need to accept data feeds from the local health boards was identified. These two sources of data can be seen in Figure 2, which was used in some form in almost all workshops after being co-produced. Later again, additional test result feeds from new purpose-built lab systems (to enable local arrangements of services to be combined with national tools) were added.

Data collection and reporting is a crucial part of a pandemic response. The team built technological solutions using a whole-system data collection model that consistently applied a data dictionary derived from World Health Organization (WHO) guidance.[16] This enabled the local health boards of NHS Scotland and PHS to collect data to inform epidemiological investigation.

The team worked with known industry software development partners, with trusted flexible capability from previous projects.[15] Organisational trust in the system and risk management were prioritised throughout the development to ensure work could progress at pace. The tools were adapted using the available evidence base and learning from approaches in other countries and services.[17,18] This approach balanced the challenge of integration and redevelopment of any external technology. It has also avoided a 'COVID-only' service, with the intention that the solutions would be a legacy for public health. Public trust in the Test and Protect system is essential for preventing the spread of COVID-19. As such, data collection was carefully considered by a range of experts to ensure only essential data was required. Data was not shared with any third-party, and all data was collected according to NHS data governance principles. A full Data Protection Impact Assessment (DPIA) was completed.

Scaling the Technology

The COVID-19 response necessitates services that can be scaled rapidly. Existing solutions had limitations in data sharing within and across organisations and remote working intensified these problems. The partnership's solution enabled a large number of contact tracers to carry out tracing without a virtual private network or additional equipment beyond a laptop. It allowed bespoke information governance processes to be applied to ensure appropriate governance for users without limiting the potential to scale and adapt to policy changes. The digital tools use an open data-exchange platform to allow for

future extensibility of the service. Extensibility is particularly relevant considering the unknowns of COVID-19. Trusted third-parties can use an application programming interface to provide services such as information provision, self-serve contact tracing, and vaccine records. The nationally standardised services allow for variation in practice by different health boards in Scotland.

National Notification Service

The NNS was the first digital tool conceived at the initial workshop in March 2020. The NNS was developed in response to a public health professional's direct request to aid automation of result delivery from COVID-19 tests carried out by NHS Scotland. The NNS has been adopted nationally in Scotland; it has now been used to process over 7 million test results. It has enabled automation of other services such as a citizen self-service contact tracing form, which has also been adopted nationally in Scotland and, at the time of writing, accounts for 64% of contact tracing data submissions.

Simple Tracing Tools

The STT were developed in recognition that to be able to contain the pandemic, contact tracing at scale was required.[19] In Scotland, contact tracing had been carried out using a proprietary Public Health system (HPZone®),[20] or local methods using general-purpose tools such as Microsoft Excel® (Microsoft, Redmond, Washington, USA). STT sought to understand the implications of a service change and ultimately informed the national case management system and service design of the National Contact Tracing Centre (NCTC).[21] STT are built on an open data-exchange platform as web applications designed for flexible access and data entry by contact tracing teams. Following an initial seven-day pilot of three health boards, STT were adopted by all 14 local health protection teams to carry out contact tracing between 28th May and 17th July 2020. During this period, 733 professional users were onboarded, who traced 1,618 index cases, 2,273 contacts, and identified 605 settings.

DISCUSSION

Collaboration

The development and implementation of two digital services in 10 weeks, used by hundreds of public health professionals across Scotland, results from the success of the collaboration between agencies, including trust in each organisation's role and expertise. The DHI brought innovation, participatory design expertise, and considerable experience in technology infrastructure[15] to NHS Scotland. PHS brought leadership, expertise, and high engagement levels with professional users (the local health boards who have responsibility for contact tracing within their geographical area).[22] NHS NSS brought together the organisational threads required for implementation including information governance, clinical governance, and Equality Impact Assessments.[23] The software development industry partners had experience working with the DHI and NSS,[15] and so the partnership could rely on their technical capacity and capability. The pandemic meant bureaucratic processes were expedited to ensure tools were deployed as soon as available, whilst participatory-design methods accelerated the design and implementation.

Challenges of Innovation During a Pandemic

As the time resource of experts was severely limited, efficient and informed decision-making was required. The pressure to resume contact tracing meant STT development had to pivot significantly from what was initially envisaged as a citizen-facing self-completion tool (which was later developed after the services described here) to a service-facing tool. All agencies accepted a riskier environment than normal practice would allow but recognised the opportunity to control specification through direct feedback into the development process during live use. In these conditions, the ability to simulate services in non-live settings gave people more confidence to make decisions and enact development. Public health services were strained due to the ongoing COVID-19 response,[24] and implementing a new service was a challenge due to the overburden of tasks. The innovation–adoption cycle[25] was visible with variation in user engagement, with some

individuals ('early adopters') highly motivated to design and adopt the service, while others were more reticent about a new digital product ('laggards'). There was a high risk of innovation overload and, although digital tools can reduce workload, there can be a significant burden in the implementation.[26] It is a reminder that technology should not be forced onto a service that does not need it, or if its deployment creates more effort than it purports to reduce.

Understanding the Design Process in Retrospect

Here, the partnership used the Cynefin framework in retrospect to better understand the design and development process.[27] It proposes that projects start from one of five domains: disorder, chaos, complex, complicated, and simple, and then move to a more well-understood domain in order. At the first workshop in March 2020, participants were in a disordered or chaotic situation with the worst-case pandemic scenario and relevant solutions both unknown. Tensions at this workshop were relatively high, and the opinion on the pandemic's scale and impact varied. Through participants' contributions at the first workshop, the stakeholder group moved from a chaotic to a complex problem domain. That is, some decisions were made, data sources were identified, and partners were either proposed or were in attendance and agreed to help. Through several more remotely run workshops, the partnership moved to the complicated domain, whereupon requirements and understanding settled. At that point, much more work still needed to be done but the design was mostly in place. At this point, expertise took over from design-led participatory design workshops. For example, industry partners began developing the service, and information governance documents were started. The stakeholders were then in the simple domain. A lot of work was still to be done, such as documentation for training, but it was only a matter of time and work before the services could be used.

Public Health Implications

This digital tool development experience has great implications for wider public health services, both in health protection and improving population health. The COVID-19 response requires a whole-systems approach with healthcare services, citizens, and political agencies collaborating and co-operating to prevent the spread of disease,[28] and mitigating the harmful effects of necessary measures such as quarantine.[29] Testing and contact tracing are key elements of this system, and digital tools can enable a whole-system approach to the containment of severe acute respiratory syndrome coronavirus 2.[1]

Throughout this process, the DHI used principles inherent to good practice in public health such as understanding the evidence base, considering and mitigating any adverse impacts on inequalities, and recognising the importance of successful engagement with the individual in population health policy.[30] Other countries have adopted a more authoritarian approach to digital tools and contact tracing,[31] which demonstrates the need to understand the broader political, cultural, and social forces in public health interventions. By understanding the importance of respect for privacy and responsible use of data,[32] the partnership was quickly able to develop a societally acceptable service for test result delivery and contact tracing. The authors believe that the services are societally acceptable due to the consent of many healthcare professionals involved in their design, the inclusion of the DHI's proposed services in the Scottish Government's early TTIS strategy,[10] and their mandated use across all 14 Scottish health boards by the Scottish Government.

COVID-19 has forced public health teams to act on a scale never seen before across the world. The pandemic's scale is a prime reason digital technology has been developed and deployed at an unprecedented pace. Digital technology can enable services to process and automate large numbers (whether it is test results, case management, or contact isolation support).[33] These digital services can allow large amounts of data to be collected by the service to enable real-time epidemiology.[3] Another considerable advantage of developing bespoke digital tools is that as collective understanding of COVID-19 has increased, they can be adapted to ensure it is capable of collecting the required data to inform risk assessment such as individual risk factors including ethnicity, and deprivation using the Scotland Index of Multiple Deprivation (SIMD),[34] and accommodate complex settings that have emerged such as factories[35] and activities.[36] The stakeholders have been able to align the tool with

changes in guidance and policy as the pandemic has progressed and lockdown eased.

CONCLUSION

The DHI, in partnership with PHS and NSS, rapidly developed and deployed two public health services in response to the pandemic, using a participatory design approach.

Digital tools should be adopted when they can enhance care, and service needs should dictate the nature of the tools (i.e., avoid digital for digital's sake). For example, the partnership chose not to develop proximity apps (as in the UK and beyond), instead focusing on a whole-system digital approach as the preferrable solution decided at the workshops by relevant stakeholders.

Digital health is becoming an integral part of all aspects of healthcare including direct clinical care, self-management, and population health management. Public health should be fully engaged in digital healthcare, as there are considerable gains to be made. This engagement should extend beyond the COVID-19 pandemic. The lessons that could be learned from this global crisis of how digital tools can inform citizens, gather real-time data, and deliver services rapidly, and at scale.[33] These lessons should apply to other public health interventions such as screening,[37] vaccination programmes,[38] and environmental exposure risk.[39]

The partnership's approach showed that digital health can have a fundamental role in public health services and can be developed at pace. To benefit from the legacy of the COVID-19 crisis, collaboration with relevant partners to inform the integration of ethical, equitable digital healthcare, and explore innovative ways of working together should continue.

Footnote

Health Protection Scotland (HPS) became part of the new organisation, PHS (Public Health Scotland) created on 1st April 2020. The function of HPS remained unchanged throughout this period.

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Liver Transplantation in Patients with Acute-on-Chronic Liver Failure: Challenging the Limits

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Abstract

Acute-on-chronic liver failure (ACLF) is one of the main causes of death on the waiting list. Liver transplantation (LT) is the only curative treatment for patients with ACLF and therefore it should be considered in all cases. However, the applicability of LT in patients with ACLF is challenging, given the scarcity of donors and the high short-term mortality of these patients. Organ allocation has traditionally been prioritised according to the model for end-stage liver disease (MELD) system. However, the accuracy of MELD score is limited in patients with ACLF. In this article, the authors review the outcomes of patients with ACLF before and after LT, highlighting its clinical course, the feasibility of LT in the sickest patients, the role of the organ allocation system, and possible indicators of futility.

INTRODUCTION

The natural history of patients with cirrhosis is characterised by the development of acute decompensating events that negatively impact their prognosis.[1,2] Even though liver transplantation (LT) is its only curative treatment, access to it is limited because the demand for organs exceeds the availability.[3]

During the last decade, it became apparent that not all acute decompensating events have the same impact in patients with cirrhosis. On the one hand, decompensations can lead to the development of acute-on-chronic liver failure (ACLF), a syndrome characterised by the development of organ failure and a high short-term mortality.[4] On the other hand, this syndrome is clinically and pathophysiologically different from mere acute decompensation, which possesses a much more favorable prognosis.[5] ACLF may occur at any stage during chronic liver disease, from compensated cirrhosis to advanced decompensation.[6]

From a pathophysiological point of view, although both ACLF and mere acute decompensation

share the same triggers, the former is characterised by the presence of an intense systemic inflammatory response.[6] Patients with ACLF exhibit features of systemic circulatory dysfunction, such as high plasma levels of renin and copeptin, and high concentrations of inflammatory cytokines, which vary according to the precipitating event and correlate with the clinical course of the syndrome.[7] All these events lead to organ failure through direct deleterious effects on microcirculatory homeostasis, mitochondrial function, and immune damage.[5,8]

Over the last decade, different definitions of ACLF have been proposed (Table 1). Depending on which definition is applied, significant differences are observed in the prevalence and incidence of ACLF. Based on the European Foundation for the study of chronic liver failure (EF-Clif) definition, the prevalence of ACLF is 23% in patients admitted for acutely decompensated cirrhosis.[4] Additionally, the in-hospital incidence was reported to be 11% in those patients who do not fulfill ACLF criteria at admission.[4] Overall, approximately one-third of patients hospitalised for acute decompensation develop ACLF during hospitalisation.[4] Nevertheless, when the American definition of ACLF was applied in a North American cohort, less than 40% of patients who met European criteria were captured by The North American Consortium for the Study of End-Stage Liver Disease (NACSELD) criteria.[9] Table 2 compares the estimated mortality according to the three main consortium definitions.[10]

Table 1: Prevalence and definitions of acute-on-chronic liver failure according to the three main consortiums.

	European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) Consortium[4]	**North American Con-sortium for the Study of End-Stage Liver (NACSELD-ACLF)[9,41]**	**Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium[41,42-44]**
Prevalence	31–45%*	10–23%†	15–65%‡
Main study cohort	1,343 patients 28 liver units Eight countries Europe	2,675 patients 14 centres USA and Canada	5,228 patients 43 centres 15 countries Asia-Pacific region
Cirrhosis diagnosis	Only applies to patients with cirrhosis		Patients with chronic liver disease, whether cirrhotic or not
Primary driver of acute injury	Non-liver causes (infection, alcoholic hepatitis, gas-trointestinal bleeding, 40% without an identifiable precipitating event)		Liver causes (alcohol, acute viral hepatitis, drug-induced liver injury, autoimmune)
Key components of the model	• Liver: bilirubin • Kidney: creatinine/dialysis • Coagulation: PT-INR • Brain: encephalopathy grade • Circulatory: median arterial pressure, use of vasopressors • Respiratory: PaO_2 or SpO_2/FiO_2	• Liver • Kidney: dialysis • Coagulation • Brain: encephalopathy grade • Circulatory: median arterial pressure, use of vasopressors • Respiratory: mechanical ventilation	• Liver: bilirubin, PT-INR, lactate • Kidney: creatinine • Coagulation: PT-INR • Brain: hepatic encephalopathy grade • Circulatory: lactate? • Respiratory

Table 1 continued.

	European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) Consortium[4]	North American Con-sortium for the Study of End-Stage Liver (NACSELD-ACLF)[9,41]	Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium[41,42-44]
Failure definition	• Liver failure: bilirubin >6 mg/dL • Renal failure: creatinine >2 mg/dL or use of renal replacement therapy • Coagulation failure: INR >2.5 • Brain failure: West Haven Criteria for encephalopathy Grade 3 or 4. • Circulation failure need for pressor support or terlipressin use. • Respiratory failure: PaO2/FiO2 >100–<200 or SpO2/FiO2 >89–<214	• Renal failure: need for renal replacement therapy • Brain failure: West Haven Criteria of encephalopathy Grade 3 or 4 • Shock: need for vasopressor support or a mean arterial pressure <60 mm Hg • Respiratory failure: need for BiPAP or mechanical ventilation	Liver failure: serum bilirubin (>5 mg/dL) and coagulopathy failure (INR >1.5 or prothrombin activity <40%); complicated with the development of clinical ascites and/or encephalopathy.
Diagnosis of ACLF	Any of the following: • Kidney failure • Creatinine 1.5–1.9 mg/dL and/or mild-to-moderate hepatic encephalopathy, plus another failure • Presence of two or more organ failures	Presence of at least two organ failures	Liver failure plus AARC score model >5
Grades of ACLF	1–3	0–4[§]	1–3
ACLF grades	• Grade 1: includes 3 subgroups: patients with single kidney failure; patients with single failure of the liver, coagulation, circulation, or respiration who had a serum creatinine level 1.5–1.9 mg/dL and/or Grade 1 or 2 hepatic encephalopathy, and patients with single cerebral failure who had serum creatinine level ranges from 1.5-1.9 mg/dl • Grade 2: includes patients with 2 organ failures •Grade 3: includes patients with 3 organ failures or more	Patients are stratified according to the number of organ failures (two, three, or all four organ failures, respectively)	Liver failure grading system based on five variables: serum bilirubin, INR, serum lactate, serum creatinine, and HE grade (AARC model) The result of the score defines ACLF grade: • Grade 1: 5–7, • Grade 2: 8–10 • Grade 3: 11–15

*Estimated over patients hospitalised for acutely decompensated cirrhosis.

[†]Estimated over patients with acutely decompensated cirrhosis precipitated or not by infection.

[‡]Estimated over patients with a first episode of acute liver deterioration due to an acute insult directed to the liver.

[§]Number of organ failures.

AARC: Asian Pacific Association for the Study of Liver Acute-on-Chronic Liver Failure Research Consortium; ACLF: acute-on-chronic liver failure; BiPAP: bilevel positive airway pressure; FiO_2: fraction of inspired oxygen; HE: hepatic encephalopathy; INR: international normalised ratio; PaO_2: partial pressure of arterial oxygen; PT-INR: prothrombin time and international normalised ratio; SpO_2: oxygen saturation as measured by pulse oximetry.

Table 2: Mortality of patients according to the three main consortium definitions.

	European Association for the Study of the Liver - Chronic Liver Failure (EASL-CLIF) Consortium[4]	North American Consortium for the Study of End-Stage Liver (NACSELD-ACLF)[9,42]	Asian Pacific Association for the Study of the Liver (APASL) ACLF Research Consortium[43]
Models to predict mortality	Chronic Liver Failure Consortium Organ Failure (CLIF-OF) www.efclif.com	North American Consortium for End-Stage Liver Disease (NACLSELD) www.nacseld.org	APASL ACLF Research Consortium (AARC) www.aclf.in
Model components	CLIF-C ACLF (for patients with ACLF) or CLIF-C AD Score (for patients with acute decompensation non-ACLF) CLIF-OF, age, white-cell count	Organ failures, age, white-cell count, serum, albumin, Model for End-Stage Liver Disease Score, and presence of infection	Bilirubin (md/dL), HE Grade, INR, lactate (mmol/lit), creatinine (mg/dL)
Mortality at 28 days	33%	28%	42%
Mortality at 90 days	51%	40%	56–68%
Mortality in most severe ACLF grades	80% at 28 days in patients with Grade 3 ACLF	77% at 30 days in patients with four OFs	86% at 28 days in patients with Grade 3 ACLF
Prognostic accuracy for mortality predicting 30-day mortality (AUROC)	0.83 (95% CI: 0.79–0.91)	0.85 (95% CI: not available)	0.78 (95% CI: 0.71–0.82)

ACLF: acute-on-chronic liver failure; AUROC: area under the receiver operating characteristic; CI: confidence interval; OF: organ failure.

CLINICAL ASPECTS OF ACUTE-ON-CHRONIC LIVER FAILURE

ACLF is a highly dynamic syndrome.[4] Although it is associated with elevated mortality, a significant proportion of patients reverse the organ failures and recover. Therefore, Gustot et al.[11] proposed to assess the evolution of ACLF at 3–7 days, considering that it correlates better with short-term prognosis. While there may be variability, approximately one-half of the patients who are admitted with Grade 1 ACLF resolve it. This is less frequent in patients with Grade 2 or 3 ACLF, in whom reversal or improvement to a lower grade is estimated to occur in 35% and 16% of individuals, respectively.[11] In contrast, progression to higher grades has been reported in 21% and 51% of patients with Grades 1 and 2 ACLF, respectively. The worse outcomes are expected in patients with Grade 3 ACLF because approximately 70% do not improve over time and 80% die at 90 days.[11]

Recently, Trebika et al.[12] described three different clinical courses in patients admitted for acute decompensation without ACLF. The first one, which was termed 'pre-ACLF', constituted patients who developed ACLF within 90 days from the acute decompensating event. The

second one, termed 'unstable decompensated cirrhosis', was characterised by readmissions but without the development of ACLF. The third one, represented by patients without readmissions or development of ACLF, was termed 'stable decompensated cirrhosis'. The three clinical courses showed different pathophysiology and prognosis, as well as variability in the degree of systemic inflammation. This classification could guide the selection of the most appropriate setting for patient management and guide the decisions regarding the urgency of LT. [12]

Finally, it is important to highlight that, although a greater number of organ failures is associated with higher mortality, it has recently been shown that certain organ failures, such as those of extra-hepatic origin, can have a negative effect on the prognosis, independently of the ACLF grade.[13]

ROLE OF LIVER TRANSPLANTATION IN PATIENTS WITH ACUTE-ON-CHRONIC LIVER FAILURE

ACLF can occur in patients who are already listed for LT or be the reason why they are listed. It was reported that 31% of the patients undergoing liver transplantation with ACLF were already on the waiting list when this syndrome developed.[28]

The CANONIC study was the first to report the outcomes after LT in a select and reduced group of patients with ACLF. The study estimated a 1-year post-LT survival of 75% in comparison to a mortality of 23% in those patients who were not transplanted.[4] Subsequently, numerous studies evaluated post-transplant survival and complications at 30 days, 90 days, 6 months, 1 year, and 5 years.[14-19] According to a recent meta-analysis, including 22,238 patients with ACLF and applying the European definition, the 1-year post-LT survival was 85% in those patients who were transplanted and 28% in non-transplanted patients. When analysing patients who were transplanted with ACLF and those who were transplanted without ACLF, the 1-year survival was 86% and 92%, respectively. Similarly, the 5-year post-LT survival was 67% and 81%, respectively.[20]

The experience of LT in patients with ACLF is increasing worldwide, positioning it as the only curative treatment. Nevertheless, the available data is heterogeneous and it is unclear whether LT is beneficial in very sick patients with extra-hepatic organ failures.[15-17] Although there is no precise definition to define LT futility, experts from European and American societies consider that post-transplant survival should be greater than 50% at 5 years.[21] However, in daily practice, several challenges are faced regarding how to quickly identify which patients with ACLF will benefit from LT, what is the precise time to LT, and how to select the appropriate donors.

Even though the presence of extra-hepatic compromise, such as circulatory, respiratory, or brain failure, is associated with lower transplant-free survival than coagulation and liver failure, there is agreement across scientific societies that patients with ACLF Grade 1 and 2, as well as those patients who have recovered from an ACLF episode, should be listed for LT.[22] However, LT for patients with ACLF with three or more failing organs (ACLF-3) is still controversial, and will be discussed in the following section.

