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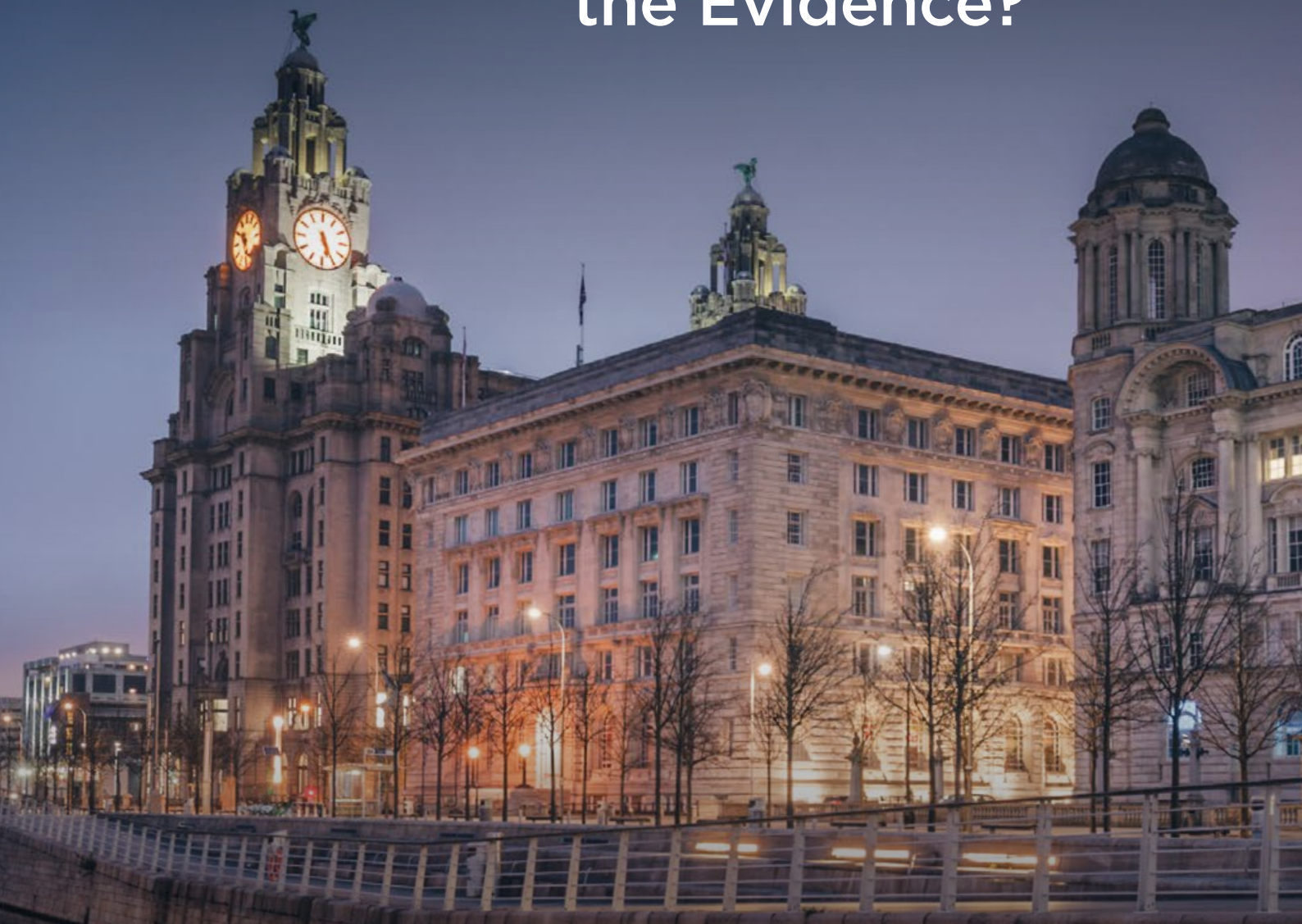
EMJ

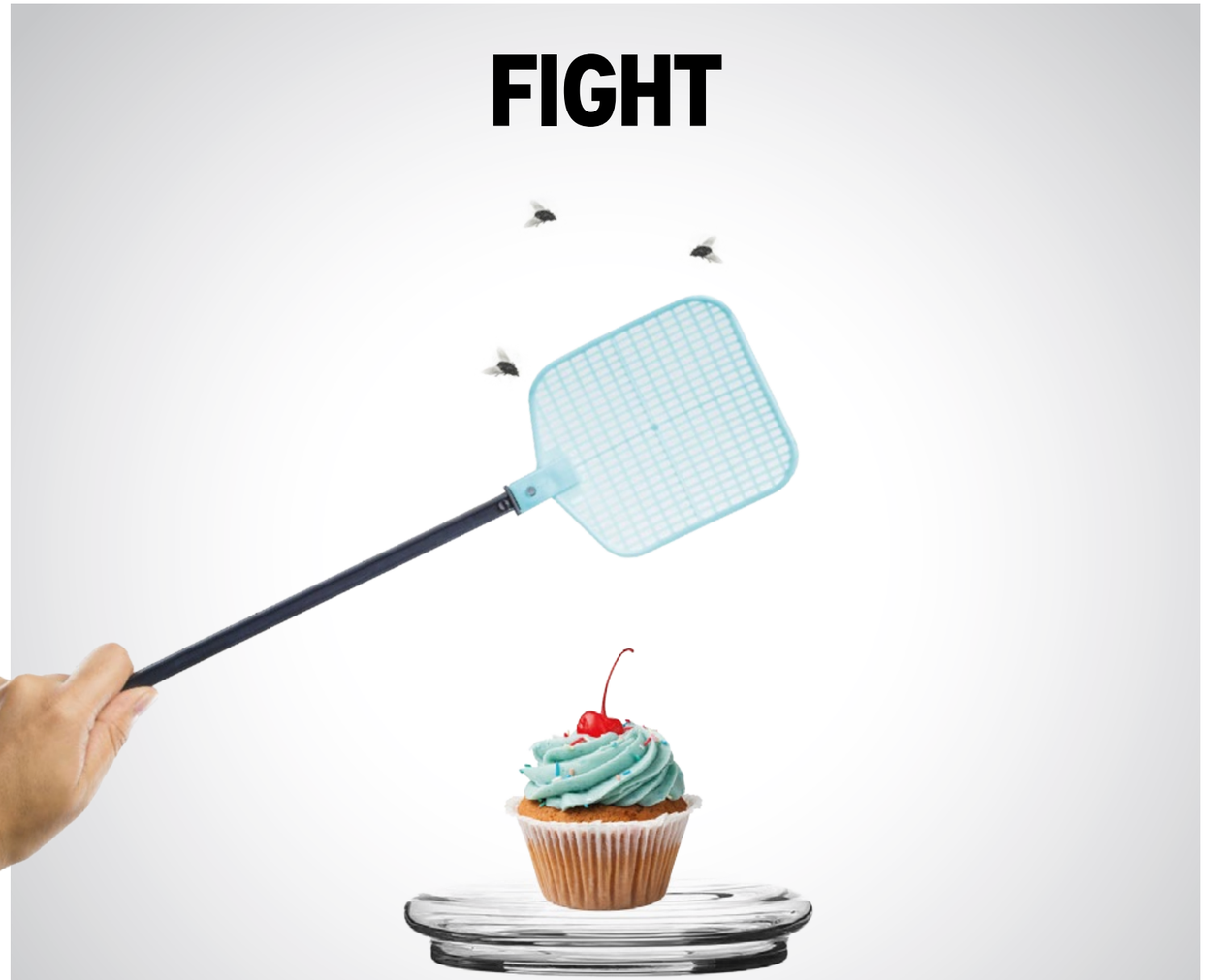
Editor's Pick

The Correlation Between Stroke and COVID-19: Where is the Evidence?



Emerging Treatments for Crohn's Disease: Cells, Surgery, and Novel Therapeutics

Pancreatic β-Cell Senescence: Mechanisms and Association with Diabetes



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]

kyntheum®▼
Brodalumab

IN THE FIGHT AGAINST PSORIASIS THINK RECEPTOR BLOCKADE

LEO

Contents

"...the scientific excellence, partnerships, and all-round comradeship we have seen over the last year have been nothing short of exceptional and provide a beacon of hope for the successes that are to come."

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 6.1

Welcome

Dear Readers,

It is with great delight that I welcome you to the first *EMJ* flagship journal of the year, containing scientific developments from a range of therapeutic areas. As we make pace in 2021, we begin to see the innovation in science that will truly make a mark in healthcare. Last year laid witness to the spread of the coronavirus disease (COVID-19) pandemic, which dominated headlines and shaped the world around us; while a clock striking midnight on the 1st of January does not miraculously change the state of the world, the scientific excellence, partnerships, and all-round comradeship we have seen over the last year have been nothing short of exceptional and provide a beacon of hope for the successes that are to come.

We begin our latest issue with the Editor's Pick, an investigative review on the impact that COVID-19 has on the incidence of stroke. Stroke is now the second-leading cause of death globally, and while mortality rates from the disease are decreasing, incidence is following an upward trajectory. Emerging infectious diseases, such as COVID-19, present new challenges, with current research suggesting the role they play in stroke aetiology. Here, Pittams et al. aim to bring further insight into the interplay between the two disease entities in order to advance the current therapies for pathogen-induced stroke.

For the endocrinologists among you, El-Badri et al. give an insightful review into pancreatic β-cell senescence. An ageing society means that more and more people are experiencing age-induced senescence. Age also brings a decrease in pancreatic β-cell proliferation and glucose homeostasis and eventually the possible development of diabetes, which in turn contributes to β-cell senescence. This paper discusses these interlinking pathophysiologies in great detail.

If dermatology is your specialty, then we have two papers of interest: one by Queirós et al. who discuss the common cutaneous alterations observed in the newborn; and a second by Tognetti et al. who review the current knowledge in the field of syphilis diagnosis and treatment. We hope that the interdisciplinary collection of articles in this flagship journal will facilitate the cross-pollination of ideas across the therapeutic spectrum.

All that remains is to give a huge thank you to the Editorial Board, authors, peer reviewers, and editors, without whom we could not publish such high-quality content. Finally, I would like to thank you, the readers, for your loyalty, and we hope that you enjoy the latest issue of our flagship journal *EMJ*

Spencer Gore

Chief Executive Officer, EMG-Health

Foreword

Dear Readers,

It is with great pleasure that I welcome you to our first *EMJ* flagship journal of 2021. With the new year comes new innovation, advancements in medicine, and, in light of the coronavirus disease (COVID-19) pandemic, persevering hope and ambition that our science and technologies will carry us on a path back to a new normal. Certainly, this issue will feature COVID-19 peer-reviewed articles; yet within the pages of *EMJ* can be found an abundance of other therapy areas: microbiology, dermatology, diabetes, respiratory, cardiology, nephrology, and gastroenterology.

Our Editor's Pick this issue tackles the effect that COVID-19 is having on the predicted rise in stroke incidence. With stroke being the second-leading cause of death globally, and almost one in 20 patients with a confirmed diagnosis of COVID-19 expected to experience a stroke, Pittams et al. seek to achieve a better understanding of the current evidence between these disease entities and what role infectious diseases play in stroke aetiology.

As you run through the pages of *EMJ*, you will uncover the narrative review by Meade et al. of alternative treatments that are under investigation for Crohn's Disease. With biological therapies providing only 30–50% efficacy after 1 year, new pharmacological interventions such as stem cell therapies and transplants, as well as nonpharmacological strategies, are being explored; these strategies are currently in late-phase trials, with the hope of implementation in clinical practice in the near future. Reading on, a research paper by Ikechukwu et al. aims to assess the physical activity level and the factors affecting exercise participation among patients with and without diabetes. The study, which took place in Nigeria, identified diabetes as a barrier to physical activity involvement and highlighted the need for public awareness on the importance of exercise in the prevention and management of diabetes.

The above details only some of the content this issue of *EMJ* has to offer and I look forward to your uncovering the wealth of material within the journal's pages. I would like to thank all the authors and peer reviewers for their time and efforts spent helping to produce this excellent issue.

Professor László Vécsei

University of Szeged, Szeged, Hungary

Rare 2030 Final Policy Conference: Summary of the Recommendations of the Rare 2030 Foresight Study

Evgenia Koutsouki
Editor

Citation: EMJ. 2021;6[1]:12-14.

IMPROVING the lives of people living with a rare disease in Europe has been an overarching aim of the Rare 2030 Foresight Study, a two-year study that collected input from various partners, including patient groups, practitioners, and key opinion leaders. By identifying twelve political, economic, sociocultural, technological, ethical, and legal trends, the study produced eight recommendations to help establish new and improved policies for rare diseases in Europe.[1] The virtual Rare 2030 Final Policy Conference that took place on February 23rd saw the various stakeholders come together to present and comment on these recommendations.[2]

FRAMEWORK STRATEGY AND EARLY DIAGNOSIS

The first of these recommendations pertains to long-term, integrated European and national plans and strategies for rare diseases. Kate Bushby, the lead researcher for the 2030 Project, explained that in light of new technology and progress in the field of rare diseases, there was a need to align these efforts into a new framework. It had become increasingly obvious that the previous framework and national plans were becoming outdated and inconsistent. Yann Le Cam, European Organisation for Rare Diseases (EURORDIS), emphasised that despite the progress made in the last 15 years, there are still unmet clinical needs for the 30 million people living with rare diseases in Europe. The new vision is to embed all the efforts in an integrated framework at the European level, which will then be supported nationally to ensure it is implemented on a day-to-day basis. New funding will ensure that there is a new cohesive plan for every person with a rare disease across Europe and will ensure that rare diseases remain a public health priority in Europe.

When it comes to the speed of and access to diagnosis, earlier, faster, and more accurate diagnosis is a key goal of the recommendations. An ambitious goal has been set to have every person with an identifiable rare disease diagnosed within six months of seeking medical attention. According to Le Cam, setting ambitious objectives will help to improve performance and potentially see the European Union (EU) become a world leader in biotechnology. Le Cam also highlighted the need to adopt a holistic approach to the needs and care of patients, powered by data: "As opposed to 10 years ago where process outcomes were measured, we are now in a position to have qualitative and quantitative objectives, and have a real impact

on society, on quality of life, and on economies." Of course, diagnosis for people with currently undiagnosable conditions will remain an ongoing challenge; however, the recommendations state that despite the absence of a diagnosis, these people would still have access to the best possible care and support.

EQUALITY OF ACCESS

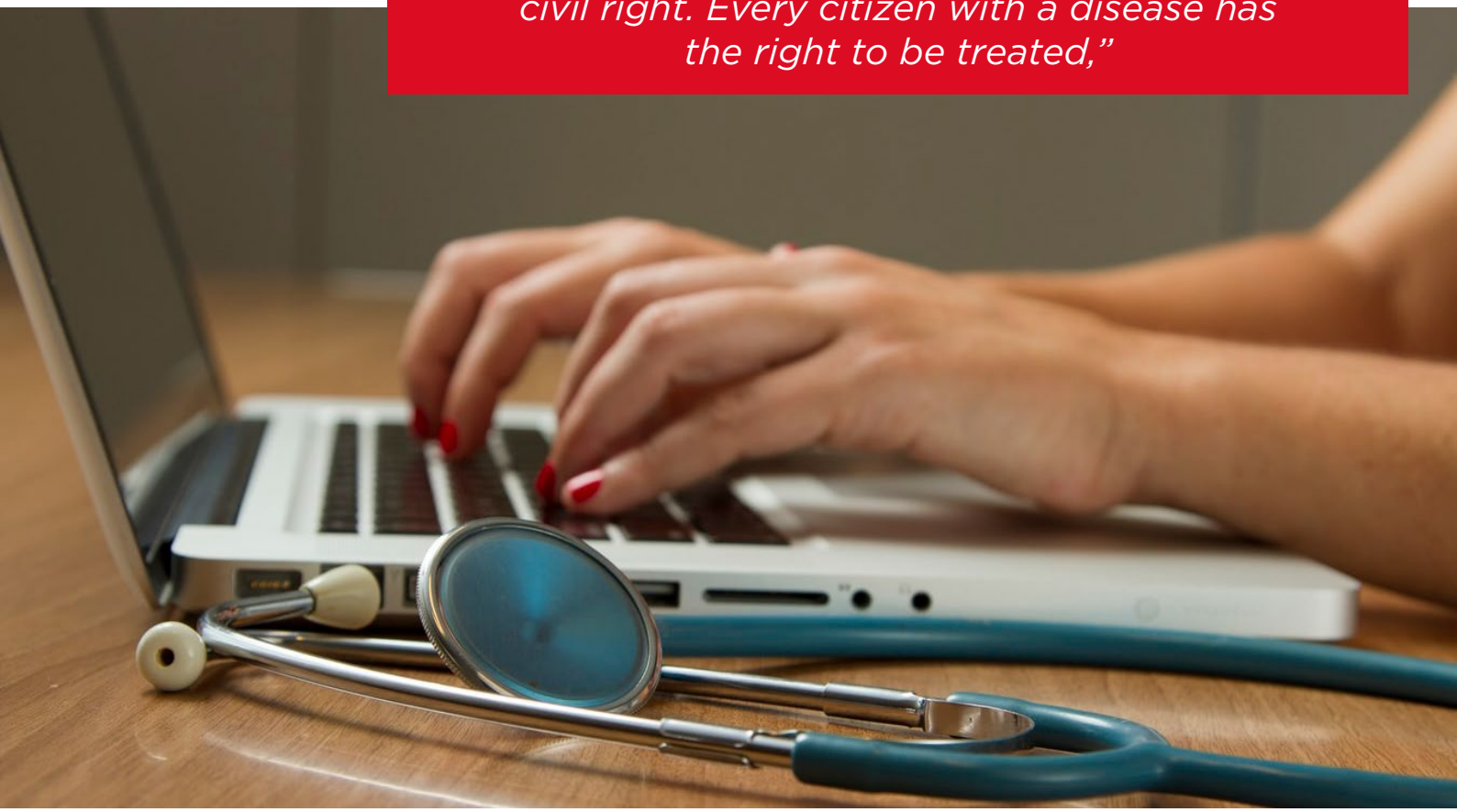
Access to services is a theme that runs throughout the recommendations, as the third recommendation addresses access to high-quality healthcare. Adopting an approach to rare diseases at the EU level means that all citizens can have access to diagnosis, care, and treatment, whether close to home or across national borders. "It is a matter of equality, it is a matter of civil right. Every citizen with a disease has the right to be treated," commented Prof Maurizio Scarpa, MetabERN.

Putting people at the forefront of such an initiative is the key to its success; therefore, there is a great need to ensure equal opportunities and integration of people living with rare diseases, which is what the fourth recommendation focusses on. Giovanna Giuffrè, ISINNOVA, commented that trends observed during the coronavirus disease (COVID-19) pandemic can help for understanding challenges and opportunities that are relevant to patients with rare diseases. Giuffrè commented that during the pandemic there have been trends of increased inequality and reduced cohesion in healthcare, while at the same time opportunities have arisen in digital health, artificial intelligence, and multi-stakeholder collaboration in research.

PARTNERSHIPS AND ADVOCACY

The next recommendation focusses on establishing a culture in which people living with rare diseases can be empowered to actively participate in research and innovation, leading to the creation of partnerships in the public and private sectors. Le Cam commented that the fundamental change proposed by this recommendation would be a change from collaboration to partnering. "What we need for success is a change of culture for an active

"It is a matter of equality, it is a matter of civil right. Every citizen with a disease has the right to be treated,"



"the Rare 2030 Recommendations, with an inclusive and collaborative approach, can be a key factor in actively spreading awareness to debunk stereotypes and stigmas."

and meaningful participation of patients," Le Cam emphasised.

This need for partnership with patients and their representatives was reinforced by the findings of surveys that were carried out between 2016 and 2021, which have shown that 9 out of 10 patient representatives wish to be more involved in the research ecosystem, help researchers, and participate more in research projects as official partners and co-investigators.

Encouraging innovation and efficiency in the development of rare disease therapies would not only improve organisation, but would also help management of care. Creating greater incentives for research and promoting international partnerships between organisations and among different sectors are key to achieving this goal. Lucia Monaco, Fondazione Telethon, explained that emphasis should be placed on identifying unmet needs, "with particular attention to diseases that are neglected by research and development." Monaco also explained that "to accelerate excellent science in rare diseases, funders should support the translation of innovation from bench to the clinic and promote access to existing infrastructures."

ACCESSIBLE DATA AND THERAPIES

Over recent decades, the dissemination of data has become an important aspect of research and innovation. Data are the focus of the seventh recommendation: more specifically, the collection and integration of data on rare diseases. One of the key objectives is ensuring that such data are encoded under the uniform nomenclature of Orphanet. Integrating these data under a federated European system will encourage collaboration and help to promote progress in research and potential treatments. However, Bushby emphasised that "we are custodians of these data, they don't belong to us. They belong to the patient, they belong to the community, and making sure that sharing is done in a meaningful way for the right reasons is probably the best that we can hope to achieve as time goes on."

The final recommendation seeks to ensure that preventative technologies and therapies are accessible to all people in Europe living with a rare disease. Ultimately, the long-term goal is to form an environment ripe for investment, to establish robust pharmaceutical and biotechnology manufacturing presences in Europe, combined with better patient access and health monitoring.

Among the stakeholders consulted for these recommendations were the 2030 Young Citizens. Fanni-Laura Mäntylä, representing Rare 2030 Young Citizens, commented that "the Rare 2030 Recommendations, with an inclusive and collaborative approach, can be a key factor in actively spreading awareness to debunk stereotypes and stigmas."

It is clear that a new era is beginning for rare diseases in Europe, which will see a more integrated, accessible, and cross-border approach, encouraging innovation, research, and development in the field, while keeping people at the heart of the approach, leaving no European citizen behind.

References

1. Rare 2030: Foresight in Rare Diseases Policy; EURORDIS-Rare Diseases Europe. Recommendations from the Rare 2030 Foresight Study. 2021. Available at: http://download2.eurordis.org/rare2030/Rare2030_recommendations.pdf. Last accessed: 8 March 2021.
2. Rare 2030: Foresight in Rare Diseases Policy. Feb 23 - Final Policy Conference. 2021. Available at: https://www.rare2030.eu/key-events/feb-2021-policy-conference/. Last accessed: 8 March 2021.

Addressing the Unmet Need in Treatment of Nonmelanoma Skin Cancers: Interviews with Two Key Opinion Leaders

Interviewees: Axel Hauschild,[1] Salvador Martín Algarra[2]

1. Department of Dermatology, University of Kiel (UKSH), Kiel, Germany
2. Medical Oncology, Clinica Universidad de Navarra, Pamplona, Spain

Disclosure: Prof Dr Hauschild has received clinical trial support from Amgen, Bristol Myers Squibb, Merck Serono, MSD, Novartis, Philogen, Pierre Fabre, Provectus, Regeneron, and Roche; speaker's honoraria from Amgen, Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, Provectus, and Roche; and consultancy fees from Amgen, Bristol Myers Squibb, Merck Serono, MSD, Novartis, OncoSec, Philogen, Pierre Fabre, Provectus, Regeneron, and Roche. Dr Algarra has received clinical trial support from Amgen, Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, and Roche; speaker's honoraria from Amgen, Bristol Myers Squibb, MSD, Novartis, Pierre Fabre, and Roche; and consultancy fees from Amgen, Bristol Myers Squibb, Merck Serono, MSD, Novartis, Pierre Fabre, Regeneron, Roche, and Sanofi.

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Interview Summary

Nonmelanoma skin cancers (NMSC) are a diverse group of cutaneous malignancies and are the most common forms of human neoplasia worldwide.[1] The incidence of these diseases has increased during the last three decades[2,3] and there are up to 3 million new cases of NMSC every year.[4] There are geographical variations in incidence based on different ultraviolet (UV) exposure rates, with the highest incidence of NMSC in Australia.[3] The incidence of NMSC is increasing and yet these cancers are considered to be neither clinically, nor from a research perspective, as relevant as other tumours. The majority of NMSC are basal cell carcinomas (BCC) and cutaneous squamous cell carcinomas (CSCC). Advanced (locally advanced and metastatic) BCC and CSCC are associated with poor outcomes and are underserved in terms of treatment. Medical therapy improvements in advanced NMSC have not occurred as rapidly as those seen in melanoma, and there is a clear unmet need in the systemic treatment of patients with NMSC.

For this article, the EMJ conducted interviews in July 2020 with two key opinion leaders, Prof Dr Axel Hauschild from Germany and Dr Salvador Martín Algarra from Spain, both of whom have a wealth of experience and expertise in managing NMSC, to gain their perspectives on a range of topics in this area. The experts gave valuable insights into several pertinent issues in NMSC treatment and discussed significant recent developments in the field.

The article discusses the incidence of and current treatment landscape for NMSC and highlights the unmet need in the treatment of these diseases. New biological therapies with a different mechanism of action and their inclusion in a treatment algorithm for previously difficult-to-treat patients are considered. Screening and prevention of these diseases are also explored.

NONMELANOMA SKIN CANCERS: INCIDENCE AND PROFILE

Increasing Incidence of Nonmelanoma Skin Cancers

Prof Hauschild explained that the major reason for the increasing incidence of NMSC, particularly CSCC, is changing UV exposure patterns, and that individuals with high sun exposure 30–40 years ago are now presenting with actinic keratosis, precancerous lesions, and invasive CSCC. He emphasised that: "Patients are not developing only one tumour, but multiple primary tumours." These tumours form anywhere on the body but 80% occur in sun-exposed areas, such as the face and ear edges and, in males with androgenic alopecia, on the scalp. Prof Hauschild considered a minor reason for increasing NMSC incidence is the growing numbers of immunosuppressed patients, particularly organ transplant recipients, who have multiple NMSC, particularly CSCC, because immunosuppression is allowing the tumours to grow rapidly; these patients may present with more advanced disease.[5]

According to Dr Algarra, "NMSC is a very serious disease that is growing in incidence due to several known factors, including greater leisure exposure to the sun,[6,7] but there are several other factors that also need to be considered. Human papillomavirus[8] and other viruses could also play a role in the incidence and development of these diseases." He also considered that age is another very serious factor because there is a growing elderly population and the incidence of these tumours increases with age.[9]

Dr Algarra highlighted the increasing incidence of NMSC with higher ambient air pollution. A study of routine healthcare data from around 1.9 million people in Saxony, Germany, showed an increase in particulate matter with aerodynamic diameter of <10 µm (PM10) was associated with a 52% increase in relative risk of NMSC.[10]

Statin use has also been associated with higher incidence of NMSC,[11] which Dr Algarra suggested is "something quite provocative," particularly as the use of statins is increasing. Also, Dr Algarra mentioned that additional factors, such as socioeconomic or smoking status, genetic predisposition, pesticides, or other commonalities of the modern lifestyle, may be relevant to the growing incidence of these tumours.

The Major Difference Between Nonmelanoma Skin Cancers Is the Tendency to Metastasise

Prof Hauschild explained that BCC almost never metastasises (he has seen only two cases of metastatic BCC in his 30-year career), is locally aggressive, and could, in principle, invade bones (this is very rarely observed in CSCC). The incidence of locally advanced BCC has been reported as 0.8% in a large USA study,[12] whereas a Danish study showed a 14-year cumulative incidence proportion of metastatic BCC of 0.0039% among individuals with a history of previous BCC and 0.0001% in the general population.[13]

The major difference between BCC and CSCC is the tendency for the latter to metastasise, with metastatic CSCC observed as often as locally advanced disease. The most important risk factor for metastatic CSCC is maximum (vertical) tumour thickness.[14] Tumour thickness of >6 mm equates to a 30% chance of metastases, <2 mm thickness equates to 0%, and 2–6 mm thickness has a rating between 0 and 30%. Immunosuppression, localisation on the lip or ear, differentiation grade, and perineural invasion are also risk factors.

Why Do Nonmelanoma Skin Cancers Have a Lower Profile than Melanoma Skin Cancers?

When asked why NMSC are not as often discussed or as high profile as melanoma skin cancers, Prof Hauschild explained: "The incidence of NMSC is very high, with BCC the most common tumour in humans followed by, most likely, CSCC. There is less research in NMSC compared with melanoma because cases of locally advanced and metastatic NMSC are very rare, representing about 2% of CSCC patients. In the vast majority of cases, you are excising the lesions, so the surgery is doing the job."

Continuing this theme, Dr Algarra explained that the incidence of melanoma is lower than that of NMSC, but melanoma is a more aggressive disease. Dr Algarra considered: "There are biological reasons that make these tumours [NMSC] less dramatic and, therefore, not as relevant to general public awareness. Furthermore, local measures cure NMSC in the large majority of patients, NMSC is more

common in ageing populations (melanoma is more common in younger populations), and those rare cases that metastasise usually do not behave in such an aggressive way as melanoma. All these facts make cutaneous melanoma more relevant than NMSC for the news, the media, the clinicians, and the researchers." He continued: "Nevertheless, it is very important to consider that there is a subset of NMSC patients who cannot be treated with local measures and progress to mutilating or metastatic disease, with very limited or no treatment options. These particular patients deserve as much attention and medical commitment as those with advanced melanoma or Merkel cell carcinoma."

The Unmet Need in Treatment of Nonmelanoma Skin Cancers

Dr Algarra described a "darker phase" in NMSC: "When NMSC relapses after one or several surgeries, it is well proven that radiation therapy could help to control the disease, but there is a considerable number of patients who relapse, progress after radiation therapy, are not surgically treatable, and may be wrongly considered not suitable for any treatment." Dr Algarra emphasised: "Advanced NMSC patients, particularly those with BCC or CSCC, are sometimes neglected. We have experienced that in other challenging diseases. NMSC patients deserve a serious commitment from a basic, translational, and clinical research point of view." He explained that most professionals in the field accept that sometimes there is "nothing you can do after local treatment," but these usually elderly patients, who may not be able to care for themselves or have other medical and psychological difficulties, "deserve an evidence-based medical approach that considers the pros and cons of active treatments."

TREATMENT LANDSCAPE

Although Dr Algarra considered NMSC to be a group of diseases that may not be as relevant for the medical oncology community as breast cancer, prostate cancer, or melanoma, he reiterated that it is a very serious matter that needs to be approached with enthusiasm and professionalism. He stated: "Recent advances in biology, translational research, and clinical research have shown clearly that these patients can be treated and may benefit from the newest approved agents. We need to develop not only algorithms but also attitudes to confront the disease in a very serious way."

Locally Advanced Disease: A Relatively New Concept

Prof Hauschild explained that in major guidelines worldwide, such as the National Comprehensive Cancer Network (NCCN)[15] and the European Association of Dermato-Oncology (EADO)[14,16] guidelines, the first treatment option is the excision of the primary tumour, and that in CSCC and BCC there is a relatively new term, 'locally advanced', which is not well defined. "The interdisciplinary tumour board says we can excise or irradiate the tumour, but it will be very difficult," he explained, "so if there is an alternative, such as systemic treatment, they would prefer the systemic treatment, and this is how the hedgehog pathway inhibitors (HPI) sonidegib and vismodegib have been developed for advanced BCC, and why cemiplimab and other programmed cell death receptor 1 (PD-1) antibodies have been introduced to the field for CSCC."

Introduction of a Different Mechanism of Action: Programmed Cell Death Receptor 1 Inhibitors in Nonmelanoma Skin Cancers

PD-1 inhibitors are new biological therapies with a different mechanism of action: they bind to PD-1 and block its interaction with programmed death ligands 1 (PD-L1) and 2 (PD-L2), representing a new treatment pathway for NMSC.[17-19]

Clinical responses to the PD-1 inhibitor cemiplimab (Libtayo® [Sanofi, Paris, France], the first medicine approved by the U.S. Food and Drug Administration [FDA] and European Commission for CSCC that has spread or cannot be cured by surgery or radiation[20]) in patients with advanced CSCC who were not candidates for curative surgery or radiation therapy have been shown in Phase I and II studies,[21-23] with longer-term results presented at the 2020 American Society of Clinical Oncology (ASCO) Annual Meeting showing durable responses that deepened over time.[24,25] Across all groups combined, with 15.7 months' median duration of follow-up, complete response (CR) rates were

16.1% (n=31) and in the metastatic group with the longest follow-up (Group 1 in Table 1), the CR rate was 20.3% (n=12), increased from 6.8% (n=4) in the 2017 primary analysis.[21,25,26]

There has also been a recent focus on cemiplimab in patients with advanced BCC who had progressed on, or were intolerant of, prior HPI therapy. In a pivotal, single-arm, open-label study,[28] objective responses were seen in 29% of patients with locally advanced BCC and in 21% of patients with metastatic BCC, with approximately 85% of patients who responded to cemiplimab maintaining their response for at least 1 year.[27]

Table 1: Duration of follow-up and tumour response to cemiplimab.

	Group 1: mCSCC 3 mg/kg every 2 weeks (n=59)	Group 2:* laCSCC 3 mg/kg every 2 weeks (n=78)	Group 3: mCSCC 350 mg every 3 weeks (n=56)
Primary analysis, CR % (n)	6.8% (4)	12.8% (10)	5.4% (3)
Approximately 1 year of follow-up, CR % (n)	16.9% (10)	12.8% (10)	16.1% (9)
Approximately 2 years of follow-up, CR % (n)	20.3% (12)	NE	NE

*Among 23 patients with laCSCC who were included in the prespecified Group 2 interim analysis, there were no CR.

CR: complete response; laCSCC: locally advanced cutaneous squamous cell carcinoma; mCSCC: metastatic cutaneous squamous cell carcinoma; NE: not evaluable.

Where do Hedgehog Pathway Inhibitors and Programmed Cell Death Receptor 1 Inhibitors Fit into the Treatment Landscape for Nonmelanoma Skin Cancers?

Prof Hauschild noted that the guidelines specify excision, with irradiation a further option if excision is not feasible; however, nowadays very few tumours are irradiated. "For locally advanced and, in particular, metastatic BCC, in the past there were HPI in first-line,[16] and there was no second-line treatment. Following the press release[27] from Regeneron [Tarrytown, New York, USA] and Sanofi on cemiplimab[20] in BCC, cemiplimab will potentially become a second-line treatment of choice for BCC. For CSCC, cemiplimab has replaced chemotherapy and any sort of epidermal growth factor receptor (EGFR) inhibitor treatment such as cetuximab," he outlined.

The introduction of PD-1 inhibitors has created a change in clinical practice and guidelines. Prof Hauschild explained: "Cemiplimab is now the treatment of choice for patients with locally advanced or metastatic CSCC, and this is good because we needed something that is more effective than chemotherapy and EGFR inhibitors, with few and mainly short-lasting responses." Furthermore, the introduction of PD-1 inhibitors in BCC gives physicians another treatment choice for patients in whom the options after failure on HPI are very limited. Prof Hauschild declared: "In general, we should give the best available agents in first line and not in second line; we should not wait for the progression of the tumour." Furthermore, Prof Hauschild considered that "the data and the patient selection in clinical trials for CSCC reflect the real world."

Dr Algarra acknowledged that several recent advances in the field have totally changed the treatment paradigm for NMSC and attempts to rescue with other local treatments, such as electrochemotherapy,[29-31] are no longer the only tools to overcome these diseases. "We have to be prepared to use these new treatments, which have proved to be active even in situations that were qualified in the past as unsurmountable."

Dr Algarra specified that a clear algorithm is needed to show how to use HPI and PD-1 inhibitors: "We must be aware that the indications for these treatments are going to grow because they are approved and recognised as active in

metastatic disease." He clarified: "They must also be considered in locally advanced disease to avoid mutilation, and even in less advanced disease if the tumour location compromises the physical and psychological health of the patient." Dr Algarra envisions there will be room for adjuvant treatment:[32] "We have to move from the current approval in advanced disease to the not so uncommon high risk of relapse scenario. In this sense we are eagerly awaiting the results of the clinical trials."

When asked about the integration of biological treatments and immunotherapy into the treatment algorithm for NMSC, Dr Algarra responded that from a real-life point of view, it may be a challenging task because of the need to consider resectability, which depends on the size and location of the tumour, number of prior relapses, and local treatment used; patient-related issues, such as comorbidities, dependence, and socio-labour needs; and regulatory issues, such as local agencies' approval, costs, hospital regulations, and pharmacy and multidisciplinary team consensus.

Treatment Options for Patients with Basal Cell Carcinomas Who Progress on Hedgehog Pathway Inhibitors

According to Prof Hauschild, "the only option at the moment for BCC patients is to be treated with PD-1 inhibitors in clinical trials or as an off-label treatment. Now that cemiplimab has shown a 29% response rate in second line and 85% of the responses are stable for at least 1 year,[27] it is very clear that a PD-1 inhibitor like cemiplimab is likely to be approved and we ought to ask our payers/insurance companies to get such a treatment in this setting. Cemiplimab is doing a good job here and I would love to see studies in first line but they are not currently available." He listed other treatment options as chemotherapy, irradiation, or best supportive care.

In terms of timing for PD-1 inhibitor treatment in patients with BCC, Prof Hauschild clarified: "I would give the HPI a chance for at least 8–12 weeks, by which time you will know if the patient is responding. This does not mean that you have a CR immediately, but if you see a partial response you can continue in the hope that a CR comes later."

When asked about duration of PD-1 treatment in patients who have relapsed or do not respond on HPI, Prof Hauschild rationalised: "The duration of treatment is not even defined for melanoma, so typically you treat with a goal to reach a CR, and a CR within 12 months is fine. My impression is that in CSCC, responses are extremely fast, so after just one infusion (i.e., within 3 weeks) we see a response." In many patients, a response can be seen as quickly as within 8–12 weeks, but in other patients the response may take longer. Prof Hauschild considered that "this is very attractive because it can work so fast in some patients".

What about Patients with Nonmelanoma Skin Cancer Who Are Not Eligible for Hedgehog Pathway Inhibitors and Programmed Cell Death Receptor 1 Inhibitors?

Prof Hauschild explained there is no age limit for the use of HPI and PD-1 inhibitors, so in principle every patient can be treated. However, organ transplant recipients are at risk of organ rejection with PD-1 inhibitor use, and this treatment gap is challenging. He clarified that there are few patients with HPI-refractory BCC and that these are mostly treated in clinical trials; for patients who progress on HPI, clinical trials are the only option, or PD-1 is given off-label.

SCREENING AND PREVENTION: DOES EARLY DETECTION IMPROVE NONMELANOMA SKIN CANCER PROGNOSIS?

Prof Hauschild outlined that the primary prevention of NMSC is avoidance of sun exposure and the secondary prevention is early detection through skin cancer screening. In Germany, skin cancer screening is an option every 2 years for everyone aged over 35 years, with some insurance companies supporting screening from age 20 years. This has highlighted an increased incidence of NMSC and melanoma, with mainly early cases being detected. In principle, although this has not been evaluated, screening could lead to decreased mortality from melanoma and reduced morbidity and treatment costs in NMSC.

Prof Hauschild described that "the more advanced cases of NMSC are typically treated surgically as inpatients in hospital, which is an

expensive setting, whereas the less advanced cases are treated in the ambulatory setting, which is 10 times cheaper than hospital treatment (e.g., €240 EUR versus €2,800 EUR for conventional surgery)." He listed the advantages of screening as avoidance of hospital referrals, treating with smaller margins, and decreased morbidity; however, he acknowledged that the impact of screening is difficult to evaluate because there is no prospective setting in which screened and nonscreened patients are compared.

FUTURE PROSPECTS AND CONCLUSIONS

Dr Algarra considered that there are effective biological treatments now available and clear clinical reasons to offer these treatments to patients; however, only a few skin cancer specialists are experienced in the use of these new treatments. There is a great need for education and dissemination of objective scientific information about these new therapies, mainly among dermatologists, plastic surgeons, and medical and radiation oncologists. It is also very important "to define carefully the agents approved and the right way to use them." Dr Algarra continued: "We need to approach these patients [with NMSC] with realism as well as with an open mind, considering the activity of these new agents is remarkable and they are going to have a real impact on their lives. We also need to consider that these agents may have side effects and are expensive, so the fine tuning is mandatory."

Prof Hauschild suggested the best available agents should be given as soon as possible in the first line; however, patient access to a centre of excellence where the drugs are administered may be a problem and the broad education and active collaboration of healthcare professionals in the field are needed. He noted that following the 2019 approval of cemiplimab, the FDA has approved the PD-1 inhibitor pembrolizumab for CSCC, and future areas of research include combining PD-1 inhibitors with EGFR inhibitors. In terms of the future in NMSC, Prof Hauschild concluded: "Second line is very difficult, it looks much better than years ago, but you can always do better... and the PD-1 inhibitors are making a big difference."

Dr Algarra concluded that these new biological treatments offer a real hope of increasing the quality and length of life for patients who previously had limited choices, as well as an opening for the future development of basic and translational research into the field of NMSC.

The insights of the key opinion leaders in this article clearly show that PD-1 inhibitors are changing and improving the treatment landscape for NMSC by providing alternative strategies for patients who previously had limited or no treatment options.

Biographies

Prof Dr Axel Hauschild

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Prof Hauschild is Head of the Skin Cancer Working Group at the University Hospital Schleswig-Holstein, Campus Kiel, Germany. Prof Hauschild's main clinical interests are the diagnosis and treatment of melanoma and nonmelanoma skin cancer. He has been the principal investigator of more than 100 Phase I–III clinical trials on melanoma, cutaneous lymphomas, and epithelial skin cancers. Prof Hauschild's scientific career was honoured with the German Skin Cancer Award and the German Cancer Award. He is the past president of the German Dermatologic Cooperative Oncology Group (DeCOG), and a board member of the European Association of Dermato-Oncology (EADO) and Melanoma World Society (MWS). Prof Hauschild was the congress president of the 8th World Congress on Melanoma in Hamburg (2013) and is the designated president of the 10th World Congress on Melanoma in April 2021 in Rome, Italy. He has been invited as a speaker to more than 700 conferences across the world. Prof Hauschild has published over 420 articles in peer-reviewed journals.

Dr Salvador Martín Algarra

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Dr Algarra is a consultant of medical oncology at the Clinica Universidad de Navarra (CUN) and a professor of oncology at the Medical School of the University of Navarra in Pamplona, Spain. He has been a member of the Directive Board of the CUN, President of its Educational Board, Co-Director of the Cell Therapy Area of the University of Navarra and Director of the Department of Oncology over two periods, as well as one of the founders and the past President of the Spanish Melanoma Group (Grupo Español Multidisciplinar de Melanoma, GEM). Dr Algarra's main areas of interest have been the therapeutic development of immunotherapy and targeted therapies in oncology, mainly in melanoma, sarcoma, and rare tumours. He is involved in other areas of clinical oncology as well as in translational research on immunology and biomarkers on solid tumours. His research work in these fields has been published in international journals.

References

1. Tanese K et al. Updates on the systemic treatment of advanced non-melanoma skin cancer. Front Med (Lausanne). 2019;6:160.
2. Welsh M et al. Genetic determinants of UV-susceptibility in non-melanoma skin cancer. PLoS One. 2011;6(7):e20019.
3. Lomas A et al. A systematic review of worldwide incidence of nonmelanoma skin cancer. Br J Dermatol. 2012;166(5):1069-80.
4. Al-Dujaili Z et al. Skin cancer concerns particular to women. Int J Womens Dermatol. 2017;3(1 Suppl 1):S49-51.
5. Scott FI et al. Risk of non-melanoma skin cancer in patients with a history of NMSC with the use of immunosuppressant and biologic agents in autoimmune disease. JAMA Dermatol. 2016;152(2):164-72.
6. Deady S et al. Increasing skin cancer incidence in young, affluent, urban populations: a challenge for prevention. Br J Dermatol. 2014;171(2):324-31.
7. Hubbard G et al. Promoting sunscreen use and skin self-examination to improve early detection and prevent skin cancer: quasi-experimental trial of an adolescent psycho educational intervention. BMC Public Health. 2018;18(1):666.
8. Hasche D et al. Cutaneous papillomaviruses and non-melanoma skin cancer: causal agents or innocent bystanders? Front Microbiol. 2018;9:874.
9. Garcovich S et al. Skin cancer epidemics in the elderly as an emerging issue in geriatric oncology. Aging Dis. 2017;8(5):643-61.
10. Datzmann T et al. Outdoor air pollution, green space, and cancer incidence in Saxony: a semi-individual cohort study. BMC Public Health. 2018;18(1):715.
11. Wang A et al. Relation of statin use with non-melanoma skin cancer: prospective results from the Women's Health Initiative. Br J Cancer. 2016;114(3):314-20.
12. Goldenberg G et al. Incidence and prevalence of basal cell carcinoma (BCC) and locally advanced BCC (LABCC) in a large commercially insured population in the United States: a retrospective cohort study. J Am Acad Dermatol. 2016;75(5):957-66.e2.
13. Nguyen-Nielsen M et al. The incidence of metastatic basal cell carcinoma (mBCC) in Denmark, 1997–2010. Eur J Dermatol. 2015;25(5):463-8.
14. Stratigos A et al. Diagnosis and treatment of invasive squamous cell carcinoma of the skin: European consensus-based interdisciplinary guideline. Eur J Cancer. 2015;51(14):1989-2007.
15. National Comprehensive Cancer Network®. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), NCCN Drugs & Biologics Compendium (NCCN Compendium®) Non-Melanoma Skin Cancers. 2021. Available at: https://www.nccn.org/professionals/physician_gls/default.aspx. Last accessed: 6 January 2021.
16. Peris K et al. Diagnosis and treatment of basal cell carcinoma: European consensus-based interdisciplinary guidelines. Eur J Cancer. 2019;118:10-34.
17. Ahmed SR et al. Cemiplimab-rwlc as first and only treatment for advanced cutaneous squamous cell carcinoma. Expert Rev Clin Pharmacol. 2019;12(10):947-51.
18. Hernández-Guerrero T et al. Cemiplimab for the treatment of advanced cutaneous squamous cell carcinoma. Drugs Today (Barc). 2019;55(8):485-94.
19. Markham A, Duggan S. Cemiplimab: first global approval. Drugs. 2018;78(17):1841-6.
20. Libtayo® (cemiplimab-rwlc). Prescribing information. 2019. Available at: https://www.libtayohcp.com/. Last accessed: 6 January 2021.
21. Migden MR et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. N Engl J Med. 2018;379(4):341-51.
22. Rischin D et al. Phase 2 study of 2 dosing regimens of cemiplimab, a human monoclonal anti–PD-1, in metastatic cutaneous squamous cell carcinoma (mCSCC). Abstract 5056. ESMO Congress, 30 September, 2019.
23. Migden MR et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, Phase 2, single-arm trial. Lancet Oncol. 2020;21(2):294-305.
24. Regeneron Pharmaceuticals. A Phase 2 study of REGN2810, a fully human monoclonal antibody to programmed death-1 (PD-1), in patients with advanced cutaneous squamous cell carcinoma. NCT02760498. https://clinicaltrials.gov/ct2/show/NCT02760498.
25. PM360. Libtayo® (cemiplimab-rwlc) longer-term results in advanced cutaneous squamous cell carcinoma presented at ASCO 2020 show durable responses that deepen over time. 2020. Available at: https://www.pm360online.com/libtayo-cemiplimab-rwlc-longer-term-results-in-advanced-cutaneous-squamous-cell-carcinoma-presented-at-asco-2020-show-durable-responses-that-deepen-over-time-2/. Last accessed: 6 January 2021.
26. Rischin D et al. Phase 2 study of cemiplimab in patients with advanced cutaneous squamous cell carcinoma (CSCC): longer follow up. J Clin Oncol. 2020;38(Suppl 15).