LIVER TRANSPLANTATION IN PATIENTS WITH GRADE 3 ACUTE-ON-CHRONIC LIVER FAILURE

The presence of ACLF-3 should not be considered a contraindication for LT. To date, the greatest challenges that LT presents in these patients are represented by its timing and with the donor selection process, which should ensure that the principles of utility and beneficence are fulfilled.[23] Of note, recent studies demonstrated that the presence of ACLF does not negatively impact post-transplant survival and also has no impact on long-term complications, such as chronic kidney disease.[17] However, patients with ACLF-3 were shown to have greater use of hospital resources, longer hospitalisations, and intensive care unit stays.[19,20]

In practice, many centres may not offer LT to patients with multi-organ failure, given that some of them might have lower post-transplant survival than expected.[24] However, in a retrospective cohort study published by Artru et al.,[14] a 1-year post-LT survival of 84% was reported in patients with ACLF-3. This study was the first to demonstrate excellent 1-year post-LT survival outcomes among these very sick patients. However, it should be noted that individuals in this

study who were transplanted with ACLF-3 were selected carefully.[14] More recently, analysis of the North American Registry of the United Network Organ Sharing (UNOS) presented similar results, estimating a 1-year post-LT survival of 82% in the same population.[19]

Additionally, two more recent studies evaluated post-transplant outcomes in ACLF-3 patients. The first one, published by Thrulavath et al.,[25] demonstrated in a large sample the feasibility of LT in patients with multi-organ failure. In this study, the 1-year post-LT survival was 81%, even in patients with more than three organ failures. Although patients with respiratory failure showed lower post-transplant survival, it was estimated to be 79% at 1 year.[25] The second study evaluated long-term outcomes after LT and reported that patients with ACLF-3 at the time of LT had a 5-year survival greater than 50%. Of note, mortality in these patients occurred predominantly during the first year and plateaued thereafter, reaching similar rates to those with lower ACLF grades. The main causes of death after the first year were infection and malignancy.[19]

ISSUES REGARDING FUTILITY IN LIVER TRANSPLANTATION

As mentioned, there is agreement that LT in patients with single organ failure or two organ failures (ACLF-2) is associated with favourable outcomes. Even though good results were shown after LT in patients with ACLF-3, a subgroup of patients might be too sick to benefit from it.[23] Given the shortage of donors, the early timing of LT, the donor quality, and the likelihood of spontaneous recovery are important elements that should be considered (Figure 1).[24,27]

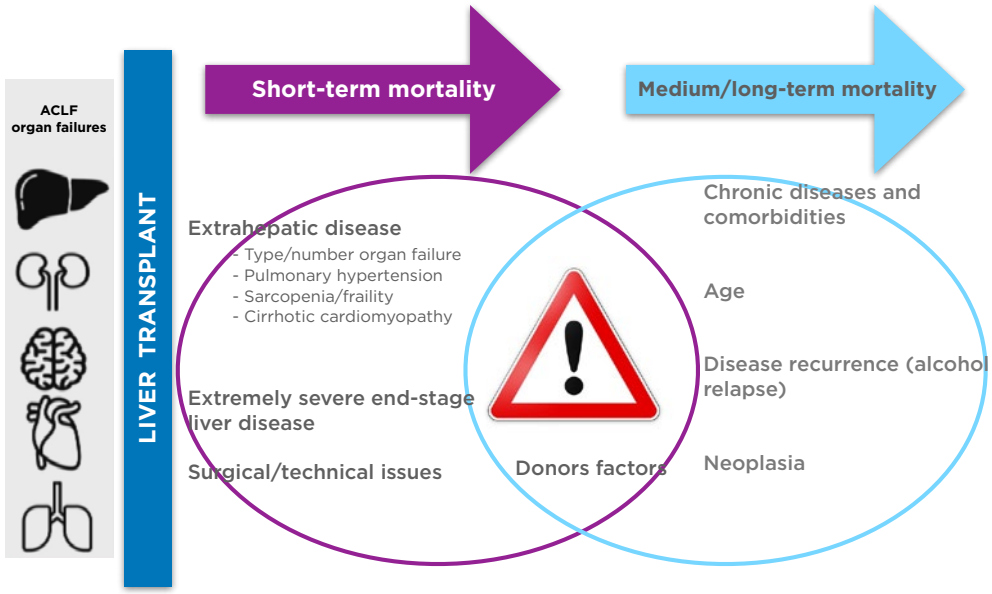

Figure 1: Main drivers of mortality after liver transplantation.[27]

Studies of LT and ACLF-3 include heterogeneous populations. Optimising survival after LT involves several factors in addition to the presence of acute-on-chronic liver failure. Some of them have relevance in the short-term post-transplant mortality, such as the type and number of organ failures at the moment of LT, the presence of sarcopenia/frailty, pulmonary hypertension, and the presence of myocardial dysfunction. Other factors are relevant for the medium/long-term outcomes, such as other comorbidities (e.g., diabetes, cardiovascular disease, chronic kidney disease), disease recurrence (e.g., alcohol relapse, deficit of adequate nutritional and physical activity planning), and oncological diseases. The type and quality of the donor organ, as well as the timing to accept it, can have an impact at any point in the post-transplant. Even though the current scores might help predict short-term and long-term post-transplant mortality, there is still a place for its improvement. It seems that the CLIF ACLF score is an accurate tool to predict survival without LT but is suboptimal to predict outcomes after LT.

ACLF: acute-on-chronic liver failure; CLIF: Chronic Liver Failure; ESLD: end-stage of liver disease; LT: liver transplantation.

The controversy arises because several studies reported poor post-transplant outcomes in patients with ACLF-3, which might be driven by the haemodynamic instability and the requirement for mechanical ventilation at the time of LT.[16,19,24] With the purpose of identifying patients who might have a poor post-transplant prognosis, Sundaram et al.[19] reported that a donor risk index greater than 1.7 was associated with greater mortality while LT within 30 days of listing was associated with greater survival. Additionally, in an abstract presented at The Liver Meeting 2020, held by the American Association for the Study of Liver Diseases (AASLD), a dynamic model was designed in order to determine the ideal timing regarding when to stop waiting for an optimal quality donor and accept a marginal quality organ.[27]

In a larger UNOS registry study, the improvement of patients with ACLF-3 at listing to ACLF 0–2 at transplantation enhanced post-LT survival, particularly in those who reversed the circulatory or brain failures or who were weaned from the mechanical ventilator.[29] This study also showed that patients transplanted after improving or resolving ACLF had greater post-LT survival than those who underwent LT with ACLF Grade 3.[29] However, less than 25% of the patients with ACLF-3 on the waiting list improved the degree of ACLF. Therefore, even though it seems that it would be advisable to perform the LT after recovering organ failures, this might not be possible for the majority of patients with ACLF-3.[29]

Meanwhile, Artzer et al.[30] were the first to publish a LT futility score for patients with ACLF-3 (transplantation for ACLF-3 model [TAM] score), which was generated from a retrospective, multicentre cohort study of five European centres. The score includes arterial lactate, mechanical ventilation support, white blood cell count, and age, and proposed a cut-off point that predicted a survival probability of less than 10%.

Overall, prospective data from large multi-centre studies are needed in order to resolve the controversy surrounding LT in these very sick patients. There is a great expectation with the prospective CHANCE study ('Liver Transplantation in Patients with Cirrhosis and Severe Acute-on-Chronic Liver Failure: Indications and Results'), which is directed by the EF-Clif and will begin enrolment in 2021.[31] The main aim of this study is to compare 1-year graft and patient survival rates after LT in patients with ACLF-2 or -3 at the time of LT with those patients with decompensated cirrhosis without ACLF, and also with transplant-free survival of patients with ACLF-2 or -3 not listed for LT.

LIMITATIONS OF THE MODEL OF END-STAGE LIVER DISEASE ALLOCATION SYSTEM

The model of end-stage liver disease (MELD) and MELD plus serum sodium (MELD-Na) allocation system has improved the outcomes of patients on the waiting list.[32,33] Patients with higher MELD and MELD-Na scores are at increased risk of ACLF. Additionally, they might predict survival in these patients.[34,35] However, none of these models incorporate determinations that represent brain, circulatory, or respiratory failure. Furthermore, they do not include biomarkers of systemic inflammation, which appear to correlate with outcomes in patients with ACLF.[36]

According to a publication by Sundaram et al.,[27] the probability of dying or being removed from the waiting list was higher in patients with ACLF-3 than in patients with acute liver failure (Status 1A in the USA). Later, a publication from the same group documented several interesting findings.[20] Firstly, in patients with ACLF-3, the MELD-Na score tended to underestimate 90-day mortality in the waiting list.[20] Secondly, the proportion of patients with ACLF-3 and MELD-Na less than 25 who died or were removed from the waiting list at 28 and 90 days was 44%.[20] This was significantly higher than what was observed in patients with a MELD-Na score greater than 35 without ACLF.[20]

Another interesting study that evaluated the performance of MELD-Na to predict 3-month mortality in patients with ACLF was published by Hearnaez et al.[37] The authors reported that MELD-Na does not fully capture the prognosis of patients with severe ACLF. Interestingly, MELD-Na was the main determinant to consider listing for LT, even in patients with ACLF-3. Approximately 65% of patients with ACLF had a MELD-Na score less than 30, suggesting that these patients have a disadvantage in the current allocation system.[36] Of note, the authors considered both the European and American definitions for the

analysis and supported a possible superiority of the former.

Given the limitations of the MELD-Na score for organ allocation, new prognostic scores have emerged specifically designed to assess the risk of mortality in patients with ACLF. The CLIF-C ACLF score computes organ failures, age, and white blood cell count.[38] The CLIF-C ACLF score showed greater accuracy in predicting mortality than the MELD and MELD-Na; however, external validation in a prospective multicentre cohort is desired (Table 2).[37,38] Moreover, the NACSELD validated a score as a predictor of inpatient mortality (NACSELD ACLF score).[39] This score, which defines extra-hepatic failures by clinical intervention (e.g., the requirement for mechanical ventilation, the use of vasopressors, or renal replacement), could predict better survival. Therefore, experts suggest that the decision to allocate LT in patients with ACLF may ultimately be guided by the CLIF-C ACLF and NASCELD ACLF scores because they might have a greater ability to predict wait-list mortality and post-transplant survival.[40] Developing a scoring system that captures essential donor and recipient factors, such as organ failure, global nutritional assessment, physical performance, and chronic conditions, is desired. This could ultimately direct a more individualised allocation approach.

FUTURE DIRECTIONS: WHAT'S NEXT?

Significant advances in the understanding of the role of LT in patients with ACLF have been achieved over the last years; however, there are still various unanswered questions. Even though LT is recommended for these patients, only one-third of the patients with ACLF-3 access LT. In this regard, performing the LT in a timely manner is challenging. Additionally, an in-depth pre-transplant evaluation of these patients might be infeasible, particularly when they present with multi-organ failure.

Most evidence concerning ACLF and LT arose from retrospective studies with important selection bias. This bias originated because patients with ACLF who were not transplanted were not analysed, among other methodological issues. Therefore, a prospective approach such as the CHANCE study might overcome these issues.

On the other hand, there is a need to develop tools to predict the development of ACLF, particularly in patients on the waiting list. Modern concepts such as sarcopenia and frailty, as well as the role of biomarkers such as cystatin C or N-terminal pro B-type natriuretic peptide, deserve further evaluation. Additionally, the role of hepatic encephalopathy and the influence of bacterial and fungal infections might help predict outcomes on the waiting list and could aid in prioritising patients.[13,28,41]

CONCLUSIONS

ACLF is a highly dynamic syndrome that, with specific criteria and proper timing, can benefit from a LT. The early identification of a window of opportunity for LT, the aggressive treatment aimed to reverse organ failures, and the judicious selection of donors have a significant impact on the waiting list and post-transplant outcomes. Until more evidence arises from prospective studies, LT teams will face challenges in dealing with these very sick patients, particularly when balancing the risks and benefits of LT and its timing.

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Hepatic Manifestations of Lysosomal Storage Disorders: Differential Diagnosis, Investigations, and Treatment, Current and Upcoming

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Abstract

Hepatomegaly can be a presenting or associated feature of an inherited lysosomal storage disorder. Thus, a high index of suspicion should be maintained in patients without an aetiologic diagnosis. Suggestive clues can be derived from family history, and/or concomitant manifestations such as anaemia, thrombocytopenia, and splenomegaly. An ophthalmologic examination may disclose relevant findings, such as the presence of a cherry red spot or gaze palsy. Each subtype presents with a broad spectrum of clinical findings, encompassing a wide range of onset from early infancy to adulthood. Diagnostic confirmation necessitates demonstration of decreased enzyme activity and/or mutation in the cognate gene. Diagnosis enables prognostication and consideration of disease-specific therapy, which is currently available for a subset. As inherited traits, diagnosis enables consideration of genetic counselling regarding reproductive risks and implications for relatives. Conditions covered in this review include Gaucher disease, Niemann-Pick diseases, and lysosomal acid lipase deficiency (Wolman disease, cholesterol ester storage disorder).

INTRODUCTION

Hepatomegaly as a clinical problem may represent a manifestation of a storage disorder; that is, a condition resulting from deficiency of an enzyme that would normally metabolise by-products of cellular turnover, and as a consequence tissue deposits build-up in various organs such as the liver, and thus, a characteristic of certain lysosomal storage disorders (LSDs).[1] LSDs are relatively rare conditions with broad systemic effects, and associated clinical features help focus evaluation in a patient presenting with hepatomegaly, with or without liver dysfunction (that is, elevated liver transaminases).

Several considerations should raise one's index of suspicion that a patient's complaint may be caused by an LSD, while screening for or after preliminary exclusion of more common disorders (e.g., infection, malignancy). LSDs are inherited conditions (mainly autosomal recessive), so obtaining a family history may provide valuable information in cases where there may be more than one similarly affected relative (e.g., sibling). Age of onset, associated clinical manifestations, and a good understanding of clinical disease

course also help to direct one's pursuit of a diagnosis. As diagnostic confirmation requires specialised testing that may not be readily available locally, it may be useful to look at a subset of LSDs, specifically, the sphingolipidoses and related conditions; and look at differentiating one from another with overlapping clinical manifestations, which hopefully leads to a request for the most appropriate investigations.

Herein, the authors describe the hepatic manifestation of three specific LSDs: Gaucher disease (GD), Niemann-Pick diseases (NPD), and lysosomal acid lipase (LAL) deficiency; and their related clinical features, means of diagnostic confirmation, and advances on the therapeutic front.

Of note, the sphingolipidoses (which encompasses Gaucher and NPD A/B) represent a subset of LSDs in which deficiency of a distinct enzyme in the sequential degradation of relevant substrates results in tissue deposits that progressively accumulate in various organs such as the liver and spleen. Except for Fabry disease, which is inherited as an X-linked trait, other conditions within this group are transmitted in an autosomal recessive fashion.[2] Incidentally, the classification of LSD was traditionally based on the chemical nature of the substrate that built up, differentiating the sphingolipidoses from another subgroup such as the mucopolysaccharidoses (MPS), characterised in the latter by accumulation in tissues of incompletely metabolised mucopolysaccharides (now referred to as glycosaminoglycans).[3] Hepatomegaly can also be found in the MPS, but other features such as the distinctive facial appearance and skeletal changes (i.e., dysostosis multiplex) help to readily distinguish these conditions from the sphingolipidoses and related conditions, the subject of this review (Figure 1).

The sphingolipidoses encompass several diseases, besides those reviewed in this paper. The grouping includes Tay-Sachs and Sandhoff disease, G_{M1} gangliosidoses, Krabbe disease, and metachromatic leukodystrophy. These conditions are dominated by primary neurologic complications in the absence of hepatosplenomegaly. Incidentally, the eponymous designation of several disorders within the group recognises the seminal contribution of the named individual(s), which preceded the identification of the underlying causal defect in all cases. For instance, GD is named after a French physician who described a young female patient who presented with splenomegaly, which on histological examination revealed the characteristic tissue deposits, prior to identification of its biochemical origin.

A related lipidosis, Wolman disease (the severe form of LAL deficiency), is named after Moshe Wolman, an Israeli physician who described the case of three siblings from a consanguineous family with xanthomas in the liver, spleen, adrenals, and other tissues, with death by 3 months of age.[4] Subsequently, attenuated cases were described with later onset, lipid deposits in the liver, and hypercholesterolaemia, termed cholesterol ester storage disease.[4] With characterisation of the cognate enzyme deficiency, the condition is now preferably called LAL deficiency. As with all the other diseases in this report, it is recognised that there can be a wide age of onset, a broad spectrum of clinical presentation, and variable rate of disease progression. To a certain extent, these observations have been attributed to the presence of residual enzyme activity; thus, a null mutation often leads to an earlier age of onset and more aggressive disease course.

The LSDs associated with hepatomegaly include GD, NPDs, and LAL deficiency. Of these, GD may be the most common, although it is likely that a significant number of patients with NPDs and LAL deficiency are being missed.

Incidentally, the group of diseases referred to as NPD (a designation proposed by Crocker and Farber in 1958) actually encompass different subtypes.[5] NPD Types A and B are caused by a deficiency of the lysosomal enzyme acid sphingomyelinase, with Type A representing the severe variant with primary central nervous system (CNS) involvement.[5] NPD Types C and D were subsequently shown to be due to defects in two distinct non-catalytic proteins.[5] In NPD Type C, 95% of cases result from mutations in a transmembrane protein (NPC1), and the rest arise from mutations in a soluble intra-lysosomal protein (NPC2).[6] Historically, NPD Type D referred to affected cases, which are descendants of an Acadian couple who lived in Nova Scotia, Canada, in the early 18th century, a consequence of founder effects (i.e., shared identity by decent).[7]

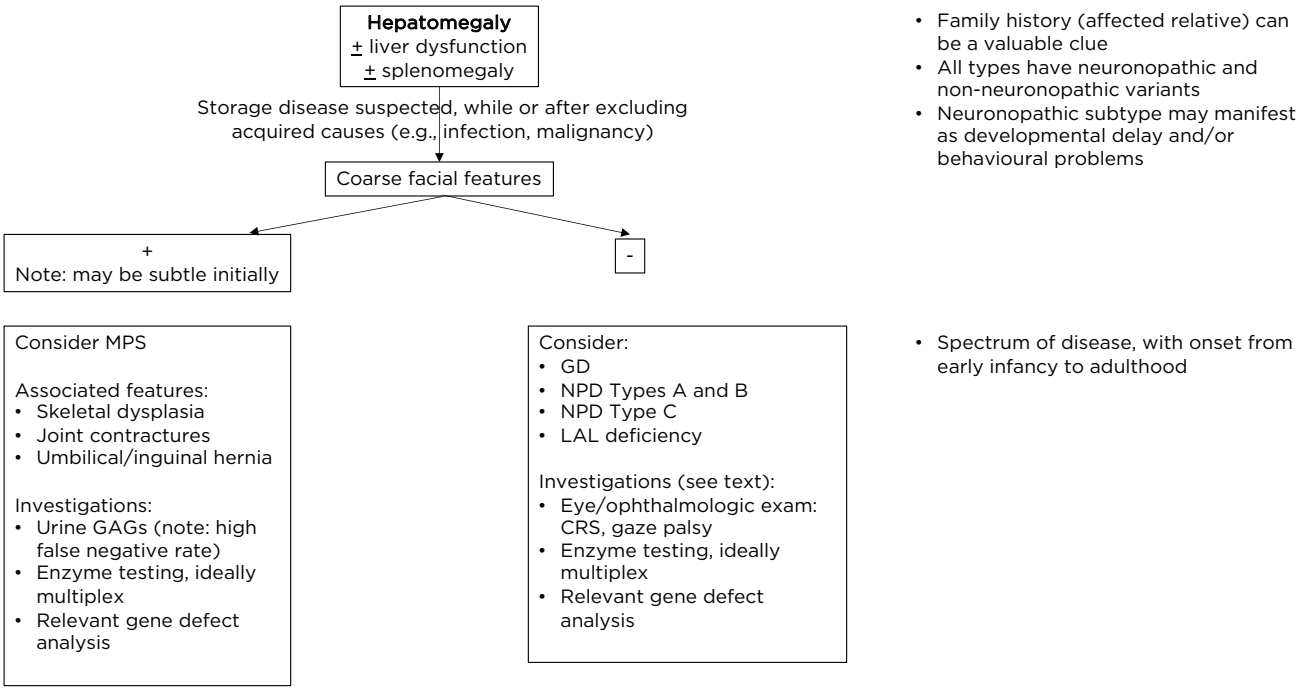

Figure 1: Clinical considerations of lysosomal storage disorders in cases of hepatomegaly, divided into those with and without coarse facial features.

CRS: cherry red spot; GAGs: glycosaminoglycans; GD: Gaucher disease; LAL: lysosomal acid lipase; MPS: mucopolysaccharidosis; NPD: Niemann-Pick disease.

NPD Type D has a more homogeneous clinical expression resembling that of less severely affected patients with NPD Type C. Subsequent studies revealed mutations in *NPC1* as the cause.

The identification of the molecular basis of several LSDs has prompted the recommendation of an alternative classification. For instance, GD and NPD Types A and B are within a set of designated enzyme deficiency disorders, whilst NPC1 is now grouped with other transmembrane protein deficiency disorders together with defects of sialin (the cause of sialic acid storage disease) and cystinosin (cystinosis).[1]

CLINICAL PRESENTATIONS

Hepatosplenomegaly is a characteristic feature of GD, although anaemia and thrombocytopenia associated with epistaxis and bruising may be major reasons affected individuals are initially referred for evaluation, in most cases through a haematologist.[8] Such may be the case, as liver function is usually preserved in these patients. However, it is recognised that adult patients with GD have an increased risk for gallstones, and it is not unusual that a referral is made first to a gastroenterologist.[9] The formation of gallstones has been related to alteration in the composition of bile in the gallbladder, accounting for non-pigment stones (as the anaemia in GD is primarily a consequence of displacement of haematopoietic elements in the bone marrow and sequestration by an enlarged spleen rather than haemolysis). Incidentally, major bleeding does not seem to be a major concern for most patients with GD, as platelet function appears to be largely intact and there is no associated deficiency in clotting factors. However, given the prevalence of GD among individuals of Ashkenazi Jewish ancestry, in whom Factor XI deficiency may also be encountered, bleeding risks may be increased in some cases.[10] Regardless, in patients with GD and thrombocytopenia it remains prudent to evaluate patients for bleeding risks prior to any major surgical or dental procedure.

Although liver dysfunction is not a typical feature of GD, cases have been described in patients who have developed cirrhosis; indeed,

liver transplantation has been undertaken in a few instances.[11] Among patients with GD and parenchymal liver disease, associated complications have included portal hypertension and hepato-pulmonary syndrome.[12] Such cases should prompt exclusion of other disease processes, such as infectious or auto-immune hepatitis, and be managed accordingly.

Bone complications, including bone pain and osteonecrosis, are major sources of morbidity in patients with GD; thus, a comprehensive evaluation of disease burden among diagnosed patients must include assessment of bone involvement.[13] Suggested bone tests include MRI, bone density, and X-rays of symptomatic sites.

Hepatomegaly is also encountered in patients with NPD. Although in this condition abnormalities in liver function tests (i.e., elevated serum transaminase levels) are often seen as storage material (sphingomyelin), which can be found in hepatic parenchymal cells. This is in contrast to GD, wherein storage (glucosylceramide) is found mainly in Kupffer cells (i.e., cells of monocyte/macrophage lineage).[5] There is considerable overlap in clinical features between GD and NPD, except for lung involvement (i.e., interstitial lung disease), which occurs more frequently in the latter.[14] Lung involvement (e.g., interstitial lung disease, pulmonary hypertension) can also be encountered in patients with GD, but this problem is seen mainly in splenectomised cases.[15]

GD and NPD Types A and B are both characterised by a spectrum of features, with primary CNS involvement occurring in a subset. Among patients with GD and CNS involvement are those with an acute (Type 2) and subacute (Type 3) disease course, with death on average before 2 years of age in the former; whilst patients with Type 3 disease live longer (beyond 30 years of age), although often with complications such as seizures.[16] Patients with GD Type 3 have a distinctive eye finding attributed to saccadic initiation failure.[16] A pertinent negative finding is the absence of a cherry red spot (CRS), characteristic of NPD Type A (also seen in Tay-Sachs disease). The CRS appearance can be accounted for by accumulation of lipids in retinal ganglion cells, with the fovea remaining and appearing unusually red and prominent against the surrounding peri-macular infiltrates. Thus, ophthalmologic investigation can be helpful in the evaluation of patients.[17] In NPD Type B, eye findings may be more subtle, described by the presence of a macular 'halo'.[18] In NPD Type C, a characteristic feature is the presence of vertical supranuclear gaze palsy.

LAL deficiency, another LSD characterised by hepatomegaly and liver dysfunction, needs to be considered in patients suspected of having a storage disorder, when the diagnosis of GD or NPD has been excluded. LAL deficiency may manifest as a severe (Wolman disease) or attenuated subtype (cholesterol ester storage disease).[4] The Wolman disease variant had been a life-limiting condition, prior to the availability of enzyme therapy. Although there had been reports of patients subjected to haematopoietic stem cell transplantation, it is not certain that significant benefits have been achieved as complications such as sinusoidal obstruction syndrome and progression to cirrhosis have been described in post-transplant cases.[20]

Non-immune hydrops fetalis (NIHF), a condition characterised by ascites, pleural and/or pericardial effusion, and skin oedema, is a rarely recognised feature of several LSDs, including GD, NPD, and LAL deficiency.[21] Other LSDs associated with reported cases of NIHF include sialidosis, galactosialidosis, infantile sialic acid storage disease, MPS Types IV and VII, G_{M1} gangliosidosis, I-cell disease, and Farber disease. These diagnoses should not be missed when features of NIHF are detected prenatally or at the time of birth, as diagnosis can inform management and also alert couples about recurrence risk with future pregnancies.

DIAGNOSIS

When suspected, the diagnosis of GD, NPD Types A and B, and LAL deficiency can be confirmed by demonstrating deficiency of the cognate enzyme (namely, acid β-glucosidase, acid sphingomyelinase, and LAL, respectively). Increasingly, most laboratories offer multiplex testing, which serves as a quality control measure for samples often shipped to a specialised diagnostic facility.[22] Most of these laboratories can now also measure several biomarkers, which may be correlated with disease burden (as discussed below). Note that measurement of enzyme activity does not reliably identify carriers,

as values may overlap with results obtained for controls. Relatives at risk may be offered carrier testing by screening for mutations detected in index cases. As NPD Type C is not an enzyme deficiency disorder, diagnosis is confirmed based on characterisation of the causal mutations in either *NPC1* (approximately 95% of cases) or *NPC2*.[6] Given the inherited nature of these conditions, affected individuals should be offered genetic counselling regarding reproductive risks and implications for relatives.

A bone marrow biopsy may be performed, given concerns clinical features may suggest a malignancy. In GD, a bone marrow biopsy may reveal the presence of lipid-engorged histocytes with a crumpled silk appearance;[23] whilst in NPD, foam cells or sea-blue histiocytes may be observed.[24] It should be noted that liquid malignancies associated with high cellular turnover may result in the presence of pseudo-Gaucher cells.[25]

In jurisdictions where the blood samples may need to be shipped out, waiting for test results may lead to some delay; so, to some extent it may be understandable why a bone marrow biopsy may be done locally to exclude malignancy. However, biochemical and/or molecular testing as noted above is still required for diagnostic confirmation of an LSD, especially prior to introduction of disease-specific therapies (discussed below).

Biomarkers

Several biomarkers, whose concentration or activity can be readily measured in blood, have been identified in patients with a sphinglipidoses and related conditions. However, most of these have been shown to be non-specific and do not necessarily correlate with disease burden (e.g., serum ferritin and angiotensin-converting enzyme in GD). Thus, several investigations have been undertaken to identify biomarkers with greater sensitivity and specificity.

In GD, the current biomarker of choice is lyso-Gb1, with screening studies undertaken in populations at risk to identify affected individuals.[26] Chitotriosidase and CCL18/PARC remain popular biomarkers but have less sensitivity and specificity.[27] Among affected individuals, studies have shown a correlation with disease burden (e.g., liver and spleen volume, bone involvement).[26]

The oxysterol species cholestane-3β, 5α, 6β-triol (C-triol) is elevated in patients with NPD Types A, B, and C and LAL deficiency.[28] Additionally, lysosphingomyelin and lysosphingomyelin-509 are both elevated in patients with NPD Types A, B, and C, although the magnitude of increase is greater in those with NPD Type C.[29]

It should be noted that no single biomarker can be fully interpreted in isolation and must be viewed as part of a wider panel of investigations informed by clinical details. Moreover, none of the biomarkers identified to date have full predictive value.

Incidentally, certain results for tests commonly available in most general hospitals may serve as clues to diagnosis. An abnormal lipid profile (elevated low-density lipoprotein cholesterol, low high-density lipoprotein cholesterol) may be found in LAL deficiency, associated with elevated alanine transaminase values.[30] A similar profile may be encountered with NPD Types A, B, and C;[31] however, lung involvement is not common in patients with LAL deficiency. On the other hand, lung involvement may not be present in the early stages of NPD Types A and B, and thus should not exclude consideration of this diagnosis. The rapid development of neurologic complications in NPD Type A is another important feature associated with the presence of a CRS on eye examination. Neurologic complications are also seen with GD Type 2, which interestingly is not associated with the CRS; as noted, a characteristic finding in Tay-Sachs disease (β-hexosaminidase deficiency), associated with neurologic complications but not with hepatomegaly.[32]

Of note, epidemiologic investigations have shown individuals with GD have an increased risk for multiple myeloma (MM) and Parkinson's disease (PD).[33,34] With MM, it appears this increased risk may be related to gammopathy as a consequence of chronic B-cell stimulation, wherein the incompletely metabolised lipids act as an antigen and trigger an aberrant immune response.[35] In some patients, this drives the clonal proliferation of plasma cells and the development of MM. The basis for the increased risk for PD in GD is under intense scrutiny as it appears the risk is true not only for affected individuals but also for carriers.[34] In any case, although the risk for either MM or PD is increased compared to the general population, when looking at a group of patients with GD the

proportion of individuals who eventually develop these comorbidities is small. However, at present there is no means for identifying those who go on to develop these problems. Thus, serial monitoring of patients should include screening of serum protein electrophoresis/γ-globulin profile for early detection of MM, and neurologic assessment for features suggestive of PD.

MANAGEMENT

Disease-specific therapies are commercially available for some LSDs and remain investigational for others (Table 1).[36]

Through the years, different approaches have been examined. Those that have achieved regulatory approval include enzyme replacement therapy, the straightforward provision of a recombinant formulation to make up for the deficiency; substrate reduction therapy, the use of a small-molecule agent that inhibits the synthesis of a precursor to limit its build-up in tissues; and pharmacologic chaperone, which is also a small-molecule agent that helps restore the functional conformation of a defective enzyme resulting from misfolding, to spare it from premature degradation and facilitate its delivery to the lysosome.

Enzyme therapy involves the regular intravenous administration of a protein, which has limited access beyond the blood–brain barrier. Antibodies may also form against a recombinant formulation, and when neutralising lead to a loss of efficacy. Small-molecular therapies are administered orally and may be subject to first-pass metabolism; there is also a potential for drug interaction. In the case of pharmacologic chaperones, action may be limited to amenable mutations; that is, gene defects that do not lead to major structural changes (e.g., deletions) that are irreparable.[37]

Enzyme therapy for GD, which is commercially available, has led to significant improvement in quality of life for treated individuals; however, it does not impact on ultimate neurologic prognosis for those with primary CNS involvement.[38]

Table 1: Sphingolipidoses associated with hepatomegaly: diagnosis, clinical features, and therapeutic approaches.

Disorder	GD	LAL deficiency	NPD
Diagnosis	Measurement of glucocerebrosidase enzyme activity *GBA1* gene sequencing	Measurement of lysosomal acid lipase enzyme activity Genetic sequencing	Measurement of acid sphingomyelinase enzyme activity for NPD Types A and B
Gene	*GBA1* Over 400 pathogenic variants Very rarely due to *PSAP* (codes for activator protein, Saposin C)	*LIPA* At least 120 pathogenic variants	For non-catalytic proteins, *NPC1* (>95%) and *NPC2*, diagnostic confirmation based on mutation analysis *SMPD1*: NPD Types A and B
Subtypes	GD Type 1 (non-neuronopathic) GD Type 2 (severe neuronopathic) GD Type 3 (variable neuronopathic)	Wolman disease, the most severe variant and usually fatal in first year CESD, a later-onset, variable, and attenuated clinical course	NPD Type A (neuronopathic) NPD Type B (non-neuronopathic) NPD Type C (broad spectrum, from early to late onset disease)
Enzyme	Acid β-glucosidase	LAL	NPD Types A and B: acid sphingomyelinase NPD Type C: defect is in non-catalytic proteins
Substrate	Glucosylceramide (glucocerebroside)	Un-hydrolysed cholesteryl esters and triglycerides	Sphingolipid and cholesterol accumulation Sphingosine, plays central role in NPD Type C pathogenesis

Table 1 continued.

Disorder	GD	LAL deficiency	NPD
Biomarkers	Chitotriosidase, an enzyme produced by activated macrophages. Correlates with visceral involvement. Used to monitor response to treatment PARC/CCL18, an inflammatory chemokine; correlates with chitotriosidase Lyso-Gb1, a biomarker with highest sensitivity and specificity	Abnormal lipid profile/liver function test results: high LDL, low HDL, and high ALT Chitotriosidase may also be elevated	C-triol: circulating oxysterol Lyso-SM-509 plasma lysosphingomyelin (higher specificity for NPD Type C) Chitotriosidase may also be elevated
Special features	Oculomotor apraxia (neuropathic type) Multiple myeloma Parkinsonism Osteonecrosis and 'bone crisis'	Thrombocytopenia, uncommon Lung involvement, uncommon	NPD Type A: CRS in macula NPD Type B: macular 'halo' NPD Type C: supranuclear gaze palsy and psychiatric symptoms
Treatment			
General	Measures essentially obviated by enzyme therapy: blood transfusion, liver transplantation, and splenectomy	Statins may be indicated May be precluded by enzyme therapy: HSCT; and liver transplant	Supportive
ERT	Imiglucerase (Cerezyme; Sanofi Genzyme, Cambridge, Massachusetts, USA) Velaglucerase (VPRIV; Shire Pharmaceuticals, Lexington, Massachusetts, USA) Taliglucerase alfa (Elelyso; Protalix BioTherapeutics, Karmiel, Israel; Pfizer Inc., New York City, New York, USA)	Sebelipase alfa (Kanuma; Alexion Pharmaceuticals, Boston, Masachusetts, USA) ARISE trial	Recombinant acid sphingomyelinase under investigation for NPD Type B
SRT	Miglustat (Zavesca; Actelion Pharmaceuticals, Allschwil, Switzerland) Eliglustat (Cerdelga; Sanofi Genzyme)	ND	NPD Type C: Miglustat (Zavesca)
Chaperones	Ambroxol, currently undergoing trial Isofagamine, failed Phase II trial in 2009	ND	ND

ALT: alanine transaminase; CESD: cholesterol ester storage disease; CRS: cherry red spot; ERT: enzyme replacement therapy; GD: Gaucher disease; HDL: high-density lipoproteins; HSCT: haematopoetic stem cell transplant; LAL: lysosomal acid lipase; LDL: low-density lipoproteins; ND: no data; NPD: Niemann-Pick disease SRT: substrate reduction therapy.

Thus, enzyme therapy is often withheld from those with GD Type 2 but represents the mainstay of therapy for those with Types 1 and 3 disease; in the latter, problems such as seizures are managed symptomatically. As noted, enzyme/protein replacement therapy would not be expected to access the brain, because of the blood–brain barrier; this has prompted investigations of the potential of small-molecule drugs that may either inhibit substrate synthesis or act as a pharmacologic chaperone. Eliglustat (Sanofi Genzyme, Cambridge, Massachusetts, USA), an oral substrate synthesis inhibitor, has been shown to be safe and effective in patients with GD Type 1 naïve to therapy or switched from a prior regimen of intravenous enzyme therapy.[39] Although eliglustat appears to cross the blood–brain barrier, as a P-glycoprotein analogue it is rapidly effluxed; thus, a sufficient drug concentration within the CNS is not achieved. There have been limited investigations involving drugs, such as isofagamine, which act as a pharmacologic chaperone.[40] With regards to treatment for CNS involvement, there are ongoing investigations examining the potential of ambroxol and other agents.[41]

Enzyme therapy is also now available for patients with LAL deficiency, and clinical trials have revealed increased survival in patients with the severe subtypes with salutary changes in lipid profile to a less atherogenic make-up in the attenuated cases, which would be anticipated to reduce long-term complications associated with atherosclerosis (e.g., myocardial infarction, stroke), although this remains to be shown.[42] It is likely that early treatment may halt or delay progression to cirrhosis and liver failure in patients with LAL deficiency, but this also needs to be demonstrated. A particular challenge for attenuated subtypes is the variability in disease progression, so long-term follow-up will be required to ascertain the types of patients most likely to benefit and the appropriate time to initiate therapy.

Enzyme therapy for NPD Type B remains investigational, although the outcome of ongoing clinical trials has demonstrated its relative safety and effectiveness in leading to resolution of the systemic manifestations of disease, as observed with enzyme therapy for GD.[43]

As NPD Type C is not an enzyme deficiency disorder, studies have focused on pharmacologic treatments that may be potentially safe and effective. Miglustat, an orally administered substrate synthesis inhibitor, has been shown to ameliorate some features of disease and improve survival, although responses have not been uniform across patient populations, perhaps because of diagnostic delays prior to treatment initiastion.[44] The rationale for the use of miglustat is based on reducing the build-up of substrates, primarily gangliosides. Unlike miglustat, cyclodextrin (2-hydoxypropyl-β-cyclodextrin) does not reduce the rate of substrate synthesis but it has been found to mobilise cholesterol by mechanisms not fully understood. When administered to the mouse and cat models of NPD Type C1, cyclodextrin was shown to extend life, reduce cerebellar pathology, and delay the onset of ataxia.[45] Clinical trials with cyclodextrin, administered either intravenously or intraventricularly, are underway.[46] Another drug under consideration is arimoclomol, a small-molecule co-inducer of heat shock proteins that is currently in clinical trials for NPD Type C; *in vitro* studies involving fibroblasts obtained from affected individuals have shown recombinant human heat shock protein 70 improved the binding of several sphingolipid-degrading enzymes to their essential co-factor bis(monoacyl)glycerophosphate, and the potential for reducing tissue substrate storage.[47]

In patients with LAL deficiency, the use of lipid-lowering drugs has been considered as a means of reducing cardiovascular comorbidity.[48] However, its use may not obviate the need for enzyme therapy as such an approach would not lead to eliminating damage to the liver, which can develop in affected individuals. Regardless, it raises the prospect of combination therapy to promote an optimal outcome, but this requires closer examination.

CONCLUSION

In patients, whether children or adults, presenting with hepatomegaly as a finding or chief complaint, a high index of suspicion should be maintained that the clinical problem may be caused by a lysosomal storage disease. A positive family history for similar manifestations may be a valuable clue, given the conditions

described (namely, GD, NPDs, and LAL deficiency) are all inherited autosomal recessive traits. However, the absence of a family history should not exclude diagnostic consideration and investigations should continue when other clinical manifestations are suggestive (e.g., presence of anaemia, thrombocytopenia, splenomegaly, lung involvement, and/or bone disease). Neurologic involvement may also be encountered in a subset of these conditions.

Diagnostic confirmation in these instances is established based on demonstration of the underlying enzyme deficiency, complemented by molecular genetic testing. An exception is with NPD Type C, as the underlying cause lies with either a gene defect encoding a transmembrane or soluble non-catalytic protein; thus, molecular genetic testing is required. Changes in concentrations of several biomarkers may provide additional clues, but as with diagnostic confirmation the availability of such testing may be limited to specialised laboratories. For these sphingolipidoses and related conditions, carrier screening can be performed reliably by genetic testing, when the causal mutation segregating in the family is identified.

Enzyme therapy is available for GD and LAL deficiency and under investigation for NPD Type B, whilst therapeutic trials for NPD Type C explore different pharmacologic options. Early diagnosis is key to achieving a favourable clinical outcome. Of recent interest are comorbidities that have become a focus of research, as they have been recognised as part of perhaps an expanded spectrum of disease, now that the cardinal features have been effectively managed by therapeutic options (e.g., MM and PD in GD). Despite their rarity, valuable lessons have been learned as we await the promise of gene therapy. A principal unmet need is treatment for the CNS manifestations.

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Portal Hypertension in Non-alcoholic Fatty Liver Disease in the Era of Non-invasive Assessment

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the emerging global health problems due to an increase of burden worldwide. It has been known that NAFLD is strongly associated with metabolic syndrome. The progression of NAFLD is a complex and multifactorial mechanism. Portal hypertension is still the main key in liver disease progression management. In NAFLD, portal hypertension might occur in the non-cirrhotic condition. Hepatic vein pressure gradient measurement has been considered as the gold standard for portal pressure assessment; however, due to its invasiveness and the need for a high-expertise centre, it is considered a non-practical measurement tool in clinical practice. Many other non-invasive parameters have been developed to replace the invasive measurement; however, there are still some limitations with regard to the technical issue, patient's condition, and its accuracy in the different stages of the disease. Therefore, the authors review portal hypertension related to the clinical course of NAFLD, and the development of portal pressure evaluation in patients with NAFLD.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) is considered as one of the fastest emerging global health priorities due to the continuous increase of burden worldwide.[1,2] The progression of NAFLD itself is a complex and multifactorial mechanism. A progressive liver disease in NAFLD is marked by hepatocyte injury in the form of ballooning, inflammation, and fibrosis, which is also known as non-alcoholic steatohepatitis (NASH).[3]

In NAFLD progression, one of the most common complications is portal hypertension due to extensive fibrosis with parenchymal and vascular remodelling in cirrhotic liver. Over the last two decades, the use of hepatic venous pressure gradient (HVPG) has become the most utilised measurement for portal pressure. This method, however, has been limited by the fact that it is an invasive technique and can only be conducted in highly specialised medical centres. Moreover, increasing demand for non-invasive methods is also contributed by the problem of early progression from intrahepatic vascular resistance to liver disease, even in the absence of cirrhosis.[4,5] Therefore, development of safe and reliable non-invasive methods for measurement and

monitoring of portal pressure is still important for prevention and early management in NAFLD-related portal hypertension.

AIM OF THE STUDY

This review will discuss the mechanisms behind NAFLD-related portal hypertension in the presence or absence of cirrhosis. Recent findings about non-invasive diagnostic modalities for portal hypertension, especially those related to the potential use in non-cirrhotic portal hypertension, will also be reviewed.

CLINICALLY SIGNIFICANT PORTAL HYPERTENSION IN NON-ALCOHOLIC FATTY LIVER DISEASE

Clinically significant increased portal pressure or clinically significant portal hypertension (CSPH) is defined as an increase of portohepatic gradient of at least 10 mmHg. Determination of CSPH is critical to evaluate possible complications, such as oesophageal varices or ascites, because different levels of risk and prognostic significance are represented by the degree of portal hypertension.[6,7] Portal pressure higher than 20 mmHg is also correlated with difficult variceal bleeding management.[8]

In general, portal hypertension is caused by increased resistance towards portal blood flow. Increase in hepatic vascular resistance is caused by either structural component or dynamic component in the form of increased hepatic vascular tone. Increase in portal-collateral blood flow is caused by splanchnic arteriolar vasodilation and neo-angiogenesis as a response towards increased production of splanchnic vasodilators.[9] In NAFLD, structural and functional changes, such as enlarged hepatocytes and ballooning injury, may affect the homeostasis of sinusoids since the early stage of the disease through endothelial dysfunction, disrupted sinusoidal microanatomy, and cross-talks among hepatocytes. As a result, intravascular hepatic resistance will be increased, leading to progression of NAFLD and development of portal hypertension. To sum up, development of portal hypertension in NAFLD can occur through early sinusoidal compression and microcirculatory disruption without the presence of extensive fibrosis or tissue remodelling in cirrhosis.[8,10]

As mentioned above, another important problem in NAFLD-related portal hypertension is the concept of portal hypertension without the presence of fibrosis or cirrhosis. A prospective study of 292 subjects with NAFLD showed that 17% of the subjects who did not have cirrhosis were found to have portal hypertension (HVPG >5 mmHg), in which 0.5% of the subjects had CSPH.[11] Another observational study of 354 subjects with NAFLD also demonstrated similar findings, showing that 12 out of 100 subjects with portal hypertension (only based on clinical manifestation) did not exhibit any advanced fibrosis or cirrhosis. The authors also pointed out that the only significant difference between subjects with and without portal hypertension was the severity of steatosis.[12] In contrast, a retrospective study of 261 subjects showed no significant association between histological steatosis and HVPG measurement. However, this study also showed that the presence of diabetes mellitus, one of the most predominant risk factors of NAFLD, was significantly associated with the presence of CSPH.[13] Consequently, development of non-invasive modalities that can be a prognostic indicator related to the presence of portal hypertension in patients without advanced fibrosis or cirrhosis still becomes a necessity.

ASSESSMENT OF PORTAL HYPERTENSION IN NON-ALCOHOLIC FATTY LIVER DISEASE WITHOUT CIRRHOSIS

The studies in patients with NAFLD and without cirrhosis, especially the ones utilising large-scale -omics technologies and integrative systems biology, are still considered as very scarce. An observational study by Da et al.[14] of patients with non-cirrhotic portal hypertension indicated that no significant difference was found among HVPG results of patients with portal hypertension caused by nodular regenerative hyperplasia. Unlike in cirrhosis, nodular regenerative hyperplasia often results in perisinusoidal or presinusoidal portal hypertension, which often show normal or mildly increased HVPG.[14] Other possible reasons behind the drawback of these studies may include sporadic utilisation of portal pressure measurement, especially considering its invasive nature, such as HVPG measurement, in patients with less-advanced early disease. Consequently, higher number of non-invasive

options are still necessary to overcome the lack of portal pressure measurement methods in patients with early stages of advanced liver disease.[10,14]

Magnetic resonance (MR)-based methods have demonstrated the ability to discern between portal hypertension with and without cirrhosis. In a retrospective evaluation of 41 subjects with non-cirrhotic portal hypertension, magnetic resonance elastography (MRE) also indicated a promising result, showing that increased liver stiffness measurement, as well as increased ratio of splenic stiffness measurement and liver stiffness measurement, can distinguish non-cirrhotic portal hypertension from cirrhotic portal hypertension. The study also showed that liver stiffness measurement was markedly lower in portal hypertension without cirrhosis, while the ratio between spleen stiffness measurement and liver stiffness measurement was markedly higher in portal hypertension without cirrhosis.[15] In addition, MR-based methods have been well-correlated with a wide range of HVPG measurements (3–16 mmHg). A study by Gharib et al.[16] demonstrated an independent significant correlation (p=0.015) between HVPG and MRE of the liver, with a median HVPG of 6 mmHg from 23 subjects. Liver stiffness measurement by MRE also showed significant correlation with histologic fibrosis score (p=0.004).[16]

The emerging use of non-invasive serum biomarkers, especially metabolite profiling, which incorporates genetic and environmental inputs, has been summarised in previous studies. This is particularly in line with the fact that both genetic and environmental factors play a very important role in NAFLD progression. In addition, markers of metabolic status and microbiome changes can also act as early predictors of portal hypertension in NAFLD since the pathophysiology of NAFLD also involves gut microbiota changes and metabolic syndrome.[10] Generally, the aim of metabolomics or metabolic profiling is to measure endogenous small metabolites quantitatively. Since the measured small molecular metabolites contain substrates and by-products, such as carbohydrates, fatty acids, and amino acids, the results may represent the metabolic responses in a disease or potential intermediate phenotypes.[17] On the other hand, soluble CD163 scavenger receptor and enzyme haem oxygenase-1 have been shown as Kupffer cell-specific markers, related to the microbiota disturbance in NAFLD.[10] Activation of Kupffer cells and bacterial translocation occur due to increased intestinal permeability. Activated Kupffer cells will eventually lead to increased production of inflammatory mediators and activation of hepatic stellate cells, leading to liver fibrosis. A study by Grønbaek et al.[18] also highlighted a significant correlation between circulating soluble CD163 and HVPG, indicating its role as an independent predictor for HVPG.[18] Other proteins associated with intrahepatic endothelial dysfunction and remodelling of extracellular matrix include von Willebrand factor antigen, the formation marker procollagen Type V, and osteopontin.[19] Overall, these novel biomarkers, especially when they are being measured simultaneously and/or serially, can be potentially advantageous in predicting disease progression, even in early stage diagnosis.[10]

ASSESSMENT OF PORTAL HYPERTENSION IN NON-ALCOHOLIC FATTY LIVER DISEASE WITH CIRRHOSIS

Portal pressure gradient (PPG) is known as the pressure gradient between the portal vein and inferior vena cava. Measurement of PPG represents measurement of liver portal perfusion pressure. The normal value is up to 5 mmHg.[9,10]

Hepatic Venous Pressure Gradient

Currently, HVPG measurement is considered as the gold standard technique to assess portal hypertension in liver cirrhosis. HVPG measurement is defined as the measurement of difference between wedged hepatic venous pressure and normal free hepatic venous pressure.[4,9] HVPG measurement is considered a safe technique due to its low rate of complications (<1% of the cases, mainly caused by transient cardiac arrhythmias and local injury on the site of puncture). This technique also does not have many relative contraindications, such as abnormal coagulation parameters and history of allergic reactions towards iodinated contrast.[20] In addition, HVPG measurement has also been considered as one of the best prognostic indicators in liver cirrhosis (Table 1).[6]

Table 1: Prognostic stratification of liver cirrhosis by hepatic venous pressure gradient measurement.[6-9]

Clinical Settings	HVPG (mmHg)	Increased risk of threshold
Compensated cirrhosis	10	Gastroesophageal varices, first episode of clinical decompensation in patients without varices, development of HCC, decompensation post-surgery for HCC
	12	Variceal bleeding
	16	First episode of decompensation in patients with varices
Decompensated cirrhosis	16	Variceal rebleeding
	20	Failure of controlling active variceal bleeding
	22	Mortality in alcoholic cirrhosis and acute alcoholic hepatitis
	30	Spontaneous bacterial peritonitis
Acute variceal bleeding	20	Treatment failure and increased mortality

HCC: hepatocellular carcinoma; HVPG: hepatic vein pressure gradient.