27. Sanofi. Libtayo® (cemiplimab) shows clinically meaningful and durable responses in second line advanced basal cell carcinoma. 2020. Available at: https://www.sanofi.com/en/media-room/press-releases/2020/2020-05-05-07-00-00. Last accessed: 6 January 2020.
28. Regeneron Pharmaceuticals. PD-1 in patients with advanced basal cell carcinoma who experienced progression of disease on hedgehog pathway inhibitor therapy, or were intolerant of prior hedgehog pathway inhibitor therapy. NCT03132636. https://clinicaltrials.gov/ct2/show/NCT03132636.
29. Potenza C et al. A review of the literature of surgical and nonsurgical treatments of invasive squamous cells carcinoma. Biomed Res Int. 2018;2018:9489163.
30. Jamsek C et al. Long term response of electrochemotherapy with reduced dose of bleomycin in elderly patients with head and neck non-melanoma skin cancer. Radiol Oncol. 2020;54(1):79-85.
31. Campana LG et al. Basal cell carcinoma: 10-year experience with electrochemo-therapy. J Transl Med. 2017;15(1):122.
32. Rischin D et al. A Phase III, randomised, double-blind study of adjuvant cemiplimab versus placebo post-surgery and radiation in patients with high-risk cutaneous squamous cell carcinoma (CSCC). Abstract 2716. ESMO Congress, 30 September, 2019.

The Treatment Landscape of Atopic Dermatitis: Interviews with Three Consultant Dermatologists

Interviewees: Tess McPherson,[1] Gorav Wali,[1] Philip Laws[2]

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Interview Summary

Atopic dermatitis (AD), sometimes referred to as 'atopic eczema', is a common, chronic, pruritic, Type II inflammatory skin disease which is associated with immune dysregulation and skin barrier dysfunction.[1-4] Individuals with moderate-to-severe AD have an overactive immune system, which results in signs and symptoms such as an intense, persistent itch associated with dryness, cracking, redness, crusting, and oozing of the skin.[5] AD may occur at any age but is more commonly seen during childhood, with a frequency of 10–30%.[6] Among adolescents, the estimated prevalence of AD is 8.7–18.1% in the USA,[7] 10.0–15.0% in the UK,[8] and <10.0% in most European countries.[8] The prevalence of AD in adults is 1.0–3.0%.[9] Risk factors for AD include female sex, sensitisation to inhalant and food allergens, allergic asthma and/or rhinoconjunctivitis, and the practice of certain jobs.[6] In the majority of patients, AD is lifelong (although there can be long periods of remission, recurrence is common) but not permanently debilitating and the disease can modify through life, which makes treatment of AD particularly challenging.

For this article, EMJ conducted interviews in July and August 2020 and January 2021 with three consultant dermatologists, Dr Tess McPherson, Dr Gorav Wali, and Dr Philip Laws, all of who have a wealth of experience and expertise in managing AD, to gain their perspectives on a range of topics in this area. The experts gave valuable insights into several pertinent issues in AD treatment and discussed significant recent developments in the field.

The article discusses the current treatment landscape for AD and evaluates where new biologics fit into this landscape. Strategies to maximise the use of currently available therapies are explored and the impact of the coronavirus disease (COVID-19) pandemic on dermatology services and treatment of AD is assessed.

ATOPIC DERMATITIS: IMPACT AND IMPORTANCE OF TYPE II IMMUNITY

Impact of Atopic Dermatitis

AD is associated with significant comorbidity and economic burden,[10] and significantly affects quality of life.[6,11] Although the huge quality of life impact is evident to the patient and their family, the extent of the impact may not always be perceived by healthcare professionals. The associated itching, sleepless nights, affected concentration, decreased school attendance, social isolation, and bullying have a massive impact on the overall health, quality of life, and educational attainment of children with AD. Additional, significant issues for adults with AD are absenteeism (through appointment attendance and inability to go to work because of infected skin) and presenteeism (disrupted productivity at work because they are distracted by their skin condition and cannot function at their normal level). Furthermore, Dr Laws noted that patients with AD are often conscious of the cosmetic impact of their condition, particularly if their skin is affected at high-impact sites, such as the hands, face, and scalp, which may be associated with significant shedding of scale. This widespread skin condition has been associated with mental health disorders, including anxiety[6] and attention deficit (hyperactivity) disorder[12,13] in adults and children. According to Dr Wali, atopic disease affects the whole family concerning distressed patients, time and cost of treatments, and inconveniences such as greasy bedsheets so it is important to engage, educate, and support patients and their families. Dr Laws estimated that up to one-quarter of general practitioner (GP) consultations are skin-related,[14] with patients with AD making up a significant proportion of cases,[14] and reattendance for the same problem is common[15] thereby underscoring the massive economic and healthcare burden of this condition.

Type II Immunity in Atopic Dermatitis

Dr McPherson explained that barrier dysfunction, irritant avoidance, and the concept of Type II immunity are important aspects of AD which need to be addressed and that reducing inflammation in AD is key. Dr Wali added: "Type II immunity is central to AD, but it is very complicated in terms of how it interacts with barrier function, the microbiome, and the environment and we are only just starting to piece it all together."

CURRENT TREATMENT LANDSCAPE

Topical and Systemic Treatments

Dr McPherson explained that most of her patients are referred through their GP or paediatrician and are often undertreated with basic therapies, such as intermittent use of anti-inflammatory topical agents, particularly steroids, and overuse of antibiotics. According to Dr McPherson, mild AD can often be managed very successfully with emollients, topical steroids, and patient education. In patients whose AD is not controlled with this approach, systemic treatments are routinely used, with methotrexate (MTX) a common first-line therapy.[16] If MTX is ineffective, or when side effects or the associated repeat blood testing are not tolerated, patients may receive biologics. Dr McPherson explained: "I see around 40 patients with moderate-to-severe AD per week and no more than an estimated 5–10% of patients require systemic treatments or biologics. The majority can be managed with topical treatments and patient education and if these were initiated earlier, we may be able to modify disease more systematically."

Dr Wali considered: "It is an exciting time for management of AD because there is such a broad range of treatments available and lots of new therapies on the horizon." He described the current treatment landscape as ranging from quite basic topical therapies, such as emollients, soap substitutes, cleansing baths, and topical steroids, to phototherapy, oral immunosuppressants, and ultimately, biologics and targeted therapies, such as JAK inhibitors. Dr Wali follows an integrated care pathway for AD that is dictated by the National Institute for Health and Clinical Excellence (NICE) guidelines.[17] The guidelines divide the care pathway into patients aged ≤12 years and those aged >12 years and provides guidance on how to manage AD particularly in primary care, clinical diagnosis, when to consider further investigations, and when to refer to secondary care.[17]

In agreement with Dr McPherson, Dr Wali said: "Although the treatment landscape is very broad, the vast majority of patients,

particularly paediatric patients, are managed on the first step of the ladder, with emollients, soap substitutes, topical steroids, and prompt treatment of infections." Dr Wali outlined that only a tiny percentage of paediatric patients go on to systemic treatments (mostly MTX). A larger proportion of adults seen in secondary care go on to systemic treatments, although this is difficult to define numerically as most patients are GP-referred, having failed to respond to topical therapies. Only a relatively small number of adult patients receive biologics.

Dr Laws indicated there is a "phobia" around the use of topical steroids, with patients reluctant to use these treatments as they thin the skin. He explained that GP and dermatologists educate their patients about skin care and how to treat their skin optimally using topical steroids; however, at dispensing, the last stage, pharmacists may warn patients about the skin-thinning effect of topical steroids. Although appropriate, if overly cautious, this warning may create anxiety, uncertainty, and confusion for patients. Dr Laws highlighted educational gaps in understanding of skin care and treatment. He specified that GP training in dermatology is often limited to a brief introduction to the therapeutic area during undergraduate training and then is mostly supported through learning from other GP and continuing medical education when they are in practice (most GP do not have attachments in dermatology). Similarly, there is also limited substantive formal dermatology training for community pharmacists on how to use topical steroids. This has the potential to result in conflicting messages to patients from different healthcare professionals about their skin care treatment. Unless the story remains consistent, or broadly similar, it unpicks the confidence the patient has in their skin care regimen, so they are left feeling that they are potentially doing things that are risky or dangerous.

New Era of Treatments in Atopic Dermatitis

Biologics are injectable drugs which use an antibody to treat a disease at the immune system level. The biologic dupilumab[18] blocks interleukins from binding to their cell receptors, which keeps the immune system from overreacting, thereby lowering inflammation and decreasing symptoms of AD. Dupilumab was the first, and is currently the only, approved biologic in the European Union (EU) and USA for the treatment of moderate-to-severe AD in adolescents (>12 years) and adults who are candidates for systemic therapy (EU) or who are inadequately responsive to standard of care (USA). The favourable efficacy, safety, and economic impact of dupilumab compared with standard of care for uncontrolled moderate-to-severe AD has been reported.[19] Tralokinumab[20] has shown positive results in Phase III clinical trials, and nemolizumab[21,22] and lebrikizumab[23] are new biologics for AD that showed promising results in Phase IIb clinical trials.

Where do Biologics Fit into the Treatment Landscape for Atopic Dermatitis?

Dr Wali proposed there will always be a need to use topical treatments before receiving biologics as they are easily accessible and a majority of patients with AD can be managed effectively with emollients and topical steroids. Dr Laws noted that several nonsteroidal topical therapies in development also show promise and will potentially move clinicians and patients away from topical steroids. However, whether biologics should come before oral immunosuppressants will be down to safety profile, experience, and cost. Patients receiving oral immunosuppressants need to be monitored and may require many blood tests and may experience potentially severe side effects. There are no major safety concerns with biologics, including dupilumab, apart from conjunctivitis. Dr Wali speculated: "As we gain more experience, maybe biologics could become first-line for moderate-to-severe AD but I foresee oral immunosuppressants will continue to be used before moving on to biologics, particularly because of the cost of treatment."

Continuing this theme, Dr Laws perceived biologics to have a very important role in AD, particularly considering the limitations of systemic therapies, including low response rates, tolerability, and side effects, and the fact that biologics are licensed for AD whereas MTX is not. He stated: "If cost was not a factor, we would be using more novel therapies. The potential for these therapies to transform the lives of patients with moderate-to-severe AD unresponsive to topical therapies is enormous." He explained that some of his patients with severe AD who he has managed for many years and had a 15–

20% improvement on systemic therapy (disease was tolerable) were switched to a biologic and saw enormous improvement in their disease. As an example, Dr Laws referred to one of his first patients with long-term AD who was switched from systemic therapy to biologics. One morning soon after the switch, the patient woke up in a panic because something was missing: after around 20 years of itching, the absence of this sensation was unrecognisable and transformational.

Are Biologics Potentially Disease-Modifying and Can They Prevent Atopic March?

There have been clinically meaningful and statistically significant improvements in AD signs and symptoms, including pruritus, and quality of life with biologics in adolescents with moderate-to-severe AD,[24,25] for whom there are limited treatment options.[26-28] Dr McPherson thought that biologics could be potentially disease-modifying with earlier treatment in younger patients and may prevent atopic march, food allergies, allergic rhinitis, and asthma, but she questioned whether more aggressive early treatment with topical steroids to modify local inflammation could achieve the same result and studies were needed to evaluate this. The BEEP trial showed that emollients administered twice per day to babies aged up to 6 months from high-risk atopic families did not prevent development of AD.[29,30] Dr McPherson added: "Having dupilumab and the future options of other biologics has been a game changer; however, biologics have not been used for long enough to establish whether they are disease-modifying or just stabilise disease, particularly in AD, which typically fluctuates in severity over time." Dr Wali reiterated that Type II immunity is complex, and we do not know whether targeting cytokines will transform AD. Dr Laws suggested that increased understanding of the pathogenesis of AD will enable targeting of specific aspects of the disease pathway, in contrast to historically cruder methods of immunosuppression with drugs such as cyclosporin, MTX, and mycophenolate. Whether this has a disease-modifying effect is an important research question that will need investigation. He stated: "As more treatment options become available for AD, there will be increased understanding of the impact of blocking different parts of the pathway and how this affects not only response but also side effects."

Maximising the Use of Currently Available Treatments in Mild Atopic Dermatitis

Dr McPherson considered: "Development of biologics has made us look at other therapies for AD in more detail and has shown us that topical treatments, if done well and supported by good patient education, can be very effective in mild AD. This is a really important thing to remember."

Dr Wali agreed: "Using basic treatments like topical steroids and emollients that have been around for a long time and are proven to work is important and we need to always remember that they are there. In terms of disease modification, it may be that just using these treatments early and well could help prevent atopic diseases." One of the difficulties with adolescents is they do not want to be different from their peers; they may not want to apply creams and topical treatments. Educating and engaging adolescents with AD and encouraging them to take ownership and control of their treatment can be just as good a way to manage their disease as progressing them on to other therapies.

A Comprehensive Care Package is Needed for Atopic Dermatitis

Dr Laws drew a parallel between AD and psoriasis, a principal element of inflammatory dermatoses, with one of the main differences being psoriasis is an immune-mediated disease whereas AD is immune-mediated with a barrier dysfunction, and the latter is crucial in the development of AD. He referred to AD as the "poor relation to psoriasis" as there are fewer treatment options and limited services for AD compared with psoriasis, for which there have been numerous treatments for the past 15–20 years, and a greater number of dedicated clinics enabling better patient management. There have been some excellent studies investigating AD disease characteristics but the advent of novel therapeutic options for AD, renewed interest, and better investment in this disease area will see greater insights over the coming years. Dr Laws intimated that the relatively slower progress in AD research compared with psoriasis was a result

of AD being perceived as a nuisance skin problem that people grow out of and is consequently not taken seriously enough to warrant appropriate funding and research.

Dr Laws shared his concern about how much suboptimal management of AD in primary care may be impacting on referrals to secondary care. If patients were treated early and optimally in primary care, he reasoned, this may reduce chronic disease burden and circumvent the need for patient referral to secondary care. Once the itch/scratch cycle is established in a patient, it becomes part of a chronic disease pathway and is extremely difficult to reverse. His approach is to treat aggressively in the early phase to control disease, with appropriate support to reduce the risk of skin atrophy and side effects of topical steroids. In a proactive treatment response, patients gain confidence in how to manage their skin disease and avoid suboptimal response, patient fatigue, and disease chronicity associated with a more cautious approach.

According to Dr Laws: "One of the main aspects of AD treatment that is often neglected is ongoing skin care with appropriate use of emollients regardless of coadministered systemic or biologic treatment options." More specialist clinics and support and educational reinforcement from specialist nurses, physician associates, and other healthcare professionals around the importance of continuous and effective skin care is vital to provide optimal care for patients. He added: "There is a need for a comprehensive care package that covers the basic treatments as well as the high-cost drugs, with closer integration and engagement with GP."

GUIDELINES

There are various guidelines for the management of AD.[31-33]

NICE Guidance for Biologics in Atopic Dermatitis

NICE guidance[17] is straightforward for use of biologics in AD: the criterion for biologics is failure to respond to, or contraindication to, a systemic immunosuppressant. Anyone who has had a systemic immunosuppressant for AD is, by definition, someone with moderate-to-severe disease. However, there is a requirement to numerically define improvement on treatment to enable therapy to continue. NICE set a threshold of ≥50% reduction in the Eczema Area and Severity Index score (EASI 50) from when treatment started and ≥4-point reduction in the Dermatology Life Quality Index (DLQI) from when treatment started.[17]

The NICE guidance is nonspecific in some areas and is therefore open to broad interpretation and can be used flexibly, which may mean that a wide range of treatment pathways/regimens are adopted in the different clinics across the country. Such differences in interpretation of the guidance are not ideal from a patient access perspective. Dr Laws postulated that there is perhaps a need for an open and detailed discussion nationally around the interpretation of the guidelines and the impact on patients and the healthcare system.

Have the Guidelines Kept Up with Progress in Atopic Dermatitis?

The NICE guidelines in AD have not been updated for over a decade. There is a paucity of comprehensive, standardised, and integrated national and local treatment guidelines for AD in the UK. Available guidelines describe siloed primary care AD management and there is a lack of clarity for treatment in secondary care. Recent advances in AD treatment have failed to prompt guideline updates.

There has been great scientific and clinical progress in AD, including the development of biologics, and the field is rapidly changing. Dr McPherson thought the treatment guidelines were keeping up with the introduction of new biologics as far as possible. She explained that good evidence is required for new medicines to be introduced and this may have been stalled by the coronavirus disease (COVID-19) pandemic.

Dr Wali acknowledged that it is early days for biologics in AD and, so far, the guidelines have kept up to date. He admitted it will be trickier when more biologics come through in terms of which ones to use, when, and in whom. He expected the field to change significantly with the introduction of new biologics and the guidelines may struggle to keep up.

DERMATOLOGY SERVICES AND TREATMENT OF ATOPIC DERMATITIS IN THE COVID-19 PANDEMIC

Guidance During the COVID-19 Pandemic

There has been considerable COVID-19-related guidance for patients, including information on teledermatology consultations,[34] and general recommendations[35] from the European Academy of Dermatology and Venereology (EADV) and the COVID-19 resource centre of the European Academy of Allergy and Clinical Immunology (EAACI).[36] When asked whether the guidance has been useful and specific enough during the COVID-19 pandemic, Dr McPherson reflected that the guidelines have been pragmatic and possibly a little overcautious regarding shielding advice but the priority was for patients to be kept as safe as possible based on the available information. Dr McPherson considered: "The guidelines in dermatology have been appropriate and the science has been magnificent. The world of science working together has been great despite not always being supported by politics."

Dr Wali found the British Association of Dermatologists (BAD) Guidelines helpful during the pandemic, particularly the table in which patients are triaged based on immunosuppressants and comorbidities, and the guidance on shielding.[32] He considered that there was a real sense of learning as you go along, and advice regarding shielding, face masks, and swabbing was confusing, so better structures need to be in place to deal with future pandemics.

Changes to Services

The impact of the COVID-19 pandemic on dermatology services has been significant, requiring all participants, including patients, to change. Continuity of patient care, support, and management of disease have been possible using digital technology during the pandemic, and although the service has had to adapt quickly, it has been maintained to a safe degree. Dr Wali explained that apart from improved remote working, the COVID-19 pandemic has prompted the development of a triage system for patient referrals. All referrals require the GP to send photographs of their visible symptoms of the disease and the patient is triaged to keep mild-to-moderate cases in the community and refer more severe cases for further care. For referred patients, the GP also organises community screening blood tests. The triage system enables more care in the community, the patient is more prepared, and more information is available beforehand, thereby minimising appointment times and enabling treatment to start earlier.

Dr Wali acknowledged: "The COVID-19 pandemic had a massive impact on services, but also provided an opportunity to change and improve technology, remote consultations, and email advice." Video consultations and patient-provided photographs are not ideal but assist with diagnosis and are effective for follow-up. Some patients may opt to continue remote consultations, particularly paediatric cases for which home appointments can be easier and more comfortable for the patient and their family.

Video and telephone reviews were also advocated by Dr Laws, who acknowledged the digital technological advances adopted during the pandemic and declared he would like to see "a drive towards more patient-initiated follow-up [with certain parameters in place] for patients whose AD is well controlled to reduce appointment and travel time and lessen appointment fatigue for the patient as well as decreasing the burden on healthcare services."

Dr McPherson surmised: "Routine patient-reported outcomes are not so easily recorded virtually as they are in the clinic, which means there is a lot of information we are no longer capturing. Although the pandemic set up is not ideal, a quick fix, or sustainable, it has been an excellent response to a difficult situation."

Immunosuppressants and Biologics in the COVID-19 Era

All three consultant dermatologists interviewed considered there was not enough evidence to stop the use of biologics during the COVID-19 pandemic; there are no signals that patients on biologics are more likely to contract COVID-19 or experience severe COVID-19. Two small studies conducted in Italy indicated that there is no evidence of increased risk with dupilumab in patients with AD who also have COVID-19.[37,38] Furthermore, the European Task Force on Atopic Dermatitis (ETFAD) did not consider dupilumab

to increase risk for viral infections.[39] There was also no evidence of risk with immunosuppressants in the COVID-19 era, according to studies from Spain[40] and Italy.[41]

Although some patients developed anxiety about using immunosuppressants (usually MTX) and biologics (dupilumab) during the pandemic and decided themselves to stop treatment, the consultant dermatologists did not consider alterations to treatment necessary. Stopping treatment would result in a flare-up, increased exposure to healthcare, and potentially COVID-19.

The pandemic did impact on patients starting immunosuppressants or biologics. These treatments were delayed rather than introduced when there was less access to healthcare for regular blood tests (MTX) and injections (dupilumab).

Dr Laws elaborated on the difference in patient attitude in the first and second waves of the pandemic to explain the probable slight increase in biologics prescribing in the second wave compared with the first. A perceived reluctance to initiate biologics in the first wave paralleled an optimism that the pandemic would soon be over, and patients appeared to delay starting such treatments accordingly. There appeared to be a more balanced view of the pandemic during the second wave and patients received more reassurance from clinicians, who now had a better idea of the nature and impact of the pandemic and a clearer view of the implications of using biologics in this situation. The clearer perspective meant patients appeared to be more willing to consider new treatments. Dr Laws specified that some clinicians appear to have proactively chosen biologics (dupilumab) over standard immunosuppressive therapies because of the perceived risk in the COVID-19 era and that the targeted nature of biologics suggested potentially lower risk, less monitoring, and decreased healthcare contact, all of which are important in a pandemic.

FUTURE PROSPECTS AND CONCLUSIONS

Dr McPherson summarised: "This is an exciting and rapidly moving field. The introduction of biologics for AD has been a major step forward for a minority of patients with recalcitrant, problematic disease that could not be controlled with the available treatments." Dr McPherson's concern was not to push biologics to patients who do not necessarily need them, and she would like to see better alignment and a more scientific approach when new products are introduced. Dr McPherson emphasised: "We should not lose sight that topical steroids can be extremely effective in mild AD and may have a modifying role, and we must ensure research is done in this area before rolling out a more systemic cytokine approach."

Dr Wali highlighted: "The future in AD is exciting, with lots of new treatments coming through targeting the different disease pathways. Increasing understanding of Type II immunity will evolve further treatment options, including for patients who are currently struggling." Dr Wali considered if therapies modify Type II immunity and atopic disease and prevent atopic march, this could potentially transform the management of atopic diseases generally. He added: "Service delivery will change according to technology with remote consultations and follow-up, which will benefit the patients in terms of less travel and will enable delivery of a better service."

Dr Laws considered: "The future for the treatment and management of AD is very exciting. There are around 30 treatments in development, and several current clinical trials are so far showing very positive responses. Biologics are dramatically effective, transformational treatments for patients with moderate-to-severe AD." He described how patients in their working prime who are often unable to work because of their condition are delighted with their response to biologic therapy and the positive impact on their lives. He highlighted: "Some of my patients with AD are suicidal; to be able to tell them about new treatments currently available or in the pipeline that will impact on their condition is incredible. As a clinical community, the challenge we must seek is to balance these therapeutic advances with good skin care education and guidance in conjunction with a comprehensive clinical service meeting the needs of the individual patient."

Biographies

Dr Tess McPherson

Consultant Dermatologist and Senior Clinical Lecturer, Oxford University Hospitals, Oxford, UK

Dr Tess McPherson is a consultant dermatologist, senior clinical lecturer, and clinical lead for Paediatric and Adolescent Dermatology at Oxford University Hospitals (since 2012).

Dr McPherson's medical training included undergraduate medicine at the University of Cambridge, Cambridge, UK, international research working for the World Health Organization (WHO) in South America, and an academic training post at the Weatherall Institute of Molecular Medicine (WIMM), Oxford, UK, studying immunology of eczema. This was followed by a paediatric dermatology training fellowship at Birmingham Children's Hospital, Birmingham, UK.

Dr McPherson was lead clinician on a National Institute for Health Research (NIHR)-funded project to develop a web resource for young adults with skin disease.[42]

In Oxford she has established an award-winning dermatology service with psychological support for adolescents with skin conditions.[43]

Dr McPherson is Secretary (President-Elect) of the British Society of Paediatric Dermatology (BSPD). She is active in national and international paediatric dermatology, including developing clinical guidelines and patient information for the British Association of Dermatology (BAD), monitoring effects of medications on children and young people (BADBIR registry), and works with charities and patient groups.

Dr Gorav Wali

Consultant Dermatologist and Honorary Senior Clinical Lecturer, Oxford University Hospitals, Oxford, UK

Dr Gorav Wali is a consultant dermatologist and honorary senior clinical lecturer at Oxford University Hospitals.

Dr Wali completed undergraduate medical training at Oxford University. He then undertook general medical and dermatology specialist training in Oxford University Hospitals and the Thames Valley Deanery, London, UK. Following appointment as Consultant in Oxford University Hospitals, he has co-led the inflammatory dermatosis service, including the use of biologics, and has developed the paediatric dermatology service. He is actively involved in clinical research and has been principal investigator for clinical trials in eczema and hidradenitis suppurativa.

Dr Philip Laws

Consultant Dermatologist and Senior Honorary Lecturer, Leeds Teaching Hospitals NHS Trust, Leeds, UK

Dr Philip Laws is a consultant dermatologist and senior honorary lecturer at Leeds Teaching Hospitals NHS Trust.

Dr Laws undertook dermatology training in Salford Royal Hospital, Manchester, UK, which included a medical education fellowship. He subsequently completed a medical dermatology fellowship in Toronto, Canada. Following this he was appointed to a consultant post in Leeds where he has co-led the inflammatory dermatosis service. His research interests include psoriasis, atopic dermatitis, and connective tissue diseases. He has been principal investigator and chief investigator in several clinical trials.

References

1. Boothe WD et al. Atopic dermatitis: pathophysiology. Adv Exp Med Biol. 2017;1027:21-37.
2. Avena-Woods C. Overview of atopic dermatitis. Am J Manag Care. 2017;23(Suppl 8):S115-23.
3. Guttman-Yassky E et al. Atopic dermatitis: pathogenesis. Semin Cutan Med Surg. 2017;36(3):100-3.
4. Suga H, Sato S. Novel topical and systemic therapies in atopic dermatitis. Immunol Med. 2019;42(2):84-93.
5. Giavina-Bianchi M, Giavina-Bianchi P. Systemic treatment for severe atopic dermatitis. Arch Immunol Ther Exp (Warsz). 2019;67(2):69-78.
6. Ricci G et al. Atopic dermatitis in adolescence. Dermatol Reports. 2011;4(1):e1.
7. Shaw TE et al. Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health. J Invest Dermatol. 2011;131:67-73.
8. Odhiambo JA et al. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol. 2009;124(6):1251-8.e23.
9. Deckert S et al. Nonallergic comorbidities of atopic eczema: an overview of systematic reviews. Allergy. 2014;69(1):37-45.
10. Shrestha S et al. Burden of atopic dermatitis in the United States: analysis of healthcare claims data in the Commercial, Medicare, and Medi-Cal databases. Adv Ther. 2017;34(8):1989-2006.
11. Drucker AM. Atopic dermatitis: burden of illness, quality of life, and associated complications. Allergy Asthma Proc. 2017;38(1):3-8.
12. Yaghmaie P et al. Mental health comorbidity in patients with atopic dermatitis. J Allergy Clin Immunol. 2013;131(2):428-33.
13. Strom MA et al. Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. Br J Dermatol. 2016;175(5):920-9.
14. Schofield J et al. Skin conditions in the UK: a health care needs assessment. Centre of Evidence Based Dermatology, University of Nottingham. 2009. Available at: https://www.nottingham.ac.uk/research/groups/cebd/documents/hcnaskinconditionsuk2009.pdf. Last accessed: 26 January 2021.
15. Le Roux E et al. The content and conduct of GP consultations for dermatology problems: a cross-sectional study. Br J Gen Pract. 2020;70(699):e723-30.
16. Irvine AD et al. A randomized controlled trial protocol assessing the effectiveness, safety and cost-effectiveness of methotrexate vs. ciclosporin in the treatment of severe atopic eczema in children: the TREatment of severe Atopic eczema Trial (TREAT). Br J Dermatol. 2018;179(6):1297-306.
17. National Institute for Health and Care Excellence (NICE). NICE Guidelines. Eczema overview. 2021. Available at: https://pathways.nice.org.uk/pathways/eczema#path=view%3A/pathways/eczema/eczema-overview.xml&content=view-index. Last accessed: 1 September 2020.
18. European Medicines Agency (EMA). Dupixent (dupilumab): summary of product characteristics. 2019. Available at: https://www.medicines.org.uk/emc/product/10619/smpc. Last accessed: 1 September 2020.
19. Agache I et al. Efficacy and safety of dupilumab for moderate-to-severe atopic dermatitis: a systematic review for the EAACI Biologicals Guidelines. Allergy. 2020;DOI:10.1111/all.14510. [Epub ahead of print].
20. Wollenberg A et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled Phase III trials (ECZTRA 1 and ECZTRA 2). Br J Dermatol. 2020;DOI:10.1111/bjd.19574.
21. Heymann WR. The 2020 vision for nemolizumab in atopic dermatitis. American Academy of Dermatology Association (AAD). 2020. Available at: https://www.aad.org/dw/dw-insights-and-inquiries/2020-archive/march/nemolizumab-in-atopic-dermatitis. Last accessed: 1 September 2020.
22. Kabashima K et al. Nemolizumab in patients with moderate-to-severe atopic dermatitis: randomized, Phase II, long-term extension study. J Allergy Clin Immunol. 2018;142(4):1121-30.e7.
23. Guttman-Yassky E et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a Phase 2b randomized clinical trial. JAMA Dermatol. 2020;156(4):411-20.
24. Regeneron Pharmaceuticals and Sanofi Genzyme. Dupilumab efficacy and safety in adolescents with moderate-to-severe atopic dermatitis: results from a multicenter, randomized, placebo-controlled, double-blind, parallel-group, Phase 3 study. NCT03054428. https://clinicaltrials.gov/ct2/show/NCT03054428.
25. Cork MJ et al. Dupilumab in adolescents with uncontrolled moderate-to-severe atopic dermatitis: results from a Phase IIa open-label trial and subsequent Phase III open-label extension. Br J Dermatol. 2020;182(1):85-96.
26. Wollenberg A et al. ETFAD/EADV eczema task force 2015 position paper on diagnosis and treatment of atopic dermatitis in adult and

paediatric patients. J Eur Acad Dermatol Venereol. 2016;30(5):729-47.

27. Sidbury R et al. Guidelines of care for the management of atopic dermatitis: section 3. Management and treatment with phototherapy and systemic agents. J Am Acad Dermatol. 2014;71(2):327-49.
28. Ring J et al. Guidelines for treatment of atopic eczema (atopic dermatitis) part II. J Eur Acad Dermatol Venereol. 2012;26(9):1176-93.
29. Chalmers JR et al. Effectiveness and cost-effectiveness of daily all-over-body application of emollient during the first year of life for preventing atopic eczema in high-risk children (The BEEP trial): protocol for a randomised controlled trial. Trials. 2017;18(1):343.
30. Chalmers JR et al. Daily emollient during infancy for prevention of eczema: the BEEP randomised controlled trial. Lancet. 2020;395(10228):962-72.
31. National Institute for Health and Care Excellence (NICE). NICE COVID-19 Rapid Guidelines. Dermatological conditions treated with the drugs affecting the immune response. 2020. Available at: https://www.nice.org.uk/guidance/NG169. Last accessed: 1 September 2020.
32. British Association of Dermatologists (BAD). British Association of Dermatologists Guidelines. 2020. Available at: https://www.bad.org.uk/healthcare-professionals/clinical-standards/clinical-guidelines. Last accessed: 1 September 2020.
33. European Academy of Dermatology and Venereology (EADV). Guidelines for treatment of atopic eczema (atopic dermatitis) Part I and Part II. JEADV. 2012;26(9):1176-93.
34. European Academy of Dermatology and Venereology (EADV). Dermatology during times of social distancing. 2020. Available at: https://www.eadv.org/cms-admin/showfile/9_Dermatology%20during%20times%20of%20social%20distancing.pdf. Last accessed: 1 September 2020.
35. European Academy of Dermatology and Venereology (EADV). COVID-19: recommendations and general advice for patients. 2020. Available at: https://www.eadv.org/cms-admin/showfile/General%20advice%20for%20patients_%20COVID-19%20Corner_.pdf. Last accessed: 1 September 2020.
36. European Academy of Allergy and Clinical Immunology (EAACI). EAACI Resource Centre COVID-19. 2020. Available at: https://www.eaaci.org/4702. Last accessed: 1 September 2020.
37. Ferrucci S et al. Safety of dupilumab in severe atopic dermatitis and infection of COVID 19: two case reports. J Eur Acad Dermatol Venereol. 2020;34(7):e303-4.
38. Carugno A et al. No evidence of increased risk for Coronavirus Disease 2019 (COVID 19) in patients treated with dupilumab for atopic dermatitis in a high-epidemic area - Bergamo, Lombardy, Italy. J Eur Acad Dermatol Venereol. 2020;DOI:10.1111/jdv.16552.
39. Wollenberg A et al. European Task Force on Atopic Dermatitis statement on severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and atopic dermatitis. J Eur Acad Dermatol Venereol. 2020;34(6):e241-2.
40. Montero F et al. Coronavirus disease 2019 (COVID-19) in autoimmune and inflammatory conditions: clinical characteristics of poor outcomes. Rheumatol Int. 2020;40(10):1593-8.
41. Scirè CA et al. COVID-19 in rheumatic diseases in Italy: first results from the Italian registry of the Italian Society for Rheumatology (CONTROL-19). Clin Exp Rheumatol. 2020;38(4):748-53.
42. Health Talk. Eczema (young people). 2017. Available at: https://healthtalk.org/eczema/overview. Last accessed: 10 February 2021.
43. De Vere Hunt I et al. Establishing and developing a teenage and young adult dermatology clinic with embedded specialist psychological support. Clin Exp Dermatol. 2019;44(8):893-6.

Is CD37-Targeted Therapy a Viable Alternative in the Treatment of Diffuse Large B-cell Lymphoma? Interviews with Two Key Opinion Leaders

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Interview Summary

Diffuse large B-cell lymphoma (DLBCL) is an aggressive lymphoma and the most frequent non-Hodgkin lymphoma (NHL) in adults, accounting for 30–40% of cases. The standard of care (SOC) in first-line treatment of patients with DLBCL is the CD20 antibody rituximab in combination with cyclophosphamide, doxorubicin, vincristine, and prednisolone (R-CHOP). Despite improvements in response and survival with R-CHOP chemotherapy, approximately 40% of patients with DLBCL will eventually relapse and 10% are resistant to first-line treatment (primary refractory).[1] High-dose chemotherapy followed by autologous stem cell transplantation (ASCT) is a salvage option for relapsed or refractory DLBCL.[2] For patients in whom first-line treatment fails, and even more so for those who are not candidates for ASCT, prognosis is poor and the majority will succumb to the disease.[3,4] Outcomes in refractory DLBCL have demonstrated that the survival from the start of salvage therapy was consistently poor, with a median overall survival (OS) of 6.3 months from the start of therapy.[3] Therefore, an unmet need exists for more effective therapies in the second- and third-line settings.[5] Furthermore, most patients with DLBCL are diagnosed at 60 years of age or older. Challenges to optimal therapy among older individuals include unfavourable biological features of DLBCL, geriatric vulnerabilities, suboptimal treatment selection, and low tolerance to aggressive chemotherapy toxicities.[6,7] Several emerging therapies have demonstrated favourable efficacy and toxicity profiles compared with historical chemotherapy regimens, thus facilitating effective treatment for elderly patients in the relapsed or refractory setting. A novel approach to targeted treatment is antibody–drug conjugates (ADC). The major therapeutic advantage of ADC is their ability to selectively deliver a potent cytotoxic agent to target cancer cells, thereby minimising off-target effects.[2] Novel

targeted therapies that offer a chance for complete and durable response, and with an improved tolerability profile compared with current SOC, may reset expectations for DLBCL therapy.

UNMET NEED IN DIFFUSE LARGE B-CELL LYMPHOMA

Professor Grzegorz S. Nowakowski

DLBCL is the most common type of NHL. The prevalence of DLBCL in NHL cases ranges from 30% to 58% in Europe, and 25% to 35% in the USA.[8] The disease is aggressive and patients typically present with rapidly enlarging lymphadenopathy, extranodal involvement, and constitutional symptoms, necessitating immediate treatment.[9] Although DLBCL can affect children and young adults, it is most commonly diagnosed in those aged between 65 and 74 years, with a median age of 66 years at diagnosis.[10,11] The SOC for first-line treatment is chemoimmunotherapy with R-CHOP, which leads to cure in approximately 60% of patients. Unfortunately, for the 40% of patients with refractory disease or who relapse (R/R), outcomes are particularly poor.[12,13] Most relapses occur early on within 1–2 years of remission and only 10–15% will achieve cure with additional therapy.[14,15]

Positron emission tomography combined with CT (PET-CT) is now a routine part of staging DLBCL.[16] This, coupled with physical examination and bloodwork, are the primary methods for monitoring patients and quantifying prognosis.[17] Stratification of patients with DLBCL can be done on a clinical and molecular basis. Highly valuable clinical prognostic predictors in patients with DLBCL include the variables of the International Prognostic Index (IPI); patients with a high IPI (typically 3–5) have poorer outcomes.[9,18] There are two major biologically distinct molecular subtypes of DLBCL: germinal centre B-cell (GCB) and activated B-cell (ABC). ABC DLBCL is associated with substantially worse outcomes when treated with standard chemoimmunotherapy. In addition to GCB and ABC subtypes, 'double-hit' lymphomas (DHL; approximately 5–10% of patients) and double-expressor lymphomas, which overexpress MYC and protein BCL2 (or less likely, BCL6), are aggressive DLBCL and are also associated with a poor prognosis.[19] Triple-hit lymphoma is a rarer subtype of B-cell NHL where rearrangements are present in all three genes (*MYC*, *BCL2*, and *BCL6*).[20] Unfortunately, none of these molecular classifiers currently impact the selection of therapy for patients, with the possible exception of DHL, which can occasionally be treated with more aggressive therapy in younger patients.[21] For most other patients, regardless of clinical risk features and molecular features, the standard treatment is R-CHOP.

For patients with R/R disease, salvage therapy with high-dose chemotherapy and ASCT may offer a chance for a cure, but several factors may limit the utility of this approach. Patients who are older or have comorbidities may be inappropriate candidates for this approach, and patients with disease that is unresponsive to second-line chemotherapy may have poorer rates of long-term survival and incur added toxicity from the chemotherapy. To proceed to ASCT, patients require a response to the salvage therapy to begin with. Unfortunately, only approximately 50–60% of the R/R patients have a sufficient response to proceed to transplant.[15] Even when including patients who undergo high-dose, salvage chemotherapy and subsequent ASCT, patients with R/R DLBCL have median 1-year and 5-year survival rates of 41% and 27%, respectively.[9,22,23] Hence, in a search for improved outcomes in the R/R setting, clinical studies have focussed on DLBCL subtypes, especially in those ineligible for transplant or who have relapsed following transplant. An alternative option for patients in the relapsed setting is chimeric antigen receptor (CAR) T-cell therapy, which entails the genetic modification of autologous T cells via cloned DNA plasmids carrying a viral recombinant vector in addition to T-cell receptor-expressing genes. Unfortunately, as in ASCT, this is an intensive therapy, it is logistically complex, and it may not be available to all patients because of comorbidities and performance status, or rapidly progressive and symptomatic disease not allowing time for apheresis and

CAR-T preparation, but also due to cost and limited access. Finally, not all patients will be willing and have enough social support to travel to treating centres to undergo this complex and time-intensive therapy.[24]

Unfortunately, many people still relapse after CAR-T therapy. Other recent entrants to the R/R DLBCL treatment landscape include the ADC polatuzumab vedotin-piiq, the selective inhibitor of nuclear export selinexor, and the anti-CD19 monoclonal antibody tafasitamab-cxix.[25] Unfortunately, even with these novel agents, there remains a huge unmet need in this space. The majority of patients will relapse or progress after a period of time on these agents, and this can occur relatively early if they are nonresponders. There are also unique challenges in the third-line treatment of these patients. Firstly, tolerance to chemotherapy decreases with further lines of therapy. Furthermore, the ability to tolerate full-dose chemotherapy is also dependent on comorbidities, age, and performance status. Therefore, the doses of chemotherapy often require reduction in this patient population, which ultimately reduces the effectiveness,[26] and the outcomes in older patients are generally worse than in younger patients. The other reason for possible worse outcomes is biology; for example, DHL and ABC-DLBCL are associated with worse outcomes, and these occur more commonly in elderly patients. Then there is the issue of comorbidities; for example, renal and kidney dysfunction often require an adjustment of the chemotherapy doses, thereby further reducing efficacy.[27] Lastly, there are logistical issues for attending centres of excellence that can deliver the more complicated treatments, such as CAR T-cell therapy. This is especially true for the elderly and those who may live in rural settings. There is also a significant wait time and evaluation of those patients.[24] Many of these patients will have rapidly progressive disease so they may progress in the time it requires to appropriately evaluate these patients and manufacture the CAR T-cell therapy, to the point that therapy cannot be used. It is important to note that in the past, subsequent lines of therapy were not highly effective and there may be a mindset, especially in older patients who have tried a first-line chemotherapy that did not work, that they are not willing to give it another try. Hopefully, this will change because of more effective and better-tolerated second-line treatment options, with many more in development.

There are now several approved therapies and many more in development, which will be approved shortly. There are several CD19 therapies available and in development, including naked antibodies, conjugated antibodies, bispecific antibodies, and CAR T-cell therapy,[28] so targeting CD19 is clonally successful but has become a crowded space. A better understanding of the biology and of CD19 is needed before deciding how these therapies can impact CD19 expression and resistance to next-line therapy still targeting CD19. With an increasing number of treatment options, the next challenge will be 'how to sequence treatment?' This is where the art of medicine takes precedence, as it really depends on the patient situation, preferences, performance status, comorbidities, and toxicities from the previous treatment. In this context, alternative targets, such as CD37, are of huge interest: a novel target, potentially avoiding resistance to CD19-targeting compounds.

CD37 THERAPY FOR DIFFUSE LARGE B-CELL LYMPHOMA

Professor Wojciech Jurczak

The treatment spectrum for DLBCL has expanded significantly in recent years, particularly for patients with R/R disease. Mechanisms of action differ greatly among agents, reflecting the complex pathophysiology and genetic variations of the disease.[24] The SOC for patients with R/R disease is salvage therapy with salvage chemotherapy (typically platinum-based), with ASCT consolidation in responding cases.[15] Alternative approaches for those ineligible for ASCT include gemcitabine-based combination regimens, polatuzumab vedotin with bendamustine/rituximab (objective response rate [ORR]: 45%; median OS: 12.4 months; median duration of response: 10.3 months),[29] and tafasitamab with lenalidomide (ORR: 58.8%; complete response [CR] rate: 41.3%; median duration of response: >24 months).[30-33] Patients failing two lines of therapy may also be treated by selinexor (ORR: 28.3%; CR rate: 13%)[34,35] or pixantrone-based regimens.[36,37] CAR T-cell therapy plays an important role in the relapsed/refractory DLBCL

setting, with reported 2-year remissions and a CR rate of 40% of patients (25% in DHL subtype).[1]

ADC are emerging as highly potent treatment options, combining chemotherapy and immunotherapy. This approach comprises a monoclonal antibody conjugated to the cytotoxic payload via a chemical linker that is directed toward a target antigen expressed on the cancer cell surface, reducing systemic exposure and therefore toxicity. The benefit of this group of agents is the ability to combine treatment modalities safely and effectively. In fact, the addition of a CD79b-targeted ADC, polatuzumab vedotin piiq, to bendamustine and rituximab more than doubled OS in patients with R/R DLBCL. The combination produced a CR rate of 40% and a median progression-free survival of 9.5 months.[29,38]

Other drugs in development include CD37-targeted agents. CD37 (tetraspanin TSPAN26) is a B-cell surface antigen widely expressed on mature B cells. CD37 is involved in immune regulation and tumour suppression. CD37 forms complexes with other tetraspanins and major histocompatibility complex (MHC) Class II antigens on B cells. CD37 is also important for T-cell–B-cell interaction, IgG/IgA production, and a balance between immune responses and tolerance.[37] The loss of CD37 results in increased IL-6 signalling and STAT3 activation, which are both known to be involved in the pathogenesis of haematological malignancies.[39] Oostindie et al.[40] demonstrated that the combinations of hexamerisation-enhanced CD20 and CD37 antibodies co-operated in C1q binding and induced superior and synergistic complement-dependent cytotoxicity in patient-derived cancer cells, compared with the single agents. Consistent with these data, a strategy of dual-ligand immunoliposomes of anti-CD20 combined with anti-CD37 demonstrated highly specific targeting to both leukaemia cell lines and B-cell chronic lymphocytic leukaemia patient cells. Compared with the single-antibody immunoliposomes, the combination demonstrated superior delivery efficiency and apoptosis induction to B-cell chronic lymphocytic leukaemia patient cells. These findings provide novel insights into the mechanisms of synergy in antibody-mediated, complement-dependent cytotoxicity, provide a rationale to enhance the co-operativity and therapeutic efficacy of antibody combinations, and provide a preferred strategy of personalised nanomedicine for the treatment of B-cell malignancies.[41]

Naratuximab emtansine (IMGN529 or Debio 1562 [Debiopharm, Lausanne, Switzerland]) is an investigational ADC comprising a CD37-targeting antibody conjugated to the maitansine-derived microtubule disruptor DM1 via a succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate (SMCC) linker, forming a nonreducible thioether bond (Figure 1). The CD37 antigen is widely present on the surface of cancerous blood cells in NHL, but absent on normal stem cells and plasma cells. Targeting the CD37 antigen on blood cancer cell surfaces can help to promote cancer cell death by specifically delivering the cytotoxic payload DM1. Naratuximab emtansine binds with high affinity and specificity to CD37, obstructing cell proliferation pathways while allowing internalisation, processing, and intracellular release of the DM1 payload. As a result of its ability to disrupt microtubule assembly, DM1 subsequently induces cell cycle arrest and apoptosis.[42]

A first-in-human, Phase I trial in 49 adult patients with R/R B-cell NHL found that the most frequent treatment-emergent adverse events (AE) over all dose levels tested were fatigue (39%), neutropenia (37%), pyrexia (37%), and thrombocytopenia (37%). AE that led to treatment discontinuation occurred in 10 patients (20%). Eight patients (16%) had treatment-related serious AE, the most common being Grade 3 febrile neutropenia. Five (13%) of 39 response-evaluable patients achieved an overall response (one CR and four partial responses), four of which occurred in the subgroup of patients with DLBCL (Table 1).[43] A preclinical study found that the combination of naratuximab emtansine and rituximab was more potent than either agent alone, and the benefit of this combination was associated with increased apoptotic induction and cell death.[44]

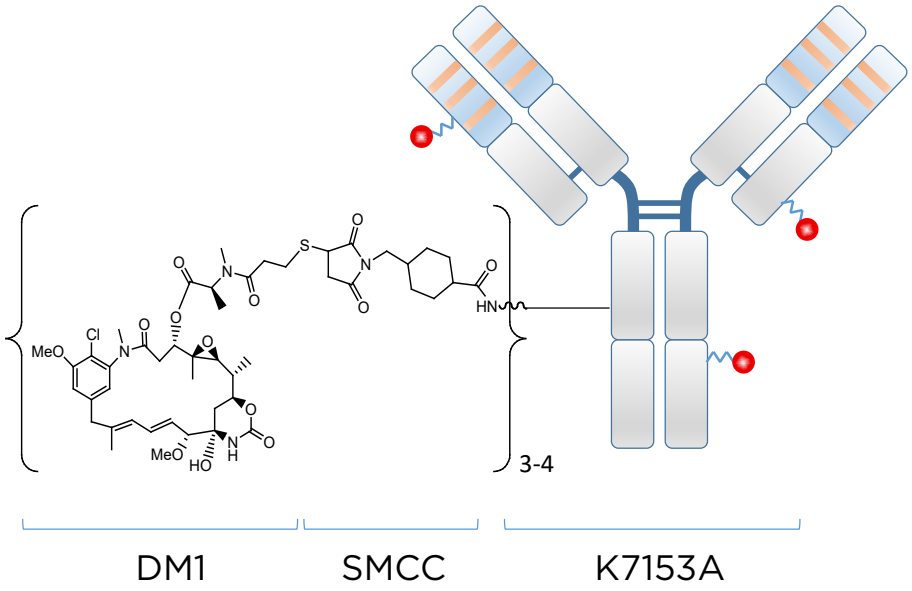

Figure 1: Naratuximab emtansine: an innovative antibody–drug conjugate targeting CD37.
DM1: microtubule disruptor; SMCC: succinimidyl-4-(N-maleimidomethyl)cyclohexane-1-carboxylate.

Table 1: Disease subtypes and duration of response for patients with an objective tumour response.

Dose (mg/kg)	Best overall response	Lymphoma (Grade/subtype)	Duration of response (months)
0.2	PR	FL (Grade 3)	2.0
0.4	PR	DLBCL (GCB)	2.0
0.4	PR	DLBCL (GCB)	1.0
1.0	CR	DLBCL (non-GCB)	4.2
1.0	PR	DLBCL (unclassified)	8.4

First-in-human, Phase I trial assessing the safety and preliminary activity of naratuximab emtansine in adult patients with relapsed or refractory B-cell non-Hodgkin's lymphoma. The primary objective was to determine the maximum tolerated dose and recommended Phase II dose.[43]
CR: complete response; DLBCL: diffuse large B-cell lymphoma; FL: follicular lymphoma; GCB: germinal centre B cell; PR: partial response.

These findings, taken in combination with additional studies showing that the combination of naratuximab emtansine and rituximab was highly efficacious in multiple xenograft models, suggest a novel mechanism whereby the potency of naratuximab emtansine can be enhanced by CD20 binding, which results in the increased internalisation and degradation of naratuximab emtansine leading to the generation of greater amounts of cytotoxic catabolite.[39-45] Overall, these data provide a biological rationale for the enhanced activity of naratuximab emtansine in combination with rituximab, and support the ongoing Phase II[46] clinical evaluation of naratuximab emtansine in combination with rituximab in patients with R/R DLBCL. The objective of this Phase II study of 100 patients is to establish the safety and efficacy profile using two different administration regimens. Results of this Phase II study are promising, with durable responses and mild adverse

events; further results will be released in due course. Naratuximab emtansine in combination with rituximab may be a very promising treatment option and could become a SOC for a subpopulation, including the elderly, for patients with relapsed/refractory DLBCL. The very favourable toxicity profile of naratuximab emtansine allows treatment of patients with severe comorbidities, where few other therapeutic options are available.

In conclusion, the promising data from recent trials highlight the importance of understanding the unique prognoses and responses that DLBCL subtypes confer on patient outcomes. The establishment of DLBCL subtypes as prognostic and therapeutic response factors will further fuel a search for more specific molecular targets in the disease process. In addition, new therapeutic options with distinct mechanisms of action are needed to address the unmet medical need, which still exists for DLBCL, particularly in the first-line treatment of patients who are elderly or frail, and in the relapse/refractory setting for patients who are unfit for ASCT or who relapse afterwards.

References

1. Patriarca A, Gaidano G. Investigational drugs for the treatment of diffuse large B-cell lymphoma. Expert Opin Investig Drugs. 2021;30(1):25-38.
2. Chin CK et al. Autologous stem cell transplantation for untreated transformed indolent B-cell lymphoma in first remission: an international, multi-centre propensity-score-matched study. Br J Haematol. 2020;191(5):806-15.
3. Crump M et al. Outcomes in refractory diffuse large B-cell lymphoma: results from the international SCHOLAR-1 study. Blood. 2017;130(16):1800-8.
4. Klink AJ et al. Real-world management and outcomes of patients with relapsed/refractory diffuse large B-cell lymphoma treated in the United States. J Clin Pathways. 2020;6(1):44-53.
5. Harris LJ et al. Novel therapies for relapsed or refractory diffuse large B-cell lymphoma. Int J Mol Sci. 2020;21(22):8553.
6. Di M et al. Challenges and opportunities in the management of diffuse large B-cell lymphoma in older patients. Oncologist. 2021;26(2):120-32.
7. Nowakowski G et al., "Standard of care in first-line therapy of DLBCL," Lenz G, Salles G (eds.), Aggressive Lymphomas (2019), Cham: Springer, pp.145-55.
8. Dulac EJ et al. The burden of illness and prevalence in diffuse large B-cell (DLBCL) and follicular (FL) lymphomas. Blood. 2013;122(21):5619.
9. Liu Y, Barta SK. Diffuse large B-cell lymphoma: 2019 update on diagnosis, risk stratification, and treatment. Am J Hematol. 2019;94(5):604-16.
10. Khan Y et al. Retrospective analysis of elderly patients with DLBCL: single center experience with FIL. J Clin Oncol. 2019;37(15 Suppl):e19024.
11. National Cancer Institute. Cancer stat facts: NHL – diffuse large B-cell lymphoma (DLBCL). 2018. Available at: https://seer.cancer.gov/statfacts/html/dlbcl.html. Last accessed: 4 March 2021.
12. Modvig L et al. Clinical and treatment-related features determining the risk of late relapse in patients with diffuse large B-cell lymphoma. Br J Haematol. 2017;179(1):75-82.
13. Gisselbrecht C et al. Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era. J Clin Oncol. 2010;28(27):4184-90.
14. Sanz L et al. Risk of relapse and clinico-pathological features in 103 patients with diffuse large-cell lymphoma in complete response after first-line treatment. Eur J Haematol. 1998;61(1):59-64.
15. Gisselbrecht C et al. Rituximab maintenance therapy after autologous stem-cell transplantation in patients with relapsed CD20(+) diffuse large B-cell lymphoma: final analysis of the collaborative trial in relapsed aggressive lymphoma. J Clin Oncol. 2012;30(36):4462-9.
16. Khan AB et al. PET-CT staging of DLBCL accurately identifies and provides new insight into the clinical significance of bone marrow involvement. Blood. 2013;122(1):61-7.
17. Yamamoto M et al. Prediction of prognosis for patients with diffuse large B-cell lymphoma refractory to or in first relapse after initial R-CHOP therapy: a single-institution study. Anticancer Res. 2017;37(5):2655-6.
18. Sehn LH et al. The revised International Prognostic Index (R-IPI) is a better predictor of outcome than the standard IPI for patients with diffuse large B-cell lymphoma treated with R-CHOP. Blood. 2007;109(5):1857-61.
19. Nowakowski GS, Czuczman MS. ABC, GCB, and double-hit diffuse large B-cell lymphoma: Does subtype make a difference in therapy selection? Am Soc Clin Oncol Educ Book. 2015;e449-57.
20. Lymphoma Australia. Double hit and Triple hit (DL & TL). 2020. Available at: https://www.lymphoma.org.au/types-of-lymphoma/non-hodgkin-lymphoma/aggressive-fast-growing-b-cell-nhl/double-hit-and-triple-hit-dl-tl/. Last accessed: 17 February 2021.
21. Riedell PA, Smith SM. Double hit and double expressors in lymphoma: definition and treatment. Cancer. 2018;124(24):4622-32.
22. Elstrom RL et al. Response to second-line therapy defines the potential for cure in patients with recurrent diffuse large B-cell lymphoma: implications for the development of novel therapeutic strategies. Clin Lymphoma Myeloma Leuk. 2010;10(3):192-6.
23. McMillan A et al. Post relapse survival rates in diffuse large B-cell lymphoma. Blood. 2016;128(22):4204.
24. Chaplin S; Prescriber. CAR-T cell therapy: personalised immunotherapy for cancer. 2018. Available at: https://wchh.onlinelibrary.wiley.com/doi/pdf/10.1002/psb.1725. Last accessed: 4 March 2021.
25. Wang L et al. New agents and regimens for diffuse large B cell lymphoma. J Hematol Oncol. 2020;13(1):175.
26. Muss HB et al. p16 a biomarker of

aging and tolerance for cancer therapy. Transl Cancer Res. 2020;9(9):5732-42.

27. Nastoupil LJ et al. Diffuse large B-cell lymphoma: current treatment approaches. Oncology (Williston Park). 2013;26(5):488-95.

28. Hammer O. CD19 as an attractive target for antibody-based therapy. MAbs. 2012;4(5):571-7.

29. Sehn LH et al. Polatuzumab vedotin in relapsed or refractory diffuse large B-cell lymphoma. J Clin Oncol. 2020;38(2):155-65.

30. MorphoSys US Inc. Highlights of prescribing information: MONJUVIÒ (tafasitamab-cxix) for injection, for intravenous use. 2020. Available at: https://www.monjuvi.com/pi/monjuvi-pi.pdf. Last accessed: 3 February 2021.

31. Duell J et al. Subgroup analyses from L-Mind, a Phase II study of tafasitamab (MOR208) combined with lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma. Blood. 2019;134(Suppl 1):1582.

32. MorphoSys. MorphoSys and Incyte Announce Long-Term Follow-Up Results from L-MIND Study of Tafasitamab in Patients with r/r DLBCL. 2020. Available at: https://www.morphosys.com/media-investors/media-center/morphosys-and-incyte-announce-long-term-follow-up-results-from-l-mind. Last accessed: 26 June 2020.

33. Salles GA et al. Single-arm Phase II study of MOR208 combined with lenalidomide in patients with relapsed or refractory diffuse large B-cell lymphoma: L-Mind. Blood. 2018;132(Suppl 1):227.

34. Karyopharm Therapeutics Inc. Highlights of prescribing information: XPOVIO® (selinexor) tablets, for oral use. 2020. Available at: https://www.karyopharm.com/wp-content/uploads/2019/07/NDA-212306-SN-0071-Prescribing-Information-01July2019.pdf. Last accessed: 3 February 2021.

35. Kalakonda N et al. Selinexor in patients with relapsed or refractory diffuse large B-cell lymphoma (SADAL): a single-arm, multinational, multicentre, open-label, Phase 2 trial. Lancet Haematol. 2020;7(7):e511-22.

36. Pettengell R et al. Pixantrone plus rituximab versus gemcitabine plus rituximab in patients with relapsed aggressive B-cell non-Hodgkin lymphoma not eligible for stem cell transplantation: a Phase 3, randomized, multicentre trial (PIX306). Br J Haematol. 2020;188(2):240-8.

37. Zinzani PL et al. Effectiveness and safety of pixantrone for the treatment of relapsed or refractory diffuse large B-cell lymphoma in every-day clinical practice: the Italian cohort of the PIXA Registry. Acta Haematol. 2020:1-5.

38. Genentech, Inc. Highlights of prescribing information: POLIVY® (polatuzumab vedotin-piiq) for injection, for intravenous use. 2020. Available at: https://www.gene.com/download/pdf/polivy_prescribing.pdf. Last accessed: 3 February 2021.

39. Elfrink S et al. High frequency of inactivating tetraspanin CD37 mutations in diffuse large B-cell lymphoma at immune-privileged sites. Blood. 2019;134(12):946-50.

40. Oostindie SC et al. CD20 and CD37 antibodies synergize to activate complement by Fc-mediated clustering. Haematologica. 2019;104(9):1841-52.

41. Yu B et al. Targeted drug delivery and cross-linking induced apoptosis with anti-CD37 based dual-ligand immunoliposomes in B chronic lymphocytic leukemia cells. Biomaterials. 2013;34(26):6185-93.

42. ADC Review. Naratuximab emtansine | IMGN529 (K7153A) | Debio 1562 | Drug Description. 2020. Available at: https://www.adcreview.com/naratuximab-emtansine-imgn529-k7153a-debio-1562-drug-description/. Last accessed: 4 March 2021.

43. Stathis A et al. Safety, tolerability, and preliminary activity of IMGN529, a CD37-targeted antibody-drug conjugate, in patients with relapsed or refractory B-cell non-Hodgkin lymphoma: a dose-escalation, Phase I study. Invest New Drugs. 2018;36(5):869-76.

44. Hicks SW et al. The antitumor activity of IMGN529, a CD37-targeting antibody-drug conjugate, is potentiated by rituximab in non-Hodgkin lymphoma models. Neoplasia. 2017;19(9):661-71.

45. Bobrowicz M et al. CD37 in B cell derived tumors—more than just a docking point for monoclonal antibodies. Int J Mol Sci. 2020;21(24):9531.

46. Debiopharm International SA. Study to evaluate the efficacy and tolerability Debio 1562 in combination with rituximab in patients with relapsed and/or refractory DLBCL and other forms of NHL. NCT02564744. https://clinicaltrials.gov/ct2/show/NCT02564744.

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Treatment may be continued until disease progression or unacceptable toxicity. ***Dose modifications:*** No dose reductions are recommended. Dosing delay or discontinuation may be required based on individual safety and tolerability. Recommended modifications to manage adverse reactions are provided in Table 1 of the SPC. **Special Populations:** ***Paediatric (<18 years):*** Safety and efficacy has not been established. ***Elderly:*** No dose adjustment is recommended. ***Renal impairment:*** No dose adjustment is recommended, however there are limited data for LIBTAYO in patients with severe renal impairment (CLcr15-29ml/min). ***Hepatic impairment:*** No dose adjustment is recommended for patients with mild hepatic impairment. LIBTAYO has not been studied in patients with moderate or severe hepatic impairment. **Contraindications:** Hypersensitivity to the active substance or to any of the excipients. **Precautions and Warnings:** ***Traceability:*** To improve traceability of biological medicinal products, the name and the batch number of the administered product should be clearly recorded. ***Immune-related adverse reactions (IRARs):*** IRARs may involve any organ system. Most IRARs initially manifest during treatment however, they can occur after discontinuation of cemiplimab. IRARs affecting more than one body system can occur simultaneously, such as myositis and myocarditis or myasthenia gravis, in patients treated with cemiplimab or other PD-1/PD-L1 inhibitors. Patients treated with cemiplimab should be monitored for signs and symptoms of IRARs. IRARs should be managed with cemiplimab treatment modifications, hormone replacement therapy (if clinically indicated), and corticosteroids. For suspected IRARs, patients should be evaluated to confirm an IRAR and to exclude other possible causes, including infection. Depending upon the severity of the adverse reaction, cemiplimab should be withheld or permanently discontinued. ***Immune-related pneumonitis:*** defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, has been observed. Patients should be monitored for signs and symptoms of pneumonitis and causes other than immune related pneumonitis should be ruled out. Patients with suspected pneumonitis should be evaluated with radiographic imaging as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids. ***Immune-related diarrhoea or colitis:*** defined as requiring use of corticosteroids with no clear alternate aetiology, has been observed. Patients should be monitored for signs and symptoms of diarrhoea or colitis and managed with cemiplimab treatment modifications, anti-diarrhoeal agents, and corticosteroids. ***Immune-related hepatitis:*** defined as requiring use of corticosteroids with no clear alternate aetiology, including fatal cases, have been observed. Patients should be monitored for abnormal liver tests prior to and periodically during treatment as indicated based on clinical evaluation and managed with cemiplimab treatment modifications and corticosteroids. ***Immune-related endocrinopathies:*** defined as treatment-emergent endocrinopathies with no clear alternate aetiology, have been observed. ***Thyroid disorders (Hypothyroidism/Hyperthyroidism):*** Thyroid disorders can occur at any time during the treatment. Patients should be monitored for changes in thyroid function at the start of treatment and periodically during the treatment as indicated based on clinical evaluation. Patients should be managed with hormone replacement therapy (if indicated) and cemiplimab treatment modifications. Hyperthyroidism should be managed according to standard medical practice. ***Hypophysitis:*** Immune-related hypophysitis has been observed. Patients should be monitored for signs and symptoms of hypophysitis and managed with cemiplimab treatment modifications, corticosteroids and hormone replacement, as clinically indicated. ***Adrenal insufficiency:*** Patients should be monitored for signs and symptoms of adrenal insufficiency during and after treatment and managed with cemiplimab treatment modifications, corticosteroids and hormone replacement, as clinically indicated. ***Type 1 Diabetes mellitus:*** Immune-related type 1 diabetes mellitus, including diabetic ketoacidosis, has been observed. Patients should be monitored for hyperglycaemia and signs and symptoms of diabetes as indicated based on clinical evaluation and managed with oral anti-hyperglycaemics or insulin and cemiplimab treatment modifications. ***Immune-related skin adverse reactions:*** defined as requiring use of systemic corticosteroids with no clear alternate aetiology, including severe cutaneous adverse reactions (SCARs), such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) (some cases with fatal outcome), and other skin reactions such as rash, erythema multiforme, pemphigoid, have been reported in association with cemiplimab treatment. Patients should be monitored for evidence of suspected severe skin reactions and exclude other causes. Patients should be managed with cemiplimab treatment modifications and corticosteroids. For symptoms or signs of SJS or TEN, refer the patient for specialised care for assessment and treatment and manage patient with treatment modifications. Cases of SJS, fatal TEN and stomatitis occurred following 1 dose of cemiplimab in patients with prior exposure to idelalisib, who were participating in a clinical trial evaluating cemiplimab in Non-Hodgkins Lymphoma (NHL), and who had recent exposure to sulfa containing antibiotics. Patients should be managed with cemiplimab treatment modifications and corticosteroids as described above. ***Immune-related nephritis:*** defined as requiring use of corticosteroids with no clear alternate aetiology, has been observed in patients receiving cemiplimab. Monitor patients for changes in renal function. Patients should be managed with cemiplimab treatment modifications and corticosteroids. ***Other IRARs:*** Other fatal and life-threatening IRARs have been observed in patients receiving cemiplimab including paraneoplastic encephalomyelitis, meningitis and myositis. Evaluate suspected IRARs to exclude other causes. Patients should be monitored for signs and symptoms of IRARs and managed with cemiplimab treatment modifications and corticosteroids as clinically indicated. Solid organ transplant rejection has been reported in the post-marketing setting in patients treated with PD-1 inhibitors. Treatment with cemiplimab may increase the risk of rejection in solid organ transplant recipients. The benefit of treatment with cemiplimab versus the risk of possible organ rejection should be considered in these patients. Cases of graft versus-host disease have been reported in the post-marketing setting in patients treated with other PD-1/PD-L1 inhibitors in association with allogeneic hematopoietic stem cell transplant. ***Infusion-related reactions:*** Cemiplimab can cause severe or life-threatening infusion-related reactions. Patients should be monitored for signs and symptoms of infusion-related reactions and managed with cemiplimab treatment modifications and corticosteroids. Cemiplimab should be interrupted or the rate of infusion slowed for mild or moderate infusion-related reactions. The infusion should be stopped and cemiplimab should be permanently discontinued for severe (Grade 3) or life-threatening (Grade 4) infusion-related reactions. ***Patients excluded from clinical studies:*** Patients that had active infections or that were immunocompromised were not included in the main study. ***Fertility, Pregnancy and Lactation:*** No clinical data available on the possible effects of cemiplimab on fertility. No effects observed in fertility study on cynomolgus monkeys. Women of childbearing potential should use effective contraception during treatment with cemiplimab and for at least 4 months after the last dose of cemiplimab. Cemiplimab, as an IG4, has the potential to be transmitted across the placenta from the mother to the developing foetus. Cemiplimab is not recommended during pregnancy and in women of childbearing potential not using effective contraception unless the clinical benefit outweighs the potential risk. It is unknown whether cemiplimab is secreted in human milk. If a lactating woman chooses to be treated with cemiplimab, she should be instructed not to breastfeed while being treated with cemiplimab and for at least 4 months after the last dose. ***Interactions:*** No pharmacokinetic drug-drug interaction studies have been conducted with cemiplimab. The use of systemic corticosteroids or immunosuppressants before starting cemiplimab, except for physiological doses of systemic corticosteroid (≤10 mg/day prednisone or equivalent), should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of cemiplimab. However, systemic corticosteroids or other immunosuppressants can be used after starting cemiplimab to treat IRARs. **Adverse Reactions:** ***Very common:*** Diarrhoea, Fatigue, Pruritus and Rash. ***Common:*** Alanine aminotransferase increased, Arthralgia, Arthritis, Aspartate aminotransferase increased, Blood alkaline phosphatase increased, Blood creatinine increased, Hepatitis, Hyperthyroidism, Hypothyroidism, Infusion related reaction, Musculoskeletal pain, Pneumonitis, Stomatitis, Dyspnoea. ***Uncommon:*** Adrenal insufficiency, Central nervous system inflammation, Chronic inflammatory demyelinating polyradiculoneuropathy, Encephalitis, Guillain-Barre syndrome, Hypophysitis, Immune thrombocytopenic purpura, Keratitis, Meningitis, Muscular weakness, Myasthenia gravis, Myocarditis, Nephritis, Neuropathy peripheral, Paraneoplastic encephalomyelitis, Pericarditis, Polymyalgia rheumatica, Sjogren's syndrome, Thyroiditis, Type 1 diabetes mellitus, Vasculitis. ***Rare:*** Myositis. ***Not Known:*** Solid organ transplant rejection **UK List price:** £4650 per vial. **Legal Category:** POM. **Marketing Authorisation Number:** EU/1/19/1376/001. **Marketing Authorisation Holder:** Regeneron Ireland U.C., Europa House, Harcourt Centre, Harcourt Street, Dublin 2, Ireland. **For more information please contact:** Sanofi, 410 Thames Valley Park Drive, Reading, Berkshire, RG6 1PT, UK. uk-medicalinformation@sanofi.com **Date of preparation:** August 2020.

Adverse events should be reported. Reporting forms and information can be found at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store. Adverse events should also be reported to the Sanofi Drug Safety department on Tel: 0800 0902314.

Alternatively, send via email to UK-drugsafety@sanofi.com

Conditional approval: LIBTAYO has been authorised under a 'conditional approval' scheme. This means that further evidence on this medicinal product is awaited.

References: 1. LIBTAYO (cemiplimab) Summary of Product Characteristics. Regeneron Pharmaceuticals, Inc. **2.** KEYTRUDA (pembrolizumab) Summary of Product Characteristics. Merck Sharp & Dohme Limited. **3.** OPDIVO (nivolumab) Summary of Product Characteristics. Bristol-Myers Squibb Pharmaceuticals Limited.

CSCC, Cutaneous squamous cell carcinoma; PD-1, Programmed cell death-1.

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The Correlation Between Stroke and Coronavirus Disease (COVID-19): Where is the Evidence?

EDITOR'S PICK

The Editor's Pick for this issue of *EMJ* is the fantastic investigative review by Pittams et al., which aims to understand the role that the coronavirus disease (COVID-19) plays in stroke aetiology. As a multifactorial disease, many of the modifiable and genetic risk factors of stroke have been well researched, yet still undetermined is the role played by infectious diseases in stroke pathophysiology. Further insight into the interplay between these two disease entities is vital both for understanding stroke aetiology and advancing the therapies needed to fight pathogen-induced stroke.

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Abstract

Stroke is the second leading cause of death globally. Despite the decreasing trend in stroke mortality, its incidence and prevalence follow an upwards trajectory that is envisaged to continue for years to come. Previous literature has suggested a role for infectious disease in stroke aetiology; however, the pathophysiological basis for this has never fully been understood. Emerging infections, such as coronavirus disease (COVID-19), present new challenges that must be addressed, to prevent them from contributing to the predicted rise in stroke incidence. Almost one in 20 patients diagnosed with COVID-19 experience a stroke thereafter, hence achieving better understanding of the interactions between these disease entities is of major clinical significance.

INTRODUCTION

Stroke is a cerebrovascular disease, whereby blockage or rupture of a cerebral artery results in cerebral infarction or haemorrhage, respectively.[1] It is the second most common cause of death globally, accounting for 80.5 deaths per 100,000 population.[2] While the mortality rate of stroke appears to be decreasing,[2] its prevalence is envisaged to rise over coming years, with a predicted increase in both stroke incidence and survival contributing to this.[3] Its multifactorial nature means that many of the modifiable and genetic risk factors implicated in stroke aetiology have been well researched. However, the role of infectious agents in provoking cerebrovascular events has often been undermined.[4,5]

The relationship between stroke and infectious disease is complex. The neurological sequelae of stroke and infectious diseases may overlap, creating diagnostic uncertainty,[6] and prior stroke is a poor prognosticator in coronavirus disease (COVID-19) infection.[7] Additionally, several infectious agents have been directly implicated in the development of stroke.[8-10] Some of these remain poorly investigated. This is particularly true for emerging infections, such as COVID-19, which pose a new opportunity to understand stroke pathophysiology.

Several mechanisms have been implicated in stroke secondary to infection.[11-14] However, stroke in patients with COVID-19 is likely the result of several processes acting synergistically, rather than a single mechanism in isolation. Treatments for pathogen-induced stroke should be centred around counteracting these pathological pathways. However, without adequate understanding of the pathophysiology of stroke in infectious disease, it is difficult to optimise a management plan for when the two occur simultaneously. In this review, the authors aim to better understand the pathophysiology of stroke in infectious disease, and in particular COVID-19 infection. The authors hope that this will enable management and treatment strategies to become nuanced, optimising the care of patients experiencing a stroke following COVID-19 infection.

METHODS

The databases searched included MEDLINE, SCOPUS, Embase, Cochrane Library, and Google Scholar. The review question had two main parts: 1) pathophysiological mechanisms of stroke in infection; and 2) management strategies for patients with concurrent infection and stroke. A separate search was conducted for each of these. If the search retrieved papers applicable to the entire article, the results were shared between different parts of this review. Keywords included "stroke", "cerebrovascular accident", "brain", "nervous system", "infection", "COVID-19", "coronavirus", "SARS-CoV-2", and "infectious disease". Part 1 also included "pathophysiology", "cause", and "trigger", while Part 2 included "treatment", "management", and "strategies". After reviewing the search results, some search terms were restricted to title and abstract fields. Each of the search terms were imputed as keywords and then combined as MeSH terms to ensure a comprehensive search. The last literature search was on 23rd July 2020.

All articles retrieved were independently screened by two authors, and consensus was reached by consulting the senior author if there were any discrepancies. Studies met the inclusion criteria if they discussed stroke and infection with respect to pathophysiology and treatment. The main exclusion criteria were non-English language studies, editorials, commentaries, and studies for which the full text was unavailable. No restriction was placed on publication year to ensure all relevant studies were captured. The search results are presented in a narrative manner throughout this article and a summary table is displayed in the pathophysiology section of the results.

PATHOPHYSIOLOGY OF STROKE IN INFECTIOUS DISEASE

In recent years, some great insight into the association between infection and stroke has been achieved. However, the true extent of this has proved difficult to determine because of the differences in definitions and criteria for stroke and infection between studies. Various mechanisms have been proposed with two main themes, as outlined in Table 1.[15-23]

Table 1: Brief overview of the proposed pathophysiological mechanisms of stroke in viral infections, including coronavirus disease (COVID-19).

Proposed mechanisms		Supporting evidence
Inflammation	Increased levels of TNFα	Van der Poll et al.,[15] 1990 Manousakis et al.,[16] 2009
	Increased levels of IL-6	Huber et al.,[17] 1999 Amlie-Lefond et al.,[18] 2016
	Increased circulating leukocytes	Rivers et al.,[19] 1975
	Inhibition of anticoagulant factors, e.g., proteins C and S	Esmon et al.,[20] 1991 Hesselvik JF et al.,[21] 1991
Direct causation (selected examples)	HIV	Ortiz G et al.,[22] 2007 Miller EC et al.,[23] 2016
	Herpes-zoster virus	Miller EC et al.,[23] 2016
	Varicella-zoster virus	Miller EC et al.,[23] 2016

First, inflammation may increase stroke tendency. Increased levels of inflammatory mediators have been detected in stroke patients following infection, compared with those without;[24] suggesting that activation of inflammatory pathways may in turn contribute towards a procoagulant state. It is thought that inflammation can give rise to increased atherosclerosis, plaque rupture, and thrombosis, eventually leading to ischaemic stroke.[9] Infarction may also be a result of cerebral vasculitis; this has previously been reported in patients with tuberculosis, meningitis, and syphilis.[9,24]

There are several pathways that have been suggested to increase coagulation when stimulated by inflammation. Rivers et al.[19] reported that endotoxin-induced monocytes promote coagulation through their expression of thromboplastin. Several cytokines, such as TNFα, have also been implicated in activating the common pathway of coagulation in severe infection.[15] TNFα may also be procoagulant due to its inhibition of the fibrinolytic system.[16]

Similarly, one of the main cytokines that has been highlighted as a key player in the disease progression, from infection to stroke, is IL-6. In murine models, the presence of IL-6 increased the progression of fatty atheromas found in atherosclerosis, a major risk factor for stroke.[17] Alongside promotion of procoagulant factors, there may be concurrent inhibition of the anticoagulant modulators proteins C and S.[20,21] Ortiz et al.[22] agreed that protein S deficiency may be an additive mechanism for initiating infarction. There is accumulating evidence that infection-induced inflammation and subsequent procoagulant state is one of the main mechanisms behind stroke postinfection. However, the specific pathways involved in this process are yet to be isolated and so further investigation is required.

Haemorrhagic strokes postinfection are investigated less frequently. One case-crossover study reported that haemorrhagic strokes were primarily associated with preceding urinary tract infection, respiratory infection, and sepsis.[25] It is thought that systemic inflammation as a consequence of systemic infection could lead to vascular endothelial cell injury, causing an intracranial haemorrhage.[9] However, further investigation is needed to fully understand this concept.

Secondly, there may be a direct causal link between the actions of infectious organisms and cerebrovascular accident.[17,18,23,25,26] For example, bacteria that cause tuberculosis and meningitis can lead to stroke through the inflammatory injury to cerebral vessels.[23] Interestingly, in the

case of viruses, there is emerging evidence that viral load is directly linked to increased incidence of stroke.[23] Initially, stroke was considered a complication of dyslipidaemia, as a side effect of highly-active anti-retroviral therapy. However, it is now thought stroke occurs as a result of virus-mediated vasculopathy. Ortiz et al.[22] suggested that vasculitis is the dominating mechanism for stroke, with hypercoagulability being a supportive mechanism.[22] Arterial remodelling leads to either stenosed or dilated vessels, causing ischaemic or haemorrhagic strokes, respectively.[23] However, it would be prudent to remember that these initial studies have small sample sizes, and include patients with HIV, which may lead to the confounding of results. Nevertheless, stroke in patients with herpes viruses, such as varicella-zoster virus and herpes simplex virus have also been associated with vasculopathy, in both adults and children when compared with age-matched controls.[23] The vasculopathy seen in varicella-zoster virus infection is histologically similar to giant cell arteritis, indicating some inflammatory involvement.[23]

The associations between infection, inflammation, and stroke are complex and remain unclear. It should be noted that many of these links are formed following retrospective cohort studies, which are weakened by recall bias and missing data. Additionally, confounding factors are often not accounted for. Therefore, further investigations are warranted, to elucidate the specific pathways employed by infective organisms.

CURRENT EVIDENCE OF THE CORRELATION BETWEEN STROKE AND COVID-19

The association between COVID-19 infection and stroke is under continued investigation as increasing reports emerge with the progression of this global pandemic. Qureshi et al.[27] reported that 4.9% of patients with a confirmed diagnosis of COVID-19 are expected to have a stroke. Worryingly, the mortality rate was reported to be as high as 38.0% among these patients with COVID-19, compared with 3.2% observed in all hospitalised stroke patients.[27] Interestingly, stroke has also been reported as the presenting complaint for COVID-19 infections. In an Italian study of 388 patients with COVID-19, nine presented with ischaemic stroke, with six of these patients admitted to intensive care and three admitted to a general ward.[28] Additionally, both Siegler et al.[29] and Yaghi et al.[30] reported a higher incidence of cryptogenic stroke in patients with COVID-19. Cryptogenic stroke refers to a stroke with an underlying cause distinct from atherosclerosis or embolism. This suggests that the underlying pathological process may be novel to infection. Given this association between COVID-19 and stroke, there has been much speculation surrounding the mechanisms responsible.

The proposed mechanisms are based on four different processes, including viral neurotropism, endothelial dysfunction, coagulopathy, and inflammation. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a neuroinvasive virus, as proven by its presence in the cerebrospinal fluid of an infected patient with encephalitis.[31] Viral presence was also noted in cerebral capillary endothelial cells in a patient with COVID-19 following autopsy.[32] This suggests that the virus may have direct effects on cerebral vessels, possibly causing endothelial dysfunction, which could lead to stroke. Endothelial dysfunction may also be mediated by angiotensin-converting enzyme 2 (ACE2) receptor binding. The binding of the virus to ACE2 receptors allows the virus to enter cells. These receptors are expressed on endothelial cells in the brain and regulate cerebral blood flow thus, viral-receptor binding may disrupt these regulatory processes, ultimately causing a stroke.[33]

Coagulopathy or a hypercoagulable state has also been associated with COVID-19. Elevated levels of D-dimer, fibrin degradation products, and fibrinogen were detected in patients with COVID-19, while antithrombin and prothrombin levels were reduced, indicating greater coagulation during infection.[32] The concentration of procoagulant markers correlated with the severity of COVID-19, suggesting that the risk of stroke is directly proportional to infection severity.[32] ACE2 receptor binding may also cause thrombosis. There is higher expression of ACE2 receptors in the heart and lungs, resulting in greater viral load at these sites. A greater immune response in the lungs can lead to hypoxia. Hypoxia is a lack of oxygen supply which generally occurs

through endothelial injury or blood stasis; two constituents of Virchow's triad, thus initiating thrombosis.[34] Similarly, an increased immune response at the coronary vessels may lead to atherosclerotic plaques being disrupted, causing plaque rupture and subsequent thrombosis. Both these processes would lead to ischaemic stroke. Furthermore, it is well known that severe infections can be complicated by disseminated intravascular coagulation which could play a part in the onset of ischaemic stroke in patients with COVID-19.[35] Another characteristic of severe COVID-19 infection is a cytokine storm, one aspect of an exaggerated immune response. This cytokine storm includes increased levels of IL-6, which has been implicated in the REasons for Geographic And Racial Differences in Stroke (REGARDS) study with increased risk of stroke, regardless of other stroke risk factors.[36]

These proposed mechanisms include direct effects of the virus as well as pathological systemic changes that may predispose to stroke. Given the complexity of the pathways involved in infection and inflammation, it would be expected that more than one of these proposed mechanisms is involved in the pathogenesis of stroke following COVID-19 infection. It would be prudent to investigate further in order to prevent cerebrovascular complications and continue the downwards trend in stroke mortality.

MANAGEMENT OF CONCURRENT INFECTION AND STROKE

Despite the worryingly high mortality rates reported in stroke patients with concurrent COVID-19 infection, there are no universal guidelines for the management of stroke in these patients. Present prophylaxis and treatments are predominantly based on what we understand already about stroke and infectious disease as separate entities, rather than when they occur simultaneously.[37,38]

Stroke may be the presenting complaint for those with COVID-19 infection;[39] therefore, guidelines recommend all potential stroke patients presenting to the emergency department are screened for COVID-19.[40-42] Use of telemedicine to assess patient stroke profile should be encouraged in order to minimise risk of transmission to hospital staff.[27,42]

Imaging investigations should be started as soon as possible, preferably within the first hour, to reduce mortality and achieve maximal functional recovery.[27,38,42] CT, CT angiography, and CT perfusion scanning may be performed.[27,41,42] Indeed, patients with COVID-19 commonly underwent CT and MRI across a series of case studies.[39,43,44] Baracchini et al.[41] proposed the usage of a mobile CT scanner for patients with suspected or confirmed COVID-19, in accordance with infection control advice, to minimise further exposure to SARS-Cov-2. Referral for intravenous thrombolysis or mechanical thrombectomy is made on a case-by-case basis, as long as benefits outweigh the risks.[27,42]

Intravenous thrombolysis is effective if administered within the first 3 hours after the cerebrovascular event. Nonetheless, studies have shown that it is not appropriate for the management of ischaemic stroke in patients with infective endocarditis, raised C-reactive protein, or raised D-dimer levels, as it may increase the risk of intracranial bleeding.[27,45] Interestingly, COVID-19 has been shown to elevate D-dimer levels.[28,46] Thus, thrombolysis should be carefully considered in infected patients, especially since hepatic function may be impaired, reducing the clearance of thrombolytic agents.[27] Poor et al.[47] have reported favourable results of thrombolysis for the treatment of pulmonary thrombi in patients who are COVID-19 positive, but there is insufficient evidence that thrombolysis would be as effective in the treatment of ischaemic stroke.[27]

The American Stroke Association (ASA) recommends the use of mechanical thrombectomy in the case of internal carotid artery or middle cerebral artery occlusion with symptom onset of less than 6 hours and a National Institutes of Health Stroke Scale (NIHSS) score above six.[48] However, two recent randomised controlled trials were able to demonstrate good efficacy of mechanical thrombectomy for up to 24 hours for patients that have had a large vessel occlusion in the anterior circulation. Patients need to fulfil eligibility criteria based on neuroimaging results, but special consideration should be given to those with a confirmed COVID-19 diagnosis given the risk of severe complications.[48,49] Of those who receive thrombectomy, 38% receive anaesthesia and of these, 14% require intubation due to complications such as respiratory failure.[27] One can expect that would be the case for

most COVID-19-positive patients experiencing respiratory symptoms. Additionally, the risk of transmission to medical staff is high.

Antiplatelet drugs, such as aspirin and clopidogrel, as well as anticoagulants (mainly enoxaparin), have been used to treat acute stroke in patients with COVID-19.[39,41,43,44] No studies have reported whether antiplatelet therapy is superior to anticoagulants or vice versa, and some patients are prescribed dual therapy.[41]

Several papers mention the use of low-molecular-weight heparin at prophylactic doses in patients with COVID-19.[28,36,38,41-44] Its effectiveness, however, remains questionable; Klok et al.[38] reported that despite enoxaparin administration, 31% of patients had thrombotic complications. The same study proposed that a more aggressive approach should be implemented, by increasing the frequency of administration or dose.[38]

FUTURE RESEARCH

The true extent of the impact COVID-19 has had on stroke will be revealed by the findings from the ongoing CASCADE study. This study aims to identify clinical predictors of stroke in patients positive for COVID-19, providing insight into the pathological pathways at play in the disease process.[50]

Ultimately, a greater understanding of SARS-CoV-2 pathogenesis is required, in order to develop preventative measures and targeted therapies.[51] Multiple theories have been formulated in regard to the correlation between COVID-19 and stroke, but further research is needed before these theories can be translated to changes in clinical practice. The implication of inflammatory processes and production of IL-6, as well as the role of ACE2 depletion, have been proposed as possible explanations for a causal relationship.[14,52] It is advisable to pursue the confirmation or rejection of these theories. Additionally, introducing neurological monitoring of patients may assist in the formulation of a timeline of disease progression in those with neurological sequelae.[52]

At present, two randomised controlled trials are reviewing the efficacy of enoxaparin as prophylactic therapy.[53,54] However, in order to develop prophylaxis and treatment guidelines, more research is needed. Further trials to investigate the aforementioned proposal of increasing the dosage of low-molecular-weight heparin are needed to ensure that its benefits outweigh the risks.[38,55] Lastly, a study comparing anticoagulant and antiplatelet therapies would be valuable to clinicians. Future retrospective and case studies should consider incorporating the decision-making process when choosing the best treatment for patients.

CONCLUSION

In this succinct review, stroke was discussed from an infectious disease perspective. Addressed were the potential pathophysiological mechanisms of stroke in patients with COVID-19, and how these can be used to inform decisions regarding both prophylaxis and treatment. The authors acknowledge that the scarcity and inconsistency of previous literature presents additional challenges when attempting to understand the complex relationship between stroke and COVID-19. Ultimately, further research is needed to enhance our understanding of both the direct effects and systemic repercussions of infection.