Upper Gastrointestinal Endoscopy

Another gold standard for evaluating oesophageal and gastric varices with the bleeding risk is an upper gastrointestinal endoscopy or oesophagogastroduodenoscopy (OGD). Oesophageal varices have been estimated to be present in 30–40% of compensated cirrhosis and up to 60% of decompensated cirrhosis.[9,21] According to Baveno VI criteria, high-risk varices are considered to be unlikely in patients with liver stiffness measurement <20 kPa from the result of transient elastography (TE) and normal platelet count.[22,23] Based on these criteria, newly diagnosed patients with liver cirrhosis must undergo an OGD examination to exclude the presence of gastroesophageal varices.[20,24]

Video Capsule

Video capsule is one of the applications of endoscopy-guided technique to overcome the invasive characteristic of an OGD. A multi-centre study conducted by Laurain et al.[25] showed that the sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of video capsule were 65%, 83%, 65%, and 83%, respectively. The diagnostic values of video capsule were lower when it was used to differentiate between small and large oesophageal varices (sensitivity: 64%; specificity: 93%; PPV: 88%; NPV: 78%; and overall accuracy: 81%). Taken together, it was concluded that the diagnostic values of video capsule were inadequate to replace OGD in patients with cirrhosis with clinical suspicion of portal hypertension.[26]

Non-invasive Modalities in the Diagnosis of Non-alcoholic Fatty Liver Disease-Related Portal Hypertension with Cirrhosis

Ultrasonography

The pathognomonic signs in portal hypertension are the presence of flow in paraumbilical vein and splenorenal collaterals, as well as reversed flow of the portal vein. Another grey-scale sign of portal hypertension is dilation of portal, mesenteric, and splenic veins. There are two ultrasound-based modalities commonly used for detecting portal hypertension: Doppler ultrasound and contrast-enhanced ultrasound (CEUS).[20,27] Different sensitivities and specificities from different signs of portal hypertension from ultrasound-based modalities are summarised in Table 2.[5]

Table 2: Summary of sensitivity and specificity values from each sign of portal hypertension obtained from ultrasound-based modalities.[5]

Signs of portal hypertension	References	Sensitivity (%)	Specificity (%)
Dilation of portal vein (>13 mm)	Bolondi et al.,[34] 1982	<50.0	90.0–100.0
Reduction of portal vein blood flow velocity	Zironi et al.,[35] 1992 Haag et al.,[36] 1999	88.0	96.0
Reversed portal vein blood flow	Gaiani et al.,[37] 1991	N/A	100.0
Increased portal vein congestion index	Moriyasu et al.,[29] 1986 Haag et al.,[36] 1999	67.0	100.0
Dilation of the splenic vein and superior mesenteric vein	Goyal et al.,[38] 1990	72.0	100.0
Reduced respiratory variation of diameter in splenic and superior mesenteric veins	Bolondi et al.,[34] 1982	79.7	100.0
Splenomegaly	Berzigotti et al.,[39] 2008	93.0	36.0
Portosystemic collateral circulation	Vilgrain et al.,[40] 1990	83.0	100.0
Increased Doppler resistive index of splenic artery	Vizzutti et al.,[41] 2007 Piscaglia et al.,[42] 2001	84.6	70.4
Increased Doppler resistive index of hepatic artery	Piscaglia et al.,[42] 2001 Schneider et al.,[43] 1999	86.0	88.0
Increased Doppler resistive index of renal artery	Berzigotti et al.,[39] 2008 Vizzutti et al.,[41] 2007	83.6	74.4
Decreased Doppler pulsatility index of superior mesenteric artery	Vizzutti et al.,[41] 2007	85.7	65.2

N/A: not applicable.

With Doppler ultrasound, evaluation of blood haemodynamics can be performed by examining portal vein velocity, congestion index, pulsatility index, and hepatic vein patterns. Measurement of portal vein velocity yields sensitivity of 88% and specificity of 96% if the mean portal vein velocity cut-off is 15 cm/sec.[28] This approach, however, has high inter-observer and inter-machine variability. In addition, the finding is also influenced by positioning of the patient. Another approach is by measuring congestion index or the ratio of portal vein cross-sectional area and portal velocity. In patients with cirrhosis and portal hypertension, congestion index was 2.5-fold higher compared to healthy patients, with a sensitivity of 67–95%.[29] In cirrhotic liver, hepatic venous waveform can also be altered due to loss of normal pulsatility in hepatic veins (likely caused by hepatic vein stenosis), which is also correlated with worse survival rate and higher Child–Pugh class.[30] A study of 121 subjects with NAFLD also demonstrated the potential use of Doppler ultrasound in evaluating hepatic blood flow in NAFLD-related portal hypertension. The authors, however, also addressed the difficulty in reproducing reliable Doppler ultrasound indices as one of the limitations of their study.[31] Moderate sensitivities have also been shown from increased Doppler resistive index of splenic (84.6%), hepatic (86%), and renal (83.6%) arteries

obtained from ultrasound-based modalities. The highest specificity, nonetheless, was observed from increased Doppler resistive index of renal artery.[5]

On the other hand, in NAFLD, CEUS has been utilised more often as a modality to distinguish NASH from steatosis by showing reduced accumulation of contrast microbubbles in NASH. The possibility of using CEUS to detect changes in hepatic vascular parameters has been evaluated by Cocciolillo et al. in a prospective study involving a quantification of portal vein and parenchymal blood flow in NAFLD and NASH subjects. The authors exhibited compelling alteration of vascular flow parameters in subjects with NAFLD and NASH in comparison to the control group by utilising CEUS. All the CEUS procedures were conducted successfully without any adverse events. Nevertheless, further studies in larger population are still necessary to validate this finding.[32,33]

Transient elastography

Initially, one-dimensional ultrasound TE had only been proposed as a method to assess liver fibrosis. TE utilises the velocity of a low frequency (50 Hz) elastic shear wave, which is propagated through liver tissue to evaluate liver stiffness.[22] In a study involving 124 subjects with recurrent hepatitis C virus infection after liver transplantation, the area under the receiver operating characteristic curve (AUROC) of TE for diagnosing CSPH was 0.94 (sensitivity: 90%; specificity: 81%; PPV: 81%; and NPV: 90%).[44] Another study by Bureau et al.[45] demonstrated that performance of TE in diagnosing CSPH in chronic liver diseases displayed higher cut-off values in alcoholic cirrhosis (34.9 kPa) when compared to viral cirrhosis (20.5 kPa).

The main advantage of using TE is the fact that it is the most widely used and validated modality with a high range of values (2–75 kPa). Despite this, the measurement can be difficult to perform in patients who are obese, patients with narrow intercostal spaces, or patients with massive ascites. TE demonstrated good reproducibility with lack of applicability (80%), depending on the experience of the operator.[7,22] In order to overcome these limitations, an effort has been made to combine TE with other non-invasive methods. Berzigotti et al.[46] evaluated the degree of portal hypertension and the presence of oesophageal varices in 117 subjects using a combination of TE, platelet count, and spleen diameter. The AUROC was higher from the combination (0.909) in comparison to each parameter, suggesting that diagnostic accuracy of TE can be improved when it is combined with other non-invasive modalities. This finding is also supported by a study in NAFLD and NASH subjects, which showed a satisfactory diagnostic performance of the combined use of transient elastography and CEUS.[33]

Shear wave elastography

The accuracy of shear wave elastography (SWE) is generally comparable with TE in evaluation of liver fibrosis. In a preliminary study performed on subjects with viral hepatitis, it was demonstrated that an acoustic radiation force impulse (ARFI) elastography had similar diagnostic accuracy with TE for diagnosing advanced fibrosis and cirrhosis.[47] This result is further supported with a meta-analysis showing no significant difference between an ARFI elastography and TE in the detection of liver fibrosis and cirrhosis.[48] Nevertheless, conflicting results about the superiority of ARFI elastography in diagnosing portal hypertension are still found from previous studies. Attia et al.[49] discovered that for diagnosing CSPH, the accuracy of liver and spleen stiffness measurement by an ARFI elastography was excellent (area under the curve [AUC] for liver stiffness: 0.929; AUC for spleen stiffness: 0.968) without any significant difference between liver and spleen stiffness measurement (p=0.79). Another study, which compared performance of ARFI and TE in diagnosing CSPH, found a significant correlation between liver stiffness measurement by ARFI (p<0.001) and TE (p<0.001) to HVPG. However, in this study, TE showed higher diagnostic accuracy compared to ARFI (AUC: 0.870 versus 0.855) without any statistically significant difference (p=0.8).[50]

Similarly, 2D SWE has also been widely used for evaluation of liver fibrosis. A prospective study by Osman et al.[51] compared the performance of 2D SWE to TE in 215 subjects with chronic hepatitis, and showed similar accuracy between both modalities. The highest sensitivity and specificity of 2D SWE were observed in evaluation of Stage F0 (sensitivity: 91.4%; specificity: 98.6%) and

Stage F4 (sensitivity: 100%; specificity: 91%). A review by Jeong et al.[52] showed a good diagnostic performance of 2D SWE in differentiating between significant fibrosis, advanced fibrosis, and cirrhosis in NAFLD subjects, with an AUROC of 75.0–92.8%. Nevertheless, a relatively high failure rate (2.7–13.0%) was still observed from the measurement of liver stiffness by this modality, especially in subjects with NAFLD and a higher BMI.

Spleen stiffness measurement

Evaluation of the association between spleen stiffness measurement (SSM) and HVPG was initially performed in subjects with hepatitis C virus-related cirrhosis by Colecchia et al.,[53] in which SSM showed the strongest correlation with HVPG. SSM also demonstrated significantly higher diagnostic accuracy for the presence of oesophageal varices compared to other modalities (AUROC: 0.94). A recent meta-analysis confirmed this finding by showing the superiority of SSM compared to liver stiffness measurement in predicting oesophageal varices (diagnostic odds ratio: 25.73 versus 9.54). SSM also exhibited higher sensitivity (87%) and specificity (75%) in adults with chronic liver diseases.[54]

Furthermore, SSM has been proposed as a diagnostic tool for early assessment of portal haemodynamic changes. A study by Santis et al.[55] observed a significantly reduced SSM ($p<0.001$) after placement of transjugular intrahepatic portosystemic shunt (TIPS). This study also found that there was no significant correlation between portal atrial gradient and liver stiffness measurement, suggesting the superiority of SSM compared to liver stiffness measurement in monitoring the modification of portal hypertension. On the contrary, Novelli et al.[56] observed similar number in increased SSM (42%) and reduced SSM (58%) after placement of TIPS. Another study of 135 subjects with cirrhosis caused by different aetiologies also demonstrated a stepwise increased diagnostic value of the SSM, in line with increased severity of portal hypertension. Significantly higher average spleen elastography measurement was obtained in subjects with oesophageal varices compared to those without any varices.[57] A review by Colecchia et al.[5] evaluated the accuracy of spleen stiffness by MRE for detecting CSPH and oesophageal varices, with the best accuracy represented by a cut-off value of 8.8 kPA.

Indocyanine green clearance

Indocyanine green (ICG) is a tricarbocyanine dye with water-soluble characteristics and with an ability to bind to albumin and α-1 lipoproteins. In the past, plasma clearance rate of ICG has a role in pre-operative assessment of the remaining liver tissues.[58] A study in subjects with compensated liver cirrhosis showed a linear correlation between ICG 15-minute retention test (ICG-r15) with HVP. ICG-r15 also demonstrated a good performance in detection of CSPH (AUC: 0.808). Meanwhile, in diagnosing oesophageal varices, the highest accuracy was shown by ICG-r15 (AUROC: 0.859) compared to other non-invasive parameters.[59]

MRI and CT

The use of MRI and/or CT is specifically recommended in clinical conditions that require more detailed assessment with accurate visualisation of portal venous system, e.g., portal cholangiopathy in portal cavernoma, evaluation of the extent of thrombosis, ectopic variceal bleeding, and prior to placement of TIPS. In detection of large oesophageal varices, the sensitivity of single-detector and multi-detector CT scan is 84–100%, while the specificity is 90–100%. Substantial irradiation and moderate inter-observer variability should be considered as the limitations of CT scan.[9,60] Previous evidence also demonstrated a significant correlation between portal pressure and all flow parameters in MRI, with meaningful correlations for portal fraction ($p<0.001$), portal perfusion ($p<0.001$), and mean transit time ($p<0.001$).[61]

Recent studies have suggested the role of MR-based elastography as an alternative method to evaluate liver elasticity. Data from a single-centre prospective study of 146 subjects with chronic liver disease showed a significantly higher AUROC value of MRE (0.994) in assessing liver fibrosis compared to ultrasound elastography and aspartate aminotransferase (AST)-to-platelet ratio index (APRI) (AUROC: 0.837 and 0.709, respectively). Interestingly, MRE also exhibited higher diagnostic performance compared to combination of ultrasound elastography and APRI (AUROC: 0.849).[62] Aside from liver fibrosis, MRE has also emerged as a potential diagnostic modality for assessing portal hypertension. Additional evidence was obtained from another study to assess the performance of 3D multi-frequency MRE for determining the degree

of portal hypertension and high-risk oesophageal varices. The spleen loss modulus demonstrated the strongest correlation with HVPG compared to other viscoelastic parameters, suggesting it to be the best parameter in the study.[54]

Subharmonic-aided pressure estimation

Subharmonic-aided pressure estimation (SHAPE) is one of the most recent non-invasive modalities to assess portal pressure.[6] The basic concept of this technique is using subharmonic emissions from microbubbles to obtain changes in ambient pressure. In general, there are three stages of subharmonic signal generation in incident acoustic power: occurrence, growth, and saturation. SHAPE depends on incident acoustic power in growth stage. An animal study using canines indicated the potential of portal vein pressure monitoring with SHAPE. A statistically significant difference was also observed in subharmonic signal amplitudes prior to and after portal hypertension condition was applied on the canines.[63]

Further evaluation of SHAPE was performed in 45 subjects with chronic liver disease. Twenty-nine percent of the subjects had NASH as the aetiology of chronic liver disease. There was a strong positive correlation between estimation of SHAPE pressure gradient and HVPG, with the strongest correlation found in the sub-group with HVPG of at least 12 mmHg. In addition, significantly higher mean SHAPE gradient was observed in subjects with higher risk of variceal bleeding (AUROC for HVPG ≥12 mmHg: 0.94; AUROC for HVPG ≥10 mm: 0.90). The estimated sensitivity and specificity of SHAPE were 100% and 81%, respectively. Overall, this preliminary study demonstrated the accuracy of SHAPE as a non-invasive tool to measure portal vein pressures in patients with chronic liver disease.[65]

Endoscopic ultrasound-guided measurement of portal pressure gradient

Previously, an animal study demonstrated comparable results between endoscopic ultrasound (EUS)-guided measurement of PPG and HVPG. Excellent correlation was exhibited between EUS and interventional radiology methods (Pearson's correlation coefficient was 0.999 for all vessels).[66] Another pilot study in humans with 28 subjects also showed high technical success rate (100%) in measuring 1.5–19.0 mmHg without any adverse events.[67] The most recent study by Zhang et al.[68] also showed similarly high technical success rate (91.7%) with similarly good correlation between EUS-guided measurement of PPG and HVPG (Pearson's correlation coefficient was 0.923; $p<0.001$). In this study, no adverse events were reported, suggesting the potential of EUS-guided measurement of PPG as a direct, safe, and accurate method in assessing portal hypertension.

COMBINATION OF NON-INVASIVE BIOMARKERS FOR NON-ALCOHOLIC FATTY LIVER DISEASE-RELATED PORTAL HYPERTENSION

The role of non-invasive biomarkers has also been emphasised in NAFLD and NASH to substitute liver biopsy as the main standard reference for assessment of the severity of NAFLD.[69] Considering the invasive nature of liver biopsy, as well as the risk of sampling bias, it is necessary to find other methods to overcome those limitations. Several indices and biomarker panels have been proposed as alternative options (Table 3). Moderate accuracy has been demonstrated by the Fatty Liver Index (FLI), which consists of BMI, waist circumference, and serum triglyceride and γ-glutamyl transferase levels. The FLI has shown sensitivity as high as 87% and AUROC of 0.84 in diagnosing fatty liver, although this test cannot be used to differentiate steatosis grades.[69] FLI, however, has been demonstrated to have independent association with liver-related mortality within 15 years (hazard ratio: 1.04) in an Italian cohort study. Moreover, FLI was also significantly associated with fibrinogen level, which was considered as a surrogate marker of inflammation.[70] Another option that can be considered is the Hepatic Steatosis Index (HSI), which consists of the ratio between serum AST and serum alanine aminotransferase (ALT), sex, BMI, and history of diabetes mellitus. Moderate accuracy (AUROC: 0.801–0.824) has been shown by HSI with high sensitivity (93.1%) and specificity (92.4%).[69,71] Another retrospective observational study in a population with HIV infection also validated the performance of HSI in diagnosing steatosis (diagnostic accuracy: 84.5%).[72]

Table 3: Summary of potential non-invasive biomarker panels for non-alcoholic fatty liver disease-related portal hypertension.

Non-invasive panels	References	Sensitivity (%)	Specificity (%)	PPV	NPV	AUROC	Limitations
FLI	Wong et al.,[69] 2018 Calori et al.,[70] 2011	87.0	64.0	N/A	N/A	0.84 (for fatty liver diagnosis) Statistically significant independent association with liver inflammation and liver-related deaths within 15 years	Sub-optimal reference standards (ultrasonography findings may be operator-dependent and show lower sensitivity towards lower grade of steatosis)
HSI	Wong et al.,[69] 2018 Lee et al.,[71] 2010 Sebastiani et al.,[72] 2015	93.1	92.4	N/A	N/A	0.801–0.824 (for NAFLD screening) 0.845 (for predicting hepatic steatosis in HIV mono-infection)	Sub-optimal reference standards (ultrasonography findings may be operator-dependent and show lower sensitivity towards lower grade of steatosis)
NFS	Lee et al.,[71] 2010	N/A	N/A	44	93	0.70–0.83 (for predicting liver-related events) 0.65–0.83 (for predicting fibrosis progression)	Varied BMI interpretation among different ethnicities
FIB-4	Lee et al.,[71] 2010	N/A	N/A	49	97	0.67–0.82 (for predicting liver-related events) 0.65–0.81 (for predicting fibrosis progression)	Moderate reproducibility because aminotransferases can fluctuate rapidly
APRI	Lee et al.,[71] 2010 Siddiqui et al.,[73] 2019	N/A	N/A	47	97	0.52–0.73 (for predicting liver-related events) 0.65–0.82 (for predicting fibrosis progression)	Modest accuracy
BARD	Harrison et al.,[74] 2008	N/A	N/A	42	97	0.81 (for predicting fibrosis Stage 3–4)	Varied BMI interpretation among different ethnicities

Table 3 continued.

Non-invasive panels	References	Sensitivity (%)	Specificity (%)	PPV	NPV	AUROC	Limitations
ARFI-spleen diameter-to-platelet ratio	Park et al.,[75] 2015	81.1 (for diagnosis of oesophageal varices) 90.0 (for high-risk varices)	84.0 (for diagnosis of oesophageal varices) 94.3 (for high-risk varices)	63.8 (for diagnosis of oesophageal varices) 72.0 (for high-risk varices)	92.7 (for diagnosis of oesophageal varices) 98.3 (for high-risk varices)	0.903 (for diagnosis of oesophageal varices) 0.946 (for high-risk varices	Relatively lower PPV indicates that unnecessary endoscopic procedures may be performed in some patients without high-risk varices
Hepascore	Huang et al.,[76] 2017	N/A	N/A	N/A	N/A	0.92 (for predicting cirrhosis) 0.83 (for predicting advanced fibrosis)	Heterogeneity between studies
ELF Test	Vali et al.,[77] 2020	93 (for cut-off score: 7.70) 36–65 (for cut-off scores: 9.80, 10.51, 11.30)	34 (for cut-off score: 7.70) 86–96 (for cut-off scores: 9.80, 10.51, 11.30)	N/A	0.83–0.98 (in settings with disease prevalence <40%)	0.81	Limited sensitivity for excluding advanced and significant fibrosis with higher cut-off scores
FAST	Newsome et al.,[78] 2020	64–100 (for rule-out zone) 4–36 (for rule-in zone)	35–86 (for rule-out zone) 25–75 (for rule-in zone)	33–83 (for rule-in zone)	73–100 (for rule-out zone)	0.74–0.95	Higher expertise and facilities may be needed to utilise this method in primary care

APRI: AST to Platelet Ratio Index; AST: aspartate aminotransferase; AUROC: area under the receiver operating characteristic curve; ELF: enhanced liver fibrosis; FAST: FibroScan-AST; FIB-4: Fibrosis-4; FLI: Fatty Liver index; HIS: Hepatic Steatosis Index; N/A: not applicable; NAFLD: non-alcoholic fatty liver disease; NFS: NAFLD Fibrosis Score; NPV: negative predictive value; PPV: positive predictive value.

To date, the most common non-invasive panels to be utilised are the NAFLD Fibrosis Score (NFS), Fibrosis-4 (FIB-4), APRI, and BARD score. NFS consists of age, BMI, diabetes mellitus, ratio of serum AST and serum ALT, platelet count, and albumin. This parameter has been validated with AUROC of 0.82.[79] On the other hand, FIB-4 index (which includes age, AST, platelet count, and ALT components) and APRI score (which includes AST and platelet count components), which were first introduced in 2003 and 2006, respectively, have also shown promising results in previous studies.[80] A systematic review by Lee et al.[23] pointed out that FIB-4, NFS, and APRI showed good prognostic accuracy for liver-related events with AUROC ranging from 0.69 to 0.92. However, FIB-4 and NFS showed superior results (AUROC: 0.67–0.82 and 0.7–0.83, respectively) compared to APRI (AUROC: 0.52–0.73) in predicting mortality. Higher accuracy for predicting fibrosis progression was also shown by FIB-4 (AUROC: 0.65–0.81) and NFS (AUROC: 0.65–0.83) in comparison to APRI (AUROC: 0.65–0.82). A

cross-sectional study by Siddiqui et al.[73] showed low PPVs and high NPVs in FIB-4, NFS, and APRI. Meanwhile, BARD score consists of BMI, ratio of serum AST and ALT, and diabetes mellitus. The AUROC was 0.81 for detection of Stage 3–4 fibrosis, with PPV and NPV of 42% and 97%, respectively.[74]

Several other models are also currently emerging as potential diagnostic tools. A combination of platelet count and ARFI elastography was also used to produce a novel model, called ARFI-spleen diameter-to-platelet-ratio score, for evaluating oesophageal varices. The use of ARFI-spleen diameter-to-platelet-ratio score demonstrated superiority compared to ARFI elastography alone in diagnosis of oesophageal varices (AUROC: 0.769) and in high-risk varices (diagnostic accuracy: 93.5%).[77] A serum model called Hepascore, which was initially developed to predict the severity of liver fibrosis in chronic hepatitis C, consists of α2-macroglobulin, hyaluronic acid, and γ-glutamyl transpeptidase. One meta-analysis showed excellent performance of Hepascore in predicting cirrhosis (AUROC: 0.92) and advanced fibrosis (adjusted AUROC: 0.83).[76] Another proposed non-invasive method is enhanced liver fibrosis (ELF) test (consists of Type III procollagen peptide, hyaluronic acid, and tissue inhibitor of metalloproteinase-1), which exhibited moderate accuracy (AUROC: 0.81) and high sensitivity (97%) in differentiating significant fibrosis in subjects with NAFLD located in high prevalence settings.[77] A new diagnostic score under development, called FibroScan®-AST (FAST™) score (Echosens, Paris, France), which combines liver stiffness measurement, controlled attenuation parameter, and AST, also indicated a satisfactory performance in subjects with NASH (AUROC: 0.80).[78]

POTENTIAL FUTURE THERAPEUTIC OPTIONS FOR NON-ALCOHOLIC FATTY LIVER DISEASE-RELATED PORTAL HYPERTENSION

Aside from lifestyle intervention, various therapeutic targets from the cellular and molecular pathophysiology of NAFLD have been addressed from previous clinical evidence, especially with the therapeutic goal of decreasing intrahepatic vascular resistance. One of the greatest-potential therapeutic targets is sinusoid vascular regulation. Statins, in particular, have been proposed as the safest and the most effective agent to repair sinusoidal microvascular dysfunction. The involvement of statins is highlighted in eNOS-NO-sGC-cGMP, signalling through the up-regulation of transcription factor KLF2 and inhibition of Ras homolog family member A/Rho-associated coiled-coil protein kinase (RhoA/ROCK) pathway. The RhoA/ROCK pathway can cause vasoconstriction through several processes, such as regulating cytoskeletal structures for liver sinusoid endothelial cells capillarisation and increasing phosphorylation of myosin light chains. Another potential agent with similar therapeutic goal is nuclear farnesoid X receptor agonists. This agent is able to lower intrahepatic vasoconstriction by stimulating endothelial nitric oxide synthase activity, inhibiting contraction of stellate cells, inducing degradation of asymmetric dimethylarginine, and up-regulating the expression of cystathionase. Moreover, nuclear farnesoid X receptor agonist has also been shown to reduce *de novo* lipogenesis.[10]

Several other sinusoidal pathophenotypes have also been addressed as potential therapeutic targets in NAFLD-related portal hypertension. As a multi-kinase inhibitor, sorafenib has been demonstrated to be capable of reducing portal hypertension in cirrhosis by inhibiting the activation of vascular endothelial growth factor and platelet-derived growth factor. The use of anticoagulant has also been considered in tackling the microthrombosis problem, which may be involved in the development of portal hypertension. The use of antibiotics (e.g., rifaximin), antioxidant, and anti-inflammatory drugs have also been utilised to manage the dynamic components of vascular resistance in NAFLD.[10]

CONCLUSION

As a growing and significant global health problem, progression and complications of NAFLD remain the most essential fields to be studied, particularly because development of portal hypertension in NAFLD can occur without any extensive fibrosis or cirrhosis. Currently, HVPG is still the gold standard for measuring portal pressure, including in patients with NAFLD-related hypertension. However, recent

evidence demonstrated that the opportunity to optimise the gold standard techniques with other non-invasive assessments should not be overlooked, especially in non-cirrhotic portal hypertension cases. Further studies are crucially required to compare the accuracy and cost-effectiveness of potential non-invasive tests for NAFLD-related portal hypertension. Currently, some potential non-invasive modalities, i.e., combined novel biomarkers and/or metabolomic, are still under development. EUS-guided measurement of PPG is also considered as a direct, safe, and accurate method in assessing NAFLD-related portal hypertension.

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Review of Rifaximin: A Summary of the Current Evidence and Benefits Beyond Licensed Use

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Abstract

Antibiotic resistance in patients with cirrhosis continues to draw significant attention. With a propensity to frequent hospitalisations, patients with cirrhosis are subject to frequent antibiotic prescription. This increases their risk of developing resistance to one or more antimicrobial agents, making management of their condition particularly challenging. Despite advancements being made in the management of liver disease, mortality rates continue to rise: almost 5-fold in those <65 years of age while remaining the leading cause of death in those 35–49 years of age. Alternative therapeutic options to prevent disease progression and cirrhosis-associated complications are urgently required; rifaximin is one such example. The medication use in patients with cirrhosis demonstrates additional benefits beyond current licensed use in the UK, that being for the prevention of hepatic encephalopathy and traveller's diarrhoea; rifaximin has especially been explored beyond current licensed use in the context of enteric-driven pathologies. Through the therapy's key central action as a broad-spectrum antimicrobial, rifaximin has the ability to modulate the gut–liver axis via removal of gut microbial products associated with the progression of cirrhosis and its sequalae.

The benefits of rifaximin use continues to gather momentum, given its non-absorbable nature and well-tolerated side-effect profile, and these require consideration. With broad-spectrum antimicrobial properties, its use may assist in overcoming the conundrum posed of antibiotic resistance amongst patients with cirrhosis. This literature review discusses the chemical and antimicrobial properties of rifaximin, its licenced indication for use, and its reported benefits beyond this, as well as concerns regarding rifaximin resistance.

INTRODUCTION

Liver disease constitutes a major global health burden, with mortality rates increasing 4-fold since the 1970s and 5-fold in those <65 years of age. Liver disease represents the leading cause of death in those 35–49 years of age, and the third most common cause of death in those 50–64 years of age in 2019.[1] Its rising incidence and rate of prevalence are largely attributable to risk factors for the most common conditions, including growing levels of alcohol consumption, the obesity epidemic, and viral hepatitis.[2,3]

Cirrhosis remains the primary driver of liver-related deaths. Pathologically, progression from inflammation to fibrosis and on to cirrhosis occurs as a result of continual exposure to a hepatic insult.[4] Treating the underlying aetiology of liver disease can slow progression, although in some cases the only cure remains liver transplantation; however, this is restricted to selected patients only and is further limited by organ supply.[5] This highlights the urgent need to explore novel therapeutic options that ameliorate disease progression and its complications.

As a result of progressive immune dysfunction, patients with cirrhosis are at risk of recurrent bacterial infections, which are recognised as a major cause for the development of liver-related complications, advancement of liver failure, and repeated hospitalisations.[6] These patients are frequently prescribed antibiotics as treatment or for infection prophylaxis, making them susceptible to developing multiple drug-resistant and extensively drug-resistant organisms, for which limited therapeutic options exist.[7,8] This review discusses the growing understanding of the possible role of rifaximin as an agent that may impact upon the trajectory of chronic liver disease, as a tool in the prevention of antibiotic resistance in chronic liver disease, and other potential areas of clinical benefit.

RIFAXIMIN

The use of rifaximin beyond its current licensed indications has been explored, especially in the context of enteric-driven pathologies. Translation into clinical practice has been hindered by a paucity of robust clinical trials. A considered review of the current understanding and uncertainties surrounding rifaximin use in decompensated cirrhosis is needed to inform appropriate future trial design, and therefore is discussed further here.

Chemical Structure

Rifaximin is a semi-synthetic, non-aminoglycoside oral antibiotic derived from rifamycin.[9] Its pyridoimidazole ring differentiates it from other rifamycin derivates and leaves rifaximin water-insoluble, therefore inhibiting absorption in the gastrointestinal tract.[10,11] Its molecular mass size of 789.9 Da enables self-association, further preventing systemic absorption.[12] Consequently, adjustments of dosing are not required.[13] Following oral administration, the concentration of detectable rifaximin in blood and urine is less than 0.4%, but up to 97.0% in stool, suggesting that its bioavailability is localised to the gastrointestinal tract.[14]

Antimicrobial Properties

Rifaximin inhibits bacterial RNA synthesis through its action on the β-subunit of bacterial DNA-dependent RNA polymerase.[15] *In vitro* studies have demonstrated that rifaximin has antibiotic coverage against Gram-positive and Gram-negative aerobic and anaerobic bacteria (Table 1). It also shows effectiveness against the protozoa *Cyrptosporidium parvuum* and *Blastocystis hominis*.[17] Rifaximin has demonstrated intermediate *in vitro* activity against various enteropathogens, with minimum inhibitory concentrations $(MIC)_{50}$ and MIC_{90} values ranging 8–64 and 16–128 µg/mL, respectively.[18,19] Yet, rifaximin achieves potent *in vivo* activity against enteropathogens, which can be explained by its extremely high luminal concentrations (4,000–8,000 µg/g) that far exceed MIC_{90} values.[18,20] Certain enteric bacteria, such as *Clostridium difficile*, have shown increased susceptibility to rifaximin with lower MIC_{50} (≤0.25 µg/mL).[16,18]

The solubility of rifaximin is 70–120 times greater in bile than in aqueous solution. This aids action in the small intestine which is bile-rich, compared to the aqueous colonic environment.[21] Encouragingly, rifaximin does not significantly alter the composition of the gut microbiota but rather selectively targets bacteria (Table 1).

Concurrently, rifaximin favours the growth of beneficial bacterial species.[22]

Table 1: Isolated bacteria for which rifaximin has anti-microbial activity.[13,16]

	Gram positive	Gram negative
Aerobic Bacteria	*Enterococcus* *Mycobacterium tuberculosis* *Streptococcus pyogenes* *Enterococcus faecalis* *Streptococcus pneumoniae* *Staphylococcus epidermidis* *Staphylococcus aureus*	*Escherichia coli* *Shigella* spp *Salmonella* spp *Yersinia enterocolitica* *Proteus* spp *Peptococcus* *Peptostreptococcus* spp *Vibrio cholerae*
Anaerobic Bacteria	*Clostridium perfringens* *Clostridioides difficile* *Peptococcus* *Peptostreptococcus* *Bifidobacterium* spp	*Bacteroides bivius-diseiens* *Bacteroides fragilis* *Helicobacter pylori* Fusobacterium spp *Klebsiella pneumoniae*

Indications for Rifaximin Use

In view of its enterically localised bioavailability, rifaximin has primarily complemented the management of gastrointestinal pathology: travellers' diarrhoea, infectious diarrhoea, small intestinal bacterial overgrowth (SIBO), irritable bowel syndrome, diverticular disease, infection prophylaxis post-colorectal surgery, and inflammatory bowel disease.[23] Over the last decade it has also emerged as a key therapeutic agent in the management of hepatic encephalopathy (HE).[24] Despite widespread use in Europe for the above conditions,[25] rifaximin is licensed only to minimise recurrent episodes of overt HE (high-quality evidence, strong recommendation)[26] and to treat travellers' diarrhoea in the UK and USA (high-quality evidence, strong recommendation),[27] as well as to manage irritable bowel syndrome with diarrhoea in the USA (moderate-quality evidence, conditional recommendation).[28-30]

Hepatic encephalopathy

Rifaximin improves the severity of acute and chronic HE by targeting deaminating enteric bacteria producing systemically absorbed nitrogenous compounds, including ammonia.[31] Concurrently, rifaximin reduces pathogenic bacterial species, thereby reconditioning the gut microbiome and reducing systemic endotoxaemia.[32]

The beneficial effects of rifaximin in the treatment of overt HE were initially established in a double-blind, placebo-controlled trial by Bass et al.,[24] demonstrating that rifaximin was associated with a 6-month risk reduction in episodes of overt HE and HE-associated hospitalisations.[24] In a further randomised controlled trial (RCT), rifaximin plus lactulose demonstrated superiority over lactulose alone in decreasing hospital stay and all-cause mortality in patients with decompensated cirrhosis (23.8% versus 49.1%; $p<0.05$).[33] These results were reinforced by a meta-analysis of 19

RCTs including 1,370 patients.[34] Rifaximin use for HE in clinical practice is further advocated by its short- and long-term safety profiles. Its tolerance is well acknowledged, especially when compared to alternative treatment options.[35,36] Furthermore, its demonstrated benefits are beyond the physical alone, and it significantly improves health-related quality of life of patients with cirrhosis with HE.[37] In light of this, rifaximin is recommended in national and international consensus guidelines as an effective adjunct to lactulose for the prevention of recurrent overt HE.[38]

Other Potential Benefits of Rifaximin

Rifaximin has been shown to effect bacterial translocation, thereby modulating the gut microbiome. Therefore, it has the potential to modify the interplay of the gut–liver axis, central to progression of cirrhosis and its sequelae.[39] Data to support this have been reported, though changes to guidelines are yet to be implemented.

Spontaneous bacterial peritonitis

With guidelines recommending the use of norfloxacin for the management of spontaneous bacterial peritonitis (SBP), Campillo et al.[40] described the effects of long-term antibiotic administration, namely increased severity of hospital-acquired, Gram-positive staphylococcal infections and quinolone resistance. Presently, antibiotic resistance poses a significant challenge in the management of infection in patients with cirrhosis, with a pressing need for alternative prophylactic antibiotics.

Organisms responsible for the development of SBP are both Gram-negative and Gram-positive. Frequently isolated Gram-negative pathogens include *Escherichia coli, Klebsiella pneumoniae*, *and Streptococcus pneumoniae*.[41] Gram-positive pathogens implicated include methicillin-resistant *Staphylococcus aureus* and enterococci.[42] As shown in Table 1, rifaximin demonstrated antimicrobial effectiveness against all these pathobionts and so its use in preventing SBP has been previously investigated.

In an RCT comparing rifaximin to norfloxacin in 262 patients affected by cirrhosis, rifaximin was superior in reducing the incidence of recurrent SBP over 6 months (3.88% versus 14.13%; p=0.04).[43] Similar findings were established for the primary prevention of SBP in patients with hepatitis-C-induced cirrhosis.[44] In a meta-analysis comparing rifaximin to various systemic antibiotics, rifaximin lowered SBP risk by 47% compared to placebo for primary prevention, and by 74% compared to systemic antibiotics for secondary prevention.[45] Prospective open-label studies have been less optimistic, demonstrating mixed results that concluded rifaximin did not consistently or reliably prevent SBP.[46] Very few studies have assessed secondary SBP occurrence in patients with cirrhosis, concomitantly prescribed antibiotic prophylaxis for SBP and rifaximin for HE. Consequently, rifaximin alone is not recommended for the treatment or prevention of SBP as per consensus guidelines.[8]

Endotoxaemia and haemodynamics

Endotoxins IL-6 and TNF-α have been shown to be associated with development of cirrhosis-associated immune dysfunction, hyperdynamic circulation, and multi-organ dysfunction. These endotoxins can potentially be influenced by rifaximin use. Kalambokis et al.[47] demonstrated in 13 patients with advanced-disease cirrhosis that rifaximin use reduced IL-6 and TNF-α, subsequently improving systemic haemodynamics, cardiac output, and plasma renin activity.[47] Furthermore, 28 days of rifaximin administration was shown to significantly lower plasma endotoxin levels and hepatovenous pressure gradient measurements, independent of β-blocker use.[48] After 5-year follow-up of the same cohort, the rifaximin-treated cohort demonstrated reduced complication rates of variceal haemorrhage, hepatorenal syndrome, and SBP, as well as survival benefit compared to the control group.[49] Rifaximin modulates gut epithelial physiology and prevents bacterial adherence and internalisation, reducing the release of pro-inflammatory cytokines (IFN-γ, IL-4, IL-6, IL-8, IL-12, and VCAM-1) implicated in cirrhosis-associated immune dysfunction.[50] Partly responsible for this phenomenon is the rifaximin-induced activation of the gut-specific pregnane-X receptor,[18] thereby suppressing NF-κB signalling, a pathway responsible for pro-inflammatory cytokine release.[51] This may help to reduce intestinal permeability, a recognised process contributing to infections in cirrhosis.[18]

Small intestinal bacterial overgrowth

The role of SIBO in bacterial infection in cirrhosis is well recognised.[6] Treatment for this condition is largely based on antibiotic therapy, for which rifaximin is one efficacious option.[52] In a meta-analysis of 32 studies and 1,331 patients, rifaximin treated SIBO in 70.8% of patients (95% confidence interval: 61.4–78.2).[53] SIBO occurs frequently in cirrhosis, but few studies have interrogated antibiotic effectiveness in this cohort. One small-scale study by Zhang et al.[54] reported that rifaximin was clinically effective in treating SIBO in 76% of patients with a confirmed diagnosis of cirrhosis.

Cirrhosis-associated morbidity

Recent evidence has proposed that rifaximin use may reduce complications associated with cirrhosis. In a Phase III RCT, 6-month-long rifaximin administration reduced the relative risk of a first cirrhosis-associated complication by 59% in patients with advanced disease.[55] In a retrospective analysis of 101 patients awaiting liver transplantation, rifaximin increased the time interval to readmission and reduced incidence of portal hypertensive complications: variceal bleeding, complications of ascites, and hepatorenal syndrome. Patients receiving rifaximin exhibited a survival benefit and were less likely to be prioritised for organ transplantation, highlighting the benefits of rifaximin.[56,57]

In addition to clinical benefits, rifaximin therapy may have wider socio-economic advantages, especially in limited resource settings. In a UK-based retrospective study, rifaximin significantly reduced 30-day readmissions and emergency department attendances, as well as hospital and critical care bed days, 6 and 12 months post-commencement of treatment,[58] incurring annual savings of 1,480–3,228 GBP per patient.[59]

RIFAXIMIN RESISTANCE

Until recently, resistance to rifaximin was thought to be uncommon.[60] This perception changed when a mutation was identified in the *rpoβ* gene. This encodes the target site of rifaximin, giving rise to concerns regarding the emergence of resistance in patients with cirrhosis on long-term rifaximin treatment.[13,61] These concerns were substantiated by an observational study of 388 patients with cirrhosis, of whom 46 (11.9%) developed *C. difficile* infection. Importantly, 30.4% of those who developed *C. difficile* infection were established on rifaximin for HE prophylaxis. Overall, *C. difficile* resistance to rifaximin was observed in 34.1% of cases and in 84.6% of patients who had previously received rifaximin. These findings stand in contrast to previous clinical studies and *in vitro* data, in which rifaximin demonstrated good antibacterial activity against *C. difficile* and in which the emergence of resistant clones was rare.[62] With resistance patterns being considerable in those with previous and no previous exposure, rifaximin resistance may be an emerging problem in cirrhosis and will require further investigation.

CONCLUSION

While it is currently licensed for the treatment of recurrent episodes of HE, the full therapeutic potential of rifaximin in liver disease may be underutilised. Rifaximin displays broad-spectrum antimicrobial activity against pathobiont enteric bacteria and demonstrates anti-inflammatory properties. It also has the ability to modulate the gut microbiome, thereby preventing bacterial translocation.[18] These processes are fundamental in the pathogenesis of cirrhosis-associated infection and therefore rifaximin use may be effective in this scenario.[6] However, there remains a lack of robust evidence in the form of adequately powered RCTs to translate these perceived benefits into clinical practice. To date, studies have focused only on the prevention of SBP, rather than all infections. There remains uncertainty regarding rifaximin resistance; yet, based on the current evidence, rifaximin use beyond the licensed indications may be a significant step forward in the management and prevention of cirrhosis-associated morbidity and mortality.

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Which Biologic Therapies to Treat Active Rheumatoid Arthritis and When?

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Abstract

Biological disease-modifying anti-arthritis drugs (bDMARD) have transformed rheumatoid arthritis (RA) treatment and allowed many patients to reach clinical remission. With the huge growth in the development of different bDMARDs, there is now a need to decide on which treatment should be prescribed to achieve optimal patient outcomes. Decisions are made by weighing up the comparative efficacy of each agent against risks, namely the risk of bacterial infections. The most powerful tools for investigating the comparative efficacy of bDMARDs are head-to-head trials that directly compare one therapy to another; however, very few trials of this type exist. Furthermore, the heterogeneity of RA calls for consideration of the comparative efficacy of therapies on an individual basis. Many studies have found associations between specific biomarkers and response to different bDMARDs to enable stratification of patient groups, although many results have not been reproducible in different cohorts. Combining predictors to create models of treatment response may be the ultimate key to finding reliable biomarkers with enough predictive power to enable a personalised medicine approach to treating RA in the clinic.

INTRODUCTION

The arrival of biologic disease-modifying anti-arthritis drugs (bDMARD) has vastly improved the outcomes of patients with rheumatoid arthritis (RA) by suppressing inflammation. Conventional synthetic biologic disease-modifying anti-arthritis drugs such as methotrexate (MTX), hydroxychloroquine, and sulfasalazine, which inhibit non-specific inflammatory pathways, are considered for first-line treatment for RA. Following an inadequate response to these agents, bDMARDs that target specific parts of the immune system may be prescribed. These act through various mechanisms such as inhibition of TNFα (adalimumab, etanercept, and infliximab), IL-6 receptor blockage (tocilizumab and sarilumab), T cell inhibition (abatacept), and B cell depletion (rituximab). More recently, the development of JAK inhibitors has marked the first targeted synthetic disease-modifying anti-arthritis drugs to enter the clinic that may be considered alongside bDMARDs.

As per the National Institute for Health and Care Excellence (NICE) guidelines, a treat-to-target strategy is employed for treating active RA to achieve remission or, if that is not possible, low disease activity. Prescribing bDMARDs in

combination with MTX is common practice as this has been shown to be more generally effective than monotherapy, likely due to the effect of MTX on autoantibody production. Although bDMARDs have revolutionised RA therapy, this is not the case for all patients, with approximately one-third of patients not responding to bDMARDs.[1] However, this comes as no surprise when the vast heterogeneity of RA pathotypes is taken into consideration. When faced with this inconsistent response and the choice between many therapies with diverse mechanisms of action, clinicians can face challenging decisions about which agent to prescribe and when.