References

1. Sacco RL et al. American Heart Association Stroke Council, Council on Cardiovascular Surgery and Anesthesia. Council on Cardiovascular Radiol-ogy and Intervention. Council on Cardiovascular and Stroke Nursing et al. An updated definition of stroke for the 21st century: a statement for healthcare professionals from the American Heart Association/ American Stroke Association. Stroke. 2013;44(7):2064-89.
2. Avan A et al. Socioeconomic status and stroke incidence, prevalence, mor-tality, and worldwide burden: an ecological analysis from the Global Bur-den of Disease Study 2017. BMC Med. 2019;17:191.
3. Stroke association. Stroke statistics. 2018. Available at: https://www.stroke.org.uk/sites/default/files/state_of_the_nation_2018.pdf. Last accessed: 23rd July 2020.
4. Grau AJ et al. Common infections and the risk of stroke. Nat Rev Neurol. 2010;6(12):681-94.
5. Jillella DV, Wisco DR. Infectious causes of stroke. Curr Opin Infect Dis. 2019;32(3):285-92.
6. Ellul MA et al. Neurological

associations of COVID-19. Lancet Neurol. 2020;DOI: 10.1016/S1474-4422(20)30221-0.

7. Trejo Gabriel y Galán JM. Stroke as a complication and prognostic factor of COVID-19. Neurología (English Edition). 2020;35(5):318-22.
8. Doheim MF et al. Association between *Helicobacter pylori* infection and stroke: a meta-analysis of 273,135 patients. J Neurol. 2020;DOI:10.1007/s00415-020-09933-x.
9. Fugate J et al. Infectious causes of stroke. Lancet Infect Dis. 2014;14:869-80.
10. Clayton TC et al. Recent respiratory infection and risk of cardiovascular disease: case-control study through a general practice database. Eur Heart J. 2008;29(1):96-103.
11. Lucchese G et al. Cross-reactivity as a mechanism linking infections to stroke. Front Neurol. 2019;10:469.
12. Kunze A et al. Recent infection as a risk factor for intracerebral and sub-arachnoid haemorrhages. Cerebrovasc Dis. 2000;10(5):352-8.
13. Epstein S et al. Infection and atherosclerosis: emerging mechanistic para-digms. Circulation. 1999;100(4):e20-8.
14. Hess D et al. COVID-19-related stroke. Transl Stroke Res. 2020;11(3):322-5.
15. Van der Poll T et al. Activation of coagulation after administration of tu-mour necrosis factor to normal subjects. N Engl J Med. 1990;322(23):1622-7.
16. Manousakis G et al. The interface between stroke and infectious disease: in-fectious diseases leading to stroke and infections complicating stroke. Curr Neurol Neurosci Rep. 2009:9(1):28-34.
17. Huber SA et al. Interleukin-6 exacerbates early atherosclerosis in mice. Ar-teriscler Thromb Vasc Biol. 1999;19(10):2364-7.
18. Amlie-Lefond C et al. varicella zoster virus: a common cause of stroke in children and adults. J Stroke and Cerebrovasc. 2016;25(7):1561-9.
19. Rivers RPA et al. The endotoxin-induced coagulant activity of human mon-ocytes. Br J Haemoatol. 1975;30(3):311-6.
20. Esmon CT et al. Inflammation and coagulation: linked processes potentially regulated through a common pathway mediated by protein C. Thromb Haemost. 1991;66(1):160-5.
21. Hesselvik JF et al. Protein C, protein S and C4b-binding protein in severe infection and septic shock. Thromb Haemost. 1991;65(2):126-9.
22. Ortiz G et al. Mechanisms of ischaemic stroke in HIV-infected patients. Neu-rology. 2007;68(16):1257-61.
23. Miller EC et al. Infection and stroke: an update on recent progress. Curr Neurol Neurosci Rep. 2016;16(1):2.
24. Grau AJ et al. Recent infection as a risk factor for cerebrovascular ischae-mia. Stroke. 1995;26(3):373-9.
25. Sebastian S et al. Infection as a stroke trigger. Stroke. 2019;50(8):2216-8.
26. Shindler-Itskovitch T et al. *Helicobacter pylori* infection and prevalence of stroke. 2018;24(1):e12553.
27. Qureshi A et al. Management of acute ischemic stroke in patients with COVID-19 infection: report of an international panel. Int J Stroke. 2020;15(5):540-54.
28. Lodigiani C et al. Venous and arterial thromboembolic complications in COVID-19 patients admitted to an academic hospital in Milan, Italy. Throm-bosis Res. 2020;191:9-14.
29. Siegler JE et al. Cerebrovascular events and outcomes in hospitalised pa-tients with COVID-19: The SVIN COVID-19 Multinational Registry. Int J Stroke. 2020; 1747493020959216. [Epub ahead of print].
30. Yaghi S et al. SARS-CoV-2 and stroke in a New York healthcare system. Stroke. 2020;51(7):2002-11.
31. Moriguchi T et al. A first case of meningitis/encephalitis associated with SARS-coronavirus-2. Int J Infect Dis. 2020;94:55-8.
32. Reddy ST et al. Cerebrovascular disease in patients with COVID-19: a re-view of the literature and case series. Case Rep Neurol. 2020;12(2):199-209
33. Paniz-Mondolfi A et al. Central nervous system involvement by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). J Med Virol. 2020;92(7):699-702.
34. Gupta N et al. The stimulation of thrombosis by hypoxia. Thromb Res. 2019;181:77-83.
35. Van der Poll T et al. Coagulation and sepsis. Thromb Res. 2016;149:38-44.
36. Jenny NS et al. Inflammatory cytokines and ischaemic stroke risk: the RE-GARDS cohort. Neurology. 2019;92(20):2375-84.
37. Orsucci D et al. Neurological features of COVID-19 and their treatment: a review. Drugs Context. 2020;9:2020-5-1.
38. Klok F et al. Incidence of thrombotic complications in critically ill ICU pa-tients with COVID-19. Thromb Res. 2020;191:145-7.
39. Avula A et al. COVID-19 presenting as stroke. Brain Behav Immun. 2020;87:115-9.
40. Mao L et al. Neurologic manifestations of hospitalized patients With Coro-navirus Disease 2019 in Wuhan, China. JAMA Neurol. 2020;77(6):1-9.
41. Baracchini C et al. Acute stroke management pathway during coronavirus-19 pandemic. Neurol Sci. 2020;41(5):1003-5.
42. National Institute for Health and Care Excellence (NICE). Clinical guide for the management of stroke patients during the coronavirus pandemic. 2020. Available at: https://www.nice.org.uk/Media/Default/About/COVID-19/Specialty-guides/Specialty-guide-Stroke-and-coronavirus.pdf. Last ac-cessed: 7th January 2020.
43. Morassi M et al. Stroke in patients with SARS-CoV-2 infection: case series. J Neurol. 2020;267(8):2185-92.
44. Beyrouti R et al. Characteristics of ischaemic stroke associated with COVID-19. J Neurol Neurosurg Psychiatry. 2020;jnnp-2020-323586.
45. Robinson T et al. Thrombolysis in acute ischaemic stroke: an update. Ther Adv Chronic Dis. 2011;2(2):119-31.
46. Grasselli et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome: a multicentre prospective observational study. Lancet Respir Med. 2020;S2213-2600(20)30370-2.
47. Poor HD et al. COVID-19 critical illness pathophysiology driven by diffuse pulmonary thrombi and pulmonary endothelial dysfunction responsive to thrombolysis. Clin Transl Med. 2020;10(2):e44.
48. Ren Z et al. Indications for mechanical thrombectomy – too wide or too narrow? World Neurosurg. 2019;127:492-9.
49. Mokin M et al. Indications for thrombectomy in acute ischemic stroke from emergent large vessel occlusion (ELVO): report of the SNIS Standards and Guidelines Committee. J Neurointerv Surg. 2019;11(3):215-20.
50. Abootalebi et al. Call to Action: SARS-CoV-2 and CerebrovAscular Disor-dErs (CASCADE). J Stroke Cerebrovasc Dis. 2020;29(9):104938.
51. Ntaios G et al. Characteristics and outcomes in patients with COVID-19 and acute ischemic stroke: The Global COVID-19 Stroke Registry. Stroke. 2020:10.1161/STROKEAHA.120.031208.
52. Whittaker A et al. Neurological manifestations of COVID-19: a systematic review and current update. Acta Neurol Scand. 2020;142(1):14-22.
53. Faculdade de Medicina de Ribeirão Preto. Full versus prophylactic hepa-rinization for the treatment of severe forms of SARS-Covid-19: clinical, randomized, open and controlled study - HeSAcovid trial. U1111-1251-4283. http://www.ensaiosclinicos.gov.br/rg/RBR-949z6v/.
54. CHU de Saint Etienne. Evaluation of

the concentration-effect relationship of enoxaparin for thromboembolic prevention in COVID-19 resuscitation patients. COV-ENOX study. EudraCT 2020-001823-15. https://www.clinicaltrialsregister.eu/ctr-search/trial/2020-001823-15/FR.

55. Abou-Ismail M et al. The hypercoagulable state in COVID-19: incidence, pathophysiology, and management. Thromb Res. 2020;194:101-15.

Emerging Treatments for Crohn's Disease: Cells, Surgery, and Novel Therapeutics

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Abstract

It was predicted that the biological era might alter the natural history of Crohn's disease, preventing the well-documented inflammation–fibrosis–fistulisation sequence. However, despite the development of novel biological therapies, average efficacy at 1 year remains at 30–50%, with this number decreasing as second-line therapies are regularly required. Currently, new advanced therapies are under investigation to provide alternatives to available treatments. In addition, novel, nonpharmacological strategies are also being explored. Surgical intervention, currently inevitable in a significant proportion of patients, necessitates that prevention of postoperative recurrence is an important research focus and recent studies have shed light on the long-term efficacy of early operative interventions and emerging surgical techniques. Cellular therapies, including stem cell therapy for perianal disease, stem cell transplantation, and harnessing the therapeutic potential of regulatory T cells, are in various stages of development. These could conceivably change the landscape of Crohn's disease management. Dietetic interventions offer a lower risk alternative that may be used as an adjunct to other therapies or where immunosuppression is unfavourable. Choosing between these therapeutic options depends on multiple factors, including the associated risk–benefit profile, available alternatives, as well as patient preference. In practice, optimal management is guided by a multidisciplinary team where pharmacological, nonpharmacological, and surgical strategies can be simultaneously explored. This narrative review aims to provide an update on advanced therapies under investigation in clinical trials and offer insights into novel, nonpharmacological approaches with a focus on interventions entering late-phase trials that will be relevant to clinical practice in the near future.

INTRODUCTION

Despite the development of multiple biological therapies for Crohn's disease (CD), remission rates at 1 year from individual agents are still only 30–50%. This decreases as second-line therapies are required and 80% of patients eventually require surgery in their lifetime.[1] Early pharmacotherapies (such as anti-TNF) have a broad mechanism of action and are relatively 'blunt' tools used to dampen the dysregulated immune response in CD. As our understanding of the aetiopathogenesis of CD has improved, newer treatments have been developed targeting more specific pathways. Several nonpharmacological options, which can be used alongside pharmacotherapy, are also available or currently under investigation. This article focusses on novel therapies entering late-phase clinical trials with the aim of providing an overview of those therapies that are likely to be included in clinical practice shortly.

NOVEL PHARMACOLOGICAL THERAPIES

The therapies discussed below are summarised in Figure 1 according to their stage in clinical trials.

Anti-Adhesion Molecules

The recruitment of leukocytes to the vascular endothelium of inflamed tissue involves communication between integrins, cell adhesion molecules located on the surface of leukocytes, and endothelial adhesion molecules. Antagonism of this interaction limits the migration of leukocytes to the intestinal mucosa inhibiting intestinal inflammation.[2] Vedolizumab was the first therapeutic agent in this class, but newer agents are showing promising results.

Etrolizumab targets the β7 subunit of both the α4β7 and the αEβ7 molecules. The Phase III BERGAMOT trial[3] randomised 300 patients with moderate-to-severe CD to receive either placebo or subcutaneous etrolizumab (105 mg every 4 weeks or 210 mg at 0, 2, 4, 8, and 12 weeks) in a 1:2:2 ratio. Compared to placebo, both active arms had higher rates of clinical remission by Week 6 and endoscopic remission (ER) at Week 14 (105 mg: 21%, 210 mg: 17.4%, placebo: 3.4%). There were no differences between the placebo and active arms regarding adverse events (AE). Common AE included headache, fatigue, abdominal pain, and nasopharyngitis. There were no occurrences of progressive multifocal leukoencephalopathy.[3] These promising results suggest a rapid effect and acceptable safety profile; the maintenance phase is currently underway.

IL-23 Antagonists

The IL-23 pathway has been associated with immune-mediated, chronic inflammatory diseases, including CD,[4] and gene polymorphisms of the IL-23 receptor are associated with the development of CD.[5,6] Blockade of IL-23 also has effects on IL-12 due to the shared p40 subunit, which is the mechanism of action for ustekinumab. However, animal models suggest that IL-12 has a beneficial role in infection prevention and immune response to cancer.[7,8] Therefore, agents that selectively target the p19 subunit (unique to IL-23), may have an advantage over agents that target both IL-12 and IL-23, and appear to have similar side-effect profiles.[4,9] Four such agents are in various stages of development. Guselkumab has been shown in case reports to be effective in the treatment of CD.[10] The others are currently being investigated in randomised controlled trials (RCT).

In a Phase II RCT, mirikizumab led to higher rates of endoscopic response and remission, and clinical remission (CR) in patients with moderate-to-severe active CD.[11] Patients were randomised to 200 mg, 600 mg, or 1,000 mg intravenous mirikizumab or placebo induction. At Week 12, endoscopic response and remission rates were significantly higher in the 600 mg (37.5% and 15.6%) and 1,000 mg (43.8% and 20.3%) groups compared to placebo (10.9% and 1.6%). This effect was mirrored with regards to CR; the maintenance phase is underway.

A recent Phase II trial investigating intravenous risankizumab induction in CD randomised patients to placebo, 200 mg, or 600 mg every 4 weeks. Higher rates of CR were noted amongst those in the 600 mg group (37%) versus placebo (15%).[4] ER rates were higher at both doses of risankizumab (200 mg: 15%, 600 mg: 20%, placebo: 3%).

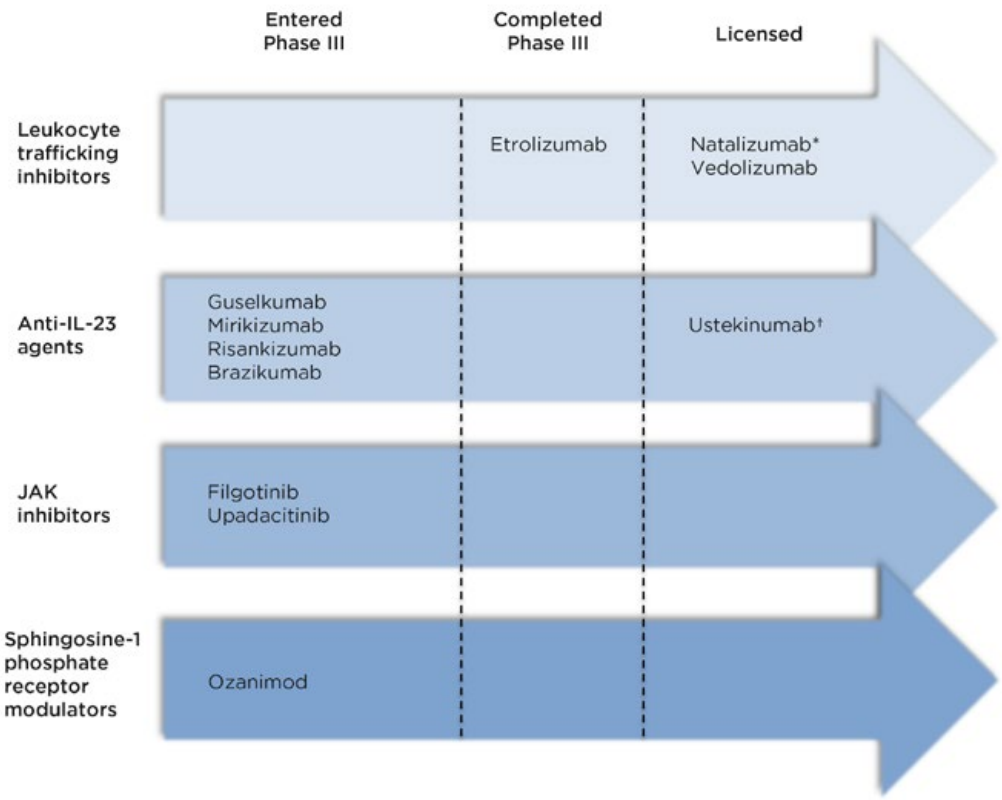

Figure 1: Recently licensed and late-stage pipeline drugs for the treatment of Crohn's disease.

*Not licensed in Europe

†Anti-IL-12 and IL-23

Notably, a near universal prior anti-TNF exposure rate was reported (93% exposed, 79% refractory). The open-label extension demonstrated Week 48 CR and ER rates of >70% and >50%, respectively.[12]

Similarly, brazikumab demonstrated a higher Week 8 clinical response rate compared to placebo (49.2% versus 26.7%; p=0.01). From a biomarker point of view, higher baseline serum concentrations of IL-22, a cytokine for which expression is induced by IL-23, were associated with greater likelihood of response.[9]

JAK Inhibitors

The downstream effects of inflammatory cytokines are often mediated by the intracellular JAK-signal transducer and activator of transcription signalling pathway. JAK inhibitors are small-molecule inhibitors of this pathway. Tofacitinib, a JAK1/3 inhibitor, has shown excellent response rates in ulcerative colitis that has not been replicated in CD (43.0% 10 mg tofacitinib twice daily versus 36.7% placebo; p=0.39).[13] Reported side effects of JAK inhibitors include infections, viral reactivation (particularly herpes zoster), dyslipidaemia, and the potential for thromboembolic events.[14-16] Two selective JAK1 inhibitors (filgotinib and upadacitinib) are currently under investigation.

The Phase II FITZROY study reported promising outcomes for filgotinib in moderately-to-severely active CD.[17] At Week 10, CR in patients on 200 mg filgotinib was double that of placebo (47% versus 23%; p=0.008). No differences were noted in endoscopic outcomes, but the maintenance phase may yield better results. There were no significant differences in AE. One episode of herpes zoster reactivation and four serious infections (3%) occurred in the filgotinib arm versus none for placebo.

The Phase II CELEST study of upadacitinib in moderate-to-severe CD was recently published.[18] Here, 220 patients were randomised to placebo

or varying doses of upadacitinib. Significantly higher rates of ER were seen at the 24 mg doses (14–22%) compared with placebo (0%), though no difference in Week 16 CR rate was seen. There were three cases of herpes zoster reactivation, but none led to treatment discontinuation. No thromboembolic events were reported. Intestinal perforation was initially reported with tofacitinib, however, only two cases were noted in patients treated with upadacitinib, both occurring in regions of active luminal CD. Larger and longer-term studies will be needed to clarify whether this is causative or a result of lack of efficacy and thus progressive disease.

Selective inhibition of JAK1 appears to result in an increased anti-inflammatory effect with an improved safety profile (reduced rates of herpes zoster reactivation and thromboembolic events). This is because of reduced impact on haematopoietic cells and natural killer cells, which occurs with JAK2 and JAK3 inhibition.[19]

Sphingosine 1-Phosphate Receptor Modulators

Interactions within lymph nodes between the five different sphingosine 1-Phosphate (S1P) receptors and their ligands govern lymphocyte migration from lymph nodes into the circulatory system. By binding to S1P1 and S1P5 receptors, ozanimod causes the internalisation of these receptors limiting the emergence of B and T lymphocytes into the bloodstream and therefore, to inflamed intestinal tissue, preventing the propagation of inflammation.[20]

Recently, the STEPSTONE trial programme reported results from their open-label, uncontrolled Phase II trial.[21] Patients with active disease received 1 mg ozanimod daily and underwent colonoscopy at Weeks 12 and 52 to assess endoscopic and clinical response. Score reductions of ≥25% and ≥50% in Simple Endoscopic Score for Crohn's Disease (SES-CD) were seen in 43.3% and 26.7% of patients respectively, with larger reductions seen in those patients with less active baseline endoscopic disease. CR (Crohn's Disease Activity Index [CDAI] decrease ≥100) and CR (CDAI <150) at Week 12 were seen in 66% and 46% of patients, respectively. Common side effects included nasopharyngitis, deranged liver function, arthralgia, rash, and hypertension. Rarely, nonselective agonism of S1P3 receptors may lead to bradycardia or macular oedema.[22,23]

Dual Biologic Therapy

Despite the advances noted above, patients with refractory disease are often not eligible for clinical trials. The use of dual biologic therapy is an emerging practice, often in patients where an additional agent is required to treat perianal disease or extraintestinal manifestations. Two case series have recently been published comprising 40 patients in total (32 with CD).[24,25] Rates of clinical and endoscopic response were 41% versus 100% and 26% versus 93%, respectively. Nine out of 12 AE were infective in aetiology; none were serious despite a high frequency of concomitant steroid and immunomodulator use.

NONPHARMACOLOGICAL THERAPIES

Stem Cell Therapy

Luminal disease

Immune reconstitution therapies, such as stem cell transplantation (SCT), have generated attention for some time within inflammatory bowel disease (IBD) circles.[26-29] Although reduction in CD activity was initially acknowledged as a collateral benefit of treatment for synchronous haematological disorders, the use of SCT as a treatment for CD has recently been explored. Following immunoablative conditioning, patients receive stem cells, either from a human leukocyte antigen (HLA) matched donor (allogeneic) or themselves, having been harvested prior to conditioning. Conceptually, allogeneic transplant resets the immune system at a genetic level, while autologous transplant replaces an aberrant immune milieu with uncommitted stem cells.[28] The ideal result is complete resolution of inflammation, but failing that, a 'resetting' of therapeutic response to previously failed therapies is also a highly valuable outcome.[26]

ASTIC was an RCT of autologous stem cell transplant in patients with CD refractory to at least three immunosuppressive agents.[28] Patients underwent transplant or standard of care, with the option of delayed transplant at

1 year. While the stringent primary outcome of treatment-free sustained remission at 1 year was not met (defined as CDAI <150, no use of corticosteroids or immunosuppressive drugs for the preceding 3 months, and no endoscopic or radiological evidence of active [erosive] disease anywhere in the gastrointestinal tract), more transplanted patients required no active treatment and had improved clinical and endoscopic disease activity than standard of care. In the subsequent pooled analysis of all patients who underwent transplant, 38% met the conventional endpoint of 3-month steroid-free CR, with 50% achieving complete endoscopic healing.[29] However, the risks associated with transplantation are significant such that the trial was prematurely discontinued, with one death as a result of sinusoidal obstructive syndrome, along with a high rate of serious AE (34 in 13 transplanted patients versus five in four control patients in the 100 days following conditioning and transplantation; median difference: 1 [0–2] more serious AE; p=0.02).[28] As a result, the ASTIClite study[26] was designed to assess the safety and effectiveness of autologous stem cell transplant using a lower intensity mobilisation and conditioning regimen. Unfortunately, this trial has also been discontinued as a result of safety concerns.[26] Accordingly, these safety concerns currently relegate SCT as a last-line treatment in refractory disease where the potential benefit is balanced against the considerable risks.

Perianal disease

Perianal disease is a common and debilitating phenotype of CD with disappointing long-term response rates to current therapies.[30] This unmet need has necessitated an ongoing search for novel therapeutic approaches. The use of mesenchymal stem cells for treatment of perianal CD was first described in 2003.[31] Adipose tissue-derived cellular aspirates are known to contain pluripotent stem cells capable of myogenic, chondrogenic, and adipogenic differentiation.[32,33] Furthermore, mesenchymal stem cells show immunomodulatory properties, migrating to sites of active inflammation and secreting anti-inflammatory cytokines and upregulating $CD4^+$ regulatory T cells (Treg).[34] Multiple clinical studies using varying protocols have shown promise.[35-38] In a Phase III placebo-controlled RCT, a significantly greater proportion of stem cell (darvadstrocel)-treated patients achieved clinical and radiographic fistula healing at Week 24 (50% versus 34%; p=0.024) with a favourable safety profile.[35] The treatment showed durability and clinical and radiographic healing occurred in 56.3% of treated patients versus 38.6% controls (p=0.01) at 1 year.[36] This resulted in the European approval of darvadstrocel, and a second, similar study is currently underway in the USA (ADMIRE-CD II). A European registry (INSPIRE) has been established to capture real-world effectiveness and safety.[39] Currently, cost remains a significant barrier to treatment uptake.

Regulatory T Cell-Based Therapies

There is increasing appreciation of the notion that IBD is a disease of immune imbalance, with excessive inflammatory stimuli relative to insufficient numbers or functioning of down-regulatory immune mediators.[40] Treg primarily function to control self-tolerance, tissue inflammation, and long-term immune homeostasis by exerting inhibitory effects on effector Treg.[41] Animal models have highlighted their integral role in protecting against intestinal inflammation specifically,[42] with transfer of Treg into mouse models of colitis resulting in amelioration of disease.[43] In humans, loss of immune homeostasis as a result of quantitative and qualitative deficiencies in Treg is recognised as a driver of inflammation in CD.[40,41] As a result, there is growing interest in the therapeutic potential of transferring healthy Treg into patients with IBD, as has been shown to be feasible with reassuring safety data in other immune mediated diseases.[41]

The effectiveness of Treg in IBD is thought to relate to their ability to home to the inflamed gut.[43] This, in itself, presents a challenge given that gut inflammation does not necessarily produce a specific antigenic target. A Phase I/IIa study using Treg specific for ovalbumin (a food antigen) in 20 patients with active CD showed promise, with at least 40% experiencing a clinical response.[44] A placebo-controlled trial of retinoic acid receptor-α-treated T-regs in CD is planned in the UK (TRIBUTE) with retinoic acid receptor-α having been shown to induce integrin α4β7 expression by Treg, potentially improving gut trafficking.[41]

Diet

In conjunction with a rapid growth in interest among patients,[45] there is increasing scientific and medical recognition of the role of diet in the pathogenesis and treatment of IBD. Postulated mechanisms by which dietary manipulation may be beneficial include microbial modulation as well as effects on intestinal cell tight junctions and the mucous membrane.[46,47] Exclusive enteral nutrition (EEN), consisting of the provision of a patient's entire nutritional requirements through a liquid formula diet, has been demonstrated to be superior to corticosteroids in the induction of remission in paediatric CD.[48-50] Despite issues with acceptability of EEN amongst adults, it has an established role in preoperative optimisation of patients with CD to reduce risk of complications,[51] and there is evidence to supports its use in the setting of a new CD diagnosis.[52,53]

The CD exclusion diet (CDED) plus partial enteral nutrition (PEN) has been compared to EEN in a paediatric RCT, showing better tolerability and equivalent Week 6 corticosteroid-free remission.[54] In the following 6 weeks, CDED plus PEN maintained remission while transfer to a free diet plus PEN did not. The CDED involved daily consumption of lean protein, starches, and fibres to act as substrates for short-chain fatty acid (SCFA)-producing bacteria. SCFA, such as butyrate, act as energy sources for colonic epithelium, perhaps explaining why low levels of SCFA may be related to IBD pathogenesis.[47] The diet also involves exclusion of foods hypothesised to contribute to dysbiosis and negatively affect intestinal barrier and immune function.

Faecal Microbiota Transplantation

Faecal microbiota transplantation (FMT) has been shown to be a potential therapeutic option for induction of remission in ulcerative colitis. A recent systematic review of four RCT showed superior pooled remission rates compared with placebo.[55] In CD, a pilot RCT randomised 24 patients, who had achieved steroid-induced CR to receive FMT or placebo via colonoscopy.[56] A reduction in Crohn's Disease Endoscopic Index of Severity (CDEIS) at Week 6 was noted in the FMT group (p=0.03). CD flare rates were numerically higher in the placebo group. Alpha diversity improved in the FMT cohort, but this was transient with normalisation at Week 14. This is consistent with earlier studies which suggested a 'wearing off' effect over time and a reported clinical benefit with sequential FMT therapies.[57,58] A number of studies have also been limited by AE or disease flares.[59] Given the heterogeneity amongst patients with CD, it seems that FMT may only benefit a proportion. However, further well-designed prospective studies in carefully selected patients are warranted to further elucidate its therapeutic role.

SURGERY

The lifetime risk of surgery for CD remains at about 80%. Five years postoperatively, 45% of patients have clinical postoperative recurrence (POR) and 20% have POR requiring further surgery. Only 22% have complete mucosal normality at 18 months.[60] Despite the increased use of biologics over the last decade, data remain conflicting as to whether this has reduced the need for surgery.[61,62]

Novel Surgical Techniques

The European Crohn's and Colitis Organisation (ECCO) guidelines recommend a stapled ileocolic side-to-side anastomosis, which is associated with fewer postoperative complications than a hand-sewn end-to-end technique.[63] However, conflicting data exist regarding rates of POR amongst these anastomotic constructions.[64,65] Novel approaches to reduce POR focus on the timing of surgery and exclusion or excision of the mesentery when constructing an anastomosis. Although mesenteric resection has been discussed for decades, uptake of this approach has been low due to the technical difficulties of safely disentangling an inflammatory mass without perforation, and achieving haemostasis whilst dividing a hypervascular and hypertrophied mesentery.[66]

A retrospective cohort (n=64) demonstrated that extensive mesenteric resection versus conventional ileo-colic resection (with limited mesenteric excision) was associated with a reduced likelihood of subsequent surgery (2.9%; n=1/34 versus 40%; n=12/30; p=0.003) and a shorter (but statistically insignificant) resection length. Here, 92% of reoperations in both cohorts occurred within 2 years. Furthermore, 10% (n=3) of cases in the conventional

cohort (versus 0% undergoing extensive excision) required a third operation resulting in a cumulative reoperation rate of 40%. The degree of macroscopic fat wrapping, assessed intraoperatively, was associated with sites of the most severe mucosal disease, clinical disease severity, and risk of surgical recurrence.[66] Further studies are under way to provide higher grade evidence with regard to the efficacy of this technique.[67,68]

The Kono-S (large lumen, hand-sewn anti-mesenteric functional end-to-end anastomosis) (Figure 2) was first performed in 2003 and has also been shown to reduce POR. A retrospective cohort study between 2003 and 2013 included 208 patients. Average Rutgeerts score was 2 at 5 years with no anastomotic surgical recurrence at 10 years. Additionally, 49% received postoperative infliximab but this did not significantly affect the surgical POR rate.[69] This led to the SupREMe-CD Study, an RCT comparing the Kono-S with conventional stapled ileocolic side-to-side anastomosis. Patients were enrolled between 2016 and 2019 (n=83) with primary or recurrent CD. All patients received 3 months of postoperative metronidazole (as tolerated) and medical prophylaxis (at clinical discretion as per their perceived recurrence risk). On multivariate analysis, the only variable that significantly contributed to disease recurrence was the type of anastomosis. Kono-S resulted in reduced endoscopic recurrence (of any grade) at 1 year (22% versus 62%, p=0.001; reduced Rutgeerts score ≥3, 13% versus 35%, p=0.001) and delayed time to clinical recurrence (hazard ratio: 0.37, p<0.001).[70] A similar USA-based trial is still recruiting, although interestingly, the design has no postoperative prophylaxis and assesses endoscopic recurrence at 3 months.[71] Results from longer-term follow-up of these trials clearly has the potential to change clinical practice.

As compelling as these data are, the pathophysiology that underlies the apparent benefit of the Kono-S remains elusive and it is unclear whether mesenteric inflammation drives mucosal inflammation or if it is a secondary phenomenon. It has been hypothesised that extensive mesenteric excision leads to greater lymph node resection, reducing inflammatory cell signalling and trafficking. Another hypothesis is that there may be mesenteric-dependent and independent CD phenotypes.[72] Perhaps the techniques above lead to a 'resetting' of the complicated bidirectional signalling pathways, described by Li et al.,[73] such that an anti-inflammatory state subsequently predominates.

Positioning of Surgery in Treatment Algorithms

The timing and indication for surgery is also critical. Long-term follow up data from the LIR!C trial have recently been presented.[74] Early laparoscopic ileocolic resection was compared with infliximab in patients with inflammatory ileocaecal CD failing conventional treatment (steroids or immunomodulation). There was no difference in the duration of effect of the initial strategy, but the use of prophylactic immunomodulation postoperatively significantly decreased the risk for additional treatment or surgery in either arm. Five years postresection, 22% were off all treatment, 52% were taking immunomodulators (prophylactic or step-up) or required steroids, and only 26% required biologic therapy. In the infliximab arm, 50% proceeded to surgery, 38% continued TNF therapy, and 14% required additional treatment (with or without continued TNF therapy). Primary surgery has already been shown to result in equivalent quality of life scores in the short term; if the chance of surgical recurrence remains negligible beyond 10 years with still only a quarter requiring biologic therapy, then surgery may become a favourable first line option in the future.[74,75]

CONCLUSION

Several novel strategies in late phase clinical trials are showing promising results. From a pharmacological perspective, both risankizumab and upadacitinib will be available shortly and for those not eligible for clinical trials the use of dual biologic therapy may increase. It is likely that a significant proportion of patients will experience loss of response and need to explore alternatives. Harnessing the host's immune response with cellular therapies is an exciting and complex field. However, it is not without risk, and at present, they remain reserved for patients with severe and refractory disease who have few, or no other viable options.

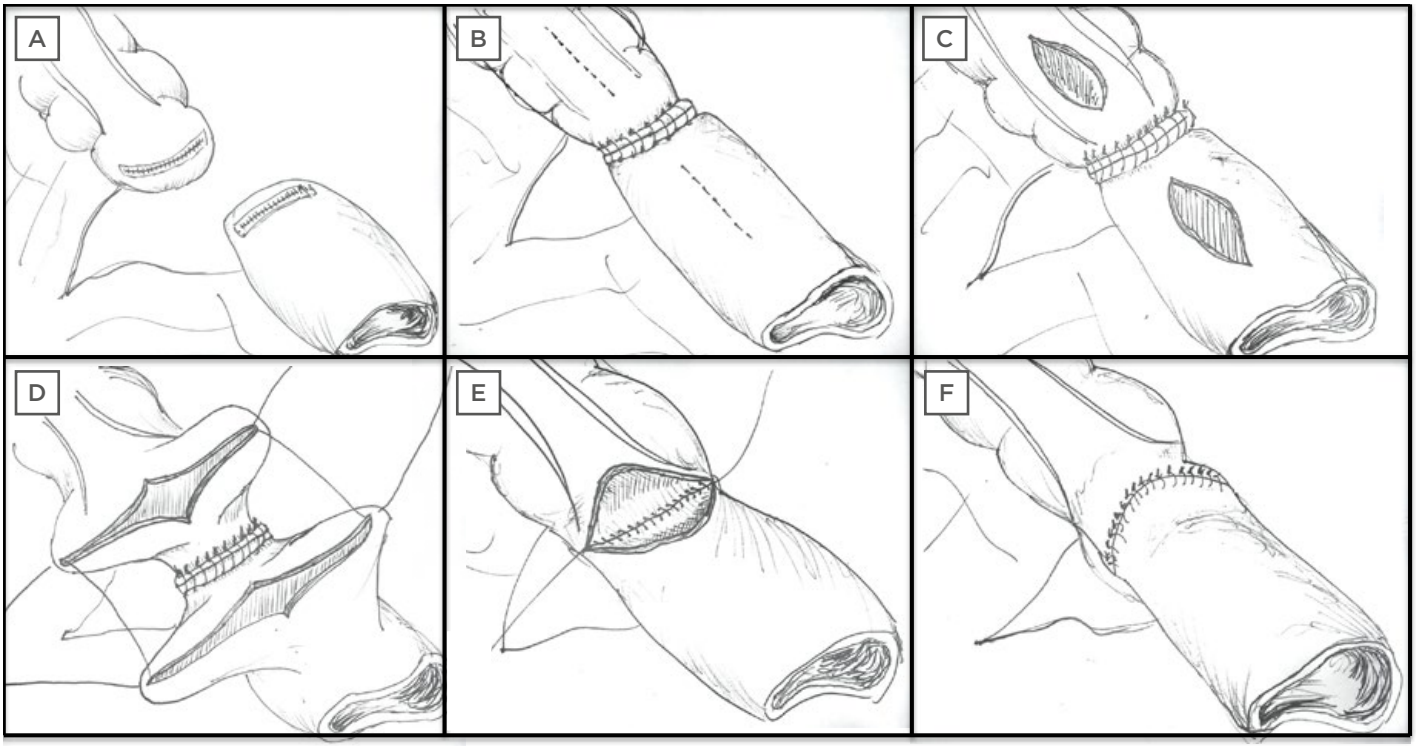

Figure 2: Steps involved in the construction of a Kono-S anastomosis.

The mesentery of the resected segment remains *in situ* but is excluded from the anastomosis with a supporting column to prevent anastomotic distortion. **A)** Resection margins, **B)** supporting column created at the posterior/mesenteric border, **C)** new enterotomy for primary anastomosis to anterior/antimesenteric border, **D–F)** suturing and formation of primary Kono-S anastomosis.

The application of stem cells for perianal disease, however, has a much more favourable risk–benefit profile, and should ongoing studies confirm efficacy, they may fundamentally alter perianal disease management pathways. Expansion of Treg cells *ex vivo* remains a challenge[41] which will need to be overcome before larger trials can take place to investigate efficacy. In comparison to cellular therapies, dietetic interventions offer a low-risk option, but higher-grade evidence is required, and it is likely that these therapies will continue to be used alongside conventional therapy or in patients who are averse to immunosuppression.

Novel surgical techniques offer the potential to avoid repeated resection. Even more compelling, may be to combine the treatments described above and perform early laparoscopic ileocolic resection in inflammatory ileocaecal CD with either a Kono-S anastomosis or extensive mesenteric excision. Bearing this in mind, one may reasonably expect even higher rates of treatment-free remission, with time to POR potentially extending beyond a decade.

References

1. Tamilarasan AG et al. Recent advances in monoclonal antibody therapy in IBD: practical issues. Frontline Gastroenterol. 2019;10(4):409-16.
2. Park SC, Jeen YT. Anti-integrin therapy for inflammatory bowel disease. World J Gastroenterol. 2018;24(17):1868-80.
3. William S et al. Etrolizumab as induction therapy in moderate to severe Crohn's disease: results from BERGAMOT cohort 1. Am J Gastroenterol. 2018;113:S3.
4. Feagan BG et al. Induction therapy with the selective interleukin-23 inhibitor risankizumab in patients with moderate-to-severe Crohn's

disease: a randomised, double-blind, placebo-controlled Phase 2 study. Lancet.2017;389(10080):1699-709.

5. Geremia Aet al. IL-23-responsive innate lymphoid cells are increased in inflammatory bowel disease. J Exp Med. 2011;208(6):1127-33.
6. Duerr RH et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. Science. 2006;314(5804):1461-3.
7. Brunda MJ et al. Antitumor and antimetastatic activity of interleukin 12 against murine tumors. J Exp Med. 1993;178(4):1223-30.
8. Stobie L et al. The role of antigen and IL-12 in sustaining Th1 memory cells *in vivo*: IL-12 is required to maintain memory/effector Th1 cells sufficient to mediate protection to an infectious parasite challenge. Proc Natl Acad Sci U S A. 2000;97(15):8427-32.
9. Sands BE et al. Efficacy and safety of MEDI2070, an antibody against interleukin 23, in patients with moderate to severe Crohn's disease: a Phase 2a study. Gastroenterology. 2017;153(1):77-86.e6.
10. Grossberg LB. A case report of successful treatment of Crohn's disease and psoriasis with guselkumab. Inflamm Bowel Dis. 2019;25(7):e84.
11. Sands B et al. Efficacy and safety of mirikizumab (LY3074828) in a Phase 2 study of patients with Crohn's disease. United European Gastroenterol J. 2019;7(8):92.
12. Ferrante M et al. Long-term safety and efficacy of risankizumab treatment in patients with Crohn's disease: final results from the Phase 2 open-label extension study. J Crohns Colitis. 2020;14(Suppl 1):S024-5.
13. Panés J et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two Phase IIb randomised placebo-controlled trials. Gut. 2017;66(6):1049-59.
14. Kavanaugh A et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). Ann Rheum Dis. 2017;76(6):1009-19.
15. Sandborn WJ et al. Venous thromboembolic events in the tofacitinib ulcerative colitis clinical development programme. Aliment Pharmacol Ther. 2019;50(10):1068-76.
16. Winthrop KL et al. Herpes zoster and tofacitinib therapy in patients with rheumatoid arthritis. Arthritis Rheumatol. 2014;66(10):2675-84.
17. Vermeire S et al. Clinical remission in patients with moderate-to-severe Crohn's disease treated with filgotinib [the FITZROY study]: results from a Phase 2, double-blind, randomised, placebo-controlled trial. Lancet 2017;389(10066):266-75.
18. Sandborn WJ et al. Efficacy and safety of upadacitinib in a randomized trial of patients with Crohn's disease. Gastroenterology. 2020;158(8):2123-38.e8.
19. Danese S et al. JAK selectivity for inflammatory bowel disease treatment: does it clinically matter? Gut. 2019;68:1893-9.
20. Hindryckx P et al. The expanding therapeutic armamentarium for inflammatory bowel disease: how to choose the right drug[s] for our patients? J Crohns Colitis. 2017;12(1):105-19.
21. Feagan BG et al. Early histological improvement demonstrated with oral ozanimod in patients with moderately to severely active Crohn's disease in the STEPSTONE trial. J Crohns Colitis. 2019;13(Suppl 1):S450.
22. Danese S et al. Targeting S1P in inflammatory bowel disease: new avenues for modulating intestinal leukocyte migration. J Crohns Colitis. 2018;12(Suppl 2):S678-86.
23. Feagan BG, Sandborn WJ, Danese S, et al. Ozanimod induction therapy for patients with moderate to severe Crohn's disease: a single-arm, Phase 2, prospective observer-blinded endpoint study. Lancet Gastroenterol Hepatol. 2020;5(9):819-28.
24. Ribaldone DG et al. Dual biological therapy with anti-TNF, vedolizumab or ustekinumab in inflammatory bowel disease: a systematic review with pool analysis. Scand J Gastroenterol. 2019;54(4):407-13.
25. Yang E et al. Efficacy and safety of simultaneous treatment with two biologic medications in refractory Crohn's disease. Aliment Pharmacol Ther. 2020;51(11):1031-8.
26. Snowden JA et al. Autologous stem cell transplantation in refractory Crohn's disease - low intensity therapy evaluation (ASTIClite): study protocols for a multicentre, randomised controlled trial and observational follow up study. BMC gastroenterol. 2019;19(1):82.
27. Burt RK et al. Autologous nonmyeloablative hematopoietic stem cell transplantation in patients with severe anti-TNF refractory Crohn disease: long-term follow-up. Blood. 2010;116(26):6123-32.
28. Hawkey CJ et al. Autologous hematopoetic stem cell transplantation for refractory Crohn disease: a randomized clinical trial. JAMA. 2015;314(23):2524-34.
29. Lindsay JO et al. Autologous stem-cell transplantation in treatment-refractory Crohn's disease: an analysis of pooled data from the ASTIC trial. Lancet Gastroenterol Hepatol. 2017;2(6):399-406.
30. Molendijk I et al. Disappointing durable remission rates in complex Crohn's disease fistula. Inflamm Bowel Dis. 2014;20(11):2022-8.
31. García-Olmo D et al. Autologous stem cell transplantation for treatment of rectovaginal fistula in perianal Crohn's disease: a new cell-based therapy. Int J Colorectal Dis. 2003;18(5):451-4.
32. Mizuno H et al. Myogenic differentiation by human processed lipoaspirate cells. Plast Reconstr Surg. 2002;10(1)9:199-209.
33. Zuk PA et al. Multilineage cells from human adipose tissue: implications for cell-based therapies. Tissue Eng. 2001;7(2):211-28.
34. Carvello M et al. Mesenchymal stem cells for perianal Crohn's disease. Cells 2019;8(7):764.
35. Panés J et al. Expanded allogeneic adipose-derived mesenchymal stem cells (Cx601) for complex perianal fistulas in Crohn's disease: a Phase 3 randomised, double-blind controlled trial. Lancet. 2016;388(10051):1281-90.
36. Panés J et al. Long-term efficacy and safety of stem cell therapy (Cx601) for complex perianal fistulas in patients with Crohn's disease. Gastroenterology. 2018;154(5):1334-42. e4.
37. Dietz AB et al. Autologous mesenchymal stem cells, applied in a bioabsorbable matrix, for treatment of perianal fistulas in patients with Crohn's disease. Gastroenterology. 2017;153(1):59-62. e2.
38. Molendijk I et al. Allogeneic bone marrow–derived mesenchymal stromal cells promote healing of refractory perianal fistulas in patients with Crohn's disease. Gastroenterology. 2015;149(4):918-27. e6.
39. Zmora O et al. INSPIRE: design and implementation aspects of a registry of complex perianal fistulas in Crohn's disease patients treated with darvadstrocel. J Crohn's and Colitis. 2019;13:S357-S8.
40. Maul J et al. Peripheral and intestinal regulatory CD4+ CD25high T cells in inflammatory bowel disease. Gastroenterology. 2005;128(7):1868-78.
41. Clough JN et al. Regulatory T-cell therapy in Crohn's disease: challenges and advances. Gut. 2020;69(5):942-52.
42. Read S et al. Cytotoxic T lymphocyte–associated antigen 4 plays an essential role in the function of CD25+ CD4+ regulatory cells that control intestinal inflammation. J Exp Med. 2000;192(2):295-302.
43. Mottet C et al F. Cutting edge: cure of colitis by CD4+ CD25+ regulatory T cells. J Immunol. 2003;170(8):3939-43.

44. Desreumaux P et al. Safety and efficacy of antigen-specific regulatory T-cell therapy for patients with refractory Crohn's disease. Gastroenterology. 2012;143(5):1207-17. e2.
45. Limdi JK et al. Dietary practices and beliefs in patients with inflammatory bowel disease Inflamm Bowel Dis. 2015;22(1):164-70.
46. Levine A et al. Evolving role of diet in the pathogenesis and treatment of inflammatory bowel diseases. Gut. 2018;67(9):1726-38.
47. Levine A et al. Dietary guidance for patients with inflammatory bowel disease from the international organization for the study of inflammatory bowel disease. Clin Gastroenterol Hepatol. 2020;18(6):1381-92.
48. Grover Z, Lewindon P. Two-year outcomes after exclusive enteral nutrition induction are superior to corticosteroids in pediatric Crohn's disease treated early with thiopurines. Dig Dis Sci. 2015;60(10):3069-74.
49. Levine A et al. Comparison of outcomes parameters for induction of remission in new onset pediatric Crohn's disease: evaluation of the porto IBD group "growth relapse and outcomes with therapy" (GROWTH CD) study. Inflamm Bowel Dis. 2014;20(2):278-85.
50. Swaminath A et al. Systematic review with meta-analysis: enteral nutrition therapy for the induction of remission in paediatric Crohn's disease. Aliment Pharmacol Ther. 2017;46(7):645-56.
51. Heerasing N et al. Exclusive enteral nutrition provides an effective bridge to safer interval elective surgery for adults with Crohn's disease. Aliment Pharmacol Ther. 2017;45(5):660-9.
52. Narula N et al. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev. 2018;4(4):CD000542.
53. Lamb CA et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut. 2019;68(Suppl 3):s1-106.
54. Levine A et al. Crohn's disease exclusion diet plus partial enteral nutrition induces sustained remission in a randomized controlled trial. Gastroenterology. 2019;157(2):440-50.e8.
55. Costello SP et al. Systematic review with meta-analysis: faecal microbiota transplantation for the induction of remission for active ulcerative colitis. Aliment Pharmacol Ther. 2017;46(3):213-24.
56. He Z et al. Multiple fresh fecal microbiota transplants induces and maintains clinical remission in Crohn's disease complicated with inflammatory mass. Sci Rep. 2017;7(1):4753.
57. Li P et al. Timing for the second fecal microbiota transplantation to maintain the long-term benefit from the first treatment for Crohn's disease. Appl Microbiol Biotechnol. 2019;103(1):349-60.
58. Wang H et al. The safety of fecal microbiota transplantation for Crohn's disease: findings from a long-term study. Adv Ther. 2018;35(11):1935-44.
59. Gutin L et al. Fecal microbiota transplant for Crohn disease: a study evaluating safety, efficacy, and microbiome profile. United European Gastroenterol J. 2019;7(6):807-14.
60. De Cruz P et al. Crohn's disease management after intestinal resection: a randomised trial. Lancet. 2015;385(9976):1406-17.
61. Zhao M et al. Treatment outcomes of inflammatory bowel disease in the biological era—a nationwide retrospective cohort study in three Nordic countries: results from the TRINordic study. J Crohns Colitis. 2020;14(Suppl 1):S036-7.
62. Frolkis AD et al. Risk of surgery for inflammatory bowel diseases has decreased over time: a systematic review and meta-analysis of population-based studies. Gastroenterology. 2013;145(5):996-1006.
63. Gionchetti P et al. 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 2: surgical management and special situations. J Crohns Colitis. 2017;11(2):135-49.
64. Guo Z et al. Comparing outcomes between side-to-side anastomosis and other anastomotic configurations after intestinal resection for patients with Crohn's disease: a meta-analysis. World J Surg. 2013;37(4):893-901.
65. Simillis C et al. Meta-analysis of the role of granulomas in the recurrence of Crohn disease. Dis Colon Rectum. 2010;53(2):177-85.
66. Coffey CJ et al. Inclusion of the mesentery in ileocolic resection for Crohn's disease is associated with reduced surgical recurrence. J Crohns Colitis. 2018;12(10):1139-50.
67. Jewish General Hospital. Extended mesenteric excision in ileocolic resections for Crohn's disease. NCT04266600. https://clinicaltrials.gov/ct2/show/NCT04266600.
68. Li Y et al. Mesenteric excision surgery or conservative limited resection in Crohn's disease: study protocol for an international, multicenter, randomized controlled trial. Trials. 2020;21(1):210.
69. Kono T et al. Kono-S anastomosis devised for surgical prophylaxis of anastomotic recurrence in Crohn's disease: a multicenter study in Japan and the United States. Dis Colon Rectum. 2015;58:e121-2.
70. Luglio G et al. Surgical prevention of anastomotic recurrence by excluding mesentery in Crohn's disease: the SuPREMe-CD study - a randomized clinical trial. Ann Surg. 2020;272(2):210-7.
71. Weill Medical College of Cornell University. Study of the Kono-S anastomosis versus the side-to-side functional end anastomosis. NCT03256240. https://clinicaltrials.gov/ct2/show/NCT03256240.
72. Wickramasinghe D, Warusavitarne J. The role of the mesentery in reducing recurrence after surgery in Crohn's disease. Updates Surg. 2019;71(1):11-2.
73. Li Y et al. The role of the mesentery in Crohn's disease: the contributions of nerves, vessels, lymphatics, and fat to the pathogenesis and disease course. Inflamm Bowel Dis. 2016;22(6):1483-95.
74. Stevens T et al. Reduced need for surgery and medical therapy after early ileocaecal resection for Crohn's disease: long-term follow-up of the LIR!C trial. J Crohns Colitis. 2020;14(Suppl 1):S003-4.
75. Ponsioen CY et al. Laparoscopic ileocaecal resection versus infliximab for terminal ileitis in Crohn's disease: a randomised controlled, open-label, multicentre trial. Lancet Gastroenterol Hepatol. 2017;2(11):785-92.

Pancreatic β-Cell Senescence: Mechanisms and Association with Diabetes

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Abstract

Senescence occurs as a part of the cellular response to different stressors. With increasing age, continuous exposure to stressors leads to age-induced senescence. Pancreatic β-cell proliferation and glucose homeostasis also decrease with age, which results in a decrease in β cell mass and, eventually, the possible development of diabetes. This process is mediated through impaired cell cycle regulators, along with specific increases in cell cycle inhibitors, telomere shortening, and defective DNA repair mechanisms. Diabetes contributes to β-cell senescence through hyperglycaemia, dyslipidaemia, oxidative stress, and inflammation. β cells isolated from patients with Type 2 diabetes mellitus have been shown to have senescence markers, such as senescence-associated secretory phenotype genes and β-galactosidase. In this paper, the authors discuss the mechanisms of cellular senescence, how senescence is impacted by the diabetic microenvironment, and the possible mechanisms and factors contributing to β-cell senescence.

INTRODUCTION

Cellular senescence is a stress response to remove cell damage through immune system activation. The term 'senescence' was originally coined in 1961 by Hayflick and Moorhead.[1] Insufficient insulin production and secretion are key features of diabetes. Normal ageing leads to a decline in the replication of insulin-producing β cells in the pancreatic islets.[2] However, a dysfunctional response affecting these β cells has been shown to be involved in diabetes pathogenesis. Decreased insulin secretion, owing to pancreatic cell dysfunction, has been linked to numerous factors, such as increased oxidative stress, endoplasmic reticulum stress, autoimmunity, and inflammation.[2] Given that these are common characteristics of cellular senescence, it has been suggested that pancreatic β-cell dysfunction occurs through the induction of cellular senescence.[3] In this review, the authors provide evidence for the involvement

of cellular senescence in diabetes pathogenesis, its underlying molecular mechanisms, and the relationship between the diabetic microenvironment and β-cell senescence.

THE MECHANISM OF CELLULAR SENESCENCE

In aged tissue, altered gene expression promotes an increase in the secretion of proteins relevant to senescence. These proteins include senescence-associated secretory phenotype (SASP) proteins and senescence messaging secretome (SMS) proteins, such as amphiregulin, EGF, BMP, FGF, VEGF, and WNT. Csf1, IL8, Cxcl15, and Ccl2 proteins activate immune cells, including natural killer cells and macrophages. Moreover, the secreted proteins upregulate proteases (MMP, elastin, plasminogen activators, and collagen), survival factors, immune modulators, chemokines, and cytokines (for example, CXCL1, IL-6, IL-1β, IL-8, CXCL2, IL-1α, and CCR2 receptors).[4] Lastly, SASP proteins shed cell surface molecules, inflammatory growth factors, and exosomes in the tissues' microenvironment, increasing the overall stress response.[4] As DNA damage causes senescence through reactive oxygen species or oncogenic signalling,[1] oncogenic activation of RAS protein results in DNA damage, telomere shortening, and oxidative stress. DNA damage activates the DNA damage response, inducing p21Waf1/Cip1 and p16Ink41 cyclin-dependent kinase inhibitors, leading to cell cycle arrest (Table 1).[5-9]

Table 1: Proteins involved in the stimulation of cell senescence signalling pathways.

Protein name	Target gene	Senescence mechanisms	Function and pathway	References
Ubiquitin-conjugating enzyme E2 C	*UBE2C*	SASP Oxidative stress-induced senescence DNA damage/ telomere stress-induced senescence	*In vitro* catalyses 'Lys-11'- and 'Lys-48'-linked polyubiquitination Acts as an essential factor of the APC/ Cand mitotic exit Protein involved in growth arrest	Young, Narita,[6] 2009
Histone H2B Type 1-K	*H2BC12*	Oxidative stress-induced senescence SASP DNA damage/ telomere stress-induced senescence Oncogene-induced senescence	G2/M DNA damage checkpoint Results from errors of replication	Young, Narita,[6] 2009
Transcription factor E2F3	*E2F3*	Oncogene-induced senescence Oxidative stress-induced senescence DNA damage/ telomere stress-induced senescence SASP	Transcription activator found in the promoter region of the cell cycle regulation and DNA replication genes The DRTF1/E2F complex functions in the regulation of the cell cycle G1/S phase	Young, Narita,[6] 2009

Table 1 continued.

Protein name	Target gene	Senescence mechanisms	Function and pathway	References
Protein MDM4	*MDM4*	Oncogene-induced senescence Oxidative stress-induced senescence SASP DNA damage/ telomere stress-induced senescence	Inhibits p53/TP53- and TP73/p73-mediated cell cycle arrest	Young, Narita,[6] 2009
E3 ubiquitin-protein ligase MDM2	*MDM2*	Oncogene-induced senescence Oxidative stress-induced senescence SASP DNA damage/ telomere stress-induced senescence	Inhibits p53/TP53- and p73/TP73-mediated cell cycle arrest	Young, Narita,[6] 2009
Cellular tumour antigen p53	*TP53*	Oxidative stress-induced senescence Formation of SAHF Oncogene-induced senescence DNA damage/ telomere stress-induced senescence	Induces growth arrest Plays a role in cell cycle regulation Inhibits CDK7 kinase activity during DNA damage to stop cell cycle progression In addition, phosphorylation of TP53 by MAPKAPK5 (PRAK)-activated downstream MAP3K5-p38 MAPK signalling activates TP53 and contributes to cellular senescence	Moiseeva et al.,[7] 2009
Retinoblastoma-associated protein	*RB1*	Oncogene-induced senescence Formation of SAHF	Regulates G0-G1 transition when phosphorylated by CDK3/cyclin-C The underphosphorylated, active form of RB1 interacts with E2F1 and represses its transcription activity, leading to cell cycle arrest	Baek, Ryeom,[8] 2017

Table 1 continued.

Protein name	Target gene	Senescence mechanisms	Function and pathway	References
Transcription factor Sp1	*SP1*	Oncogene-induced senescence SASP Oxidative stress-induced senescence	Plays a role in DNA damage response Regulates RNF112 to protect cells in response to oxidative stress	Baek, Ryeom,[8] 2017
Polyubiquitin-B	*UBB*	Oncogene-induced senescence SASP Oxidative stress-induced senescence	Has different functions depending on the Lys residue Lys-11-linked is involved in cell cycle regulation Lys-70-linked is involved in DNA damage responses	Young, Narita,[6] 2009; Baek, Ryeom,[8] 2017
Polyubiquitin-C	*UBC*	Oncogene-induced senescence SASP Oxidative stress-induced senescence DNA damage/ telomere stress-induced senescence	Cell cycle check point Has different functions depending on the Lys residue Lys-11-linked is involved in cell cycle regulation Lys-70-linked is involved in DNA damage responses	Young, Narita,[6] 2009; Baek, Ryeom,[8] 2017
Cyclin-dependent kinase 2	*CDK2*	SASP DNA damage/ telomere stress-induced senescence	Cyclin E/CDK2 prevents oxidative stress-mediated, Ras-induced senescence by phosphorylating MYC Involved in G1-S phase DNA damage checkpoint that prevents cells with damaged DNA from initiating mitosis	Young, Narita,[6] 2009
Cyclin-dependent kinase 4	*CDK4*	Oncogene-induced senescence SASP Oxidative stress-induced senescence	Promotes cell cycle in G1/S transition and regulates the cell cycle during the G1/S transition Evasion of oncogene-induced senescence due to defective p16INK4A binding to CDK4 and CDK6	Young, Narita,[6] 2009; Baek, Ryeom,[8] 2017

Table 1 continued.

Protein name	Target gene	Senescence mechanisms	Function and pathway	References
Mitogen-activated protein kinase 3	*MAPK3*	Oncogene-induced senescence Oxidative stress-induced senescence SASP	MAPK1/ERK2 and MAPK3/ERK1 are two MAPK that play an important role in the MAPK/ERK cascade. This cascade has a role in the initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells	Young, Narita,[6] 2009; Baek, Ryeom,[8] 2017
Mitogen-activated protein kinase 1	*MAPK1*	Oxidative stress-induced senescence DNA damage/ telomere stress-induced senescence	MAPK1/ERK2 and MAPK3/ERK1 are the two MAPK that play an important role in the MAPK/ ERK cascade. The MAPK/ERK cascade also plays a role in initiation and regulation of meiosis, mitosis, and postmitotic functions in differentiated cells by phosphorylating a number of transcription factors	Agger K et al.,[9] 2009
Cyclin-dependent kinase 4 inhibitor C	*CDKN2C*	Oncogene-induced senescence SASP Oxidative stress-induced senescence	Inhibits cell growth and proliferation, depending on endogenous retinoblastoma protein RB	Young, Narita,[6] 2009; Baek, Ryeom,[8] 2017; Agger K et al.,[9] 2009
Cyclin-dependent kinase 4 inhibitor D	*CDKN2D*	Oncogene-induced senescence SASP Oxidative stress-induced senescence	Inhibits CDK4 and CDK6 in T cells, promoting cell cycle regulation Involved in cell cycle arrest	Young, Narita,[6] 2009; Baek, Ryeom,[8] 2017; Agger K et al.,[9] 2009
Ubiquitin-40S ribosomal protein S27a	*RPS27A*	Oncogene-induced senescence SASP Oxidative stress-induced senescence	Cell cycle check point Has different functions depending on the Lys residue Lys-11-linked is involved in cell cycle regulation Lys-70-linked is involved in DNA damage responses	Young, Narita,[6] 2009; Baek, Ryeom,[8] 2017; Agger K et al.,[9] 2009

Table 1 continued.

Protein name	Target gene	Senescence mechanisms	Function and pathway	References
Ubiquitin-60S ribosomal protein L40	*UBA52*	Oncogene-induced senescence SASP Oxidative stress-induced senescence	Cell cycle check point Has different functions depending on the Lys residue Lys-11-linked is involved in cell cycle regulation Lys-70-linked is involved in DNA damage responses	Young, Narita,[6] 2009; Baek, Ryeom,[8] 2017; Agger K et al.,[9] 2009
Cyclin-dependent kinase 6	*CDK6*	Oncogene-induced senescence SASP Oxidative stress-induced senescence	Promotes initiation of cell cycle exit during cell differentiation, preventing cell proliferation Delays senescence Promotes the proliferation of beta cells in pancreatic islets of Langerhans	Young, Narita,[6] 2009; Baek, Ryeom,[8] 2017; Agger K et al.,[9] 2009
Transcription factor E2F1	*E2F1*	Oncogene-induced senescence Oxidative stress-induced senescence	Transcription activator binds DNA with DP proteins through the E2 recognition site, 5′-TTTC[CG]CGC-3′, found in the promoter region of genes involved in cell division regulation	Agger K et al.[9] 2009
Histone H2A Type 1-B/E	*H2AC4*	Oxidative stress-induced senescence SASP DNA damage/telomere stress-induced senescence	Core component of nucleosome Also plays a role in cell transcriptional regulation	Young, Narita,[6] 2009; Agger K et al.[9] 2009
Histone H2B Type 1-J	*H2BC11*	Oxidative stress-induced senescence SASP DNA damage/telomere stress-induced senescence	Core component of nucleosome Also plays a role in cell transcriptional regulation	Young, Narita,[6] 2009; Agger K et al.[9] 2009

Table 1 continued.

Protein name	Target gene	Senescence mechanisms	Function and pathway	References
Histone H2A.Z	*H2AZ1*	Oxidative stress-induced senescence SASP DNA damage/ telomere stress-induced senescence	Cell cycle regulation	Young, Narita,[6] 2009; Agger K et al.[9] 2009
Histone H2A-Bbd type 1 H2AB1	*H2AB1*	Oxidative stress-induced senescence SASP DNA damage/ telomere stress-induced senescence	Cell cycle and transcriptional regulation	Young, Narita,[6] 2009; Agger K et al.[9] 2009
Histone H2AX	*H2AFX*	Oxidative stress-induced senescence SASP DNA damage/ telomere stress-induced senescence	Required for checkpoint-mediated arrest of cell cycle progression	Young, Narita,[6] 2009; Agger K et al.[9] 2009
Cyclin-A2	*CCNA2*	SASP DNA damage/ telomere stress-induced senescence	Cyclin, which controls both the G1/S and the G2/M transition phases of the cell cycle	Young, Narita,[6] 2009
Histone H2A Type 1-D	*H2AC7*	Oxidative stress-induced senescence SASP DNA damage/ telomere stress-induced senescence	Cell division and transcriptional regulation	Young, Narita,[6] 2009; Agger K et al.[9] 2009
Histone H2B Type 1-O	*HIST1H2BO*	Oxidative stress-induced senescence SASP DNA damage/ telomere stress-induced senescence	Core component of nucleosome Also plays a role in cell transcriptional regulation	Young, Narita,[6] 2009; Agger K et al.[9] 2009

APC/C: Anaphase promoting complex/cyclosome; SAHF: senescence-associated heterochromatin foci; SASP: senescence-associated secretory phenotype.

THE DIABETIC MICROENVIRONMENT MEDIATES CELLULAR SENESCENCE

The diabetic microenvironment is characterised by chronic hyperglycaemia; imbalanced lipid breakdown (dyslipidaemia); increased formation of reactive oxygen species;[10] and a distinct, reduced antioxidant potency that leads to cellular inflammation. This state of simultaneous glucotoxicity, lipotoxicity, and inflammation paves the way for the micro- and macrovascular complications of diabetes.[11]

Aguayo-Mazzucato et al.[12] isolated β cells from 8-month-old rats based on the activity of the senescence marker β-galactosidase (β-gal). β-gal-positive cells showed upregulation of senescence genes and a decline in β cell markers, such as Ins1, Mafa, Nkx6.1, and Pdx1. SASP genes, such as *TNF* and *CXCL1*, were upregulated in β-gal-positive cells. An increase in p16Ink4a was also observed in conditioned media from β-gal-positive cells. In β-gal-positive cells in mouse models of insulin resistance, SASP were acquired through either continuous administration of S961, an insulin receptor blocker, or through a high-fat diet. In the S961 model, there was a reversal of all the previous parameters, including a decrease in SASP gene expression back to the normal level within 2 weeks of terminating the drug. When the research group tested senolytic therapy by administering B/B homodimeriser, which causes a loss of cells expressing p16Ink4a, an improvement of β-cell senescence and a reduction of SASP parameters in aged mice were achieved. Glucose-mediated insulin secretion was also improved.[12]

β-gal positivity was higher in islet cells of older patients and patients with Type 2 diabetes mellitus. SASP, such as CCL4 and IL-6, beside p16Ink4a, were increased in β-gal-positive cells. The senescence marker insulin-like growth factor 1 receptor (IGF1R) was found to be higher in islets from patients with Type 2 diabetes mellitus <40 years of age; this denotes premature β-cell senescence. Additionally, the expression of p53-binding protein 1 (p53BP1) was higher in islets from patients with Type 2 diabetes mellitus.[13] Aguayo-Mazzucato et al.[12] reported a differential expression in age-related genes in young compared to older β cells; whereas Kcnq5 and Fgfr1 were upregulated in younger mice, while IGF1R, CD99, and Bambi were upregulated in older mice. An observed age-dependant increase in IGF1R staining in the human pancreata was also observed,[13] and aged islets displayed better staining with IGF1R, which was associated with defective insulin secretion.[13] This may indicate premature β-cell senescence in patients with Type 2 diabetes mellitus.[13] These markers, IGF1R and p53BP1, showed heterogenic distribution in older β cells of the same islet and between islets.[13]

MECHANISM OF AGEING OF β CELLS

Age-Associated β-Cell Growth Arrest

The balance between β-cell proliferation and growth arrest is important in maintaining a proper β cell mass sufficient for glucose haemostasis. While β cells normally have a low replication rate, under certain conditions, such as pancreatic injury, their proliferation increases to cope with the pancreas' deficient metabolic function.[14] Physiologically and with increased age there is a decrease in β cell replication.[15] Similarly, with age the human pancreata showed deteriorated β-cell replication[15] and a decrease in the expression of cell cycle and cell proliferation regulator FoxM1.[16] Also, with β-cell ageing, there is a decrease in the expression of pdx1, the transcription factor which is responsible for β-cell division and maturation.[15] Isolated human pancreata from healthy donors aged 7–66 years showed a decline in β-cell proliferation starting at age 16 years.[15] Also, pancreata at autopsy from 124 individuals with diabetes and obesity aged 61–83 years showed reduced β-cell replication.[17] The relationship between the decrease in β cell mass and signs of diabetes is still under investigation. In healthy donors with impaired fasting glucose level, there was a decrease in β cell mass.[17] In another study, there was a reduction in β cell mass by 24% in patients with diabetes after 5 years of disease onset, which became worse with time.[18] This decrease in β cell mass may be inherent because of defects in cell cycle regulators such as *CDKN2A* and *CDKN2B*. These genes reduce β-cell proliferation as a compensatory mechanism during maturation.[19] β-cell dysfunction associated with diabetes and defective insulin secretion leads to impaired glucose clearance, further causing a reduction in β cell mass.[20]

Mechanism of Age-Related β-Cell Growth Arrest: Cell Cycle Mechanism

Any insult to the genetic material caused by stress leads to suspension of the cell cycle. The passage of the cell cycle from G1 to S, then from S to G2, and then finally to mitosis, is regulated by cell cycle checkpoints. These checkpoints grant the cells the time needed to correct any damage to their DNA. This mechanism prevents the passage of damaged or mutated genetic materials to the next cell generations. A set of enzymes called cyclin-dependent kinases (CDK) control and regulate the cell cycle.[21] CDK are protein kinases that are only active when complexed with their cyclin subunit and are inactive when alone.[22]

Mechanism of Age-Related β-Cell Growth Arrest: Cell Cycle Regulation in β Cells

β cell cycle activators

D-cyclins are cycle activators which regulate cell proliferation by regulating the cell's progress from the G to the S phase.[23] D-cyclins include D1–3 cyclins that complex with CDK4. Cyclin D2-null mice suffer from decreases in islet mass and, later in life, diabetes owing to a severe reduction in β-cell proliferation.[23] In the absence of cyclin D2, cyclin D1 could partially replace cyclin D2. In the double mutant form, severe reductions occur in β-cell proliferation and diabetes follows early in life. Cyclin D is upregulated, as is β-cell proliferation, in murine β cells following partial pancreatectomy, which serves as a model of β-cell regeneration. Transgenic mice in which cyclin D1 or D2 were overexpressed showed enhanced β-cell proliferation.[24,25] Significant increases in β-cell proliferation were observed in mice that expressed a single point mutation at site 280 of cyclin D2, promoting its consistent activation, regardless of age. Using adenovirus to overexpress cyclin D1 in human and rat islets significantly enhanced β-cell proliferation. In contrast to rodent cells, human β cells showed high expression of cyclin D3, with lower expression of cyclin D1 or D2.[26] When overexpression of cyclin D3 in human islets *in vitro* was complexed with CDK6, but not other cyclins, a significant increase in β-cell proliferation was observed.[26]

Cyclin-CDK interactions led to a reduction in cell cycle inhibitors, thus inducing cell proliferation.[27] The β cell mass of *CDK4*-null mice showed a severe reduction, both postnatally and at 17 weeks, reaching only 10% when compared to the β cell mass of the wild type.[28] *CDK4*-knockout mice showed smaller organs and pancreata, indicating replication defects;[29] and developed diabetes because of their defective β-cell replication, causing a defective β cell mass. Interestingly, this effect was not due to apoptosis or autoimmunity.[29] Transgenic mice with mutated *CDK4*, so as not to be inhibited by cell cycle inhibitor p16INK4a, showed up to a 10-fold increase in islet size. However, this increase was not associated with an increase in glucose-induced insulin secretion.[30] Sertad1 (Sei1) is a protein that is expressed in pancreatic islets and aids cyclin/CDK4 stabilisation through the inhibition of p16INK4a.[31] Sei1-null mice showed defective insulin production owing to a reduced islet cell mass, which was also found to be independent of apoptosis. Using adenovirus to deliver CDK4 into human or rat β cells resulted in enhanced β-cell proliferation, which further increased when accompanied by cyclin D1 transfection.[32] Knock-in mice in which CDK4 was upregulated showed enhanced β-cell proliferation and β-cell hyperplasia.[30] Using CDK4R24C, β-cell specific knock-in mice also showed the previous results.[33] CDK4 knock-in also resulted in the reversal of diabetes in obese mouse models (db/db41) through the enhancement of β-cell replication.[34] This replication was improved after partial pancreatectomy in CDK4R24C mice,[35] indicating the therapeutic potential of CDK4.[36]

The *CDK5R1* gene encodes p35, which is responsible for the activation of cdk5. In Type 2 diabetes mellitus, CDK5R1 becomes hypomethylated and consequently activated, leading to upregulation of CDK5. CDK5 activation causes defective expression of Pdx1 that subsequently leads to failed mature β-cell maintenance and may lead to a form of maturity-onset diabetes of the young (MODY4).[36]

CDK6 was not detected in murine islets but was shown to be critical for β-cell replication in humans.[26] The effect of age on cyclin D and CDK levels has not yet been examined. CDK2 is expressed in pancreatic islets, but its level is downregulated with age.[28] In mice, CDK2 level decreased significantly at 11 months of age in comparison to a younger age.[37] Deletion of CDK2 resulted in enhanced islet senescence and, eventually, diabetes.[38]

β cell cycle inhibitors and β-cell senescence

Cell cycle inhibitors include the INK4/ARF family: p16INK4a, p15INK4b, p18INK4c, and p19INK4d; as well as the CIP/KIP family: p21Cip1, p27Kip1, and p57Kip2. The INK4/ARF family interrupts D cyclin binding to CDK4 and CDK6, while the CIP/KIP family acts by binding to cyclin D, E, and A, and CDK.[39] Overexpression of murine CDK inhibitors (CDKI), through induced overexpression or inhibition of their epigenetic regulators, resulted in cell cycle arrest and β-cell ageing.[40] On the other hand, loss of CDKI or their epigenetic regulators led to islet hyperplasia.[41,42]

β cell cycle inhibitors and β-cell senescence: p27Kip1

Postnatally, the level of p27 was found to be upregulated in mature β cells. Postnatal deletion of p27 resulted in a significant increase in β-cell proliferation and a consequent increase in islet mass;[43] no increase in islet mass or hyperplasia was observed in adult mice, indicating a state of postnatal β-cell quiescence, mediated by cell cycle arrest. After induction of diabetes using streptozotocin, p27-null mice showed increased β-cell proliferation and reversal of diabetes.[42] In two other diabetes models, accumulation of p27 in the nucleus was noted in β cells.[41] Additionally, p27-deficient mice exhibited enhanced glucose tolerance that was further improved by the deletion of p27.[44]

In this model, the deletion of p27 allowed for β-cell replication and prevented the development of diabetes.[44] Using the mouse model of overexpressed p27, specifically RIP-CDKn1b in β cells, a significant decrease in cell replication was shown, resulting in the development of diabetes.[41] Furthermore, cadaveric islet samples from individuals with diabetes showed increased nuclear p27, indicating that p27 is a main regulator in response to increased β-cell requirement.[41]

Regulation of p27 is critical in the cell cycle; it is regulated by E3 ubiquitin ligase S-phase kinase-associated protein 2 (SKP2) and is degraded through E3 ubiquitin ligase SKP2 ubiquitination. In β cells lacking SKP2, p27 upregulation is concomitant with a decrease β-cell proliferation and with senescence, leading to the development of diabetes.[45] The multiple endocrine neoplasia type 1 (*MEN1*) tumour suppressor gene acts through a complex with histone methyltransferase to enhance expression of certain genes.[46] *MEN1*-null mice (*MEN1*-/-) showed increased β-cell proliferation and islet hyperplasia.[47] Individuals with mutations in Menin, the product of MEN1, present with pancreatic islet tumours. Mice that are heterozygous to *MEN1* (*MEN1*+/-) showed simultaneous decreases in the level of p27 and p18, resulting in islet hyperplasia (Figure 1).[46,48]

β cell cycle inhibitors and β-cell senescence: p21

p21 is a CDKI which halts the cell entrance to the S phase.[49] p21 is the downstream effector of the p53 senescence pathway. Upregulation of CDK4 or cyclin D1 increased p21 levels in the nucleus, denoting its importance in regulating the cell cycle.[50] However, in a murine model of p21 deficiency, normal islet proliferation took place, indicating that there may be other cell cycle regulators that compensate for p21 function.[51] Minamino et al.[52] showed that oxidative stress enhances the expression of p21.

Treatment of isolated rat β cells with hydrogen peroxide led to elevated levels of p21 and suppression of insulin production.[53] Induction of p21 in rat islets was followed with induction of diabetes.[53]

β cell cycle inhibitors and β-cell senescence: p16

With age, β cells show upregulation of cell cycle inhibitors, such as the tumour suppressor protein p16Ink4a.[54] CDK4 and CDK6 complex with cyclin D, phosphorylating pRB and activating the transcription factor E2F, which permits the transition from G to S phase. With age, p16Ink4a sequesters CDK4 and CDK6 and thus inhibits interaction with D cyclins.[54] Transgenic mice with β cells overexpressing p16Ink4a showed significant reduction in β-cell replication at 26–32 weeks, comparable to older mice.[54] p16Ink4a-null mice showed no age-related reduction in β-cell replication; β cells from mice of 60 weeks of age proliferated similar to younger mice that were 10 weeks of age.[54]

p16 gene locus INK/ARF is epigenetically regulated by polycomb-group proteins. These proteins regulate stem cell self-renewal by modifying the INK/ARF locus.[55] Expression of BMI-1 polycomb proteins decrease with age

and have an inhibitory role on p16. Knockout of *BMI-1* resulted in higher expression of p16 and p19, along with a consequent decrease in β-cell proliferation. Furthermore, inhibition of *BMI-1*, caused by premature senescence due to an increased expression of p16, led to a decrease in β cell mass and impaired glucose tolerance (Figure 1).[48,56]

The enhancer of zeste homology 2 (EZH2) is another polycomb protein that is more expressed in younger mice. It acts as an inhibitor of p16 and p19 through H3K27 trimethylation of Ink4a and Arf.[40] *EZH2*-null mice show a decrease in β-cell proliferation and eventually develop diabetes.[40] *EZH2* and p16 double-null mice were able to reverse this diabetes.

p38 mitogen-activated protein kinase (p38 MAPK) is expressed in response to cellular stressors.[57] p38 MAPK inhibits BMI-1 and thus p38 activation, leading to an increase of p16 and p19.[58] Aged islets showed more upregulated p38 MAPK compared to younger islets.[59] In p38 MAPK-deficient mice, global inhibition of CDKI was observed with age.[59] Induction of diabetes using streptozotocin in these mice showed partial reversal, caused by enhanced β-cell proliferation. The oncoprotein Wip1 is an inhibitor for p38 MAPK and its level is reduced with ageing. Thus, deletion of Wip1 in mice resulted in an upregulation of p38 MAPK and development of ageing-associated diabetes. However, induced expression of Wip1 resulted in a decrease in p38 MAPK and, consequently, a decrease in p16 expression, p19 expression, and the reversal of diabetes (Figure 1).[48,59]

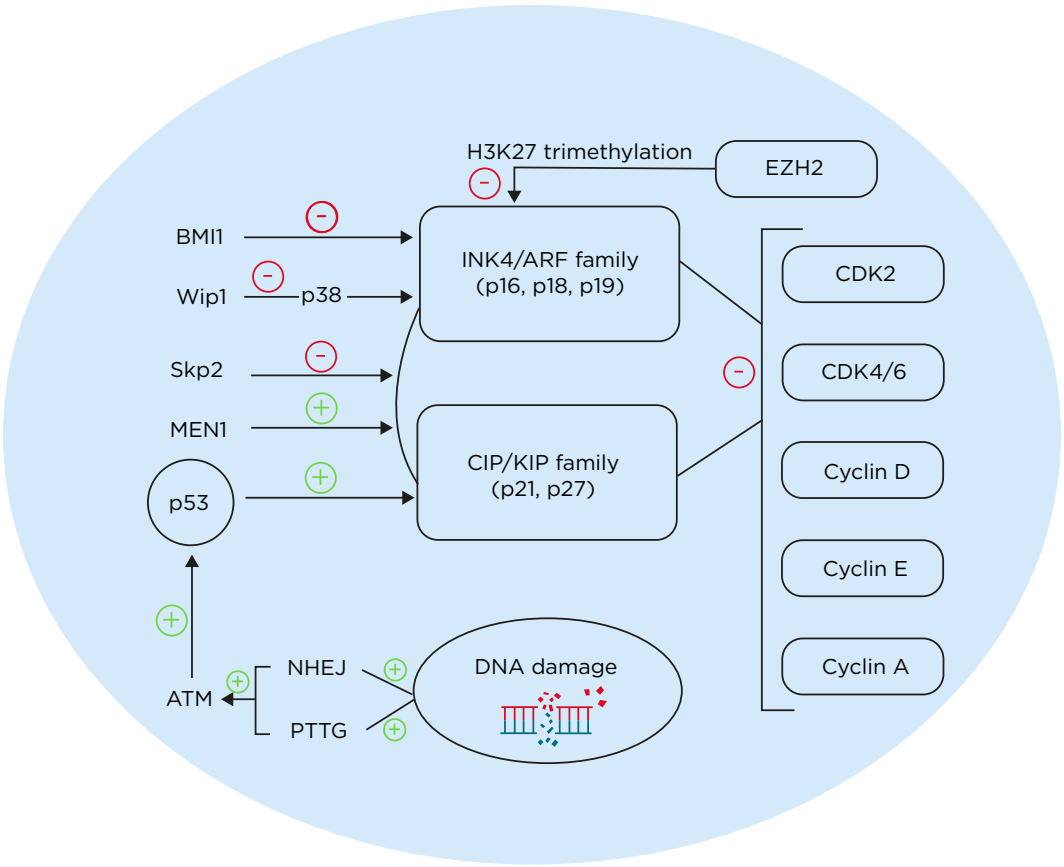

Figure 1: Different pathways affecting cell cycle regulation in pancreatic β cells.

ATM: ataxia telangiectasia mutated gene; *BMI1*: BMI1 proto-oncogene; CDK: cyclin-dependent kinase; EZH2: enhancer of zeste 2 polycomb repressive complex 2 subunit; *MEN1*: multiple endocrine neoplasia tumour suppressor gene; NHEJ: non-homologous end joining; *PTTG*: pituitary tumour transforming gene; Skp2: S-phase kinase-associated protein 2; Wip1: wild-type p53-induced phosphatase 1.

Created with BioRender.com.[48]

CELLULAR STRESSORS AND β-CELL SENESCENCE

The Role of Telomere Shortening

Telomeres are repeated DNA sequences located at the end of chromosomes that shorten with every cell cycle as a result of double-stranded breaks and DNA damage. These breaks activate the p53 apoptosis pathway or p21-mediated senescence.[60] In mice deficient in the telomerase RNA template (TERC), an impaired glucose tolerance occurred that was partially corrected by deleting p53.[61] In these mice, β-cell proliferation and islet mass decreased, which were caused by telomere shortening due to deficient TERC.[62] *TERC*-null mice who were exposed to β cell stress through a high-fat diet showed significantly impaired glucose tolerance associated with insulin insensitivity.[52] Higher levels of p53 and cellular ageing in the fat pads of these mice may have contributed to the observed insulin resistance.

DNA Repair Dysfunction

DNA repair mechanisms, such as nonhomologous end joining (NHEJ), are the main pathway for repairing double-strand breaks.[63] Deletion of DNA ligase IV, which is responsible for fixing the DNA ends as a part of the NHEJ pathway, leads to the activation of p53, p21-mediated β-cell senescence, decreased proliferation, and, eventually, diabetes.[64] Individuals with diabetes thus show higher DNA damage, concomitant with reduced DNA repair efficiency.[65]

The NHEJ pathway effectors can be subdivided into two groups: the DNA end recognition and processing complex, composed of the DNA-dependent kinase catalytic subunit (Ku70/80 heterodimer and DNA-PKcs) and the DNA repair factor Artemis; and the DNA ligation complex (DNA ligase IV, XRCC4, Cernunnos/XLF).[63] Ku70/80 have the ability to bind and phosphorylate the pancreatic duodenal homeobox-1 protein (PDX-1), which is the main transcription factor in pancreatic development, through recruitment of DNA-PKcs.[66] An increase in DNA damage stimuli leads to increased DNA-PKcs and PDX-1 degradation. Defective NHEJ pathways were reported in deficient pituitary tumour transforming genes.[67] In mice deficient in pituitary tumour transforming genes, upregulated p53 and p21 levels concomitant with increased DNA damage were observed, and this led to β-cell senescence.[68]

Ataxia telangiectasia mutated protein (ATM) is a protein kinase and cell cycle regulator that acts upon DNA damage. It phosphorylates and activates many effectors, including tumour suppressor p53, and thus aids in DNA repair and prevention of cellular senescence.[69] In ATM-deficient mice, impaired glucose tolerance and, eventually, diabetes developed.[70] Induction of ATM in β cells without DNA damage using chloroquine injection in two diabetes models (ob/ob, db/db) reduced fasting and random blood glucose.[71] Oxidative stress also enhanced ATM regulation of metabolic activity, and thus prevented development of diabetes induced by oxidative damage of β cells.[72]

CONCLUSION

In this review, the authors provided an overview of how the diabetic microenvironment causes cellular senescence and the relation of β-cell senescence to the development of diabetes. CDKI upregulation may induce β-cell senescence; thus, inhibition of CDKI may represent a therapeutic approach to enhance β cell mass. *MEN1* deletion increased β-cell proliferation through inhibition of the CDKI p27 and p18. In addition, gestation-induced β-cell proliferation was caused by decreases in *MEN1*, reflecting a possible therapeutic effect of *MEN1* in diabetes. Regulating Wip1 impacts ageing-associated β-cell proliferation, as induction of Wip1 resulted in a decrease of p38 MAPK. Enhancement of Wip1 may thus present a promising therapeutic approach for diabetes. The pathogenesis of patients with Type 2 diabetes mellitus and β-cell senescence was related to an increase in SASP factors. However, more studies are needed to directly relate the connection between SASP factors with the pathogenesis of diabetes in aged β cells, and the role of senolytic therapies in the reversal of impaired β-cell proliferation in ageing individuals.

References

1. Hayflick L, Moorhead PS. The serial cultivation of human diploid cell strains. Exp Cell Res. 1961;25(3):585-621.
2. Cerf ME. Beta cell dysfunction and insulin resistance. Front Endocrinol (Lausanne). 2013;4:37.
3. Burton DGA, Faragher RGA. Cellular senescence: from growth arrest to immunogenic conversion. Age (Dordr). 2015;37(2):27.
4. Coppé J-P et al. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumour suppressor. PLoS Biol. 2008;6(12):2853-68.
5. Cesare AJ et al. The telomere deprotection response is functionally distinct from the genomic DNA damage response. Mol Cell. 2013;51(2):141-55.
6. Young AR, Narita M. SASP reflects senescence. EMBO Rep. 2009;10(3):228-30.
7. Moiseeva O et al. Mitochondrial dysfunction contributes to oncogene-induced senescence. Mol Cell Biol. 2009;29(16):4495-507.
8. Baek KH, Ryeom S. Detection of oncogene-induced senescence in vivo. Methods Mol Biol. 2017;1534:185-98.
9. Agger K et al. The H3K27me3 demethylase JMJD3 contributes to the activation of the INK4A-ARF locus in response to oncogene- and stress-induced senescence. Genes Dev. 2009;23(10):1171-6.
10. Rizwan H et al. High glucose augments ROS generation regulates mitochondrial dysfunction and apoptosis via stress signalling cascades in keratinocytes. Life Sci. 2020;241:117148.
11. Chapman MJ et al. Triglyceride-rich lipoproteins and high-density lipoprotein cholesterol in patients at high risk of cardiovascular disease: evidence and guidance for management. Eur Heart J. 2011;32(11):1345-61.
12. Aguayo-Mazzucato C et al. Acceleration of β cell ageing determines diabetes and senolysis improves disease outcomes. Cell Metab. 2019;30(1):129-42.e4.
13. Aguayo-Mazzucato C et al. β cell ageing markers have heterogeneous distribution and are induced by insulin resistance. Cell Metab. 2017;25(4):898-910.e5.
14. Desgraz R et al. β-cell regeneration: the pancreatic intrinsic faculty. Trends Endocrinol Metab. 2011;22(1):34-43.
15. Reers C et al. Impaired islet turnover in human donor pancreata with ageing. Eur J Endocrinol. 2009;160(2):185-91.
16. Krupczak-Hollis K et al. Growth hormone stimulates proliferation of old-aged regenerating liver through forkhead box m1b. Hepatology. 2003;38(6):1552-62.
17. Butler AE et al. Beta-cell deficit and increased beta-cell apoptosis in humans with Type 2 diabetes. Diabetes. 2003;52(1):102-10.
18. Rahier J et al. Pancreatic beta-cell mass in European subjects with Type 2 diabetes. Diabetes Obes Metab. 2008;10(Suppl 4):32-42.
19. Saxena R et al. Genome-wide association analysis identifies loci for Type 2 diabetes and triglyceride levels. Science. 2007; 316(5829):1331-6.
20. Leahy JL et al. Targeting beta-cell function early in the course of therapy for Type 2 diabetes mellitus. J Clin Endocrinol Metab. 2010;95(9):4206-16.
21. van Heeringen C et al. Prefrontal 5-HT2a receptor binding index, hopelessness and personality characteristics in attempted suicide. J Affect Disord. 2003;74(2):149-58.
22. Coudreuse D, Nurse P. Driving the cell cycle with a minimal CDK control network. Nature. 2010;468(7327):1074-9.
23. Pestell RG et al. The cyclins and cyclin-dependent kinase inhibitors in hormonal regulation of proliferation and differentiation. Endocr Rev. 1999;20(4):501-34.
24. Zhang X et al. Overexpression of cyclin D1 in pancreatic β-cells in vivo results in islet hyperplasia without hypoglycemia. Diabetes. 2005;54(3):712-9.
25. He LM et al. Cyclin D2 protein stability is regulated in pancreatic beta-cells. Mol Endocrinol. 2009;23(11):1865-75.
26. Fiaschi-Taesch NM et al. Induction of human β-cell proliferation and engraftment using a single G1/S regulatory molecule, cdk6. Diabetes. 2010;59(8):1926-36.
27. Chudnovsky Y et al. Melanoma genetics and the development of rational therapeutics. J Clin Invest. 2005;115(4):813-24.
28. Martín J et al. Genetic rescue of Cdk4 null mice restores pancreatic beta-cell proliferation but not homeostatic cell number. Oncogene. 2003;22(34):5261-9.
29. Mettus RV, Rane SG. Characterization of the abnormal pancreatic development, reduced growth and infertility in Cdk4 mutant mice. Oncogene. 2003;22(52):8413-21.
30. Rane SG et al. Loss of Cdk4 expression causes insulin-deficient diabetes and Cdk4 activation results in beta-islet cell hyperplasia. Nat Genet. 1999;22(1):44-52.
31. Sugimoto M et al. Regulation of CDK4 activity by a novel CDK4-binding protein, p34SEI-1. Genes Dev. 1999;13(22):3027-33.
32. Cozar-Castellano I et al. Induction of β-cell proliferation and retinoblastoma protein phosphorylation in rat and human islets using adenovirus-mediated transfer of cyclin-dependent kinase-4 and cyclin D1. Diabetes. 2004;53(1):149-59.
33. Hino S et al. In vivo proliferation of differentiated pancreatic islet beta cells in transgenic mice expressing mutated cyclin-dependent kinase 4. Diabetologia. 2004;47(10):1819-30.
34. Miyawaki K et al. Transgenic expression of a mutated cyclin-dependent kinase 4 (CDK4/R24C) in pancreatic β-cells prevents progression of diabetes in db/db mice. Diabetes Res Clin Pract. 2008;82(1):33-41.
35. Lee J-H et al. Cdk4 regulates recruitment of quiescent β-cells and ductal epithelial progenitors to reconstitute β-cell mass. PLoS One. 2010;5(1):e8653.
36. Wei F-Y et al. Cdk5-dependent regulation of glucose-stimulated insulin secretion. Nat Med. 2005;11(10):1104-8.
37. Hinault C et al. Differential expression of cell cycle proteins during ageing of pancreatic islet cells. Diabet Obes Metab. 2008;10(s4):136-46.
38. Kim SY et al. Loss of cyclin-dependent kinase 2 in the pancreas links primary β-cell dysfunction to progressive depletion of β-cell mass and diabetes. J Biol Chem. 2017;292(9):3841-53.
39. Frank CL, Tsai L-H. Alternative functions of core cell cycle regulators in neuronal migration, neuronal maturation, and synaptic plasticity. Neuron. 2009;62(3):312-26.
40. Chen H et al. Polycomb protein Ezh2 regulates pancreatic beta-cell Ink4a/Arf expression and regeneration in Diabetes Mellitus. Genes Dev. 2009;23(8):975-85.
41. Uchida T et al. Deletion of Cdkn1b ameliorates hyperglycemia by maintaining compensatory hyperinsulinemia in diabetic mice. Nat Med. 2005;11(2):175-82.
42. Georgia S, Bhushan A. p27 regulates the transition of beta-cells from quiescence to proliferation. Diabetes. 2006;55(11):2950-6.
43. Georgia S, Bhushan A. β cell replication is the primary mechanism for maintaining postnatal β cell mass. J Clin Invest. 2004;114(7):963-8.