This article will outline the current literature to compare different bDMARDs in terms of benefits and risks, and discuss how it may be possible to stratify patients to move towards a personalised medicine approach.

METHODS

The authors conducted database searches for screening studies for inclusion in the review from their inception to 1st January 2021. Data were retrieved from databases including PubMed, Ovid Medline, and Embase. Keywords for searches included: "rheumatoid arthritis", "clinical trial", "biological therapy", "comparison", "efficacy", "infection risk", "treatment", "response", "predicts", "biomarker", and "personalised medicine." A total of 11,616 papers were retrieved including duplicates. After review by the authors, articles were excluded if they were out of the remit of the review; e.g., including other agents or diseases, were not published in English, or included animal studies only. A total of 144 abstracts were screened and 70 papers were included in this article. This is not a systematic review or meta-analysis. Where possible, clinical trial data and biomarker results were organised in tabulated form (Tables 1 and 2).

Table 1: Head-to-head trials of biologic agents for the treatment of rheumatoid arthritis.

Trial	Study type	Monotherapy or combination	Drug	Result
ADCTA[2]	Superiority	Mono	TCZ versus ADA	TCZ superior to ADA
MONARCH[3]	Superiority	Mono	SAR versus ADA	SAR superior to ADA
AMPLE[4]	Non-inferiority	+ MTX	ABT versus ADA	ADA non-inferior to ABT
EXXELERATE[5]	Superiority	+ MTX	CTZ versus ADA	CTZ is not superior to ADA
RED SEA[6]	Non-inferiority	+ MTX	ADA versus ETC	ADA non-inferior to ETC
RA-BEAM[7]	Superiority	+ MTX	BARI versus ADA and PL	BARI superior to ADA
ORBIT[8]	Non-inferiority	Not specified	TNFi versus RTX	RTX non-inferior to TNFi
SIRROUND-H[9]	Superiority	Mono	SRK versus ADA	SRK superior to ADA for improvement in DAS28 but non-superior for ACR50 response
ORAL Strategy[10]	Non-inferiority	+ MTX	TOF versus ADA	TOF non-inferior to ADA

Trials that did not directly compare biological agents or did not measure treatment response were excluded.

ABT: abatacept; ACR50: American College of Rheumatology 50; ADA: adalimumab; BARI: baricitinib; CTZ: certolizumab pegol; DAS28: Disease Activity Score 28; ETC: etanercept; MTX: methotrexate; PL: placebo; RTX: rituximab; SAR: sarilumab; SRK: sirukumab; TCZ: tocilizumab; TNFi: TNF inhibitor; TOF: tofacitinib.

Table 2: Predictors of drug response for biologic agents used to treat rheumatoid arthritis.

Baseline predictor	Response	No response	Study (year)
Low BMI	TNFis	N/A	Gremese et al.,[61] (2013)
Current smoking	N/A	TNFis	Hyrich et al.,[28] (2006) Söderlin et al.,[29] (2012) Abhishek et al.,[30] (2010)
High DAS28	TNFis, ABT, TCZ	N/A	Leffers et al.,[62] (2011) Kleinert et al.,[63] (2012)
Pauci-immune synovial pathotype	N/A	CTZ	Nerviani et al.,[39] (2020)
Anti-CCP seropositivity	RTX, ABT	N/A	Gardette et al.,[64] (2014) Sokolove et al.,[35] (2016)
Higher circulating plasmablasts	RTX	N/A	Stradner et al.,[48] (2016) Vital et al.,[47] (2010) Brezinschek et al.,[46] (2012)
High serum IL-17	N/A	TNFis	Chen et al.,[54] (2011)
High serum IL-6	ETC	N/A	Shi et al.,[56] (2018)
High serum IL-33	RTX	N/A	Sellam et al.,[55] (2016)
Increased IL18RAP in whole blood	TNFis	N/A	Cherlin et al.,[53] (2020)
High serum sICAM/low CXCL13	ADA, TNFis	N/A	Dennis et al.,[65] (2014) Folkersen et al.,[59] (2016)
High serum CXCL13/low sICAM	TCZ	N/A	Dennis et al.,[65] (2014)
Low serum COMP levels	ADA	N/A	Morozzi et al.,57 (2007)
High IFN signature in peripheral blood monocytes	N/A	RTX	Thurlings et al.,[66] (2010) Raterman et al.,[45] (2012)
MRP8/13 serum levels	RTX, TNFis	N/A	Choi et al.,58 (2015)
Increased CX3CR1 and SLC2A3 in whole blood	TNFis	N/A	Folkersen et al.,[59] (2016) Julià et al.,[51] (2009)
Lympho-myeloid synovial pathotype	TNFi	N/A	Lliso-Ribera et al.,[38] (2019)
High synovial TNFα	IFX	N/A	Wijbrandts et al.,[40] (2008) Groof et al.,[41] (2016) Ulfgren et al.,[42] (2000)

ABT: abatacept; ADA: adalimumab; CCP: cyclic citrullinated peptide; COMP: cartilage oligomeric matrix protein; CXCL13: chemokine ligand 13; DAS28: Disease Activity Score 28; CTZ: certolizumab pegol; ETC: etanercept; IFX: infliximab; N/A: not applicable; RTX: rituximab; sICAM: soluble intercellular adhesion molecule; TCZ: tocilizumab; TNFis: tumour necrosis factor inhibitors.

COMPARING BIOLOGICAL THERAPIES IN TERMS OF EFFICACY

Being the oldest class of bDMARDs, TNF inhibitors (TNFis) are well-studied, which, along with their low cost, makes them a popular choice for clinicians. Therefore, the contrasting lack of data for newer forms of therapy can pose difficulties for making reliable comparisons. The most useful conclusions can be drawn from head-to-head trials that directly compare one agent to another within the same patient cohort as

opposed to using data from placebo-controlled trials or making comparisons between trials on different patient cohorts.

To date, there have only been a handful of head-to-head trials directly comparing different biological therapies. These can either be in the form of superiority trials, which are powered to determine if one therapy is better than the other, and non-inferiority trials, which investigate whether one therapy is at least as good as the other. In two superiority trials, the IL-6 inhibitors tocilizumab and sarilumab were found to be more effective than adalimumab when used as a monotherapy; additionally, in the RA-BEAM trial, baricitinib was found to have significantly greater clinical improvements than adalimumab.[2,3] Table 1 summarises findings from hitherto head-to-head trials.

There have been efforts to compare the efficacy of bDMARDs using data from various clinical trials via meta-analysis; however, many of these have not been in agreement or have been criticised in terms of methodology (e.g., combining DMARD-naïve and DMARD-inadequate responder patients or combining monotherapy and combination therapy in one analysis).[11] A recent systematic meta-analysis compared eight bDMARDs used as combined therapy with MTX.[12] One major strength of this analysis is the inclusion of similar patient populations by using aggregate results from systematic re-analyses of individual patient data performed by the study sponsor. Overall, only a few statistically significant differences were found between the bDMARDs analysed, with anakinra showing the least benefit. This is consistent with two previous meta-analyses and reflected in the NICE guidelines, which do not recommend this therapy on the balance of cost-effectiveness and clinical benefits.[13,14] In contrast, a multiple treatment comparison regression modelling approach found, when given as combination therapies, the therapies ranked as follows: certolizumab as the most effective followed by tocilizumab, anakinra, rituximab, golimumab/infliximab/abatacept, and adalimumab/etanercept as the least effective. It is interesting to note that they found a higher dose level had a significant effect on treatment and no effect was found for disease duration.[15] In summary, with only a small number of studies looking at direct comparisons in the same cohort of patients, it can be difficult to draw conclusions on the comparative efficacy of biological therapies, therefore more data from head-to-head trials are needed to help to unveil these trends.

QUALITY OF LIFE MEASURES

The most commonly used outcome measures for assessing RA disease activity are the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) criteria for remission and low disease activity used by clinicians; ACR20 is commonly used in clinical trials, which is a composite measure involving a set of five criteria. These tend to have a large contribution from measures looking at the reduction in inflammation. However, a common problem seen among patients is the persistence of fatigue and pain, even if inflammation is well controlled. This highlights the importance of considering an alternative perspective: how bDMARDs compare to each other for improving specific quality of life measures. The authors have not been able to identify any published research addressing this question, though there is some suggestion that different bDMARDs may contrast in their ability to treat certain aspects of RA. For instance, in the AMPLE trial adalimumab had a greater reduction in pain assessment score than abatacept.[4] A head-to-head trial is currently underway to investigate this finding further (BIORA-PAIN).[16]

RISK OF INFECTION

In addition to the comparative benefits of biological treatments, another aspect to consider is the comparative risk of infection between therapies. When making judgements about the safety of therapies, it is also important to note that people with RA have a risk of infection that is higher than the general population.[17] However, the added risk of infection following administration of biological agents is widely recognised, with many studies reporting this to be higher than conventional synthetic biologic disease-modifying anti-arthritis drugs. This risk has been shown to increase with dosage and is highest within the first 6 months of the first course of TNFi therapy.[18] The most common infection caused by biological therapies is pneumonia, primarily caused by the reactivation

of a latent *Mycobacterium tuberculosis* infection. In the case of TNFis, it could be postulated that TNF's role in stimulating the phagocytosis of *M. tuberculosis* may be driving this response.

Many studies have suggested a lower risk of infection for abatacept. The ATTEST trial looked at infliximab versus abatacept with MTX and found substantially lower rates of serious infections with abatacept (1.9% versus 8.5%),[19] and a meta-analysis by Salliot et al.[20] found abatacept did not significantly increase the risk of serious infection in patients with RA. More recent studies have supported these data. A multi-database cohort study found abatacept had a lower composite risk of serious infections when compared to tocilizumab.[21] Additionally, a propensity score-matched cohort study with 11,248 patients on abatacept or a TNFi found a lower risk of hospitalised respiratory infection for abatacept versus TNFis (particularly infliximab), and a large retrospective cohort study of 31,801 patients found that exposure to etanercept, infliximab, or rituximab was associated with a greater 1-year risk of hospitalised infection compared with the risk associated with exposure to abatacept.[22] This is in line with the AMPLE head-to-head study comparing adalimumab and abatacept, where adalimumab patients experienced more serious infections (3.8% versus 5.8%) and more discontinuations as a result.[4] How the risk of infection varies between other biological agents is not yet clear. Some data alludes to a lower risk for etanercept versus adalimumab,[14,23] and one head-to-head study found no differences in safety between sarilumab and tocilizumab.[24]

BIOLOGICAL SWITCHING

After at least 3 months of non-response to a bDMARD, patients are prescribed a different bDMARD; this is known as biological cycling or switching. This particular timeframe is used, as no response after 3 months is a predictor of a lack of responsiveness after 1 year of therapy on the same biological agent.[25] Patients who do not respond to therapy fall into two categories: a response that falls over time, and no initial response. Patients in the former group may have developed anti-drug antibodies, in which case cycling to another TNFi inhibitor may still show benefit; however, these antibodies may have cross-reactivity with a biosimilar.[26] Patients in the latter group may benefit from switching to a biological therapy with an alternative mechanism of action. This approach has been demonstrated to be beneficial over TNFi cycling for the majority of patients in multiple studies.[27] However, this trial-and-error method of choosing therapies is far from ideal and can lead to continued disease progression and low quality of life, while risking exposure to side effects and wasting costly therapeutics. This calls for an urgent need to uncover predictors of patient response to improve patient outcomes.

PREDICTORS OF RESPONSE

Generic Predictors of Response

Patient characteristics and clinical data have been able to draw out overall trends in treatment response. Current smoking has been associated with a lack of response to TNFis in several studies,[28-30] but this trend was not seen with a study on tocilizumab.[31] Additionally, younger age, male sex, lower BMI, shorter disease duration, no-comorbidities, low Health Assessment Questionnaire (HAQ) score, and high Disease Activity Score 28 (DAS28) predict a better response to bDMARDs.[32,33]

Current Tools

The only predictive tools currently in clinical use are testing for rheumatoid factor and anti-citrullinated protein antibody positivity. These are shown to correlate with disease severity and are associated with response to rituximab and abatacept; however, this trend is not seen with TNFis, with conflicting reports or no association found.[34,35] Blood erythrocyte sedimentation rate and C-reactive protein (CRP) levels are commonly used markers that can indicate inflammation and the requirement of more aggressive therapy, but cannot determine which bDMARD to use. The lack of current distinguishing markers further highlights the pressing need to discover more reliable predictors.

Synovial Biopsy

Histological and gene expression studies on biopsies of pre-treatment synovial tissues have enabled the classification of patients into three distinct pathotypes: lympho-myeloid

pathotypes (B cells and myeloid cells); diffuse-myeloid pathotype (macrophage-rich but few B cells); and pauci-immune pathotype (few immune cells and high in fibroblasts). Changes in synovial pathotype towards a less inflammatory pathotype (for instance from lympho-myeloid to diffuse myeloid or pauci-immune) are associated with reductions in DAS28, indicating a response to therapy.[36] The lympho-myeloid pathotype has been shown to be associated with more aggressive disease and early radiographic progression, and therefore a higher likelihood of progressing on to bDMARDs.[37] Consistent with this, a large study on 200 pre-treatment patients (PEAC) showed a significantly higher number of patients in the lympho-myeloid pathotype required biological therapy.[38] Interestingly, patients with this pathotype were predicted to require biologic therapy after 12 months, independent of disease duration, contradicting the 'early window of treatment opportunity' dogma and indicating that this stratification method has the potential to fast-track patients who are unlikely to respond to first-line therapy on to bDMARDs at disease onset. As well as predicting requirement for bDMARDs, these pathotypes may also be useful in predicting response to bDMARDs. A recent study with 37 participants showed the pauci-immune pathotype had a significantly lower response to the TNFi certolizumab pegol than the other two pathotypes.[39] This may indicate that patients with this lower inflammatory pathotype may require an alternative treatment strategy; e.g., ongoing studies are investigating treatment of pain sensitisation in RA.

The use of genetic markers in the synovium may also provide a useful tool in patient stratification. Using RNA sequencing, 3,000 differentially expressed transcripts were found between the three pathotypes in the PEAC dataset, providing greater evidence for these sub-groups.[36] The researchers also found genetic differences between patients requiring biological therapy and those who did not. The non-bDMARDs group had an upregulation of fibroblast proliferation and cartilage turnover genes, and patients requiring bDMARDs had a significantly higher upregulation of genes regulating B and T cell proliferation, differentiation, and activation as well as matrix metallopeptidase and cytokine-mediated cellular activation genes.[38] Furthermore, higher baseline levels of TNFα in the synovium has been shown to predict response to infliximab in three studies.[40-42]

These studies outline an exciting method of predicting treatment response at the site of disease, and ultrasound-guided needle biopsy is reportedly well-tolerated with low complication rates.[43] Nevertheless, the use of biomarkers obtained from urine and blood are more appealing for entering into clinical use due to ease of testing and repeatability over time in response to interventions.

Blood Biomarkers

There have been extensive research efforts to find biomarkers present in the blood that correlate with treatment response; however, the advantage of the convenience of obtaining these samples may be offset by biomarkers not being detectable away from the site of pathology. For instance, although TNF levels in the synovium have been shown to correlate with treatment response, this signature does not translate to the blood.[44] Likewise, in comparison to the 3,000 differentially expressed transcripts between the three pathotypes in the synovium, Lewis et al.[36] found just eight differentially expressed transcripts in matched peripheral blood.

These genes were associated with the more inflammatory lympho-myeloid pathotype, with seven associated with Type I IFN response (*IFI27*, *ISG15*, *IFI44L*, *OASL*, *USP18*, *RSAD2*, and *LY6E*).[36] This genetic signature has had previous interest, with some studies finding high levels of this correlates to a lack of response to rituximab.[45]

Additional blood biomarkers associated with rituximab response have been found through multiple flow cytometry studies, which have demonstrated that higher numbers of circulating plasmablasts are associated with treatment response,[46-48] and sensitive flow cytometry analysis of B-cell depletion can indicate the level of response as well as required dose.[49]

RNA sequencing of whole blood using microarrays has enabled researchers to identify biomarkers of interest and create multi-gene models of response. Using a cDNA microarray, Lequerré et al.[50] used eight transcripts to predict 18/20 patients' response to infliximab

successfully. Another eight-gene model was able to predict infliximab response with an 85.7% prediction accuracy in an independent validation set of patients.[51] Finally, Tanino et al.[52] used an Agilent whole-genome microarray to propose 10 genes that could predict response to infliximab with a 65.4% accuracy.[52] Recently, using PrediXcan software, which is more a cost-effective approach than genome-wide genotyping and RNA sequencing, an association between *IL18RAP* expression and treatment response to TNFis was found.[53]

Blood cytokine levels can be used as another predictive tool. Increased T helper 17 frequency and T helper 17-related cytokines (IL-17) in the blood, determined by flow cytometry and ELISA, are associated with lack of response from TNFis, which evidences the theory that TNFi resistance may be due to the prevalence of non-TNF pathways.[54] Additional cytokines of interest in the serum include IL-33, which has been linked to rituximab response[55] and high levels of IL-6 and survivin found to be associated with response to etanercept.[56]

Furthermore, low serum levels of cartilage oligomeric matrix protein, a protein related to cartilage turnover, have been shown to be associated with response to adalimumab in one study,[57] and significantly higher MRP8/13 serum levels were found in responders to three biological therapies, with high baseline levels increasing the odds of being a responder from 3.3 to 55.[58]

Although these are intriguing findings, many of these results have not been reproduced in other cohorts and are not able to differentiate treatment response at a level amenable to clinical use. The COMBINE study aimed to overcome this problem by using a multi-omics approach, investigating previously identified genetic and proteomic predictors of TNF response to see if these findings could be validated from a large biobank of 451 blood samples.[59] They validated 11 predictors from previous studies, which encompassed eight genes from transcriptomics literature, serum levels of soluble intercellular adhesion molecule 1 (sICAM1)/chemokine ligand 13 (CXCL13), and two single-nucleotide polymorphisms (SNPs) (rs6028945 and rs7305646) from genome-wide associated study literature and used these to explain 51% of the variation in change in DAS28-CRP. Interestingly, they found the sICAM1/CXCL13 levels, reported by Dennis et al.,[60] were the greatest predictor of response. Previous evidence has highlighted CXCL13 as a marker of interest; e.g., high CXCL13 levels have been suggested to indicate an inflammatory pathotype that may benefit from more aggressive treatment, and high synovium levels of CXCL13 correlate with high levels in the serum.[60] Table 2 summarises the predictors of drug response discussed in this article.

Multiple Predictors

Arguably the best approach is one that uses a combination of predictors. Using the PEAC dataset, a regression model was created to predict whether a patient required bDMARDs at 12 months by combining clinical and gene expression level data. The initial model included four clinical covariates: DAS28, CRP, tender joint count, and synovial pathotype, and resulted in a predictive performance of 78.8%.[38] Upon addition of genes that were identified as significantly differentially expressed between the biological and non-biological group, the sensitivity and specificity improved to 89% for penalised predictors and 90% for unpenalised clinical predictors.

The Dialogue on Reverse Engineering Assessment and Methods (DREAM): Rheumatoid Arthritis Responder Challenge took a crowdsourcing approach to encourage the development of models that predict a patient with RA's response to TNFis by making genome-wide associated study data available. Each team's model was rigorously tested by the Sage-DREAM team to rank the performance based on predefined metrics in a so-called 'challenge-assisted peer review.'[67]

The best performing model was a Gaussian process regression model combining demographic, clinical, and SNP array markers. It correctly classified 78% of patients as responders or non-responders to TNFis (with an area under the curve of approximately 0.66) as well as predicting change in DAS28 after 24 months with a Pearson's correlation coefficient of 0.405. The model relied on the kernel function, which enabled patients to be weighted based on their similarity to a paired patient and provided information on which predictors had the greatest

weights in the prediction. Additionally, this model can generate confidence intervals, which may be beneficial for application as a clinical tool. One downside of this model is that it was built using data from European descendants, so may not be translatable to other populations. It is also worth noting that the SNPs only showed a small contribution to the prediction when added to the clinical model.[68]

The Maximising Therapeutic Utility in Rheumatoid Arthritis (MATURA) consortium was formed in 2014 in response to stratified medicine being identified as a priority by the Medical Research Council (MRC) in 2011. It comprises 12 academic centres and nine industrial partners, and aims to develop tests to predict patients' responses to MTX, TNFis, rituximab, and tocilizumab. Two research work-streams are underway, one focused on synovial and blood correlates from PEAC and STRAP. The second will use blood samples and clinical information from some of the largest datasets worldwide. These work-streams will be integrated by statisticians to develop algorithms to help clinicians stratify patients.[69] Initial results indicate that biomarkers of DAS28 are detectable in genetic, transcriptomic, and DNA methylation data sets. Consistent with the best-performing DREAM model, these have little predictive power when used alone;[70] however, this collaborative effort to combine multiple predictors paves a bright future for creating a model with enough predictive power to be used in clinics.

CONCLUSION

The small number of differences found when comparing bDMARDs in terms of efficiency overall may be explained by different bDMARDs being more suited to particular patients, depending on their unique disease pathways. There is no doubt that better biomarkers will improve patient care; unfortunately, we are not yet at a stage where a model is ready for clinical use, due to low predictive values, practical barriers for obtaining certain biomarkers in clinics, and low reducibility between cohorts. Nevertheless, the flurry of recent research efforts investigating predictive tools in multiple domains, including clinical, imaging, pain and function, and blood and urine markers, may allow patient assessment on a more holistic level, providing promise for more personalised care in people with rheumatoid arthritis.

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Cardio-Metabolic Benefits of Walnuts in Type 2 Diabetes Mellitus: A Literature Review

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Abstract

Diabetes and its complications are main causes of morbidity and mortality among adults in the USA. An increase in the number of individuals with diabetes is primarily attributed to changes in dietary patterns including increased consumption of obesogenic foods and beverages. Many individuals who are overweight and obese show signs of insulin resistance and are at increased risk of Type 2 diabetes mellitus (T2DM) and cardiovascular disease. Lifestyle interventions (i.e., physical activity and nutrition) are the cornerstone of T2DM management and prevention. Prior research attests to the health benefits of consuming nuts, which have a substantial amount of mono- and polyunsaturated fatty acids, for individuals at risk for or with T2DM, and walnuts appear to be particularly promising. Walnuts are rich in nutrients, minerals, antioxidants, and vitamins that can contribute to improved cardio-metabolic risk factors in individuals at risk for or with T2DM. This review assesses the cardio-metabolic benefits of walnuts in T2DM. The authors' review indicates that the reported effects of walnuts on glycaemic control have been inconclusive, with several studies showing association with improved glycaemic control while others show no effect. Despite their high energy density and potential to contribute to weight gain, the authors' review suggests that walnuts can contribute to satiety without association with weight gain. This review also suggests that walnut consumption has been associated with improved low-density lipoprotein cholesterol levels and endothelial function but has not been associated with blood pressure improvement. Meta-analyses are warranted to quantitatively assess impact of walnut consumption on these cardio-metabolic risk factors in T2DM.