44. Rachdi L et al. Differential effects of p27 in regulation of beta-cell mass during development, neonatal period, and adult life. Diabetes. 2006;55(12):3520-8.
45. Zhong L et al. Essential role of Skp2-mediated p27 degradation in growth and adaptive expansion of pancreatic beta cells. J Clin Invest. 2007;117(10):2869-76.
46. Karnik SK et al. Menin regulates pancreatic islet growth by promoting histone methylation and expression of genes encoding p27Kip1 and p18INK4c. Proc Natl Acad Sci U S A. 2005;102(41):14659-64.
47. Crabtree JS et al. Of mice and MEN1: insulinomas in a conditional mouse knockout. Mol Cell Biol. 2003;23(17):6075-85.
48. BioRender. BioRender. Available at: https://biorender.com/. 2021. Last accessed: 8 February 2021.
49. Abbas T, Dutta A. p21 in cancer: intricate networks and multiple activities. Nat Rev Cancer. 2009;9(6):400-14.
50. Cozar-Castellano I et al. Evaluation of β-cell replication in mice transgenic for hepatocyte growth factor and placental lactogen: comprehensive characterization of the G1/S regulatory proteins reveals unique involvement of p21cip. Diabetes. 2006;55(1):70-7.
51. Cozar-Castellano I et al. The cell cycle inhibitory protein p21cip is not essential for maintaining beta-cell cycle arrest or beta-cell function in vivo. Diabetes. 2006;55(12):3271-8.
52. Minamino T et al. A crucial role for adipose tissue p53 in the regulation of insulin resistance. Nat Med. 2009;15(9):1082-7.
53. Kaneto H et al. Oxidative stress induces p21 expression in pancreatic islet cells: possible implication in beta-cell dysfunction. Diabetologia. 1999;42(9):1093-7.
54. Krishnamurthy J et al. p16INK4a induces an age-dependent decline in islet regenerative potential. Nature. 2006;443(7110):453-7.
55. Lessard J, Sauvageau G. Bmi-1 determines the proliferative capacity of normal and leukaemic stem cells. Nature. 2003;423(6937):255-60.
56. Dhawan S et al. Bmi-1 regulates the Ink4a/Arf locus to control pancreatic beta-cell proliferation. Genes Dev. 2009;23(8):906-11.
57. Han J et al. A MAP kinase targeted by endotoxin and hyperosmolarity in mammalian cells. Science. 1994;265(5173):808-11.
58. Bulavin DV et al. Inactivation of the Wip1 phosphatase inhibits mammary tumorigenesis through p38 MAPK-mediated activation of the p16(Ink4a)-p19(Arf) pathway. Nat Genet. 2004;36(4):343-50.
59. Wong ES et al. p38MAPK controls expression of multiple cell cycle inhibitors and islet proliferation with advancing age. Dev Cell. 2009;17(1):142-9.
60. Herbig U, Sedivy JM. Regulation of growth arrest in senescence: telomere damage is not the end of the story. Mech Ageing Dev. 2006;127(1):16-24.
61. Sahin E et al. Telomere dysfunction induces metabolic and mitochondrial compromise. Nature. 2011;470(7334):359-65.
62. Kuhlow D et al. Telomerase deficiency impairs glucose metabolism and insulin secretion. Ageing (Albany NY). 2010;2(10):650-8.
63. Mahaney BL et al. Repair of ionizing radiation-induced DNA double-strand breaks by non-homologous end-joining. Biochem J. 2009;417(3):639-50.
64. Tavana O et al. Absence of p53-dependent apoptosis combined with nonhomologous end-joining deficiency leads to a severe diabetic phenotype in mice. Diabetes. 2010;59(1):135-42.
65. Sliwinska A et al. Effect of gliclazide on nucleotide excision repair (NER) and non-homologous DNA end joining (NHEJ) in normal and cancer cells. J Physiol Pharmacol. 2010;61(3):347-53.
66. Lebrun P et al. Regulation of the pancreatic duodenal homeobox-1 protein by DNA-dependent protein kinase. J Biol Chem. 2005;280(46):38203-10.
67. Bernal JA et al. Proliferative potential after DNA damage and non-homologous end joining are affected by loss of securin. Cell Death Differ. 2008;15(1):202-12.
68. Wang Z et al. Pituitary tumor transforming gene-null male mice exhibit impaired pancreatic beta cell proliferation and diabetes. Proc Natl Acad Sci U S A. 2003;100(6):3428-32.
69. Zhan H et al. Ataxia telangiectasia mutated (ATM)-mediated DNA damage response in oxidative stress-induced vascular endothelial cell senescence. J Biol Chem. 2010;285(38):29662-70.
70. Miles PD et al. Impaired insulin secretion in a mouse model of ataxia telangiectasia. Am J Physiol Endocrinol Metab. 2007;293(1):E70-4.
71. Schneider JG et al. ATM-dependent suppression of stress signaling reduces vascular disease in metabolic syndrome. Cell Metab. 2006;4(5):377-89.
72. Guo Z et al. ATM activation in the presence of oxidative stress. Cell Cycle. 2010;9(24):4805-11.

Syphilis Diagnosis and Treatment: State of The Art

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Abstract

The present review summarises the current knowledge in the field of syphilis diagnosis and treatment, along with epidemiologic and historical data. A literature search was conducted in PubMed and Google Scholar, using the search terms "syphilis", "diagnosis", "dermoscopy", "management AND treatment", "laboratory tests AND syphilis", and "primary OR secondary OR tertiary OR congenital syphilis". A total of 55 out of 100 papers were included in this review. An overview of the different clinical presentation of primary, secondary, tertiary, and congenital syphilis, with particular attention to dermatologic signs and dermoscopic examination, is provided. The panorama diagnostic procedures are illustrated, along with their accuracy and recommendation. Treatment and management options of patients at different syphilis stages are provided and discussed according to the referring guidelines. The dermatologist can play a key role in providing the early and correct diagnosis and setting up in the proper management of patients with syphilis infection.

BACKGROUND

Syphilis is a chronic bacterial infection caused by *Treponema pallidum* subspecies *pallidum*, known by clinicians for hundreds of years and with more than 5 million new cases diagnosed every year worldwide, mostly in low- and middle-income countries.[1,2] Syphilis can even be associated with other sexually transmitted diseases (STD), adverse pregnancy outcomes, and acceleration of HIV transmission.[1]

The term 'syphilis' was first used in 1530 in a poem by Girolamo Fracastoro (in which Apollo curses the population with a disease that bears the name of the shepherd 'Syphilus', which angered him). Also called 'lues', plague, in Latin, the disease is of importance to both individual and public health because it has a growing incidence. Although many consider this disease as specific to the 20th century, there has been a growing trend in recent years, especially among patients under the age of 25. The fluctuating incidence of infection requires a greater effort for control and contagion management in order to avoid continuous transmission peaks. Syphilis incidence has again begun to increase dramatically in western Europe and the Americas, and now disproportionately occurs among males who have sex with males (MSM).[3,4]

T. pallidum subsp. *pallidum* is a slow-growing, motile spirochaete bacterium with a long spiral shape. Humans are its only natural host, and it cannot be cultured *in vitro*. It is closely related

to other pathogenic treponemes, including *T. pallidum* subsp. *pertenue*, which causes yaws; *Treponema carateum*, which causes pinta; and *T. pallidum* subsp. *endemicum*, which causes endemic syphilis or bejel.

EPIDEMIOLOGY

The origins of syphilis remain to be controversial.[5] According to the 'Columbian hypothesis', syphilis was brought to the Old World in 1493 by Columbus' returning seamen; on the other hand, the 'pre-Columbian hypothesis' states that the disease existed in both the Old and New Worlds prior to 1942; finally, the 'Evolutionary/Unitarian hypothesis' postulates that treponemal diseases were already distributed worldwide.[5] From the 1490s, the infection spread quickly across Europe,[6] characterised by high virulence and mortality; however, in less than one century, less virulent strains were naturally selected.

From an epidemiological point of view, syphilis has been closely associated with HIV infection transmission.[7-10] Syphilitic genital ulcers are densely infiltrated with lymphocytes (the primary target cells for HIV infection) and therefore provide a potential breach of entry for HIV acquisition, as well as a focus for HIV (and syphilis) transmission to others.[11] Rates of primary and secondary syphilis among females have more than doubled between 2014 and 2018.[12] The numbers of cases reported to the Centers for Disease Control and Prevention (CDC) increased by about 81% from 2014 to 2018 in MSM.[13] This happened especially in higher-income countries, where the use of geosocial network phone applications and/or location-based applications for sex led to an increased risk of sexually transmitted infections (STI), as well as to a reduced ability for partner notification because of anonymity.[14,15] All stages of syphilis in pregnant females pose a risk of transmission to the fetus, but it is higher with early stages of infection than with later ones, so it is strictly important to perform an optimum and continuous prevention in these patients.[16] Without treatment, the disease can progress over years through a series of clinical stages and may lead to irreversible neurological or cardiovascular complications.

CLINICAL PRESENTATION

Primary Syphilis

The primary stage of syphilis may be manifested clinically as a generally single, indurated, painless, and ulcerative chancre, which typically appears about 2–3 weeks after direct contact with another person's infectious lesion.[3] Although chancres are most often seen on the penis, they can be located at nearly any place where direct contact with infectious lesions occurs, and sometimes it is unnoticed.[17,18] The chancre begins as a macule, then papule, (Figure 1A) and rapidly develops into an erosion that is round or ovular in shape with sharp indurated margins (Figure 1B), which are pink, red, or greyish. The primary chancre can be accompanied by tender or non-tender, painless, regional lymphadenopathy with overlying nonerythematous skin. Without treatment, after a period of 3–6 weeks, primary lesions spontaneously resolve without scarring.[3] Sexual acquisition of syphilis occurs when an infectious lesion contacts the skin or mucous membrane of an uninfected person, often (but not exclusively) during oral, vaginal, or anal sex. The risk of transmission after sexual exposure is estimated at approximately 33%.[17]

Secondary Syphilis

Prodromic symptoms

Secondary syphilis is the most recognised clinical syndrome of syphilis, mostly among females or MSM. Symptoms including malaise, myalgia, sore throat, headache, or low-grade fever commonly precede or are present during secondary syphilis.[19,20] After 3–12 weeks from the resolution of a chancre or sometimes concurrently, secondary manifestations of infection result from haematogenous dissemination of spirochaetes.

Syphilitic exanthema

The rash of secondary syphilis is extraordinarily variable in appearance, involving both skin and mucous, and it could be localised or widespread. It generally appears as diffuse macular exanthema of 1–2 cm in diameter, on the trunk and extremities with scaly macules, or papules that are red-brown or 'ham coloured'. Lesions involving the palms of the hands or soles of the feet are diagnostic.

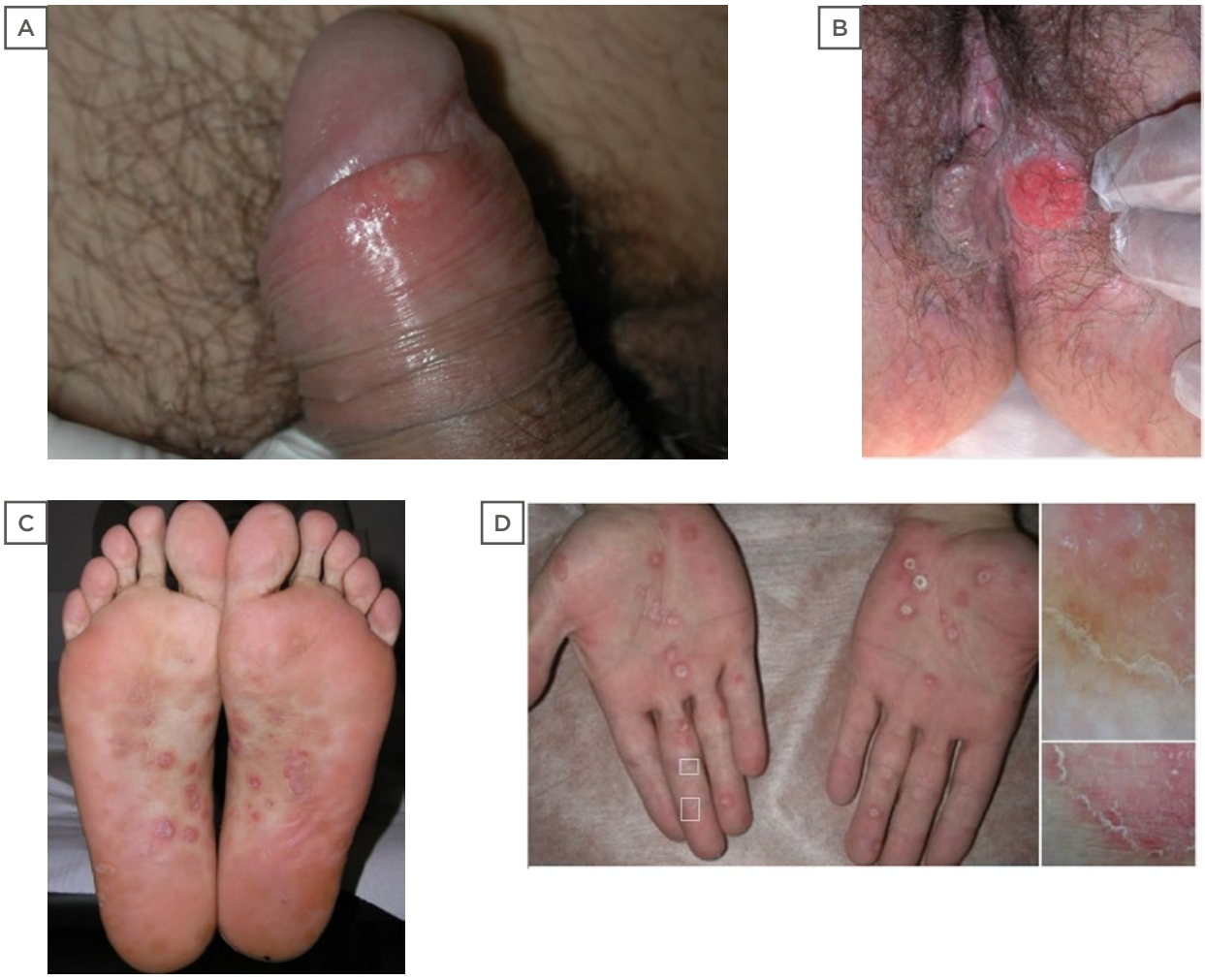

Figure 1: Clinical aspects of primary and secondary syphilis.

Two clinical presentations of the primary chancre, pathognomonic lesion of primary syphilis. A) Superficial erosion of the lesion at early stage on the glans in a 27-year-old male; B) advanced ulceration with raised indurated margins involving the perineal skin in a 34-year-old female. Secondary syphilis pathognomonic manifestations at palmoplantar sites consisting of erythematous papules with a central ring of scales (Biett's sign); C) soles of a 24-years-old male; D) and palms of a 45-year-old male. dermoscopic examination with contact polarised dermosocope (OM 17X) reveals an inward-oriented scaling collarette characterised by thick adherent white scales and erythematous centre (D, squares).

Palmoplantar lesions are often pink, red, or brown macules or papules. Syphilis papules often show on their central surface a white ring of a scaling edge, known as Biett's collarette (Figure 1C and D). In this phase, lesions can mimic any possible configuration, from annular to nodular, lichenoid, or psoriasis-like, hence the clinical differential diagnosis can be difficult.[18-20]

Mucocutaneous and adnexal signs

Cutaneous manifestations are often associated with diffuse lymphadenopathy, hepatosplenomegaly, hepatitis, alopecia,[20] periostitis, or nephrotic syndrome. Even in secondary syphilis, lesions do not scar, and heal with postinflammatory hyperpigmentation. When mucous membranes are involved, lesions can appear as highly infectious mucous patches, sometimes with an exuberant, verrucous surface resembling a wart, called condyloma lata.[19] Nail changes, including brittleness, splitting, pitting, onycholysis, onychomadesis, transverse grooves, and Beau lines, can occur.

Dermoscopic findings

The morphology of this Biett's collarette can be highlighted by polarised dermoscopy, consisting of a circular scaling edge outward-directed with moderately adherent thick white scales. Moreover, the area inside the ring results de-epithelised, thus monomorphic dotted and glomerular vessels can be seen over a diffuse, yellow/reddish background (Figure 1D). Polarised dermoscopy can reveal Biett's sign in dark-phototypes skin, where the vascular structures are less visible. In addition, dermoscopy can be very useful in differentiating the secondary syphilis lesions from other dermatological conditions exhibiting scaling collarettes, including pityriasis rosea, erythema multiforme, actinic porokeratosis, tinea corporis, erythema annulare centrifugum, granuloma annulare, annular variants of psoriasis, and subacute or discoid lupus erythematosus.

Resolution/worsening

Resolution of untreated manifestations of secondary syphilis can typically take from 4 to 12 weeks. High-risk factors (HIV infection with low CD4 count, malnutrition, MSM, previous syphilis, diabetes, and alcohol abuse) may induce lues maligna, or noduloulcerative syphilis, with asymmetric ulcers or round necrotic plaques with heaped up lamellar or rupioid crusts on the scalp, face, trunk, and extremities.

Latent Syphilis

Latent syphilis follows the untreated secondary stage, without clinical manifestations. In this phase, the infection can only be detected through serological testing.[16,21,22] Early latent syphilis can occur between the primary and secondary stages or after the resolution of secondary stage. The CDC defined a 1-year cut-off in order to differentiate between early latent and late latent syphilis; it has been highlighted that highest rate of recurrences (about 25% of treated patients) happen in the first year after infection.[16,21,22] In any stage of syphilis, it is possible to have an asymptomatic or symptomatic neurologic involvement with abnormal cerebrospinal fluid findings.[14,16]

Tertiary Syphilis

Tertiary, or late syphilis, is a systemic, multiorgan evaluation that occurs in approximately one-third of untreated but infected patients,[23,24] after a period of years or even decades, including late neurosyphilis (general paresis or tabes dorsalis), cardiovascular syphilis, or gummatous syphilis. Cutaneous lesions (noduloulcerative or gummatous) occur in 16% of patients with late clinical manifestations; these are usually single, unilateral, and asymptomatic.[23,24] Noduloulcerative lesions are superficial brown nodules, with serpiginous ulcerative evolution and central resolution. On the other side, gummas are painless destructive rubbery nodules that evolve into punched out ulcers that can grow to many centimetres and that drain necrotic material, invading deeply into tissue and bone, and healing with deeply retracted scars. The neurological involvement in tertiary syphilis is rare in the antibiotic era, but it could be either meningovascular or parenchymatous.[14] Meningovascular syphilis usually occurs from 5 to 12 years after contagion and manifestations may include haemiplegia, aphasia, and seizures. Parenchymatous manifestations are differentiated in general paresis (irritability and cognitive and memory impairments, emotional lability, and paranoia) and while tabe dorsalis (ataxia, lightning pains, visceral crises, rectal incontinence, and bladder disturbances).[25,26] Auricular and ocular syphilis can occur during any stage of infection with tinnitus and/or hearing loss, uveitis, retinitis, and retinal detachment.[18] Cardiovascular syphilis causes an inflammation of the inner lining of the artery (endarteritis)[7] and may lead to the development of aortic aneurysms (often involving the ascending aorta), aortic insufficiency, coronary-artery stenosis, and myocarditis. Syphilis in pregnancy carries significant risks for adverse outcomes, with more than 25% of affected pregnancies ending in stillbirth or spontaneous abortion.[1,22,23]

Congenital Syphilis

Congenital syphilis occurs if the *T. pallidum* is transmitted from the mother to the fetus. If the infection is transmitted within the first trimester of pregnancy, the consequences may include premature delivery, spontaneous abortion, stillbirth, nonimmune hydrops, or perinatal death.[27] If the infection is transmitted during the second to third trimester of pregnancy, the majority of infants born to mothers with untreated syphilis appear healthy and have no clinical or laboratory

evidence of infection at birth, but may develop manifestations of disease months to years later if left untreated.[27] Thus, congenital syphilis can be differentiated in early congenital (manifestations ≤2 years of age) and late congenital syphilis (manifestations ≥2 years of age). Signs described in early congenital syphilis include skin exfoliative rash (pemphigus syphiliticus), splenomegaly, adenopathy, condylomata lata, pseudoparalysis of Parrot, chorioretinitis, cataracts, periostitis, osteochondritis, nephrotic syndrome, pancreatitis, myocarditis, gastrointestinal malabsorption, and hypopituitarism (diabetes insipidus). Signs described in latent congenital syphilis include Hutchinson's teeth, Mulberry molars, interstitial keratitis, healed chorioretinitis, intellectual disability, hydrocephalus, seizures, optic nerve atrophy, juvenile general paresis, cranial nerve palsies, frontal bossing, saddle nose deformity, protuberant mandible, short maxilla, high palatal arch, saber shin, sternoclavicular joint thickening (Higouménakis sign), and clutton joints.

LABORATORY TESTS AND DIAGNOSIS

Dermatologists most often diagnose primary or secondary syphilis by observing mucocutaneous manifestations,[17-20] but every clinical hypothesis must be supported by laboratory confirmation.[28-37] Although Syphilis was first recognised in Europe in the late 15th century, interpretation of serological tests, diagnosis, and management are often challenging.[28-30] Syphilis can be diagnosed directly by the tissue, or indirectly by means of serologic tests. To date, multiple assays have been used for laboratory confirmation, with variable ranges of diagnostic accuracy, as summarised in Table 1.[30-41]

Direct Diagnosis

Microscopic observation

Since *T. pallidum* cannot be grown in culture, the direct diagnosis is obtained by the detection with darkfield microscopy of the spirochaetes in fluid or smears procured from a lesion. Indeed, the *T. pallidum* is a corkscrew, spiral-shaped organism that is 6–15 µm long and 0.1–0.2 µm wide, thus it cannot be visualised by direct microscopy and requires darkfield microscopy. This approach has high sensitivity and specificity but requires a specific microscope (paraboloid) and adequately trained physicians, so it is limited to specialised centres.[14] The CDC initially approved darkfield microscopy and PCR as criteria for the direct detection of *T. pallidum* in tissue specimens.[37] *T. pallidum* can also be visualised using immunofluorescent staining and special silver stains, nowadays limited to few centres.

Histopathology

The histopathological features reported for the primary syphilis lesion are nonspecific and limited by the ulcerative nature of the lesion itself, including ulceration, exocytosis, dense perivascular infiltrate of lymphocytes and plasma cells, and endothelial cell proliferation.[28] A bioptic specimen is more commonly obtained from papular/macular lesions of secondary syphilis.[29] The range of histopathologic findings that can be exhibited is wide, and include neutrophils in the stratum corneum, irregular/psoriasiform acanthosis, effacement of the rete ridges/elongated rete ridges, vacuolar interface with vacuolar predominance/with equal numbers of lymphocytes and vacuoles, endothelial swelling, presence of plasma cells, lymphocytes with ample cytoplasm, and interstitial inflammation.[29] Globally, the main histologic patterns reported are the combined pattern of lichenoid and perivascular inflammatory infiltrate (Figure 2A and B).[30] Unfortunately, these histopathologic features can be seen in those conditions clinically mimicking secondary syphilis popular/macular lesions, as seen with pityriasis rosea, pityriasis lichenoides, or early mycosis fungoides cases.[28] Thus, the histopathologic examination has low specificity and low sensitivity and should always be performed along with serology.[28-39] Moreover, spirochaetes can be identified by silver-based stains, the marking includes melanin too, causing overlap and difficulty in interpreting images (Figure 2C).

Immunohistochemistry

Immunohistochemistry using a monoclonal antibody to *T. pallidum* can be performed on bioptic specimens.[30,31] This method is particularly useful to reach the correct diagnosis in retrospective investigations, especially when the diagnostic suspect of syphilis was not considered on a clinical ground. The immunohistochemistry assays developed to date are multiple, and more

recently were focussed on the recombinant protein technology. Briefly, the *T. pallidum* DNA derived from *Nichols* strain genome were amplified by PCR and inserted into an expression vector and then to *Escherichia coli* cells for expression of fusion proteins with a tag sequence for efficient chromatography purification. The obtained recombinant proteins were tested as antigens in either enzyme-linked immunosorbent assay (ELISA) (e.g., Alere Determine™ Syphilis TP test; Abbott, Chicago, Illinois, USA) or Western blot format. The ELISA assay appeared to be very sensitive in the detection of *T. pallidum*, with reported rates of detection of the spirochaetes in both the epidermis and dermis, or in the dermis or epidermis only of 52%, 24%, and 20%, respectively.[30]

Indirect Diagnosis

The indirect diagnosis of syphilis currently relies on serological tests for the detection of antibodies. Two types of serologic tests for syphilis, nontreponemal and treponema-specific tests (i.e., assays for detection of specific antibodies), were largely validated for diagnostic confirmation of syphilitic infection.[32-38] However, they are affected by low specificity in some conditions (Table 1).[30-41] Thus, the research in the last year was focussed on the immunoproteasome of the *T. pallidum*, aimed to discover new highly-specific antigens and select the optimal antigen combinations for an ideal diagnostic *'T. pallidum panel'*.[39] Among them, surface-exposed proteins, adhesins, and periplasmic and flagellar proteins appeared the most promising. More recently, biochips (i.e., microarrays with orderly located molecular probes for realisation of an appreciable number of specific recognition reactions with the minimum volumes of analysed biological mater) were studied to expand the panel of *T. pallidum* antigens and recombinant proteins to be included in a unique serologic assay. A recently proposed 'immunochip' reached high diagnostic accuracy by adding new synthetic proteins (Tp0277, Tp0319, Tp0453, Tp0684, Tp0965, and Tp1038) to the already known panel of immunodominant antigens (Tp15, Tp17, Tp47, and TmpA).[33] These methods are now proposed for serological screening, allowing multiple parallel detection of specific serum IgG.[32,33]

Nontreponemal tests

Nontreponemal tests include rapid plasma regain (RPR) and venereal disease research laboratory (VDRL) tests. Both measure tissue damage caused by syphilis by detecting antibodies to cardiolipin, cholesterol, and lecithin, which are normal components of human cells.[9,21,22] When a nontreponemal test is reactive, the laboratory quantifies the amount of antibody present, expressing it as a titer. Monitoring titers over time enables the assessment of response to treatment. In many patients who are successfully treated for syphilis, a nontreponemal test ultimately becomes nonreactive (in approximately 3 months).[34-40] Persistently reactive nontreponemal tests after successful treatment typically with low titers (1:1 to 1:4) and more commonly in patients infected with HIV are called serofast reactions.[42] False positive and false negative nontreponemal test results can occur in numerous conditions.[43] False positive results can occur due to patient-related factors (i.e., intravenous drug usage, pregnancy), some autoimmune and inflammatory diseases (i.e., systemic lupus erythematosus, arthritis, ulcerative colitis, thyroiditis, vasculitis), a plethora of infectious diseases (i.e., lymphogranuloma venereum, hepatitis C virus, Epstein–Barr virus, endocarditis, leprosy, varicella, measles, mumps, malaria pinta, yaws, rickettsia, brucellosis, chancroid, tuberculosis, Lyme disease), and even in case of malignancy (e.g., colon carcinoma, lymphomas, metastatic solid cancer). Conversely, false negative results can occur in case of HIV infection, in pregnancy, or in neurosyphilis/lues maligna.

Treponemal tests

Treponemal tests measure IgM and IgG specific antibodies against *T. pallidum* using native or sonically disrupted *T. pallidum* cells as the source of total number of antigens. Some of the first developed treponemal tests include the *T. pallidum* particle agglutination (TPPA), the fluorescent treponemal antibody absorption, and the *T. pallidum* haemagglutination (TPHA) tests. More recent treponemal assays include enzyme immunoassay and chemiluminescence immunoassay. Treponemal tests are typically more sensitive than nontreponemal tests during early infection.

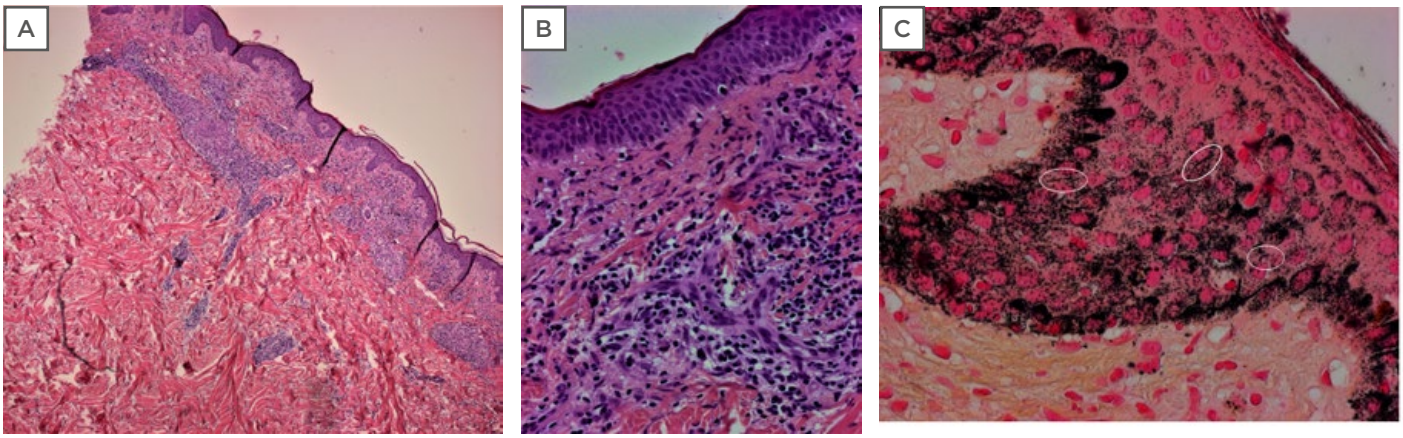

Figure 2: Histopathologic aspects of secondary syphilis.

A) Lichenoid pattern of secondar syphilis characterised by a superficial band-like infiltrate with focal infiltration of the epidermis and a deep perivascular dermal infiltrate (haematoxylin and eosin, original 400x magnification); and B) dermal infiltrate of plasma cells and histiocytes with swollen endothelium; C) Warthin–Starry silver nitrate-based stain highlights both spirochaetes (white circles) and melanin granules resulting in marked background artifacts (haematoxylin and eosin, original 400x magnification).

Table 1: Comparison of the accuracy of the different diagnostic tests used to date in primary syphilis.[30-41]

	Sensitivity (%)	Specificity (%)
DF microscopy	62.0–92.0	N/A
T. pallidum PCR	72.3–77.8	93.1–100.0
VDRL	62.5–78.4	96.0–99.0
TPHA	95.0–100.0	77.5
TPPA	86.2–100.0	99.6–100.0
RPR	62.5–76.1, 77.0–99.0	93.0–99.0
FTA-ABS	72.0–100.0	87.0–100.0
ELISA	96.0–100.0	90.0–98.0
Immunochip	94.1	100.0

DF: darkfield microscopy; ELISA: enzyme-linked immunosorbent assay based on recombinant *Treponema pallidum* antigen; FTA-ABS: fluorescent treponemal antibody absorbed test; N/A: not assessed; RPR: rapid plasma regain; *T. pallidum: Treponema pallidum*; TPHA: *Treponema pallidum* haemagglutination assay; TPPA: *Treponema pallidum* particle agglutination assay; VDRL: venereal disease research laboratory test.

IgM and IgG are often detectable 2 and 4 weeks after exposure, respectively, and in some cases within 3 days of a chancre's appearance. Regardless of stage or nonserologic tests, all patients with syphilis should undergo serologic testing with both nontreponemal and treponemal (if not known to have reactive treponemal tests because of a history of syphilis) tests. Treponemal tests are always sequent to nontreponemal tests in order to confirm or to exclude diagnostic hypothesis.[34-42,44,45]

Cerebrospinal fluid examination

Referrals for cerebrospinal fluid examination via lumbar puncture are recommended only for patients who meet one of three conditions: 1)

signs or symptoms of neurosyphilis, otic syphilis, or ocular syphilis; 2) suspected treatment failure; or 3) tertiary syphilis.[44,45] Patients with syphilis who have ocular symptoms should be referred for an ophthalmologic evaluation in addition to cerebrospinal fluid examination.

Test Interpretation

Interpretation of either can be complicated, particularly when treponemal and nontreponemal tests are discordant.[28-35] Dermatologists most often diagnose primary or secondary syphilis, which have mucocutaneous manifestations. For patients with current reactive serologies without signs or symptoms of primary, secondary, or tertiary syphilis, physicians must ascertain whether the serologies represent previously treated infection (and if so, whether treatment was successful) or new infection (and if so, determine duration of infection to stage the patient). Doing so requires eliciting a sexual and medical history and reviewing the patient's serologic history, if available.

Congenital syphilis

Maternal syphilis screening is part of routine standard of care in all pregnancies in many countries, including VDRL/RPR and TPHA/TPPA. Histological examination of the placenta and/or of the cord may reveal spirochaetes or exhibit signs of enlarged hypercellular villi, proliferative vascular changes, and acute and/or chronic villi. Adequate treatment with penicillin during pregnancy is 98% effective at preventing congenital syphilis. If the infection is left undiagnosed, treponemal infection is transferred, but most neonates are completely asymptomatic at birth. However, by the age of 3 months, newborns develop hepatomegaly, jaundice, rhinitis, generalised lymphadenopathy, or rash; serologic tests are thus required (VDRL/RPR and FTA-ABS or TPHA/TPPA). After 2 years of age, gummas and perioral fissures/scarring; facial changes, including frontal bossing, saddle nose, and prominent maxilla; anterior bowing of the shin; Hutchinson's teeth; intellectual disability; cranial nerve palsies; sensorineural hearing loss; and changes in vision (e.g., interstitial keratitis, secondary glaucoma, and corneal scarring) can occur. At this stage, long bone radiographs, chest X-ray, and head X-rays can be performed. Long bone radiographs may show pathologic fractures, metaphyseal serration, localised demineralisation, and osseous destruction, chest X-ray may show diffuse opacification of both lung fields.[30]

TREATMENT

Pre-penicillin Era

There were multiple syphilis treatments in the pre-penicillin era, and included, across the centuries, purgative agents, heat, and pyrogens. In the 19th century, mercury was widely used as oral compounds or prepared in topical salves, injections, and even fumigation, but treatment could last for years before being effective.[43] In 1908, Paul Ehrlich was awarded the Nobel Prize for the discover of arsphenamine (i.e., Salvarsan), an arsenical compound that can be considered the first modern antimicrobial agent. It was introduced at the beginning of the 1910s as the first effective treatment for syphilis and African trypanosomiasis. Salvarsan came to be used in combination with bismuth or mercury, and over 30 doses were recommended to prevent relapse and were supposed to be effective to reduce the risk of neurosyphilis, but this progression occurred in many patients anyway. Then in 1927, a Nobel prize was awarded to Julius Wagner-Jauregg for the invention of malariotherapy to treat neurosyphilis, which was based on the rational that inoculating patients with *Plasmodium vivax* induced a fever that was able to kill heat-sensitive *T. pallidum* bacteria.[46] At the time, Wagner-Jauregg concluded that malariotherapy was more effective the earlier it was used in the course of the disease and recommended combined treatment with Salvarsan. However, from 1925 to 1938, a considerable number of patients were unable to sustain this therapy, with different reported rates of mortality from 3% to 30%.

General Indications

Since 1943, penicillin has been an effective treatment for syphilis; with no reported resistance cases to date, it remains the recommended therapy. Benzathine penicillin G is the recommended treatment for syphilis in all stages.[36-41] However, it is important to estimate the schedule of treatment according to the stage, eventual pregnancy status, a possible allergy,

or whether the patient has neurosyphilis, otic syphilis, or ocular syphilis. In any case of allergy, it is suggested to use doxycycline 100 mg twice a day for 14 days in early syphilis and for 28 days in the late stage. Physicians should consider empiric treatment if, based on clinical presentation and epidemiologic risk, the index of suspicion is high, particularly if follow-up cannot be assured. Of note, CDC treatment recommendations for all stages and for neurosyphilis, otic syphilis, and ocular syphilis do not depend on HIV status or nontreponemal test titer.[44] The therapeutic schedule must be extended to the patient's partners in the same way. Treatment response is assessed clinically and serologically.[44,45]

Primary, Secondary, and Early Latent Syphilis

Treatment for both primary, secondary, and early latent syphilis consist of one administration of benzathine penicillin G 2.4 million units intramuscularly.

Late Latent Syphilis

The treatment consists of benzathine penicillin G 2.4 million units intramuscularly once a week for 3 consecutive weeks.

Tertiary Syphilis

Neurosyphilis, otic syphilis, and ocular syphilis require treatment with intravenous aqueous crystalline penicillin G for 10–14 days.

Neonatal Syphilis

As benzathine penicillin G is the only therapy with documented efficacy for treating both the pregnant individual and the fetus, pregnant patients must be desensitised and treated with penicillin.[44,45]

Treatment Reactions

Patient should be adequately and completely warned about treatment reactions. For example, penicillin G treatment might precipitate a Jarisch–Herxheimer reaction, which typically presents within 1 day as fever, headache, myalgia, and possibly worsening rash.[47-49] The hypothesised mechanism underlining the reaction could be related to a massive destruction of spirochaete, causing the release of lipoproteins, immune complex formation, and cytokine cascades, including TNFα, IL-6, and IL-8.[47] However, it is known that the reaction occurs more commonly and severely in patients with a higher clinical burden of disease and higher nontreponemal test titers. Often mistaken for a drug allergy, the reaction resolves spontaneously, typically within 24 hours. Antipyretics and hydration can be used for symptomatic relief. Pretreatments, such as acetaminophen and antihistamines, do not prevent the reaction.

MANAGEMENT AND FOLLOW-UP

Response to Treatment

Clinical and serologic follow-up should follow a determined interval at 1, 3, and 6 months after therapy. In addition, even if a nontreponemal test has been performed recently, a repeat nontreponemal test on the day of treatment should be performed to enable the evaluation of serologic response to treatment.[44,45]

Follow-up of HIV-uninfected Population

The CDC recommends clinical evaluation and nontreponemal tests at 6, 12, and 24 months for patients without HIV infection and at 3, 6, 9, 12, and 24 months for patients with HIV infection.[50] Serologic response is defined as a 4-fold or greater decline in nontreponemal test titers (e.g., from 1:64 to 1:16 or lower). Treatment failure should be considered if titer decline does not occur by 1 year for patients without HIV infection with primary or secondary syphilis and by 2 years for patients with HIV infection with early nonprimary, nonsecondary syphilis.

Follow-up of HIV-infected Population

Treatment failure should be considered if titer decline does not occur by 2 years for patients with HIV infection with primary, secondary, or early nonprimary, nonsecondary syphilis.[51]

Treatment Failure

Patients should be counselled to return for care if symptoms fail to resolve within 2 weeks. Suspected treatment failure warrants additional evaluation and management that is beyond the scope of this article. Lack of titer decline (called serologic nonresponse) affects 12–20% of patients with primary and secondary syphilis and is associated with lower baseline nontreponemal

titer, older age, late-stage infection, and possibly HIV infection. In addition, rising titers in a recently treated patient might indicate reinfection, which is not uncommon among patients with a history of syphilis.[41,52]

Additional Sexually Transmitted Infection Testing and HIV Prevention

Patients who are diagnosed with syphilis should be collaterally tested for HIV, hepatitis, and other STD, with particular attention to sexual-related vaccinations and pre-exposure or postexposure prophylaxis for HIV. The CDC recommends HIV testing for all patients with syphilis who are not known to have HIV.[42,44,45] In addition, a syphilis diagnosis within the previous 6 months is one CDC criterion for initiating pre-exposure prophylaxis. Among males (including MSM), a syphilis diagnosis is associated with a higher risk for subsequent HIV seroconversion. Eliciting a sexual and gender identity history, including the gender(s) of sexual partners, is essential to assess patients' sexual health needs. Physicians should encourage patients with syphilis to disclose their diagnosis to recent sex partner(s) to improve those persons' health and to stop onward transmission. Health departments can also assist with partner notification, if patients desire.

Ethical Considerations

Syphilis is a legally reportable disease for clinicians. Mechanisms and details of reporting depend on state or local regulations. Physician reporting, which includes stage, enables health departments to prioritise outreach efforts to primary and secondary syphilis patients who are likely to have been infectious to recent sex partners and helps with disease surveillance. Informing patients that the case will be reported, and that the public health department might follow-up with them, can facilitate subsequent positive interactions. Infants and children who are diagnosed with syphilis should have birth and maternal records reviewed to assess whether the infection was congenitally or sexually acquired. Management should be co-ordinated with a paediatric infectious disease specialist and should include evaluation for sexual abuse, typically by consulting child protection services.[44,45]

CONCLUSIONS

Syphilis, which appeared to be long forgotten before the 70s, is currently considered a public health problem. Diagnosis is still obtained late in most cases, and proper patient management and follow-up are not performed. Syphilis prevention and control efforts by national, state, and local public health agencies include disease surveillance, epidemiologic analyses, education of providers and the public, support for clinical and prevention services, outreach to recently diagnosed patients and their sex partners, and screening of persons who are at high risk for syphilis.

As summarised in the present review, that illustrates the current state of the art of syphilis diagnosis and treatment, the dermatologist who adequately knows syphilis can play a key role in providing the early and correct diagnosis and setting up in the proper management of patients.

References

1. Newman L et al. Global estimates of the prevalence and incidence of four curable sexually transmitted infections in 2012 based on systematic review and global reporting. 2015;10(12):e0143304.
2. World Health Organization (WHO). Report on global sexually transmitted infection surveillance 2015. 2015. Available at: https://apps.who.int/iris/bitstream/handle/10665/249553/9789241565301-eng.pdf?sequence=1. Last accessed: 8 February 2021.
3. Hook EW. Syphilis. Lancet 2017; 389:(10078):1550-7.
4. Public Health England (PHE). Infection report: sexually transmitted infections. 2015. Available at: https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/437433/hpr2215_STI_NCSP_v6.pdf. Last accessed: 12 January 2021.
5. Forrestel AK et al. Sexually acquired syphilis: historical aspects, microbiology, epidemiology, and clinical manifestations. J Am Acad Dermatol. 2020;82(1):1-14.
6. Melo FL et al. Syphilis at the crossroad of phylogenetics and paleopathology. PLoS Negl Trop Dis. 2010;4(1):e575.
7. Giacani L, Lukehart SA. The endemic treponematoses. Clin Microbiol Rev. 2014;27(1):89-115.
8. Darrow WW et al. Risk factors for human immunodeficiency virus (HIV) infection in homosexual men. Am J Public Health. 1987;77(4):479-83.
9. Hook EW III. Syphilis and HIV infection. J Infect Dis. 1989;160(3):530-4.

10. Stamm WE et al. The association between genital ulcer disease and the acquisition of HIV infection in homosexual men. JAMA 1988;260(10):1429-33.
11. Ghanem KG et al. The modern epidemic of syphilis. N Engl J Med. 2020;382(9):845-54.
12. Centers for Disease Control and Prevention (CDC). Sexually transmitted disease surveillance 2018. 2018. Available at: https://www.cdc.gov/std/stats18/STDSurveillance2018-full-report.pdf. Last accessed: 12 January 2021.
13. Beymer MR et al. Sex on demand: geosocial networking phone apps and risk of sexually transmitted infections among a cross-sectional sample of men who have sex with men in Los Angeles County. Sex Transm Infect. 2014;90(7):567-72.
14. Harmon ED, Robertson EW. Syphilis: a growing concern. Nurse Pract. 2019;44(8):21-8.
15. Centers for Disease Control and Prevention (CDC). Syphilis in pregnancy - 2015 STD Treatment Guidelines. 2015. Available at: https://www.cdc.gov/std/tg2015/syphilis-pregnancy.htm. Last accessed: 12 January 2021.
16. Hook EW 3rd, Marra CM. Acquired syphilis in adults. N Engl J Med. 1992;326(16):1060-9.
17. O'Byrne P, MacPherson P. Syphilis. BMJ. 2019;365:l4159.
18. Katz AR et al. Dermatologically challenging syphilis presentation. Int J STD AIDS. 2019;30(7):707-9.
19. Tognetti L et al. Unusual presentation of secondary syphilis: membranoproliferative glomerulonephritis and muco-cutaneous lesions. Int J STD AIDS. 2018;29(4):410-3.
20. Tognetti L et al. Syphilitic alopecia: uncommon trichoscopic findings. Dermatol Pract Concept. 2017;7(3):55-9.
21. Arando Lasagabaster M, Otero Guerra L. Syphilis. Enferm Infecc Microbiol Clin. 2019;37(6):398-404.
22. Barnett R. Syphilis. Lancet. 2018;391(10129):1471.
23. Jorge LM et al. Tertiary syphilis: tubero-serpiginous and tubero-ulcerous syphilids. Braz J Infect Dis. 2016;20(3):308-9.
24. Tampa M et al. Brief history of syphilis. J Med Life. 2014;7(1):4-10.
25. Olry R, Haines DE. Tabes dorsalis: Not, at all, "Elementary my dear Watson!". J Hist Neurosci. 2018;27(2):198-203.
26. Gonzalez H et al. Neurosyphilis. Semin Neurol. 2019;39(4):448-55.
27. Arrieta AC, Singh J. Congenital Syphilis. N Engl J Med. 2019;381(22):2157.
28. Engelkens HJ et al. Primary and secondary syphilis: a histopathological study. Int J STD AIDS. 1991;2(4):280-4.
29. Flamm A et al. Histopathologic features distinguishing secondary syphilis from its mimickers. J Am Acad Dermatol. 2020;82(1):156-60.
30. Rato M et al. Syphilis: relevance of immunohistochemistry for the diagnosis. JAAD Int. 2018;79(3):AB277.
31. Wang LN et al. [Sensitivity and specificity of ELISA based on recombinant Treponema pallidum antigen and rapid plasma reagin test in diagnosis of syphilis: a comparative study]. Zhonghua Yi Xue Za Zhi. 2007;87(24):1721-2. (In Chinese).
32. Kubanov A et al. Novel Treponema pallidum recombinant antigens for syphilis diagnostics: current status and future prospects. Biomed Res Int. 2017;2017:1436080.
33. Runina AV et al. Immunochip for syphilis serodiagnostics with the use of extended array of Treponema pallidum recombinant antigens. Bull Exp Biol Med. 2018;165(6):767-71.
34. Ortiz DA et al. The traditional or reverse algorithm for diagnosis of syphilis: pros and cons. Clin Infect Dis. 2020;71(1):S43-51.
35. Morshed MG, Singh AE. Recent trends in the serologic diagnosis of syphilis. Clin Vaccine Immunol. 2015;22(2):137-47.
36. Park IU et al. Performance of treponemal tests for the diagnosis of syphilis. Clin Infect Dis. 2019;68(6):913-8.
37. Tuddenham S et al. Syphilis laboratory guidelines: performance characteristics of nontreponemal antibody tests. Clin Infect Dis. 2020;71(Suppl 1):S21-42.
38. Park IU et al. Sensitivity and specificity of treponemal-specific tests for the diagnosis of syphilis. Clin Infect Dis. 2020;71:S13-20.
39. Vrbová E et al. A retrospective study on nested PCR detection of syphilis treponemes in clinical samples: PCR detection contributes to the diagnosis of syphilis in patients with seronegative and serodiscrepant results. 2020;15(8):e0237949.
40. Cornelisse VJ et al. Getting to the bottom of it: sexual positioning and stage of syphilis at diagnosis, and implications for syphilis screening. Clin Infect Dis. 2020;71(2):318-22.
41. Lin LR et al. Further evaluation of the characteristics of Treponema pallidum-specific IgM antibody in syphilis serofast reaction patients. Diagn Microbiol Infect Dis. 2011;71(3):201-7.
42. Young H et al. The architect syphilis assay for antibodies to Treponema pallidum: an automated screening assay with high sensitivity in primary syphilis. Sex Transm Infect. 2009;85(1):19-23.
43. O'Shea JG. 'Two minutes with venus, two years with mercury'--mercury as an antisyphilitic chemotherapeutic agent. J R Soc Med. 1990;83(6):392-5.
44. Workowski KA et al. Sexually transmitted diseases treatment guidelines, 2015. MMWR Morb Mortal Wkly Rep. 2015;64:(RR-03)1-137.
45. World Health Organization (WHO). WHO guidelines for the treatment of Treponema pallidum (syphilis). 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/249572/9789241549806-eng.f;jsessionid=DB5FF67A9897ED27291AEF0100114D75?sequence=1. Last accessed: 8 February 2021.
46. Austin SC et al. The history of malariotherapy for neurosyphilis. 374 Modern parallels. JAMA. 1992;268(4):516-9.
47. Pound MW, May DB. Proposed mechanisms and preventative options of Jarisch-Herxheimer reactions. J Clin Pharm Ther. 2005;30(3):291-5.
48. Yang CJ et al. Jarisch-Herxheimer reaction after penicillin therapy among patients with syphilis in the era of the HIV infection epidemic: incidence and risk factors. Clin Infect Dis. 2010;51:976-9.
49. Aronson IK, Soltani K. The enigma of the pathogenesis of the Jarisch-Herxheimer reaction. Br J Vener Dis. 1976;52(5):313-5.
50. Rolfs RT et al. A randomized trial of enhanced therapy for early syphilis in patients with and without human immunodeficiency virus infection. The Syphilis and HIV Study Group. N Engl J Med. 1997;337(5):307-14.
51. Sena AC et al. Response to therapy following retreatment of serofast early syphilis patients with benzathine penicillin. Clin Infect Dis. 2013;56:420-2.
52. Centers for Disease Control and Prevention (CDC). Preexposure prophylaxis for the prevention of HIV infection in the United States - 2017 update. 2017. Available at: https://www.cdc.gov/hiv/pdf/risk/prep/cdc-hiv-prep-guidelines-2017.pdf. Last accessed: 14 January 2021.

Management of Pulmonary Hydatid Cyst With Pleural Complications: A Case Series

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Abstract

Introduction: The aim of this observational, retrospective study was to review and describe clinical presentations and management of patients with pulmonary hydatid cysts (PHC) and pleural complications.

Methods: Complete case records from the previous 2 years were reviewed, including operative steps and follow-up of patients with PHC and pleural complications. Only four cases that presented with pleural complications were found out of 14 cases of surgically managed PHC.

Results: The most common symptoms in all patients were chest pain and fever. In all cases, the lower lobes of the lung were involved. Lung resection surgery was not required in any case. There was no postoperative respiratory failure or immediate or late mortality in any of these patients. The mean follow-up was 10 months for all these cases, with no pulmonary recurrence or complications.

Conclusion: Pulmonary parenchymal sparing surgical interventions are deemed to be the safest curative treatment for complicated PHC. Spontaneous pyopneumothorax can also be caused by complicated PHC.

INTRODUCTION

Hydatid cyst formation is a silent zoonotic disease caused by infection with *Echinococcus granulosus* metacestodes. Humans act as accidental intermediate hosts and the most common cyst sites are the liver and lung, but they may also be located in other organs, such as the brain, heart, and spleen. Because of slow cyst growth, pulmonary hydatidosis is often asymptomatic. Pulmonary hydatid cyst (PHC) often becomes symptomatic after cyst rupture in the pleural cavity or bronchus. In these cases,

PHC may be misdiagnosed with other diseases and therefore patients may receive inappropriate treatment.[1] Surgical methods for dealing with PHC include enucleation of intact cysts and cystotomy, with or without capitonnage, or lung resection for complicated or intact cysts. The ideal surgical technique and outcomes for PHC with pleural complication are unknown, and still the technique continues to be performed at the choice of the surgeon.

METHODS

On reviewing case records of patients with surgically managed PHC at the authors' institute within the last 2 years (2018–2019), only four out of 14 cases of PHC presented with pleural complications.

Of these four patients, there were two males and two females, with a mean age of 38 years. Three of these patients already had spontaneous pyopneumothorax. Two patients presented with a chest tube *in situ*. In one patient, a chest tube was used to stabilise them before operating. Another patient was found to have localised pleural thickening with a locally contained, leaking, ruptured cyst during operation. This patient had been given preoperative antihelminthic drugs after PHC diagnosis. Plain chest radiography, haematological tests, and contrast enhanced CT of the thorax with abdomen and ultrasonography was performed in all cases.

RESULTS

The most common symptoms in all four patients were chest pain and fever, followed by dyspnoea in three patients. No patients had skin eruptions, rashes, anaphylactic episodes, or haemoptysis. In three patients the cysts were unilateral. The hydatid cyst presented in the right lung in one patient and in the left lung in the other three patients. In all cases, the lower lobes of the lung were involved. The standard posterolateral thoracotomy incision was used in all cases for surgical exploration. The surgical techniques required were residual cystectomy with repair of the bronchial openings plus capitonnage and decortication. A double-lumen endobronchial tube and coverage of the uninfected area with scolicidal agent during the operative procedure and postoperative drug therapy were used in all cases to prevent recurrence. Lung resection surgery was not required in any case. Only one patient had long-standing postoperative air leak, though this proceeded to heal spontaneously. There was no postoperative respiratory failure and no patients needed long-term mechanical ventilation. There was no mortality in this case series. The mean follow-up was 10 months for all cases, and there was no pulmonary recurrence or complications. Complete case details are summarised in Table 1.

Table 1: Summary of pulmonary hydatid cases presented with pleural complications.

	Case One	Case Two	Case Three	Case Four
Age (years)	35	58	32	28
Sex	Male	Male	Female	Female
Side of pulmonary cyst	Left	Left	Left	Left and right
Site of pulmonary lobe	Lower	Lower	Lower	Lower
Associated hepatic involvement	No	Yes	No	Yes
History of animal contact	Sheep and pet dogs	Sheep and pet dogs	Pet dog	Pet dogs
Clinical manifestations	Chest pain Fever Dyspnoea Dry cough	Chest pain Fever Dyspnoea Dry cough Fatigue	Chest pain Fever Dyspnoea Dry cough	Chest pain Fever

Table 1 continued.

	Case One	Case Two	Case Three	Case Four
Preoperative complications	Left pyopneumothorax	Left pyopneumothorax	None	Left pyopneumothorax
Chest X-ray	Suggestive of left pyopneumothorax and intercostal drain *in situ*; no defined pulmonary cystic lesion (Figure 1).	Suggestive of left-sided basal haziness; empyema; blurred shadow of pulmonary cystic lesion present.	Giant pulmonary cyst (12 cm); no pleural finding.	Bilateral pulmonary cystic lesion present with left pneumothorax; empyema.
CT scan	Large left hydropneumothorax with serpiginous coiled up membranes in dependent parts, likely ruptured hydatid cyst with bronchopleural communication.	Small left hydropneumothorax with floating particles and membranes in dependent parts, a likely ruptured hydatid cyst with suspected bronchopleural communication. Few tree-in-bud nodules in left lower lobe suggestive of infective aetiology (Figure 2).	Superior segment of left lower lobe lung showing well-defined peripheral enhancing lesion (size: 12x7x6.5 mm). Hydatid cyst likely in transitional stage.	Complex cyst (size: 64x47x48 mm) in the left lower lobe of lung with air fluid levels and floating membranes, with moderate pleural effusion, consolidation in the left lower lobe. There was also a large simple cyst seen in the right lung (size: 4.6x4.0x5.9 mm) and in the right lobe of the liver.
Antihelminthic drug therapy	Postoperatively	Postoperatively	Preoperatively; started upon diagnosis and continued postoperatively	Postoperatively
Tube thoracostomy (preoperative)	Yes (already from outside)	No	No	Yes (before operation)
Surgery Incision	Left posterolateral thoracotomy	Left posterolateral thoracotomy	Left posterolateral thoracotomy	Left posterolateral thoracotomy
Intraoperative finding	Empyema with hydatid cyst contents lying freely in pleural space. Cavity with significant air leak.	Empyema with ruptured hydatid cyst. Some contents lying freely in pleural space. Cyst wall attached to cavity with minor air leak.	Localised hydatid cyst rupture attached to pleura with small extrapulmonary empyema cavity contained pus and debris. Pleural thickening. No air leak.	Empyema with ruptured hydatid cyst. Some contents lying freely in pleural space. Cyst wall attached to cavity with minor air leak.
Procedure	Cystectomy, capitonnage, and decortication.	Cystectomy, capitonnage, and decortication.	Cystotomy, capitonnage, and decortication.	Cystectomy, capitonnage, and decortication.
Postoperative complication	Prolonged air leakage, resolved in 3 weeks	No	No	No
Postoperative hospital stay	14 days	10 days	10 days	9 days
Mortality	No	No	No	No

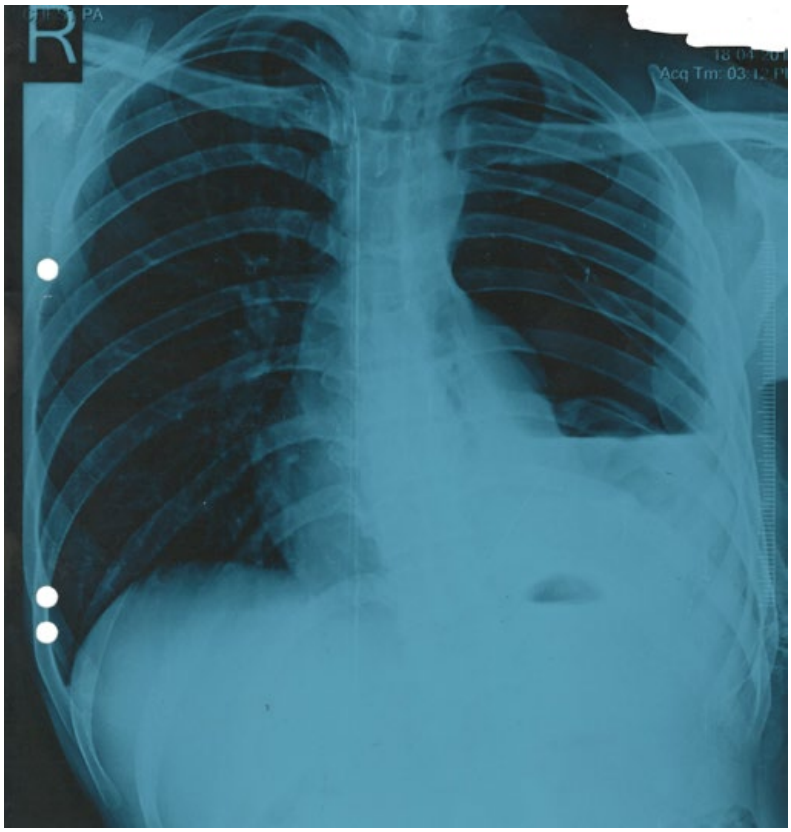

Figure 1: Chest X-ray showing massive left pneumothorax with collapsed left lung and intercostal drain *in situ* (Case One).

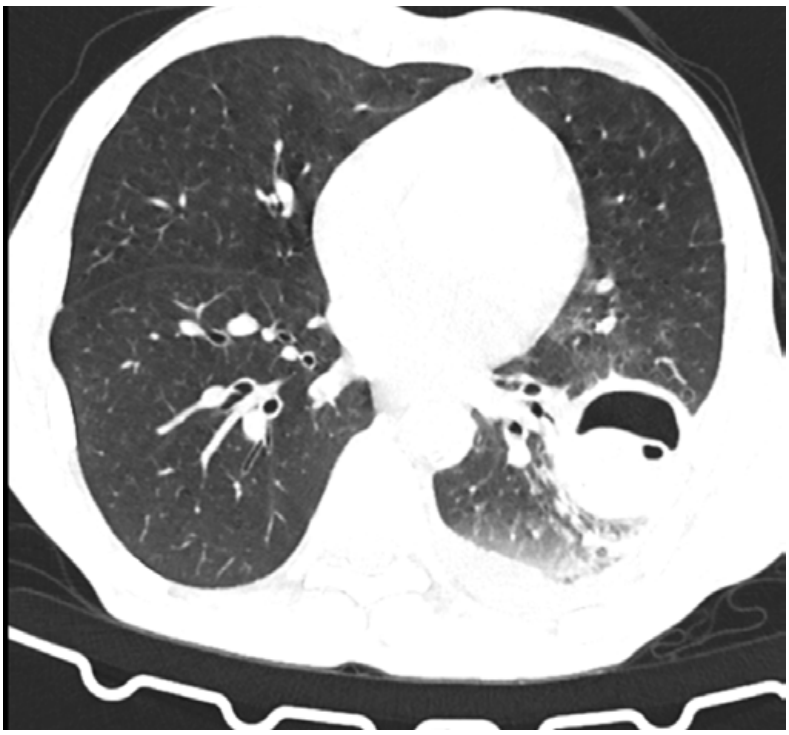

Figure 2: Chest CT scan of a patient with a cyst cavity in the posterobasal segment of the left lower lobe adhered to the lateral chest wall with loculation in the cyst and air-fluid level (perforated hydatid cyst) (Case Two).

DISCUSSION

Hydatid disease is one of the most important helminthic diseases.[1] The liver is the most effected organ, followed by the lungs (almost 25% of cases) in patients with hydatidosis. The lung may be affected when the liver is bypassed via the lymphatic system.[1] One of the unusual complications of pulmonary hydatidosis is rupture, which can occur spontaneously when it reaches 7–10 cm in diameter, secondary to an infectious process, or after coughing, trauma to the chest, or needle aspiration.[2,3] In the study by Aribas et al.[4] of 145 patients with complicated hydatid cysts of the lung, 88% had ruptured cysts and 16% had both intact and ruptured cysts. In another study involving 537 patients with PHC, 87 (16%) had ruptured cysts, with a higher incidence in cysts >10 cm in diameter (27% versus 15%).[5] Another study by Sayir et al.[6] revealed a similar percentage of rupture (18%).

The clinical appearance is inconstant for these complicated perforated hydatid cysts and depend upon the characteristics of perforation. The cyst frequently ruptures into the bronchus but in some cases it ruptures into the pleura. Usually, rupture can be classified into three types: contained, communicating, and direct. In most cases, the solid residues in the collapsed parasitic membrane cavity are the source of the recurrent infection. Coughing sputum, chest pain, haemoptysis, dyspnoea, and fever are the most common symptoms of complicated PHC.[7] Rupture of a hydatid cyst into the pleural cavity can cause pneumothorax, pleural effusion, or empyema. Cyst rupture into the pleural cavity can also result in tension pneumothorax.[8]

Serologic tests are used in the diagnosis and follow-up of patients with hydatid cysts in endemic regions because of their low cost and convenient administration. Serologic tests that can be used in the diagnosis and follow-up of hydatid cysts include *Echinococcus* indirect hemagglutination, ELISA, IgG measuring, immunoelectrophoresis, and indirect fluorescent antibody testing. CT scans of the thorax have an important role in patients with complicated PHC. There are various signs that help to diagnose a ruptured hydatid cyst in a CT scan including air crescent or meniscus, Water Lily or Camelotte, Cumbo, and air bubble and signet ring signs.[9]

Surgical treatment remains the most valid method of treatment for a PHC, regardless of whether it is symptomatic. The aim of surgical intervention is removal of the germinative membrane without causing intraoperative contamination and preventing an intrapulmonary residual cystic space. Therefore, varying techniques, such as enucleation, pericystectomy, and simple cystotomy with or without capitonnage of the pericystic space, can be chosen in appropriate conditions during the operation.[4] Surgical treatment should be performed by preserving the lung parenchyma where possible. Resection should not be avoided if complications develop (e.g., significant infection) or if there is bronchiectasis.[6] Bacterial infection is one of the most serious complications of a perforated cyst, leading to empyema. Decortication is necessary in such cases because of pleural contamination and pleural thickening.

Pulmonary resection must be avoided as much as possible. However, segmental resection, wedge resection, and lobectomy are justified when lesser procedures are excluded because of the size and number of cysts and degree of infection. The principal indications for lobectomy are large cysts involving more than 50% of the lobe, cysts with severe pulmonary suppuration not responding to treatment, multiple unilobar cysts, and a sequelae of hydatid disease such as bronchiectasis, pulmonary fibrosis, or severe haemorrhage, as capitonnage or any other procedure leads to complications in such patients.[10]

In the literature, various surgical techniques and procedures have been described for management of PHC, but in complicated scenarios, especially in pleural rupture, these procedures can be very difficult to perform because of ill-defined planes and extensive adhesions as a result of intense pleural reaction. A more feasible surgery in this case would be cystectomy or, in the case of nonsalvageable lung tissue, limited anatomical resection. Turna et al.[10] failed to show an advantage of added capitonnage procedures, but this study is demerited by its small sample size and nonstandardised criteria for defining significant postoperative air leak.

The choice between a cystectomy and a limited resection or segmentectomy usually depends on the individual surgeon's experience and

judgement about the condition of the adjacent lung tissue.[11] In this case series, three out of the four cases did not have a well-defined plane for a cystotomy. However, the lung tissue was amenable to repair and hence a cystectomy was performed, followed by capitonnage. Even similarly designed studies have shown contrasting results.[12] A large retrospective study by Yaldiz et al.[13] showed acceptably low complication rates with capitonnage. Capitonnage has been shown to have superior results in children compared to cystotomy alone.[14] The authors routinely performed capitonnage in all cases at their institute. As it is essential to have a well-expanded lung at the end of the surgical procedure, decortication was required in almost all cases of ruptured hydatid cyst into the pleural cavity.

Research has shown that 73–75% of patients may respond to medical management; however, the reported cure rates are only 25–30%. Anthelmintics weaken the cyst wall, thus increasing the likelihood of cyst rupture.[10] Every patient who has hydatid cysts of the lung should be investigated for associated cysts in the liver. Many liver cysts can be approached from a thoracic route after incising the diaphragm.[15] When bilateral cysts are present, some surgeons prefer a one-stage operation via a median sternotomy and this method is applicable when bilateral lung and liver cysts are present. A two-stage thoracotomy is preferred by some surgeons, as sternotomy carries its associated risk of mediastinitis. The side with the larger, ruptured, and infected cyst is operated on first. The period between two thoracotomies varies from 3 weeks to 2 months.[4,6]

Medical therapy with benzimidazoles is clearly valuable in disseminated disease, including secondary lung or pleural hydatidosis, in poor surgical risk patients, and in cases of intraoperative spillage of hydatid fluid. Albendazole is given in two divided doses of 10–15 mg/kg body weight/day, the usual adult daily dose being 800 mg. Therapy is most often indicated for a minimum of 3–6 months.[16] Prevention of hydatid disease can often be achieved by avoiding close contact with dogs and sheep. Careful washing of vegetables and products can also reduce infection. Prohibition of domestic slaughtering of sheep and proper offal disposal prevents dogs from consuming infected viscera, thus disrupting the life cycle of the parasite and stoping transmission. Reducing numbers of stray dogs and surveillance techniques, including coproantigen tests, could also help to reduce infections in some endemic areas.[16]

CONCLUSIONS

In this case series, presence of pyopneumothorax was found in the majority of complicated cases but ultimately good outcomes were achieved with surgical intervention. Lung-sparing surgical interventions are the most feasible and safest curative treatment for complicated PHC with rupture in pleural space, offering negligible morbidity and mortality. Further it can be concluded that complicated hydatid cyst should also be considered in the differential diagnosis of spontaneous pyopneumothorax. Use of preoperative drug therapy in these cases is not established and theoretically medical therapy can cause cyst rupture and further complications.

PATIENT CONSENT

Patients and relatives were well informed and signed consent forms regarding publishing their data and photographs. Anonymity during reporting was also taken with due care.

References

1. Kaur M, Singh R. Ruptured pulmonary hydatid cyst: the camalote sign. Indian J Clin Prac. 2013;23(12):856-8.
2. Karimi M et al. Ruptured pulmonary hydatid cyst: a case report. J Parasit Dis. 2017;41(3):899-902.
3. Puri D et al. Ruptured hydatid cyst with an unusual presentation. Case Rep Surg. 2011;2011:730604.
4. Aribas OK et al. Pleural complications of hydatid disease. J Thorac Cardiovasc Surg. 2002;123(3):492-7.
5. Usluer O et al. Surgical management of pulmonary hydatid cysts. Tex Heart Inst J. 2010;37(4):429-34.
6. Sayir F et al. Surgical treatment of pulmonary hydatid cysts, which perforated to the pleura. Eurasian J Med. 2012;44:79-83.
7. Cobanoglu U et al. Therapeutic strategies for complications

secondary to hydatid cyst rupture. Int J Clin Exp Med. 2011;4(3):220-6.

8. Kuzucu A et al. Complicated hydatid cysts of the lung: clinical and therapeutic issues. Ann Thorac Surg. 2004;77(4):1200-4.
9. Sarkar M et al. Cystic pulmonary hydatidosis. Lung India. 2016;33(2):179-91.
10. Turna A et al. Surgical treatment of pulmonary hydatid cysts: is capitonnage necessary? Ann Thorac Surg. 2002;74(1):191-5.
11. Nabi S, Waseem T. Pulmonary hydatid disease: what is the optimal surgical strategy? Int J Surg. 2010;8(8):612-6.
12. Bilgin M et al. Is capitonnage unnecessary in the surgery of intact pulmonary hydatic cyst? ANZ J Surg. 2004;74(1-2):40-2.
13. Yaldiz S et al. Capitonnage results in low postoperative morbidity in the surgical treatment of pulmonary echinococcosis. Ann of Thorac Surg. 2012;93(3):962-6.
14. Kosar A et al. Effect of capitonnage and cystotomy on outcome of childhood pulmonary hydatid cysts. J Thorac Cardiovasc Surg. 2006;132(3):560-4.
15. Yalcinkaya I et al. Surgical treatment of hydatid cyst of the lung: review of 30 cases. Eur Respir J. 1999;13(2):441-4.
16. Morar R, Feldman C. Pulmonary echinococcosis. Eur Respir J. 2003;21(6):1069-77.

‘Dry’ Pericarditis with Rapid Progression to Tamponade as a Feature of COVID-19

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Abstract

Pericardial inflammation is a recognised feature of coronavirus disease (COVID-19). The authors herein present the case of a female with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection who developed a large and life-threatening pericardial effusion over a few days following the onset of pericarditis, despite prompt commencement of treatment. This was successfully drained, and she was discharged in stable condition on oral nonsteroidal anti-inflammatory drugs and colchicine.

At 6-week follow-up she had made a full recovery, and repeat echocardiography demonstrated no recurrence of effusion or evidence of constrictive physiology.

CASE REPORT

A 63-year-old female presented to hospital with severe, central, sharp chest pain, exacerbated by deep inspiration and upon lying back. She denied cough, fever, or other systemic symptoms. Her past medical history was significant for myelofibrosis, treated with stem cell transplant and complicated by subsequent graft-versus-host disease in December 2018.

Baseline blood tests showed normal haemoglobin and total white cell count with mild lymphocytosis and thrombocytopenia. C-reactive protein was elevated at 59 mg/L (normal range 0–10), as was D-dimer at 743 µg/L (0–500). High-sensitivity troponin-I levels taken 6 hours apart were in the normal range. A chest radiograph showed a chronically elevated right hemidiaphragm but no acute pathology. Baseline 12-lead ECG showed sinus rhythm with subtle PR-segment depression and saddle ST-segment elevation in the inferolateral leads (Figure 1A). A nasopharyngeal swab, sent for reverse-transcriptase (RT)-PCR assay in line with local policy in place because of the coronavirus disease (COVID-19) pandemic, was negative for all respiratory viruses except severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2).

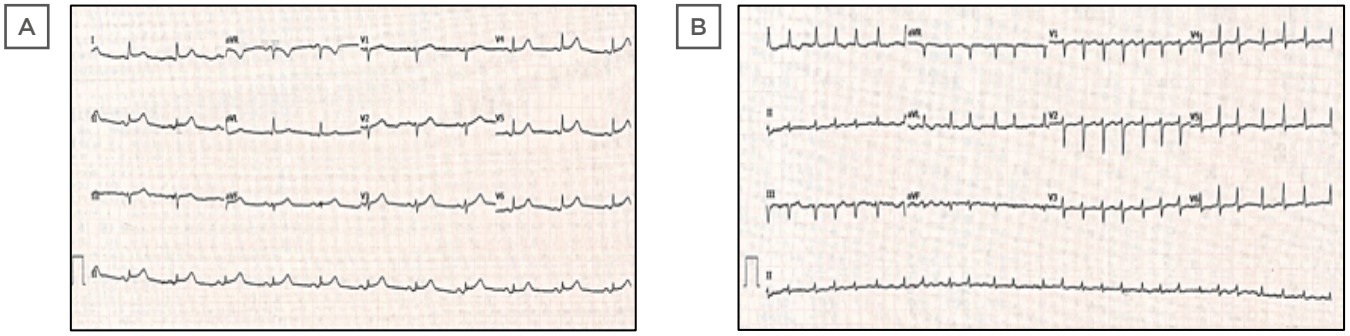

Figure 1: A) Admission ECG demonstrating sinus rhythm with PR depression and a concave ST elevation in inferolateral leads. **B)** Subsequent ECG showing new-onset atrial fibrillation at a rate of 152 beats per minute with lower voltage complexes in the limb leads and electrical alternans.

Pericarditis was the prime differential diagnosis, but in view of the clinical presentation, raised D-dimer, and history of malignancy, a CT pulmonary angiogram was performed. No pulmonary embolism was seen, but the scan demonstrated collapse and parenchymal inflammatory changes at the right lung base, and minimal pericardial thickening with no pericardial effusion (Figure 2).

The patient was commenced on oral antibiotics for lower respiratory tract infection and nonsteroidal anti-inflammatories (NSAID) for pericarditis.

Four days later she deteriorated, with temperature spikes and rising inflammatory markers. Her ECG at this time showed new-onset atrial fibrillation (AF) at a rate of 152 beats per minute, with low-voltage complexes in the limb leads and subtle beat-to-beat alternations of QRS amplitude consistent with electrical alternans (Figure 1B). Her blood pressure had fallen to 108/68; she was becoming pale, diaphoretic, and breathless; and clinical examination indicated elevated central venous pressure. Urgent transthoracic echocardiography (TTE) demonstrated a large global pericardial effusion with a maximum depth of 3.1 cm and echocardiographic features of tamponade, namely right ventricular diastolic collapse and respiratory variability in mitral valve inflow velocity of >25% (Figure 3). The left ventricular ejection fraction was well-preserved at 55%. There were no regional wall motion abnormalities or echo-bright areas of myocardium on TTE suggestive of myocarditis. Given her infective state and her precarious haemodynamic situation, emergency pericardiocentesis was undertaken at the bedside, yielding over 600 mL of serosanguinous fluid and restoring adequate blood pressure. Analysis of the pericardial fluid showed it to be a sterile, exudative effusion (fluid albumin 28 g/L against contemporaneous serum albumin 32 g/L). Cytology revealed heavily bloodstained fluid with occasional macrophages present but no malignant cells. No SARS-CoV-2 or other standard viral RNA was detected in the aspirate.

She made a good recovery thereafter, and was discharged home 48 hours later on NSAID, colchicine 0.5 mg twice per day, bisoprolol 2.5 mg once per day, and a proton-pump inhibitor. AF had resolved following drainage of the fluid and, given that the AF was thought to be triggered by atrial irritation and her CHA2DS2-VASc score was 1 (female sex), an anticoagulant was considered ill-advised.

At 6-week follow-up the patient had made a full symptomatic and functional recovery. Repeat TTE showed good left ventricular systolic function and no recurrence of effusion, nor evidence of pericardial thickening or constrictive physiology.

DISCUSSION

The authors have presented a case of lone pericarditis as the predominate presenting feature of COVID-19 infection, the most noteworthy feature of which is the rapid progression to cardiac tamponade despite prompt commencement of anti-inflammatory medication.

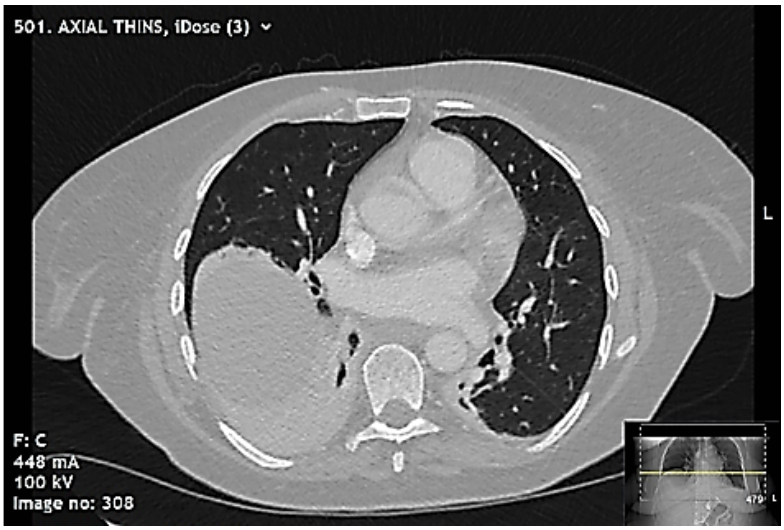

Figure 2: Selected slice from CT pulmonary angiogram demonstrating right lower zone collapse with mild inflammatory changes, mild pericardial thickening, and no pericardial effusion.

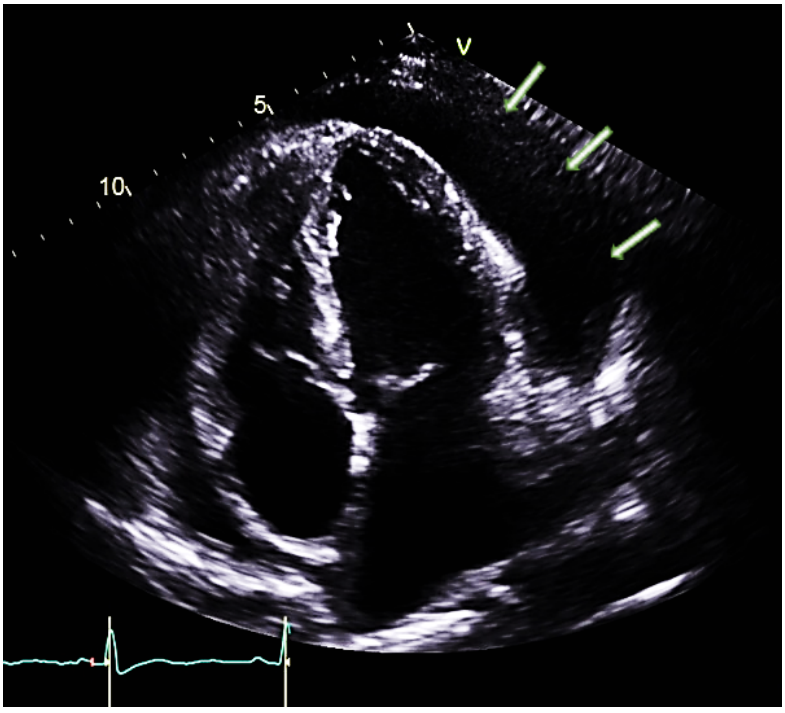

Figure 3: Transthoracic echocardiogram (apical four chamber view) demonstrating large global pericardial effusion (shown with arrows).

Following the first reported cases of COVID-19, caused by SARS-CoV-2, from Wuhan, China in December 2019, the devastating morbidity and mortality of the virus has led to an extraordinary level of global research to better understand the pathophysiology and clinical manifestations of infection. While initial concerns focussed on development of fever, coryzal symptoms, and pneumonia,[1] appreciation of the extensive range of extrapulmonary symptoms, especially cardiac, has been growing. Despite this, reports of pericardial inflammation and tamponade caused by COVID-19 remain uncommon, particularly in the absence of other systemic features; in many reports myopericarditis complicates COVID-19 pneumonia rather than occurring alone, while

tamponade, where encountered, tends to develop over a more protracted period than seen in this case.[2,3] Cardiac involvement, though, does appear to signify a poorer prognosis.[4]

The mechanism of cardiac inflammation in COVID-19 is not well understood at present, though some inferential conclusions have been made based on the pathogenicity of previous coronaviruses, namely SARS-CoV (responsible for the SARS outbreak in 2003) and the Middle East respiratory syndrome-related coronavirus (MERS-CoV). SARS-CoV-2, much like its predecessors, is known to enter myocardial cells through interaction with the angiotensin-converting enzyme-2 receptor. SARS-CoV RNA could be detected in necropsy specimens of human myocardium during the SARS pandemic[5] and significant macrophage infiltration was also noted, supporting the theory of direct viral invasion and myocardial damage as a mechanism of initial injury. Subsequent stimulation of proinflammatory cytokine production, such as TNFα, IL-6, and IL-8, then occurs. Ultimately, this can be followed by upregulation of interstitial fibrotic pathways, via Smad3-induced modulation of TGFβ signalling,[6] which mediates scarring.

Generally, viral infection is the most common cause of pericarditis.[7] Previous prospective studies have shown that pericardial effusion is a frequent complication of pericarditis, evident about 73% of the time,[8] but is typically mild. Large effusions and tamponade following pericarditis are considerably rarer, occurring in around 2–3% of cases and generally developing several weeks or months after initial presentation. In the chronic setting, large volumes of fluid (often as much 2–3 litres) can accumulate in the pericardial space without becoming clinically apparent because gradual pericardial stretch offsets any change in pericardial pressure. However, over a shorter timeframe (typically hours to days), the accretion of fluid can quickly outstrip pericardial compliance, thus only a few mL of exudate may be required for pericardial pressure to exceed right ventricular filling pressure and cause tamponade.[9] Accumulation of >600 mL pericardial fluid over 3–4 days, especially without earlier clinical manifestation, is therefore exceptional.

Whilst viral pericarditis is recognised as the most common aetiological factor, establishing direct causal correlation between viral infection and pericardial inflammation can be challenging. Ideally this would be done by demonstrating viral presence in a pericardial aspirate through culture or RT-PCR testing in a patient with concurrent clinical evidence of systemic infection with the same virus. However, in general clinical practice, as in this case, this is frequently not possible. Pierre-Yves et al.[10] proposed a systematic cascade of investigations to yield a diagnosis in pericarditis, shown in a series of 106 pericardial aspirates over a 7-year period. While a three-fold improvement in diagnostic yield was demonstrated with this method, it is worth noting that PCR gave a positive diagnosis in only 11 out of 37 cases where the diagnosis had not been reached with other methods. Successful detection of SARS-CoV-2 in pericardial fluid using PCR has, to date, been reported exceptionally rarely.[11] The diagnosis is often made based on the temporal association between infection with a biologically plausible aetiological agent and onset of pericarditis, combined with ruling out other potential causes through biochemical, immunological, and microbiological analysis of serum and pericardial fluid.

The patient in this case was started on high-dose NSAID and colchicine, as per standard international guidance.[12,13] The safety of NSAID use during the COVID-19 pandemic had been called into question. Originally, it had been suggested that NSAID use increased cellular expression of the ACE-2 receptor, which could facilitate viral binding and cellular invasion.[14] However, no clear evidence supporting this assertion has been proposed in the literature. Others had suggested a potential exacerbation of harmful systemic, particularly cardiorenal, effects in people who were unwell and dehydrated due to viral infection, which was compounded by anecdotal reports of individuals who suffered worsening symptoms following administration of ibuprofen. The World Health Organization (WHO) subsequently advised against the use of NSAID because of the potential risk of clinical worsening in patients with SARS-CoV-2 infection. However, the lack of good quality data against NSAID led to a subsequent reversal of that recommendation. Official guidance from the U.S. Food and Drug Administration (FDA) and other international medical bodies now supports NSAID use for those prescribed the drug for

a pre-existing condition or when no suitable alternative is available.[15,16] Thus, despite the initial scepticism over the potentially harmful effects of NSAID administration in patients with COVID-19, this remains the recommended treatment for pericarditis.

Colchicine is a well-established primary treatment agent for pericarditis. It exerts an anti-inflammatory effect by inhibiting microtubule formation, which in turn disrupts the nucleotide-binding oligomerisation domain-like receptor pyrin domain-containing-3 (NLRP3) inflammasome. Inhibition of the NLRP3 inflammasome downgrades the release of IL-1, which abrogates the recruitment of myeloid leucocytes, such as neutrophils, monocytes, and macrophages, to the site of injury.[17] Colchicine may also play a role in diminishing the inflammatory response in the early stages of COVID-19 infection to prevent onset of immunopathological effects including acute respiratory distress syndrome; this is the subject of investigation for several upcoming European trials.[18,19] For now, colchicine remains a favourable treatment for pericarditis in those concurrently infected with COVID-19.

Corticosteroids are indicated as adjunctive treatment for pericarditis in patients with incomplete response to NSAID and colchicine, or for those in whom these agents are contraindicated,[12] but current international guidance advocates avoidance in cases of pericarditis with infective aetiology. However, the beneficial anti-inflammatory properties of corticosteroids may offset the risk of increased susceptibility to viral replication in cases of advanced COVID-19 pneumonia when the immunopathologic response is the predominating issue.[20] Trial data to clarify the optimal timing and dosage of corticosteroid administration in patients with COVID-19 are eagerly awaited.

CONCLUSION

This case demonstrates the unusual clinical event of rapid progression from dry pericardium to cardiac tamponade over a few days despite prompt treatment with anti-inflammatory medication. It highlights the potential for patients with COVID-19-related cardiac inflammatory conditions to develop life-threatening effusions within a short timeframe, and the need to be vigilant for this. NSAID and colchicine remain first-line treatments for pericarditis in patients with COVID-19.

References

1. Guan WJ et al. Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med. 2020;41(22):2130.
2. Hua A et al. Life-threatening cardiac tamponade complicating myo-pericarditis in COVID-19, Eur Heart J. 2020;DOI:10.1093/eurheartj/ehaa253.
3. Dabbagh MF et al. Cardiac tamponade secondary to COVID-19. JACC Case Rep. 2020;DOI:10.1016/j.jaccas.2020.04.009. [Epub ahead of print].
4. Shi S et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. JAMA Cardiol. 2020;DOI:10.1001/jamacardio.2020.0950.
5. Oudit GY et al. SARS-coronavirus modulation of myocardial ACE2 expression and inflammation in patients with SARS. Eur J Clin Invest. 2009;39(7):618-25.
6. Zhao X et al. Severe acute respiratory syndrome-associated coronavirus nucleocap-sid protein interacts with Smad3 and modulates transforming growth factor-beta signaling. J Biol Chem. 2008;283(6):3272-80.
7. Ramasamy V et al. Established and novel pathophysiological mechanisms of pericardial injury and constrictive pericarditis. World J Cardiol. 2018;10(9):87-96.
8. Imazio M et al. Good prognosis for pericarditis with and without myocardial involvement: results from a multicenter, prospective cohort study. Circulation. 2013;128(1):42-9.
9. Spodick DH. Acute cardiac tamponade. N Engl J Med. 2003;349(7):684-90.
10. Pierre-Yves L et al. Molecular analysis of pericardial fluid: a 7-year experience, Euro Heart J. 2006;27(16):1942-6.
11. Farina A et al. SARS-CoV-2 detection in the pericardial fluid of a patient with cardiac tamponade. Eur J Intern Med. 2020;76:100-1.
12. Adler Y et al. 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2015;36(42):2921-64.
13. Imazio M, Adler Y. Management of pericardial effusion. Eur Heart J. 2013;34(16):1186-97.
14. Fang L et al. Are patients with hypertension and diabetes mellitus at increased risk for COVID-19 infection? Lancet Respir Med. 2020;8:e21.
15. U.S. Food and Drug Administration (FDA). FDA advises patients on use of non-steroidal anti-inflammatory drugs (NSAIDs) for COVID-19. 2020. Available at: https://www.fda.gov/drugs/drug-safety-and-availability/fda-advises-patients-use-non-steroidal-anti-inflammatory-drugs-nsaids-covid-19. Last accessed: 14

December 2020.