INTRODUCTION

In the USA, diabetes is a public health problem of epidemic proportions, affecting almost 35 million individuals.[1] An estimated 88 million adults aged 18 years and older have prediabetes, yet only one of 10 persons with prediabetes is aware.[1] Of persons with prediabetes, 15–30% are likely to develop Type 2 diabetes mellitus (T2DM) within 5 years.[1] Diabetes complications include stroke, hypertension, cardiovascular disease (CVD), blindness, kidney disease, nervous system damage, limb amputations, and biochemical imbalances that can cause acute life-threatening events.[1] Total medical costs, including lost work

and wages, for persons diagnosed with diabetes are estimated at $327 billion.[2] Medical costs for people with diabetes are more than double those for persons without diabetes.[2] Rates of cardiovascular mortality are 2–4 times higher among adults with diabetes than among those without diabetes.[1]

Persons who are obese are over 7 times more likely to develop T2DM and cardio-metabolic complications than are persons who are a healthy weight.[3,4] Excessive body weight is associated with insulin resistance.[5] Insulin resistance is associated with hyperglycaemia, dyslipidaemia, and hypertension,[5,6] which promote cellular-level alterations of vascular tissues, with resulting formation of atherosclerotic plaque that reduces endothelium-dependent vasodilation.[7,8] Most deaths among patients with diabetes are caused by atherosclerotic CVD.[9]

Glycaemic control remains the basis of diabetes care. Co-management of cardio-metabolic risk factors and prevention of their consequences are also essential to improve long-term survival. A modest reduction of as little as 5–7% of body weight can significantly improve cardio-metabolic risk factors among those at risk for and with T2DM.[10-13] Patients at risk for or with T2DM are typically advised to consume foods with a low glycaemic index (GI). Low-GI diets have been shown to improve serum lipid profiles, reduce C-reactive protein levels, and aid in weight management, reducing the development of T2DM and CVD.[14,15] Walnuts have a low GI[16] and are rich in nutrients, minerals, antioxidants, and vitamins that can improve cardio-metabolic risk factors. Walnuts are relatively high in mono- and polyunsaturated fatty acids (MUFAs and PUFAs), particularly α-linolenic acid and linoleic acid (Table 1), which are known to have favourable effects on cardio-metabolic health.[17-25] This review examines the cardio-metabolic benefits of walnuts (including improved glycaemic control, body weight, lipid profile, blood pressure, and endothelial function) in those at risk for or with T2DM.

METHOD

The authors reviewed all articles retrieved through Google Scholar and PubMed that were published from January 1999 to March 2021 using the following search terms: "walnut AND type 2 diabetes," "walnut AND diabetes," "walnut AND pre-diabetes," "walnut AND prediabetes," "walnut AND metabolic syndrome," "walnut AND overweight," and "walnut AND obesity." Inclusion criteria included animal and human studies that were published in English; study population included those at risk for (i.e., prediabetes, metabolic syndrome, obesity, and overweight) or with T2DM; utilised walnuts as an intervention; and assessed at least one of the following parameters: glycaemic control, body weight, lipid profile, blood pressure, or endothelial function. Studies that did not fall within the timeframe of the review and not meeting the inclusion criteria were excluded.

GLYCAEMIC CONTROL

Walnuts are rich in MUFAs, PUFAs, and magnesium, which have been linked to improved glycaemic control, insulin sensitivity, and insulin-secreting capacity.[24,25] Walnut inclusion in the diets of those at risk for or with T2DM has been associated with the displacement of high-carbohydrate foods.[26,27] Displacing carbohydrates from diets while substituting MUFAs and PUFAs has been shown to improve blood glucose, insulin sensitivity, and insulin secretion.[23,26] *In vitro*, 10–100 µg/mL of walnut leaf extract has been linked to increased glucose uptake in cell-based assay and inhibition of protein tyrosine phosphatase 1B in a concentration-dependent manner compared to control cells.[28] However, reported effects of walnut consumption on glycaemic control in T2DM have been considered inconclusive.

An epidemiologic study by Pan et al.[29] that prospectively followed 137,956 females without diabetes, CVD, or cancer at baseline, aged 35–77 years, for 10 years reported that walnut intake of 1–3 servings/month (1 serving=28 g), 1 serving/week, or ≥2 servings/week was associated with lower T2DM risk compared with <1 serving per month. A cross-sectional analysis by Arab et al.[30] of the population of the USA aged 18–80 years, using a sample of 34,121 individuals from the National Health and Nutrition Examination Survey (NHANES) database, reported a lower incidence of self-reported diabetes and better glycaemic control among those who consumed walnuts (i.e., 12 g or more based on a 24-hour dietary recall) compared with non-nut consumers.

Table 1: Nutrient profile of walnuts.

Nutrient	Amount per 100 g
Calories	654.0 kcal
Water	4.1 g
Protein	15.2 g
Carbohydrate	13.7 g
Sugar	2.6 g
Fibre	6.7 g
Total fatty acids	65.2 g
Saturated fatty acids	6.1 g
Monounsaturated fatty acids	8.9 g
Polyunsaturated fatty acids	47.2 g
Omega-3 fatty acids	9.1 g
Omega-6 fatty acids	38.1 g
Calcium	98.0 mg
Iron	2.9 mg
Magnesium	158.0 mg
Phosphorus	346.0 mg
Potassium	441.0mg
Sodium	2.0 mg
Zinc	3.1 mg
Copper	1.6 mg
Manganese	3.4 mg
Selenium	4.9 mcg
Phytosterols	72.0 mg
Vitamin A	20.0 IU
Vitamin C	1.3 mg
Vitamin E (α-tocopherol)	0.7 mg
Vitamin K	2.7 mcg
Thiamine	0.3 mg
Riboflavin	0.2 mg
Niacin	1.1 mg
Vitamin B6	0.5 mg
Folate	98.0 mcg
Vitamin B12	0.0 mcg
Pantothenic acid	0.6 mg
Choline	39.2 mg
Betaine	0.3 mg

A randomised controlled trial by Tapsell et al.[31] with 50 patients with T2DM who were overweight, aged 33–70 years, reported reduced fasting insulin with daily inclusion of 30 g walnuts by those counselled to consume a low-fat, weight-maintenance diet for 3 months, compared with those counselled to consume a low-fat diet without walnuts. A randomised controlled study by Zibaeenezhad et al.[32] with 100 patients with T2DM, aged 30–60 years, showed improved glycaemic control with inclusion of 15 g walnut oil daily for 3 months in their diets, compared with a control diet without walnuts. A randomised controlled study by Hosseini et al.[33] with 61 patients with T2DM, aged 40–65 years, reported that 100 mg walnut leaf extract in capsules consumed twice daily before meals for 3 months improved glycaemic control compared with placebo capsules.

Conversely, a randomised controlled study by Rabiei et al.[34] with 50 patients with T2DM, aged 30–80 years, reported that daily supplementation of 200 mg walnut leaf extract in capsules for 2 months did not improve glycaemic control or insulin sensitivity, although it reduced body weight and blood pressure compared with placebo capsules containing microcrystalline cellulose. Also, a randomised crossover-controlled study by Ma et al.[35] with 24 patients with T2DM, aged 30–75 years, found that including 56 g walnuts daily for 2 months as part of an otherwise *ad libitum* diet with dietary counselling to regulate caloric intake did not show improved glycaemic control or insulin sensitivity. Likewise, randomised crossover-controlled studies by Katz et al.[36] and Njike et al.[37] with 46 and 112 participants, respectively, aged 25–75 years and at risk for T2DM, showed no association between glycaemic control and daily inclusion of 56 g walnuts in otherwise *ad libitum* diets, with or without advice to regulate caloric intake, for 2 months or 6 months, respectively, compared with *ad libitum* diets without walnuts. Brennan et al.[38] studied 20 participants with metabolic syndrome, aged 40–75 years, and found no association between insulin resistance and consumption of 48 g walnuts in liquid meals for 4 days, compared with placebo.

In a randomised controlled study, walnut leaf powder administered twice daily at doses of either 25, 50, or 100 mg/kg for 28 days via gavage to 36 diabetic rats with *ad libitum* access to food and water improved glycaemic control compared to placebo (i.e., 10 mL/kg distilled water).[23] In another randomised controlled study, 20 diabetic-induced female albino rats fed either 21.3, 42.6 or 85.2 g walnuts over 3, 7, and 10 days, respectively, showed improved glycaemic control compared with control diets without walnuts when assessed on those days.[39,40]

Overall, while several studies showed an association between improved glycaemic control and walnut consumption or administration, several other studies with more vigorous designs failed to show such association. Therefore, the effect of walnuts on glycaemic control in T2DM may be considered inconclusive (Table 2).[26,27,29-43]

BODY WEIGHT

The effect of walnut consumption on body weight has been linked to walnuts' satiating effects. In a randomised controlled crossover study by Farr et al.,[44] walnut intake for 5 days by participants at risk for T2DM was associated with reductions in perceived hunger and appetite and with increased activation of the insula (i.e., a region of the deep brain in the cerebral cortex) to highly desirable food signals. Brennan et al.[38] reported that including walnuts in the diets of participants with metabolic syndrome for 4 days was associated with increased satiety without increasing hormones known to mediate satiety; this was likely due to an inadequate length of time to observe an increase in these hormones. In addition to their satiating effects, including walnuts in the context of a calorie-controlled diet has been associated with acutely enhanced oxidation of body fat in individuals who are overweight[45] and with the displacement of high-calorie foods from diets.[26,27]

In a randomised controlled study with 50 patients with T2DM aged 30–80 years, 2 months of daily supplementation of 200 mg walnut leaf extract in capsules significantly reduced body weight compared with microcrystalline cellulose placebo capsules.[34] In a secondary analysis of a randomised controlled study by Neale et al.[27] with 337 participants who were overweight and obese, aged 37–51 years, including 30 g walnuts daily for 3 months in individualised diet plans with servings of each food group, combined with counselling to regulate caloric intake, was

associated with significant weight loss compared with a control group receiving general advice for healthful eating and physical activity.

However, randomised crossover design studies by other investigators have found no association between weight loss and the daily inclusion of 56 g walnuts in otherwise *ad libitum* diets, or with counselling to regulate calorie intake diets, for 2 or 6 months in adults at risk for (n=46 and n=112) or with T2DM (n=24), aged 25–75 years, compared with a control otherwise *ad libitum* diet, with or without counselling to regulate calorie intake.[35-37] In addition, in another randomised controlled study by Tapsell et al.[41] of 58 patients with diabetes who were overweight, aged 35–75 years, a moderate-fat diet plan with advice to include 30 g walnuts daily for 6 months showed no association with weight loss compared with a control treatment plan utilising a standard clinical practice. In a randomised controlled trial with 100 patients with T2DM, aged 30–60 years, Zibaeenezhad et al.[32] showed no body weight loss with daily inclusion of 15 g walnut oil for 3 months in their diets, compared to their exclusion.

Some animal studies have also examined the impact of walnuts on body weight. In a randomised controlled study by Mollica et al.,[39] 36 diabetic rats administered either 25, 50, or 100 mg/kg walnut leaf extract twice daily for 28 days via gavage and provided *ad libitum* access to food and water showed significant weight gain compared with placebo (i.e., 10 mL/kg distilled water). In another randomised controlled study by Onwuli et al.,[39,40] diabetic-induced female albino rats fed either 21.3, 42.6, or 85.2 g of walnuts showed no association in body weight compared with control diets without walnuts at Days 3, 7, and 10 of assessment.

While two studies showed significant improvement in body weight, one small animal study showed weight gain with walnut inclusion in the diets, and an overwhelming majority of studies reported no association between weight loss and walnut inclusion in the diets. To be conservative with the inference of this review on the effects of walnuts on body weight, it is imperative to conclude that there is no association between walnut consumption and body weight in those with or at risk for T2DM (Table 2).

LIPID PROFILE

Daily inclusion of 48 g walnuts for 4 days by individuals with metabolic syndrome is associated with increased concentration of apolipoprotein A,[46] which may ultimately lead to an improved lipid profile. This improvement may be due to the relatively high content of omega-3 fatty acids in walnuts. Dietary omega-3 fatty acids have been associated with reduced synthesis and secretion of very-low density lipoprotein and increased removal of triglycerides from very-low density lipoprotein and chylomicron through upregulation of lipoprotein lipase.[47]

A randomised control study by Tapsell et al.[41] with 58 patients with T2DM, aged 35–75 years, reported increased high-density lipoprotein cholesterol and reduced low-density lipoprotein (LDL) cholesterol with the daily inclusion of 30 g walnuts for 6 months, together with counselling on a moderate-fat diet plan, compared with standard clinical advice without walnut supplementation. A randomised crossover-controlled trial by Tindall et al.[42] also reported improved LDL cholesterol among 45 adults who were overweight and obese, aged 35–65 years, after replacing saturated fat with walnuts (57–99 g/day) as snacks compared with vegetable oils over a 6-week period. Other randomised controlled crossover studies (n=24 and n=112, respectively)[35,37] also showed improved LDL cholesterol from baseline with daily inclusion of 56 g walnuts for 2 months and 6 months, respectively, in otherwise *ad libitum* diets, with or without counselling to regulate caloric intake of patients with or at risk of T2DM. Zibaeenezhad et al.[32] reported improved LDL cholesterol with the intake of 4 walnut oil capsules (1.25 cc) daily for 90 days compared with placebo capsule containing distilled water (1.25 cc) during a randomised controlled trial among 100 patients with T2DM, aged 35–75 years. However, a randomised crossover-controlled study by Katz et al.[36] with 46 participants at risk for T2DM, aged 30–75 years, did not report improved lipid profile with the daily inclusion of 56 g walnuts for 2 months in otherwise *ad libitum* diets, with counselling to regulate calorie intake, compared with *ad libitum* diets supplemented with walnuts.

Table 2: Summaries of the articles included in the review.

Study	Target population	Study design	Intervention	Comparison group	Results
Glycaemic control: human studies					
Arab et al.,[30] (2018)	A sample of 34,121 adults in the USA, aged 18–80 years	Cross-sectional	Consumption of approximately 12 g or more walnuts based on a 24-hour dietary recall	Non-nut consumer	Improved glycaemic control
Brennan et al.,[38] (2010)	20 patients with metabolic syndrome, aged 40–75 years	Randomised crossover controlled	Consumption of 48 g walnuts in liquid meals with 50 g frozen mango, 50 g frozen strawberries, 60 g banana, 100 g frozen berries, and 250 g pineapple juice for 4 days	Placebo shake liquid meals, containing 32 g safflower oil, 50 g frozen mango, 50 g frozen strawberries, 60 g banana, 100 g frozen berries, and 250 g pineapple	No association with insulin resistance
Hosseini et al.,[33] (2014)	61 patients with T2DM, aged 40–65 years	Randomised controlled parallel design	100 mg walnut leaf extract consumed in the form of capsules twice daily before meals for 3 months	Placebo capsules	Improved glycaemic control
Katz et al.,[36] (2012)	46 participants at risk for T2DM, aged 30–75 years	Randomised crossover controlled	56 g walnuts daily for 2 months, with counselling to regulate calorie intake	*Ad libitum* diet without walnut supplementation	No improvement in glycaemic control
Ma et al.,[35] (2010)	24 patients with T2DM, aged 30–75 years	Randomised crossover controlled	56 g walnuts daily for 2 months, with counselling to regulate calorie intake	*Ad libitum* diet without walnut supplementation	No improvement in glycaemic control
Njike et al.,[26] (2016)	112 participants at risk for T2DM, aged 25–75 years	Randomised crossover controlled	56 g walnuts daily for 6 months, with or without counselling to regulate calorie intake	*Ad libitum* diet without walnut supplementation	No improvement in glycaemic control
Pan et al.,[29] (2013)	137,956 females without diabetes, cardiovascular disease, or cancer, aged 35–77 years	Prospective cohort	Either 1 to 3 servings per month (1 serving=28 g), 1 serving per week, or ≥2 servings per week of walnut consumption	<1 serving per month walnut consumption	Lower risk of T2DM
Rabiei et al.,[34] (2018)	50 patients with T2DM, aged 30–80 years	Randomised controlled parallel design	200 mg walnut leaf extract per day for 2 months in the form of capsules	Microcrystalline cellulose capsules	No improvement in glycaemic control

Table 2 contined.

Study	Target population	Study design	Intervention	Comparison group	Results
Tapsell et al.,[31] (2009)	50 patients who were overweight with T2DM, aged 33–70 years	Randomised controlled parallel design	30 g walnuts daily for 3 months in the context of dietary counselled low-fat weight maintenance diets	Dietary counselling for low-fat diet, without walnut supplementation	Improved glycaemic control
Zibaeenezhad et al.,[32] (2016)	100 patients with T2DM, aged 30–60 years	Randomised controlled parallel design	15 g walnut oil daily for 3 months, with dietary counselling to regulate caloric intake	Calorie control diet, without walnut supplementation	Improved glycaemic control
Glycaemic control: animal studies					
Mollica et al.,[39] (2017)	36 rats with diabetes	Randomised controlled parallel design	Walnut leaf extract administered via gavage with either 25, 50, or 100 mg/kg twice daily for 28 days, with access to food and water *ad libitum*	10 mL/kg distilled water	Improved glycaemic control
Onwuli et al.,[40] (2014)	20 diabetic-induced female albino rats	Randomised controlled parallel design	Fed with either 21.3, 42.6, or 85.2 g of walnuts for 3, 7, and 10 days	Control diets, without walnut supplementation	Improved glycaemic control
Body weight: human studies					
Katz et al.,[36] (2012)	46 participants at risk for T2DM, aged 30–75 years	Randomised controlled crossover	56 g walnuts daily for 2 months, with counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	No association with weight loss
Ma et al.,[35] (2010)	24 patients with T2DM, aged 30–75 years	Randomised crossover controlled	56 g walnuts daily for 2 months, with counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	No association with weight loss
Neale et al.,[27] (2017)	337 participants who were overweight and obese, aged 37–51 years	Randomised controlled parallel design	Inclusion of 30 g walnuts daily in individualised diet plans of servings of each food group, with counselling to regulate calorie intake	General advice for healthy eating as well as guidance for physical activity	Association with weight loss
Njike et al.,[26] (2016)	112 participants at risk for T2DM, aged 25–75 years	Randomised crossover controlled	56 g walnuts daily for 6 months, with or without calorie regulation	*Ad libitum* diet, without walnut supplementation	No association with weight loss

Table 2 contined.

Study	Target population	Study design	Intervention	Comparison group	Results
Rabiei et al.,[34] (2018)	50 patients with T2DM, aged 30–80 years	Randomised controlled parallel design	200 mg walnut leaf extract per day for 2 months in the form of capsules	Microcrystalline cellulose capsules	Association with weight loss
Tapsell et al.,[41] (2004)	58 patients with diabetes who were overweight, aged 35–75 years	Randomised controlled parallel design	Moderate-fat diet plan advice to include 30 g walnuts daily for 6 months	Standard clinical practice, with follow-up advice based on clinical judgment	No association with weight loss
Zibaeenezhad et al.,[32] (2016)	100 patients with T2DM, aged 30–60 years	Randomised controlled parallel design	Inclusion of 15 g of walnuts as oil daily for 3 months	Exclusion of walnut in diets	No association with weight loss
Body weight: animal studies					
Mollica et al.,[39] (2017)	36 rats with diabetes	Randomised controlled parallel design	Walnut leaf extract administered via gavage with either 25, 50, or 100 mg/kg twice daily for 28 days, with access to food and water *ad libitum*	10 mL/kg distilled water	Association with weight gain
Onwuli et al.,[40] (2014)	20 diabetic-induced female albino rats	Randomised controlled parallel design	Fed with either 21.3, 42.6, or 85.2 g walnuts for 3, 7, and 10 days	Control diets, without walnut supplementation	No association with weight loss
Lipid profile: human studies					
Katz et al.,[36] (2012)	46 participants at risk for T2DM, aged 30–75 years	Randomised crossover controlled	56 g walnuts daily for 2 months, with dietary counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	No association in improving lipid profile
Ma et al.,[35] (2010)	24 patients with T2DM, aged 30–75 years	Randomised crossover controlled	56 g walnuts daily for 2 months, with dietary counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	Improved LDL cholesterol
Rabiei et al.,[34] (2018)	50 patients with T2DM, aged 30–80 years	Randomised controlled parallel design	200 mg walnut leaf extract per day for 2 months in the form of capsules	Microcrystalline cellulose capsules	No association in improving lipid profile
Tapsell et al.,[41] (2004)	58 patients with diabetes who were overweight, aged 35–75 years	Randomised controlled parallel design	Moderate-fat diet plan advice to include 30 g of walnuts daily for 6 months	Standard clinical practice, with follow-up advice based on clinical judgment	Improved HDL and LDL cholesterols

Table 2 contined.

Study	Target population	Study design	Intervention	Comparison group	Results
Tindall et al.,[42] (2019)	45 participants who were overweight and obese, aged 35–65 years	Randomised crossover controlled	Walnuts (57–99 g/day) as snack for 6 weeks	Vegetable oil	Improved LDL cholesterol
Zibaeenezhad et al.,[32] (2016)	100 patients with T2DM aged 35–75 years	Randomised, double-blind placebo control trial	Four walnut oil capsules (1.25 cc) daily for 90 days	Placebo capsule containing distilled water (1.25 cc)	Improved LDL cholesterol
Lipid profile: animal studies					
Mollica et al.,[39] (2017)	36 rats with diabetes	Randomised controlled parallel design	Walnut leaf extract administered via gavage with either 25, 50, or 100 mg/kg twice daily for 28 days, with access to food and water *ad libitum*	10 mL/kg distilled water	Improved lipid profile
Blood pressure: human studies					
Katz et al.,[36] (2012)	46 participants at risk for T2DM	Randomised crossover controlled	56 g walnuts daily for 2 months, with dietary counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	No association with blood pressure reduction
Ma et al.,[35] (2010)	24 patients with T2DM, aged 35–75 years	Randomised crossover controlled	56 g walnuts daily for 2 months, with dietary counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	No association with blood pressure reduction
Njike et al.,[26] (2016)	112 participants at risk for T2DM, aged 25–75 years	Randomised crossover controlled	56 g walnut daily for 6 months, with or without dietary counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	No association with blood pressure reduction
Rabiei et al.,[34] (2018)	50 patients with T2DM, aged 30–80 years	Randomised controlled parallel design	200 mg walnut leaf extract per day for 2 months in the form of capsules	Microcrystalline cellulose capsules	Associated with blood pressure reduction
Tindall et al.,[42] (2019)	45 participants who were overweight and obese, aged 35–65 years	Randomised crossover controlled	Walnuts (57–99 g/day) as snack for 6 weeks	Vegetable oil	Improved diastolic blood pressure
Zibaeenezhad et al.,[32] (2016)	100 patients with T2DM, aged 30–60 years	Randomised controlled parallel design	Inclusion of 15 g daily for 3 months of walnuts as oil in diets	Exclusion of walnut in diets	No association with blood pressure reduction

Table 2 contined.

Study	Target population	Study design	Intervention	Comparison group	Results
Endothelial function: human studies					
Berryman et al.,[43] (2013)	15 participants who were overweight and obese, aged 21–60 years	Randomised crossover controlled	Single dose of 51 g walnut oil	5.6 g ground walnut skin or 85 g ground whole walnut	Improved endothelial function
Katz et al.,[36] (2012)	46 participants at risk for T2DM, aged 30–75 years	Randomised crossover controlled	56 g walnuts daily for 2 months, with dietary counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	Improved endothelial function
Ma et al.,[35] (2010)	24 patients with T2DM, aged 30–75 years	Randomised crossover controlled	56 g walnuts daily for 2 months, with dietary counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	Improved endothelial function
Njike et al.,[37] (2015)	112 participants at risk for T2DM, aged 25–75 years	Randomised crossover controlled	56 g walnuts daily for 6 months, with or without dietary counselling to regulate calorie intake	*Ad libitum* diet, without walnut supplementation	Improved endothelial function

HDL: high-density lipoprotein; LDL: low-density lipoprotein; T2DM: Type 2 diabetes mellitus.

Also, a randomised controlled study by Rabiei et al.[34] with 50 patients with T2DM, aged 30–80 years, reported no improvement in lipid panel with supplementation of walnut leaf extract capsules compared with microcrystalline cellulose placebo capsules.

One randomised controlled study with diabetic rats by Mollica et al.[23] assessed the effects of walnut leaf extract on lipid profile. The rats receiving either 25, 50, or 100 mg/kg walnut leaf extract twice daily via gavage for 28 days, with *ad libitum* access to food and water, showed significant improvement in their dyslipidaemia compared with those given 10 mL/kg distilled water as placebo without walnut leaf extract supplementation.

With only two studies showing no association between lipid profile and the inclusion of walnut in the diets, most of the studies showed a strong association. Therefore, it may be concluded that including walnuts in the diets of individuals with T2DM has favourable effects on lipid profile (Table 2).

BLOOD PRESSURE

The relatively high content of omega-3 fatty acids, polyphenols, L-arginine, and magnesium in walnuts may play an important role in improving blood pressure. Foods rich in omega-3 fatty acids lower blood pressure by upregulating angiotensin-converting enzyme-2.[48] Foods rich in polyphenols act through the angiotensin-converting enzyme pathway by blocking this enzyme and therefore allowing blood vessels to relax, thus improving blood flow and reducing blood pressure.[49,50] In addition, polyphenols stimulate the enzyme nitric oxide synthase to increase production of nitric oxide, which causes smooth muscles in blood vessels to relax, opening the arteries to improve blood flow.

L-arginine is an amino acid used by the body to produce nitric oxide, which causes blood vessels to relax and dilate, thus lowering blood pressure.[51-53] Magnesium stimulates production of prostaglandin E1, a potent vasodilator.[54]

In a randomised controlled study of 50 patients with T2DM, aged 30–80 years, Rabiei et al.[34] demonstrated reduced office blood pressure with daily supplementation of 200 mg walnut leaf extract capsules compared with microcrystalline cellulose capsules. Likewise. Tindall et al.[42] reported improved diastolic blood pressure in 45 adults who were overweight and obese, aged 35–65 years, when replacing saturated fat with walnuts (57–99 g/day) compared with vegetable oils over a 6-week period. However, other previous randomised controlled crossover studies (n=24, n=46, and n=112, respectively), with participants aged 30–75 years, have shown no association between reduced office blood pressure and the inclusion of 56 g walnuts in otherwise *ad libitum* diets, with or without counselling to regulate caloric intake in patients with or at risk for T2DM.[32,35-37] A randomised control study by Zibaeenezhad et al.[32] with 100 patients with T2DM, aged 30–60 years, showed no improvement in office blood pressure with the daily inclusion of 15 g walnut oil for 3 months in their diets, compared to diets without walnut oil supplementation.

All studies in this review (with the exception of just two studies) showed no association in improved blood pressure with the inclusion of walnuts in the diets. Therefore, it could be concluded that there is no association with the inclusion of walnuts in the diets of those with or at risk for T2DM (Table 2).

ENDOTHELIAL FUNCTION

Walnuts are rich in L-arginine amino acids, which are known to improve vascular function. In the body, L-arginine is converted into nitic oxide, a potent neurotransmitter that helps to relax blood vessels and improve blood flow.[51-53] Also, walnuts are rich in polyphenols shown to have anti-oxidative effects *in vitro* and *in vivo* in mice with T2DM.[55] Dietary polyphenol antioxidants bind to lipoproteins to inhibit oxidative stress processes that lead to the development of atherosclerosis.[56] In addition, walnuts are rich in omega-3 α-linolenic fatty acids. Dietary omega-3 fatty acid intake has been inversely associated with the incidence of CVD. Omega-3 fatty acids are known to have an anti-inflammatory effect, which prevents the formation of pathological blood clots and also improves oxidative stress parameters.[57,58]

In the context of a randomised controlled crossover trial with 15 particpants who were overweight and obese, aged 21–60 years, Berryman et al.[43] reported significantly improved endothelial function with the consumption of a single 51 g dose of walnut oil. In a randomised controlled crossover study by Ma et al.[35] with 24 patients with diabetes, aged 35–75 years, including 56 g walnuts daily for 2 months in otherwise *ad libitum* diets with counselling to regulate calorie intake improved endothelial function compared with control *ad libitum* diets without walnut supplementation. Additionally, in other randomised controlled crossover studies, Katz et al.[36] and Njike et al.[37] (n=46 and n=112, respectively) also demonstrated improvement in endothelial function with the inclusion of 56 g walnuts daily for 2 months and 6 months, respectively, in otherwise *ad libitum* diets, with or without counselling to regulate calorie intake compared to *ad libitum* diets without walnuts in participants at risk for T2DM, aged 30–75 years.

This review suggests that all studies discussed here showed an association in improved endothelial function with the inclusion of walnuts in the diets. Therefore, it could be concluded that the inclusion of walnuts in the diets in patients with or at risk T2DM has favourable effects on endothelial function (Table 2).

DISCUSSION

Based on the body of evidence, the reported effects of walnut on glycaemic control in those at risk for or with T2DM remains inconclusive. Although epidemiologic studies, animal models, and some randomised controlled and mechanistic trials showed an association between walnut intake and glycaemic control in individuals at risk for or with T2DM, some randomised trials failed to demonstrate this association. The variation of results observed in these studies may be due to differences in doses of walnuts, types of walnuts, length of interventions, demographics

of participants, timing of introducing walnuts into their diets, and/or different dietary patterns in the context in which they were introduced. Additionally, some studies may have been underpowered. Therefore, a much larger study or meta-analysis is warranted to clearly elucidate any association in glycaemic control with walnuts.

The inclusion of walnuts in the diets of individuals at risk for or with T2DM showed no effects on body weight in most of the studies. One study showed reduced body weight with the inclusion of walnuts in the diets. This difference in results observed may be due to the ways in which walnuts were introduced into the diets of the study's participants. Some of the study's participants included the walnuts as snacks in-between meals, while others included the walnuts with their meals. Also, none of these studies were designed with body weight as the primary outcome measure. The design of a study with body weight as a primary outcome measure in which walnuts are introduced as snacks in-between meals has the potential to improve satiety to foster reduced caloric intake and body weight.

Most studies showed an association between reduced LDL cholesterol and the inclusion of 30–56 g walnuts in the diets of persons with T2DM. In addition, one study also showed improved high-density lipoprotein cholesterol. One study showed no association in lipid profile with the inclusion of 56 g walnuts in the diets of persons at risk for T2DM. Different demographics of study participants and dietary patterns may explain the differences among the results. A study designed to examine differential effects of walnuts on lipid profile in participants with different demographic and dietary patterns is warranted.

Studies consistently showed no impact on blood pressure when introducing walnuts into the diets of persons at risk for or with T2DM. The lack of effects on blood pressure may be due to less reliable techniques used to assess blood pressure in these studies, insufficient doses, and the fact that blood pressure was not the primary endpoint of these studies. There is biological credibility that the biochemical composition of walnuts may reduce blood pressure. A study design in which blood pressure is the primary outcome measure and using more reliable techniques such as an ambulatory 24-hour blood pressure monitor to assess blood pressure is needed to elucidate the effects of walnuts on blood pressure.

Walnut consumption was associated with improvement in endothelial function in those at risk for or with T2DM in prior studies. A dose-response study is needed to determine the optimal dose and frequency of walnut consumption to maintain improved endothelial function throughout the course of the day, without adversely affecting other cardio-metabolic parameters.

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A Case Report of Extensively Drug Resistant Typhoid in Karachi, Pakistan: A Major Health Concern to Curb the Outbreak

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Abstract

The disease burden of extensively drug resistant typhoid in developing countries is a major emerging issue that cannot be ignored. Since its emergence from multidrug strains, the majority of typhoid cases in Karachi, Pakistan, have been extensively drug resistant, mostly infecting younger patients. In the study, the authors analysed one such case in an adolescent male and discussed how, by the implementation of national health policies, the spread of these infectious diseases could be prevented and the overall burden on the healthcare system decreased in areas with already limited resources.

INTRODUCTION

Salmonella typhi is a flagellated gram-negative bacterium that is rod shaped and causes typhoid fever in its only host: humans.[1] The transmission of typhoid fever is mainly through "direct, person to person transmission as a result of improper hygiene and unsafe food/water handling practices" causing faeco-oral spread of the bacterium especially in "densely populated areas that lack proper sanitation and access to safe drinking water" such as in Pakistan.[2] After the ingestion of *S. typhi*, the bacterium enters the systemic circulation by crossing through the epithelium of the intestine and can disseminate to the liver, gall bladder, bone marrow, and spleen, causing symptoms such as fever that may become life threatening, generalised muscle ache, abdominal pain, and headache.[3] The treatment of typhoid is primarily through antibiotics; however, drug resistance to common antibiotics is increasing rapidly, causing major concern.[4]

Extensively drug resistant (XDR) typhoid fever has become a major health issue in some parts of the world since it began in late 2016 in Hyderabad district of Sindh, Pakistan, due to strains of *S. typhi* that are antimicrobial resistant (AMR).[5] The emergence of XDR typhoid from the already concerning multi-drug resistant typhoid has occurred due to the organism simply obtaining a plasmid that is now resistant to multiple classes of antibiotics including first-line and second-line treatment options such as trimethoprim-sulfamethoxazole, ampicillin, chloramphenicol, third generation cephalosporins, and fluoroquinolones.[6-8] It is

hypothesised that the spread of this XDR type occurred because the *S. typhi* strain acquired this plasmid from *Escherichia coli*, since researchers discovered that the isolated plasmid resembled one within a Nigerian *E. coli* sample.[7]

In Karachi, Pakistan, the incidence of XDR typhoid cases reported in major hospitals since the initial outbreak was 7,622 of out of a total 11,717 cases of typhoid, according to the National Institute of Health (NIH) Islamabad.[9] Out of these, most (42%) of those affected were children under the age of 4 years.[9] The overall attack rate was 38/100,000 population, the highest of which was found in 0–4 years age, group with 116/100,000 population, followed by the 5–9 years age group with 83/100,000 population.[9]

CASE REPORT

A previously healthy 13-year-old male, a resident of Korangi, Karachi, Pakistan, presented in the outpatient department on 13th August 2019, with the complaint of sudden onset high grade, stepladder fever for 2 weeks. It was initially 101–102 °F later climbing to 103 °F over the span of 8 days with associated rigors, chills, abdominal pain, cough, congestion, and generalised body ache. On admission, his vitals included blood pressure: 114/68 mmHg; temperature: 104 °F; pulse: 62 beats per minute; respiratory rate: 14 breaths per minute; oxygen saturation on room air: 97%; and his weight was 60 kg. The patient was alert and oriented with time, place, and person, and his Glasgow Coma Scale (GCS) was 15/15. Physical examination was remarkable for pallor, mild muscle tenderness, and abdominal tenderness, and negative for cyanosis, clubbing, oedema, icterus, lymphadenopathy, splenomegaly, and skin rash. Upon systemic examination, the cardiovascular and respiratory systems had no significant findings. His abdomen was tender with guarding present due to pain, and there was no visceromegaly. There were no signs of ascites, and normal bowel sounds were present. His neurological examination was normal. He had no bone or joint pains or swelling.

The child was prescribed paracetamol *per os, si opus sit,* and advised for investigation including complete blood count and posterior anterior chest X-ray chest PA. On the third day, when symptoms did not subside, the family came for a follow-up. The child was admitted and other investigations including a blood culture, dengue non-structural protein 1 antigen, malarial parasite, urine detailed report, urea, creatinine, electrolytes, liver function tests, and viral marker were sent. The child's vitals were monitored, and he was started on loratadine 10 mg *per os* once daily, nebulised ipratropium bromide every 6 hour for cough and congestion, and IV Ringer's lactate 75 mL/hour, IV paracetamol 1 g *si opus sit*, IV ceftriaxone 1 g twice daily for fever and antibiotic cover. Investigations revealed only mild anaemia and platelet count of 131×10^9/L, as well as, a drop in leukocytes from 7.6×10^9/L to 3.8×10^9/L. Aspartate transaminase, alanine transaminase, and γ-glutamyl transferase were deranged on liver function tests.

The chest X-ray was clear and urea, creatinine, electrolytes, and urine detailed report were normal, and hepatitis markers, dengue non-structural protein 1 antigen and malarial parasite were negative. The blood culture revealed growth of *S. typhi* that was resistant to ampicillin, ciprofloxacin, cefotaxime, co-trimoxazole, cefixime, ceftriaxone, and chloramphenicol. This strain was only sensitive to azithromycin, imipenem, and meropenem. The patient was switched from ceftriaxone to IV imipenem/cisplatin 500 mg three times a day in 1,000 mL normal saline according to sensitivity with plan to de-escalate to tablet azithromycin 500 mg twice daily. He was also given two capsules of loperamide stat, dioctahedral smectite powder twice daily, and miconazole oral gel three times a day for the complaints of diarrhoea and oral ulcers.

Fever subsided after 6 days of changing antibiotics. IV Imipenem/cisplatin was continued for a total of 7 days and then de-escalated to tablets of azithromycin when the patient's clinical condition was noted to be improving. Treatment was continued to complete a total of 14 days of therapy according to treatment guidelines set forth by the Medical Microbiology and Infectious Diseases Society of Pakistan.[10] The patient's general condition improved; he was counselled on the importance of hygienic practices for the prevention of transmissible diseases and was discharged.

DISCUSSION

Since the emergence of extensively drug resistant typhoid fever in Pakistan, the number of XDR cases has increasingly outnumbered sensitive cases, making it a progressively concerning issue in South Asia, specifically Karachi, Pakistan. The mechanism of AMR occurs via the plasmids in *S. typhi* H58 haplotype that carry resistant genes including trimethoprim-sulfamethoxazole resistance (*dfrA7*, *sul1*, *sul2*), ampicillin resistance (*blaTEM-1*), chloramphenicol resistance (*catA1*), fluoroquinolone resistance (qnr, oqxAB, or aac(6′)Ib-cr), and ceftriaxone resistance (*ESBL*).[11] These resistant genes have caused XDR typhoid to become a greater burden (about 72% more burdensome) than sensitive typhoid in Pakistan, specifically in terms of cost related to diagnosis and nursing care.[12] In a study on the frequency of XDR typhoid fever, of total 969 typhoid fever cases, 777 (80.2%) were multidrug resistant-cases and showed resistance to all three first-line antibiotics (ampicillin, chloramphenicol, and co-trimoxazole); 517 (53.3%) were XDR-typhoid fever cases, which were resistant to first- and second-line drugs (ciprofloxacin) and the third generation cephalosporin (ceftriaxone). Only two antibiotics (azithromycin and imipenem) were seen to be sensitive to all *S. typhi* cases.[13] Many studies have suggested the use of azithromycin, carbapenems, and tigecycline for treatment of XDR typhoid.[1,14,15] This "sudden emergence and rapid spread of resistant isolates underline the importance of AMR surveillance for typhoid and other enteric Gram-negative bacteria and highlight the inadequacy of relying solely on non-culture-based methods for diagnosis of typhoid (such as Widal and Typhidot tests), which do not provide susceptibility results."[11] Thus, guidelines to counteract the resistance have been set by the NIH Islamabad, which stress on the prompt confirmation of diagnosis of any and all suspected cases with blood culture and sensitivity prior to initiating empirical therapy.[16] Furthermore, it is advised that the appropriate use of specific antibiotics should be based on the culture and sensitivity reports, and to refrain from using stronger antibiotics such as azithromycin or carbapenem for uncomplicated or sensitive cases.[17]

In the authors' case, they ensured proper investigations, including a blood culture, were conducted prior to beginning empiric therapy with the recommended antibiotic. After obtaining results of the blood culture and sensitivity, the authors promptly switched antibiotic management according to the appropriate sensitivities. It is the duty of healthcare professionals to fulfil a role in halting the spread of drug resistant organisms by following the guidelines set to diagnose and treat typhoid promptly and accurately.

The World Health Organization (WHO) has also highlighted some major modifiable risk factors to contain the spread of typhoid. These include the limited resources in rural set ups to screen and confirm the diagnosis of typhoid fever, the substandard prescription and use of antibiotics, unsanitary practices, and the inadequate use of vaccines among those at high risk, notably direct contacts with patients and carriers or those in high endemic incidence areas.[2] These issues must be acknowledged and updated in Pakistan in order to curb the growing number of cases.

Poor sanitation is one of the major preventable factors contributing to the outbreak of typhoid, especially of drinking water when it is contaminated with sewage lines, increasing the risk of faeco-oral transmission of the bacteria.[18] This is heightened by poverty, overcrowding, and a lack of education in proper hygiene.[19] Some recommendations made by the NIH Islamabad include proper hand hygiene, using water that is filtered or boiled, and thoroughly washing produce prior to meal preparation.[17] The importance of hygiene is exemplified by the nations, including Europe, North America, South America, and Australia, that have proper clean water and sewage line systems, and implement a national typhoid fever surveillance.[20,21] Thus, sanitation and education about its importance are critical to prevent the spread of infectious diseases like typhoid and can successfully be accomplished through simple picture pamphlets and school programmes to spread awareness.[22] The education provided should specifically focus on how typhoid is spread, the prevention of it spread through hand washing and basic hygiene, minimising exposure to contacts, and vaccination for susceptible populations.[5] In the authors' case, the patient and his family were counselled regarding the implementation of these basic hygienic practices to prevent the transmission of typhoid.

Vaccination against typhoid exists in two forms: an injectable vaccine for those over 2 years of age and a live attenuated oral vaccine for those over 5 years of age; a third new conjugate type vaccine was prequalified by the WHO in 2017 for use in children as young as 6 months.[23] The NIH Islamabad has listed the conditions in which the vaccine is justified including for those in direct contact with patients and carriers, healthcare workers who are exposed due to their profession, "institutions where the appropriate hygienic condition cannot be met, areas of high endemic incidence," and travellers.[24] The combination of these efforts can become a powerful tool to raise awareness, prevent disease, and promote healthy living styles.

CONCLUSION

In conclusion, as the number of XDR typhoid cases rise it is becoming increasingly necessary to take action under the guidance of the NIH Islamabad and WHO at a local level in order to effectively minimise the spread of drug resistant communicable diseases. The power of community education programmes and locally set-up campaigns for the promotion of public health should not be underestimated. Although the resistant strain has already emerged, healthcare professionals can still help to curb its rapid spread, even the communities with the least resources, by emphasising and promoting the implementation of simple preventive measures.

This case highlighted the importance of high clinical suspicion and prompt diagnostic investigations including a blood culture. Compared to other existing literature that address special populations, such as pregnant females or cases in which patients present with pathognomonic features such as rose spots, the authors' case presented with no clear indication typhoid and care was taken to follow the proper guidelines regarding thorough investigations.[6,25] There were also many studies revealed during the authors' literature search that emphasised outbreaks and the global burden of typhoid cases; however, by providing this perspective of an average young male, the authors are aiming to add a case study into the existing literature to increase insight at the individual level specifically from a geographical area like Pakistan, where extensively drug resistant typhoid took its origin.[18,19,21] Lastly, the authors believe that, through this study, healthcare providers will be reminded to use antibiotics appropriately and only when necessary, to impede further antibiotic resistance.

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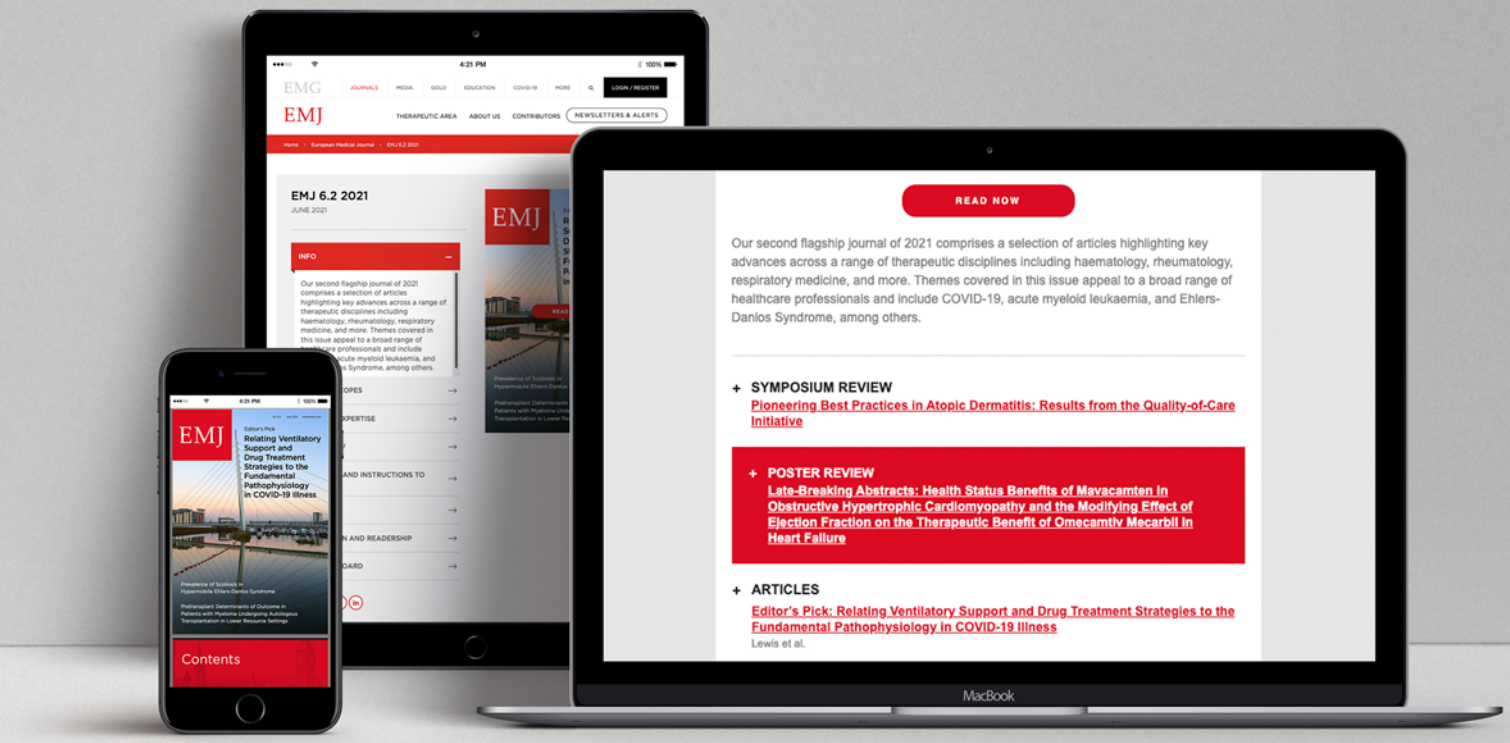

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