16. World Health Organization (WHO). The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19. 2020. Available at: https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19. Last accessed: 14 De-cember 2020.
17. Cremer PC et al. Complicated pericarditis: understanding risk factors and patho-physiology to inform imaging and treatment. J Am Coll Cardiol. 2016;68(21):2311-28.
18. Deftereos SG et al. Effect of colchicine vs standard care on cardiac and inflammato-ry biomarkers and clinical outcomes in patients hospitalized with coronavirus dis-ease 2019: the GRECCO-19 randomized clinical trial. JAMA Netw Open. 2020;3(6):e2013136.
19. Schlesinger N et al. Colchicine in COVID-19: an old drug, new use. Curr Pharmacol Rep. 2020:1-9. [Epub ahead of print].
20. Imazio M et al. Anti-inflammatory therapies for pericardial diseases in the COVID-19 pandemic: safety and potentiality. J Cardiovasc Med. 2020;21(9):625-9.

Transient Cutaneous Alterations of the Newborn

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Abstract

Neonatal cutaneous alterations are common, usually appearing at birth or during the first few days of life. Most of these conditions are physiological, benign, and transient, arising from a combination of immaturity of the newborn skin with environmental factors. Nonetheless, some of them may eventually be a clue to underlying disorders. Physicians should therefore be aware of these clinical manifestations so that parents can be reassured and, when necessary, complementary investigations can be undertaken.

INTRODUCTION

At birth, the skin of the newborn suddenly comes into contact with the extrauterine world: a dry and aerobic environment.[1] Newborn skin is 40–60% thicker than adult skin, with weaker intercellular attachment and decreased production of sweat.[2] Newborn skin is therefore more vulnerable, although structurally similar to adult skin, and trauma associated with delivery leaves its marks on it.[3] Moreover, newborn skin must rapidly adapt and mature to provide protection against infection, toxins, changes in temperature, and transepidermal water loss, which poses an additional stress.[1]

Because of these factors, cutaneous alterations are relatively common in the neonatal period.[3] Most of these conditions are physiological, benign, and transient, thus do not require therapy.[4] Nevertheless, they are frequently a cause of concern to parents, who need reassurance about its nature.

In this paper, several common cutaneous alterations observed in newborn skin are reviewed. In the first part, physiological changes are covered, including traumatic, vascular, pigmentary, and hormonal conditions. In the second part, a review of the most common rashes of the newborn is undertaken. Although not typically apparent during the neonatal period, infantile acropustulosis and eosinophilic pustular folliculitis are included as these are important in the differential diagnosis of other conditions.

PHYSIOLOGICAL ALTERATIONS

Vernix Caseosa

The vernix caseosa is a protective layer which covers neonatal skin at birth (Figure 1). It is a

complex membranous substance comprising 80% water, 10% protein, and 10% lipids, which include barrier lipids such as ceramides, free fatty acids, phospholipids, and cholesterol, partly synthesised by fetal sebaceous glands during the last trimester of pregnancy.[5] In its composition there are also shed lanugo hair and desquamated cells. *In utero*, the vernix protects neonatal skin against amniotic fluid.[1] During transition to an extrauterine environment, the vernix has several important functions including lubrication of the birth canal during parturition, prevention of water loss, and temperature regulation. It is also implicated in the development of innate immunity and facilitates reduction of skin pH to the ideal range for optimal skin function;[1,5] therefore, the vernix should be left as undisturbed as possible. Gentle bathing or dry wiping does not significantly disrupt this layer, and should therefore be the procedures of choice for newborns' hygiene.[1]

TRAUMATIC LESIONS

Sucking Blisters

Sucking blisters are estimated to occur in 1:250 live births and result from vigorous sucking by the infant during fetal life. Clinically, flaccid bullae on a noninflamed base are seen, which rupture easily, leading to linear or round erosions. Lesions are present at birth and are located mainly on the forearm, wrist, and hand. Although frequently solitary, blisters can be multiple and bilateral.[6] Diagnosis of congenital sucking blisters is one of exclusion. The absence of lesions in other body regions, the timing of onset, and the rapid resolution of the blisters, in combination with the otherwise well appearance of the neonate, are highly suggestive of this condition.[7] Differential diagnosis of sucking blisters includes congenital or neonatal herpes simplex virus infection, fetal or neonatal varicella, bullous impetigo, epidermolysis bullosa, congenital syphilis, or congenital candidiasis, among other rarer entities.[6] Sucking blisters resolve spontaneously in days to weeks without sequelae, and therefore no specific therapy is needed.[6]

Caput Succedaneum and Cephalohaematoma

Caput succedaneum refers to a collection of oedematous fluid above the periosteum, between the outermost layer of the scalp and the subcutaneous tissue. It is a common lesion seen at birth, and results from the high pressure exerted on the infant's head by the vaginal walls and uterus as the head passes through the narrowed cervix during labour.[8]

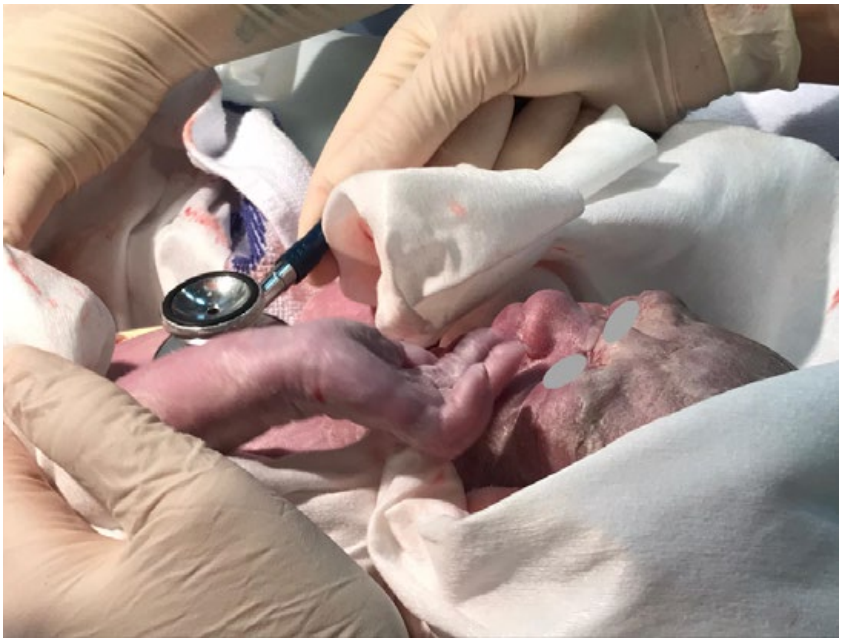

Figure 1: Vernix caseosa covering the skin of a newborn.

Although caput succedaneum may occur in the absence of risk factors, incidence increases in difficult or prolonged labours, with premature rupture of the amniotic membranes, in *primigravidae*, and in instrument-assisted deliveries. This condition is evident immediately after delivery and gradually decreases in size thereafter.[9] On physical examination, it is generally 1–2 cm in depth and has a soft, boggy feel with irregular margins. Petechiae, purpura, and an ecchymotic appearance may be present.[8]

Cephalohaematoma is a subperiosteal accumulation of blood, which occurs infrequently, with an incidence of 0.4–2.5% of all live births. It is more common in *primigravidae*, in infants with higher percentiles, and following instrument-assisted deliveries or prolonged, difficult labour and, for unknown reasons, occurs twice as often in males as in females. Because of the slow nature of subperiostial bleeding, cephalohaematomas are not usually present at birth but develop hours or even days after delivery.[9] As the bleeding continues and blood occupies the subperiosteal space, pressure acts as a tamponade to stop further bleeding. A firm, enlarged unilateral or bilateral bump covering one or more bones of the scalp characterises this lesion. Unlike caput succedaneum, cephalohaematomas do not cross suture lines.[8]

Cephalohaematoma and capput succedaneum must be distinguished from subgaleal haematomas, which, unlike the former conditions, can be life-threatening. Neonatal subgaleal haematomas are usually associated with vacuum extraction deliveries, although they have also been reported in deliveries without instrument use.[10] Observation is the primary treatment for both uncomplicated caput succedaneum and cephalohaematoma. Resolution of caput succedaneum is generally spontaneous and occurs within the first few days following birth. A cephalohaematoma may take longer to resolve, but most cases do so within 2 to 6 weeks of life.[8]

VASCULAR PHENOMENON

Acrocyanosis

Acrocyanosis is often seen in healthy newborns during the first hours of life and refers to the occurrence of peripheral cyanosis around the mouth and the extremities. It is caused by benign vasomotor changes that result in peripheral vasoconstriction and increased tissue oxygen extraction, attributed to peripheral arteriole hypertonia. Acrocyanosis is a benign condition and may persist for 24 to 48 hours. After this period, it may occasionally recur in the context of cold exposure or crying.[11] Acrocyanosis must be distinguished from central cyanosis. This is defined as a dusky appearance of the body and the mucous membranes and is always concerning beyond the first 10 minutes of life. Abnormalities in ventilation, congenital heart abnormalities, and haemoglobinopathies are amongst the main causes of central cyanosis.[11]

Cutis Marmorata

Cutis marmorata is a benign entity characterised by the appearance of a reticulated or livedoid purplish mottling of the skin, related to physiological capillary and venular vasomotion in the setting of cold exposure.[12] Cutis marmorata seems to be associated with lower gestational age and birth weight, which may be associated with the greater vulnerability of these neonates, who are therefore more likely to present with vasomotor instability.[3] This condition must be distinguished from cutis marmorata telangiectatica congenita, which is characterised by a fixed vascular change associated with subtle dermal atrophy. This entity may be associated with limb length discrepancy, vascular, osseous, ocular, and neurologic malformations.[12]

Harlequin Colour Change

Harlequin colour change presents as erythema in one half (the dependent side) and pallor in the other half of the body, usually lasting for several minutes. This condition presents in the first 3 weeks of life, commonly between Day 2 and Day 5.[11,12] Although it has been observed in neonates after the administration of anaesthetic agents and alprostadil, harlequin colour change may also occur in healthy neonates in the absence of medication. This phenomenon may occur as a result of changes in vascular tone, although it still remains unexplained. Harlequin color change is a benign and transient feature; therefore, no treatment is necessary.[13]

Salmon Patch

Salmon patch, also known as naevus flammeus, naevus simplex, or unna naevus, is a common congenital capillary malformation that is usually found in the midline.[14] It affects approximately 50% of newborns and is more frequent in those born with greater weight, at term or post-term. A slight female predominance has been observed.[15] Salmon patches arise from dilations of capillaries within the dermis, which may result from persistent fetal circulation in newborns.[4] Clinically, they present as pink or red irregular macules, which may become confluent (Figure 2A).

Lesions tend to bleach with digital pressure, and are more apparent with crying, apnoeas, fever, and changes in ambient temperature. Salmon patches occurr most frequently on the nape of the neck, the eyelids, and the glabella, and are usually transitory, disappearing during the first 2 years of life. Nearly one-half of those located in the nape of the neck and in the sacral region, and a small percentage of those located in the glabellar zone, may persist.[14,15] Salmon patches need to be distinguished from cutaneous capillary malformation, formerly referred to as 'port wine stain', a potential marker of Sturge–Weber syndrome. The variant '*en coup de sabre*' of congenital morphea is another differential diagnosis of this condition.

PIGMENTARY CHANGES

Mongolian Spot

Mongolian spot (MS) is a type of dermal melanocytosis, which presents at birth or soon thereafter as an ill-defined area of slate gray to blue/black pigmentation, usually over the sacrococcygeal or lumbar area. Both sexes are equally affected, and these lesions are more common in newborns of Asian and/or African descent.[16,17] MS arise from a defect in melanocyte migration. Melanocytes are present in dermis of the embryos at the beginning of the 10th week of gestation, and they migrate to the epidermis between the 11th and the 14th week. After Week 20, no melanocytes are found in the dermis. Failure of this migration results in the appearance of MS.[16] Clinically, MS are round, oval, or irregular macules. The colour varies from blue to green, grey, black, or a combination of any of these colours. Lesions may be single or multiple, and their size ranges from <1 cm to >20 cm. Pigmentation is more intense at the age of 1 year and gradually fades thereafter.[16,17] MS must be differentiated from other dermal melanocytoses like naevus of Ota, naevus of Ito, Hori naevus, and blue naevus.

Onset at birth, disappearance with age, absence of mucosal involvement, and no progression to malignancy favour the diagnosis of MS.

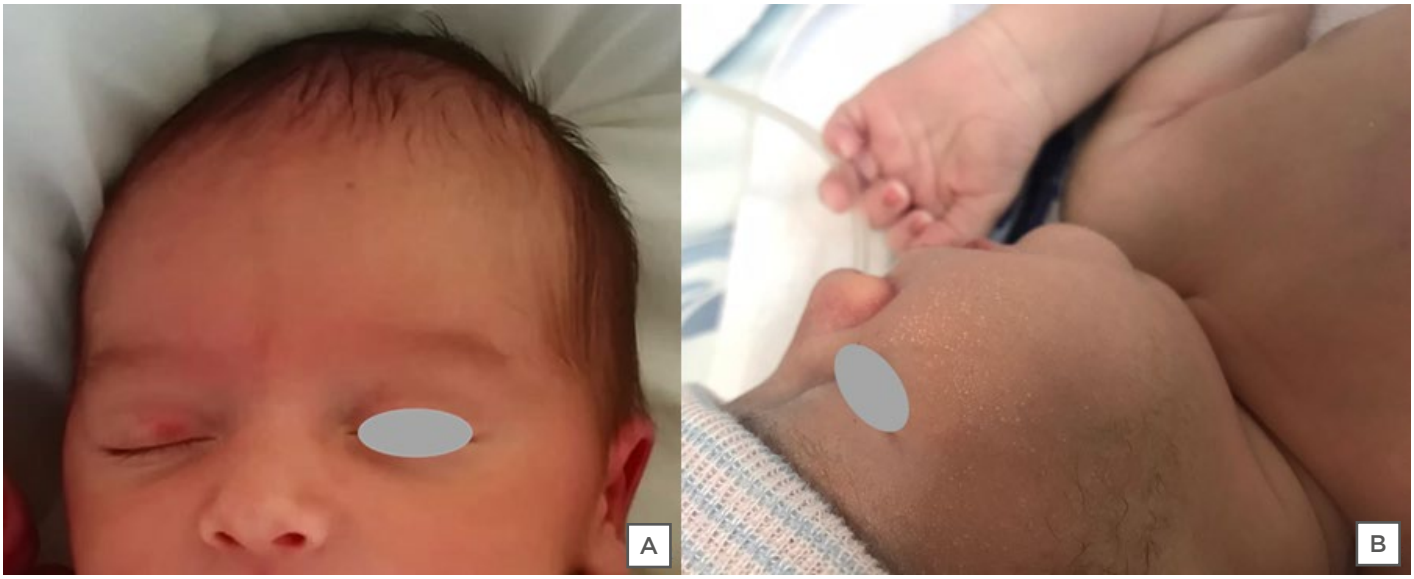

Figure 2: Physiological alterations. A) Salmon patch in the upper eyelid of a 1-week-old female. B) Milia cysts overlying the cheek of a 2-week-old newborn.

MS usually resolve by early childhood, hence, no treatment is needed if they are located in the sacral area; nonetheless, it may be required for extrasacral lesions due to cosmetic issues.[16] Although most MS are benign lesions, recent data suggested that MS may be associated with inborn errors of metabolism such as lysosomal storage diseases. Therefore, extrasacral, extensive, persistent, and dark-coloured spots should be looked upon with suspicion, especially in the presence of a consanguineous marriage or a strong family history of storage disorders.[4]

Epidermal Hyperpigmentation

Epidermal pigmentary changes are also common in newborns and include linea nigra and hyperpigmentation of the knuckles, genital, axilla, or areolar regions. Hyperpigmentation of the skin over the distal phalanges has also been described, particularly in newborns with higher phototypes.[18] This abnormal pigmentation is transient and probably represents a response to maternal and placental hormones that enter the newborn circulation. Among these hormones, oestrogen and progesterone have been reported to exert a melanocytic stimulating effect, which is also responsible for the darkening of linea alba in pregnant females. As these are transient and benign changes, no treatment is necessary.[2] Abnormal hyperpigmentation may be a sign of congenital adrenal hyperplasia; however, in this condition, there are usually associated findings such as virilised external genitalia.

HORMONAL CHANGES

Sebaceous gland hyperplasia is a common physiological phenomenon in newborns, affecting mainly full-term infants.[19,20] It is caused by high sebum secretion rates reflecting the stimulation by placentally transferred maternal androgens, particularly dehydroepiandrosterone.[2,19] Clinically, sebaceous hyperplasia is characterised by multiple, yellow to flesh-coloured tiny papules on the nose, cheeks, and chin, where the density of sebaceous glands is highest.[19,20] Sometimes the papules can coalesce into plaques without surrounding erythema. The most important differential diagnosis of this condition are milia cysts, which are epidermal inclusion cysts, usually solitary and whiter in colour.[20] Sebaceous gland hyperplasia spontaneously resolves within the first few weeks of life, and therefore no treatment is required.[19,20]

OTHER PHYSIOLOGICAL LESIONS

Epstein Pearls and Bohn's Nodules

Epstein pearls occur in 64–89% of neonates and are more common in newborns of Caucasian descent. These lesions, also known as palatal microkeratocysts of the newborn, are white-yellow cysts usually 1–3 mm in size. They are typically seen on the median palatal mouth raphe and represent epithelial tissue trapped during the palatal fusion.[20] Similar cysts on the alveolar ridges or in the periphery of the palate are called Bohn's nodules. These are keratin cysts derived from the dental lamina, and they do not require treatment as they spontaneously resolve over the first few months of life.[20]

Milia Cysts

Milia cysts are small lesions resulting from retention of keratin within the dermis. They affect approximately 40–50% of newborns and may be present at birth or appear later in infancy.[19] Milia cysts appear as tiny, white, or yellow smooth-surfaced papules 1–2 mm in diameter, most commonly located over the cheeks, forehead, nose, and nasolabial folds (Figure 2B).[19,20] Lesions may be few or numerous and are frequently grouped, with a tendency towards disappearance during the first 3 to 4 weeks of life. The most important differential diagnosis of milia cysts is sebaceous hyperplasia, which tends to be slightly more yellow.[20] No therapy is required, as lesions tend to spontaneously resolve. However, it is important to note that persistent and widespread milia may be a feature of associated syndromes such as basal naevus syndrome, Rombo syndrome, Brooke–Spiegler syndrome, or pachyonychia congenita Type II, and therefore complementary investigation should be conducted in these particular settings.

Koilonychia

Koilonychia refers to nails with a transverse and/or longitudinal concave central depression. It can be hereditary, acquired, or idiopathic. In newborns, it is frequently idiopathic, affecting particularly the hallux. In these circumstances, koilonychia tends to spontaneously regress

with growth.[21] Nonetheless, it is important to remember that these nail changes, later in life, may also be a manifestation of inflammatory skin diseases such as psoriasis, lichen planus, or secondary to systemic alterations, such as iron deficiency or endocrine disorders.[22]

Traumatic Punctate Leukonychia

Punctate leukonychia is a true leukonychia caused by alterations or imperfections in the proximal nail matrix.[21] As the nail plate has a very smooth surface in newborns, these lesions can be easily observed.[23] No specific treatment is required, as they tend to resolve with nail growth.[21]

Beau's Lines

Beau's lines of the fingernails appear at 4 weeks of life in 92% of newborns and disappear with growth, usually before 14 weeks.[21] They result from intrauterine distress or physiological alterations during birth that cause mild trauma to the proximal nail matrix, with transiently reduced nail growth.[23] Clinically, one can observe linear transverse nail plate surface depressions, which require no particular approach.[21]

COMMON RASHES

Erythema Toxicum Neonatorum

Erythema toxicum neonatorum (ETN) is a common condition, affecting neonates of all races and ethnicities worldwide. Its incidence ranges from as low as 3.7% to as high as 72%, affecting predominantly full-term neonates weighing over 2,500 g.[3,24,25] Although the pathogenesis of this condition is unknown, recent studies suggest that ETN may represent a cutaneous immune reaction to an acute, transitory attack of the commensal microflora that penetrate the newborn skin via hair follicles, a condition which presupposes a certain degree of maturity of the immune system.[3,24]

ETN is a self-limited condition, usually beginning within the first 2 days of life and resolving entirely within 6 days. Recurrence occurs in up to 11% of neonates, usually between 5 and 11 days after the original eruption.[24] This transient neonatal rash is asymptomatic and resolves without sequelae, with individual lesions rarely persisting for more than 1 day.[25] Five distinct components may be present in various combinations, which include erythematous macules, wheals, papules, small pustules, and vesicles, usually measuring 1–2 mm. The eruption usually occurs throughout the body, typically involving the trunk, face, buttocks, and thighs; the palms, soles, and genitals are spared.[24]

Diagnosis of ETN is usually clinical. A cytologic exam of pustule contents shows more than 50% eosinophils, with or without a small number of neutrophils. Peripheral blood eosinophilia up to 15% may frequently coexist. Histopathologic examination is rarely necessary, but when performed it shows superficial dermal oedema with a mild diffuse and perivascular eosinophilic infiltrate. Pustules are subcorneal or intraepidermal and are associated with the pilosebaceous orifice in most cases.[24] The differential diagnoses of ETN include sepsis, staphylococcal folliculitis, miliaria, congenital candidiasis, acne neonatorum, transient neonatal pustular melanosis, infantile acropustulosis, neonatal varicella, and occasionally incontinentia pigmenti.[24]

It is important to educate parents about the transient nature of this eruption. Although antihistamines may alter the duration of ETN, their use is not necessary as the rash does not seem to bother the child. The most useful therapy remains reassurance that the eruption is benign and will resolve without sequelae.[24]

Transient Neonatal Pustular Melanosis

Transient neonatal pustular melanosis (TNPM) is a benign condition most commonly affecting infants who are black. It affects both sexes with the same frequency and lesions are virtually always present at birth.[26] So far, the aetiology of TNPM remains unknown. Some authors consider it a variant of ETN, although this has not been confirmed.[27]

TNPM features three different morphologies, which can coexist or occur sequentially. At delivery, flaccid and superficial noninflammatory vesicopustules are usually present in the chin, forehead, nape of the neck, lower back, buttocks, and shins. These lesions are easily disrupted, leaving hyperpigmented macules with fine collarettes of scale. Finally, residual hyperpigmented macules may persist for several months.[27]

Diagnosis of TNPM is generally clinical. Cytological examination of the pustules shows polymorphonuclear neutrophils. Histological examination is rarely permorfed, but will show intra- or subcorneal pustules containing primarily neutrophils. Pigmented macules show increased melanin in basal keratinocytes. Differential diagnosis of this condition is similar to that of ETN.[26,27] As in ETN, no treatment is necessary for this condition. Parents' reassurance of its benign and self-limited nature is all that is needed.[27]

Miliaria

Miliaria is a common condition affecting up to 15% of newborns, and is commonly observed in summer months, febrile periods, or in newborns with excess clothing.[27] The most common type of miliaria in the immediate neonatal period is miliaria crystallina (MC), which is characterised by small, clear, and flaccid vesicles over healthy skin, especially on the face, neck, trunk, and occluded areas. MC is caused by obstruction of the eccrine sweat duct as it courses through the stratum corneum.[28]

Miliaria rubra (MR) is another type of miliaria, also caused by obstruction of eccrine sweat gland ducts but deeper within the spinous layer. Leakage of fluid into the lower epidermis and superficial dermis leads to local inflammation, characterised by numerous erythematous papules, vesicles, and pustules (Figure 3A).[28] MR lesions usually begin after the 2nd week of life and predominate in the trunk and intertriginous areas, where occlusion by clothing is accentuated. In hot environments, lesions on the scalp, face, and neck area may appear.[27] Rarely, MR can progress to miliaria profunda, where the obstruction of the eccrine gland duct is even deeper.[27] This type of miliaria is very rare in infants, usually occurring in older patients in tropical climates.

Diagnosis of miliaria is clinical. Cytologic examination of vesicopustule material shows a predominance of lymphocytes. Histologically, in MC, subcorneal or intracorneal vesicles centered on the acrosyryngium are seen, with little surrounding inflammation. In MR, intraepidermal spongiosis and vesicles are found, along with a chronic inflammatory infiltrate in the dermis.[27] Lesions of milaria resolve without intervention, but there is a proven benefit in lowering the environment temperature. Prevention may be accomplished by avoiding overheating and excessive swaddling.[27]

Neonatal Cephalic Pustulosis

Neonatal cephalic pustulosis (NCP) is a relatively common benign condition with prevalence estimated between 10% and 66%.[25] It usually develops within the first 2–3 weeks of life, and is characterised by multiple inflammatory papules and pustules mainly on the cheeks but also on the forehead, chin, neck, upper chest, and scalp (Figure 3B).[27] Although an inflammatory response to *Malassezia spp*. has been suggested to be involved in the pathogenesis of NCP, this has not been confirmed.[29] Diagnosis of NCP is usually clinical. A Giemsa-stained smear of pustular contents can show yeast forms, neutrophils, and inflammatory cells.[27] Although topical imidazole or hydrocortisone are sometimes prescribed, no treatment is needed for this condition as it has a self-limited course with spontaneous involution over weeks to months.

Neonatal Acne

Neonatal acne occurs in up to 20% of newborns. This condition may be evident at birth or appear during the first 4 weeks of life and is more commonly seen in males.[30] Several factors may contribute to the development of neonatal acne, including increased sebum excretion, stimulation of the sebaceous glands by maternal or neonatal androgens, and colonisation of sebaceous glands by Malassezia species.[31] Neonatal acne typically presents as small, closed comedones on the forehead, nose, and cheeks. Accompanying sebaceous hyperplasia is often noted. Less frequently, open comedones, inflammatory papules, and pustules may also develop. Several eruptions should be considered in the differential diagnosis of neonatal acne, including erythema toxicum neonatorum, transient neonatal pustular melanosis, milia, and pustular miliaria. Other entities to be considered include bacterial folliculitis, secondary syphilis, herpes simplex virus and varicella zoster virus, and skin colonisation by fungi of Malassezia species. Drug eruptions associated with hydantoin, lithium, or halogens should be considered in particular cases.[30] Neonatal acne is usually mild and self-limited, resolving spontaneously without scarring in approximately 1–3 months.[31]

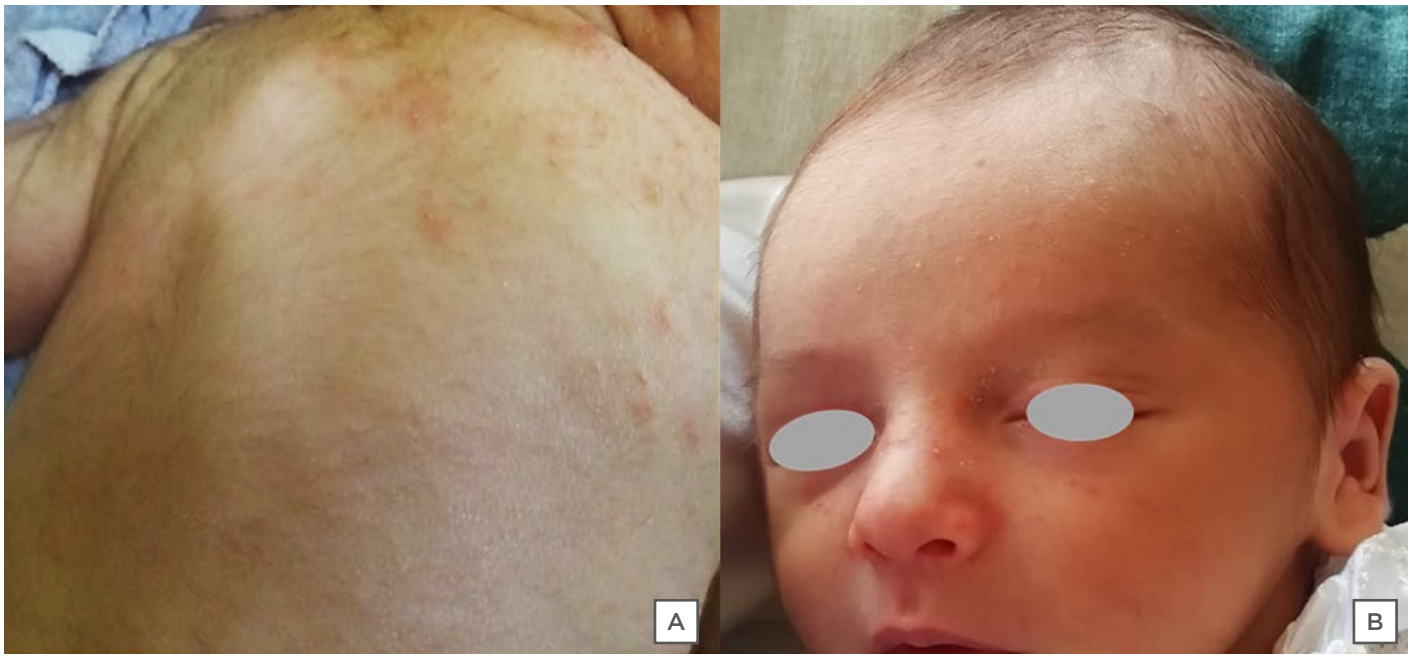

Figure 3: Common rashes. A) Miliaria rubra lesions on the back of a 2-week-old male. B) Neonatal cephalic pustulosis on the face of a 3-week-old female.

Therefore, in most cases no treatment is needed except for reassurance. If necessary, comedones may be treated with azelaic acid cream 20% or tretinoin cream 0.025–0.050%. For inflammatory lesions, erythromycin solution 2.0% and benzoyl peroxide gel 2.5% may be used. Severe or recalcitrant disease warrants a workup for congenital adrenal hyperplasia, a virilising tumour, or underlying endocrinopathy.[30]

Infantile Acropustulosis

Infantile acropustulosis (IA) is an uncommon condition, usually developing at approximately 3–6 months of age, although it can begin earlier. It is more common in males and in infants of African descent.[25] Clinically, IA is characterised by recurrent crops of pruritic vesicopustules predominantly in the palms and soles, although it can also affect the back of the hands, feet, ankles, wrists, and scalp. Eruptions usually last between 7 and 14 days, recurring every 3–5 weeks. With time, episodes usually decrease in frequency and severity, eventually resolving completely by 3 years of age.[32]

Diagnosis of IA is clinical. Cytological examination of pustular contents shows a predominance of neutrophils, with occasional eosinophils. Histopathological examination, albeit rarely perfomed, demonstrates the presence of subcorneal pustules filled primarily with neutrophils. Scabies is the main differential diagnosis of this condition, and can usually be excluded by skin scraping examination. Incontinentia pigmenti is another condition in the differential diagnosis of IA. Other clinically similar conditions, such as dyshidrotic eczema and palmoplantar pustulosis, are rare in infants. Treatment of IA is symptomatic, usually requiring potent or superpotent topical corticosteroids and oral antihistamines.[32]

Eosinophilic Pustular Folliculitis

Eosinophilic pustular folliculitis (EPF) usually affects infants between 5 and 10 months of life, with a male to female ratio of 4:1.[33] EPF is a polymorphous eruption characterised by recurrent eruptions of pruritic papules, pustules, and vesicles. Pruritic vesicopustules may coalesce, forming exudative and crusted plates located mainly on the scalp, and less commonly on the face and extremities. Eruptions are intermittent and self-limited, lasting from 1 to 4 weeks, and eventually resolving by 3 years of age.

Cytological examination of pustular contents reveals primarily eosinophils, without bacteria or other microorganisms. Histological examinations

show a dense eosinophilic infiltrate with a predominant perifollicular distribution. Peripheral eosinophilia is observed in approximately 70% of cases.[34]

Differential diagnoses of EPF predominantly include ETN, TNPM, IA, bacterial folliculitis, tinea capitis. and reactions to arthropod bites. Other rarer conditions, such as Langerhans' cell histiocytosis and the vesicular-papulo-pustular eruption associated with autosomal dominant hyper-IgE syndrome, should be considered in the appropriate clinical settings. Treatment is primarily symptomatic and similar to that of IA, including midpotency topical corticosteroids, topical tacrolimus, and oral antihistamines.[33] In more recalcitrant cases, oral dapsone and other oral antibiotics may be needed.[34]

CONCLUSION

Neonatal cutaneous alterations are common, usually appearing at birth or during the first few days of life. Most of these conditions are physiological and arise from a combination of immaturity of the newborn skin with environmental factors. Although the majority of these conditions are benign and sponteously reversible, some of them may eventually be a clue to underlying disorders. Physicians should therefore be aware of these clinical manifestations, so that parents can be reassured and, when necessary, complementary investigations undertaken.

References

1. Johnson E, Hunt R. Infant skin care: updates and recommendations. Curr Opin Pedi-atr. 2019;31(4):476-81.
2. Haveri F, Inamadar A. A cross-sectional prospective study of cutaneous lesions in newborn. ISRN Dermatol. 2014;360590.
3. Ábrahám R et al. Cutaneous lesions and disorders in healthy neonates and their relationships with maternal-neonatal factors: a cross-sectional study. World J Pediatr. 2017;13(6):571-6.
4. Techasatian L et al. Neonatal birthmarks: a prospective survey in 1000 neonates. Glob Pediatr Heal. 2019;6:2333794X19835668.
5. Nishijima K et al. Biology of the vernix caseosa: a review. J Obs Gynaecol Res. 2019;45(11):2145-9.
6. Afsar F et al. Neonatal sucking blister. Dermatol Online J. 2019;25(11):pii: 13030/qt33b1w59j.
7. Adam R, Schroten H. Picture of the month. Congenital sucking blisters. Arch Pediatr Adolesc Med. 2007;161(6):607-8.
8. Nicholson L. Caput succedaneum and cephalohematoma: the cs that leave bumps on the head. Neonatal Netw. 2007;26(5):277-81.
9. Petrikovsky BM et al. Cephalhematoma and caput succedaneum: do they always occur in labor? Am J Obs Gynecol. 1998;179(4):906-8.
10. Liu L, Antaya R. Neonatal subgaleal hematoma from trauma during vaginal delivery without instrument use. Pediatr Dermatol. 2017;34(1):e40-1.
11. Drapkin Z et al. Is my baby normal? A review of seemingly worrisome but normal newborn signs, symptoms and behaviors. Am J Emerg Med. 2019;37(6):1153-9.
12. Su J. Common rashes in neonates. Aust Fam Physician. 2012;41(5):280-6.
13. van den Berg G, Bakker H. Harlequin color change in a neonate. N Engl J Med. 2020;382(5):456.
14. Redondo P. Classification of vascular anomalies (tumours and malformations). Clinical characteristics and natural history. An Sist Sanit Navar. 2004;27:Suppl 1:9-25. (In Spanish).
15. Monteagudo B et al. Salmon patch: a descriptive study. Actas Dermosifiliogr. 2011;102(1):24-7. (In Spanish).
16. Gupta D, Thappa DM. Mongolian spots. Indian J Dermatol Venereol Leprol. 2013;79(4):469-78.
17. Zagne V, Fernandes N. Dermatoses in the first 72 hours of life: a clinical and statistical survey. Indian J Dermatol Venereol Leprol. 2011;77(4):470-6.
18. Pérez-Bescós L et al. Cutaneous hyperpigmentation of the distal phalanges in a newborn infant. An Pediatr (Barc). 2006;65(4):390.
19. Paller A, Mancini A, Hurwitz Clinical Pediatric Dermatology. A Textbook of Skin Disorders of Childhood and Adolescence (2011) 4th edition, Chicago: Elsevier Health Sciences.
20. Eichenfield L et al., Neonatal dermatology (2007) 2nd edition, Philadelphia: Saunders Elsevier Inc.
21. Starace M et al. Nail disorders in children. Skin Appendage Disord. 2018;4(4):217-29.
22. Walker J et al. Koilonychia: an update on pathophysiology, differential diagnosis and clinical relevance. J Eur Acad Dermatol Venereol. 2016;30(11):1985-91.
23. Richert B, André J. Nail disorders in children: diagnosis and management. Am J Clin Dermatol. 2011;12(2):101-12.
24. Morgan AJ et al. Erythema toxicum neonatorum revisited. Cutis. 2009;83(1):13-6.
25. Csoma Z et al. Overview of dermatologic disorders of neonates in a central regional intensive care unit in Hungary. Pediatr Dermatol. 2015;32(2):201-7.
26. Nanda S et al. Analytical study of pustular eruptions in neonates. Pediatr Dermatol. 2002;19(3):210-5.
27. Reginatto FP et al. Benign skin disease with pustules in the newborn. An Bras Dermatol. 2016;91(2):124-34.
28. Antaya R, Robinson D. Blisters and pustules in the newborn. Pediatr Ann. 2010;39(10):63-45.
29. Ayhan M et al. Colonization of neonate skin by Malassezia species: relationship with neonatal cephalic pustulosis. J Am Acad Dermatol. 2007;57(6):1012-8.
30. Serna-Tamayo C et al. Neonatal and infantile acne vulgaris: an update. Cutis. 2014;94(1):13-6.
31. Antoniou C et al. Clinical and therapeutic approach to childhood acne: an update. Pediatr Dermatol. 2009;26(4):373-80.

32. Mancini AJ et al. Infantile acropustulosis revisited: history of scabies and response to topical corticosteroids. Pediatr Dermatol. 1998;15(5):337-41.
33. Hernández-Martín Á et al. Eosinophilic pustular folliculitis of infancy: a series of 15 cases and review of the literature. J Am Acad Dermatol. 2013;68(1):150-5.
34. Fukamachi S et al. Therapeutic effectiveness of various treatments for eosinophilic pustular folliculitis. Acta Derm Venereol. 2009;89(2):155-9.

Streptococcus suis and an Incidentally Diagnosed Metastatic Colon Cancer

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Abstract

Background: *Streptococcus suis* is a zoonotic infection known to cause meningitis and sepsis, in addition to several other rare manifestations. Infection with this organism is rare in the absence of pork ingestion or a handling history.

Case presentation: The authors report the case of a 62-year-old male with no animal contact history, who presented with symptoms of urinary tract infection. It was his second infection over the course of 2 years. His urine culture was positive for *Escherichia coli* but his blood culture was positive for *S. suis*. Ultrasound of the abdomen ruled out underlying predisposing urinary pathology. However, it did show several heterogeneous liver masses with abnormal vascularity. A follow-up abdominal CT revealed a malignant neoplastic process involving the sigmoid colon with metastatic liver lesions. Colonoscopy demonstrated a fungating mass at the sigmoid colon and biopsies revealed a moderately differentiated adenocarcinoma.

Conclusion: This case suggests the possibility of associated colon cancer in patients presenting with *S. suis* with no explicit history of animal or pork contact. It also proposes the existence of an association between colon cancer with *Streptococcus* species other than *bovis*.

BACKGROUND

Streptococcus suis is a zoonotic gram-positive bacterium that is usually acquired through direct contact with swine or pork. In humans, this organism can present as acute meningitis, septicaemia, infective endocarditis, or other manifestations.[1] Patients with *S. suis* meningitis can develop permanent hearing loss. Male sex and occupations with direct swine or pork contact are considered risk factors.[1,2] In this article, the authors raise awareness of *S. suis* infection in the Middle East and explore all the common associations with *S. suis* by reporting the first case in the United Arab Emirates with bacteraemia, colon cancer, and no prior swine or pork contact.

CASE PRESENTATION

A 62-year-old Pakistani male presented with dizziness, nausea, and burning in micturition for 1 month prior to presentation. The patient also reported a 4 kg weight loss over a 3-month period. There was no history of fever. Past medical history was significant for diabetes and heart

failure with reduced ejection fraction (40%), as well as one previous history of extended-spectrum β-lactamase *Escherichia coli* cystitis 2 years ago. Social history was absent of direct animal contact and pork handling or eating. However, the patient reported eating meat from restaurants for 1 month prior to the onset of his symptoms. There was no recent travel history; the last time he left the country was over 1 year ago.

Upon initial presentation, his vitals were blood pressure 117/77 mmHg, pulse 78 beats per minute, temperature 37.2 °C, respiratory rate 18 breaths per minute, and saturation of oxygen 95% on room air. His physical examination did not reveal any abnormalities.

Laboratory investigation showed a white blood cell count of 13.4 per mm^3, with 78% neutrophils and a haemoglobin count of 9.7 g/dL. The serum C-reactive protein (112.6 mg/dL) and procalcitonin (0.17; low risk for progression to severe sepsis) levels were elevated. Urinalysis showed positive nitrates with leukocyte esterase +3 and white blood cell count 10–15 per high-power field. Liver function tests showed alkaline phosphatase of 164 unit/L, alanine transaminase 16 unit/L, aspartate aminotransferase 28 unit/L, γ-glutamyl transferase 123 unit/L, bilirubin 0.7 mg/dL, albumin of 2.7 g/dL, and globulin of 3.9 g/dL.

As the patient was vitally stable with no signs of pyelonephritis, he was discharged on oral cefuroxime for 7 days after cultures from urine and blood were obtained. Three days later, the patient was called back to the hospital as his urine culture was growing extended-spectrum β-lactamase positive *E. coli* and his blood culture revealed the presence of gram-positive cocci in chains.

At presentation, the patient stated a partial improvement in the severity of his symptoms with the persistence of nausea. His vitals were blood pressure 133/83 mmHg, pulse 85 beats per minute, temperature 36.6 °C, respiratory rate 16 breaths per minute, and saturation of oxygen 100% on room air. He was admitted and started on a daily dose of intravenous ertapenem 1 g.

The patient's culture result was identified as *S. suis* 2 days after admission by means of matrix-assisted laser desorption/ionisation time-of-flight (MALDI-TOF) through the automated mass spectrometry microbial identification VITEK system (BioMérieux, Marcy-l'Etoile, France). *S. suis* sensitivity was specifically requested for ertapenem as the patient was already prescribed it, and it was found to be sensitive. For his presenting anaemia with a mean corpuscular volume of 83, a blood film and iron studies were performed. The results were consistent with chronic anaemia.

A transthoracic echocardiogram was performed to exclude infective endocarditis and showed an ejection fraction of 35% with no vegetation.

Repeated blood cultures were negative, reducing further the likelihood of infective endocarditis. A renal ultrasound was performed to rule out any predisposing underlying urinary pathology to his recurrent infections. The ultrasound showed a normal urinary tract but revealed the presence of multiple heterogeneous liver masses with abnormal vascularity on the Doppler study (Figure 1). The serology for hepatitis B, C, and HIV was negative. Triphasic liver CT showed a malignant neoplastic process involving the sigmoid colon with metastatic liver lesions (Figure 2), as well as mesenteric and portocaval lymphadenopathy.

Colonoscopy was later performed, which showed a fungating mass with superficial ulcerations at the sigmoid colon (Figure 3). Biopsies obtained showed Grade 2 moderately-differentiated adenocarcinoma. No culture was obtained from the mass.

He was discharged in a stable condition after completing 10 days of ertapenem for his urinary tract infection and *S. suis* bacteraemia. A follow-up appointment with the oncology clinic was planned but the patient decided to travel to his home country for continuity of care.

DISCUSSION

S. suis is a gram-positive facultative anaerobe that is coccoid in shape and presents in chains or pairs.[2] First identified in humans in 1968,[3] *S. suis* have since been reported to cause meningitis, sepsis, arthritis, and infective endocarditis. In a few reports, it has also caused endophthalmitis and osteomyelitis.[4-7]

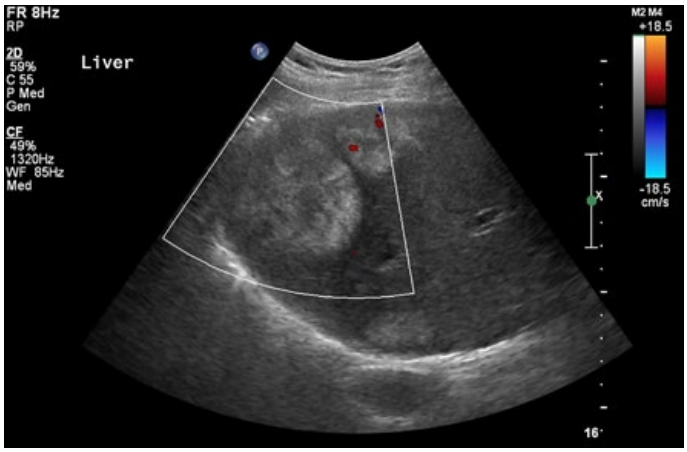

Figure 1: Ultrasound image of the liver showing multiple variable sizes of hyperechoic to hypoechoic heterogeneous masses in the liver showing no abnormal vascularity.

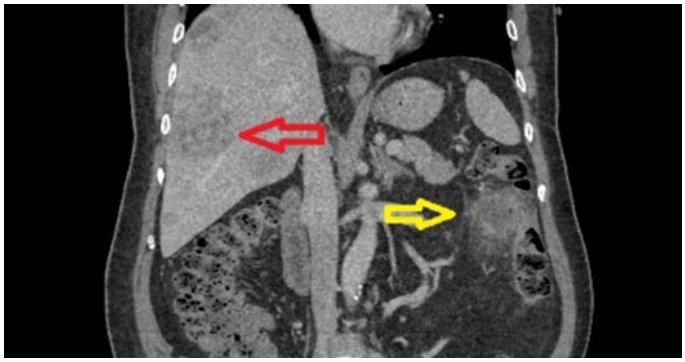

Figure 2: Coronal cut of abdominal CT in the portovenous phase showing the same sigmoid colon lesion (yellow arrow) as well as the liver metastasis (red arrow).

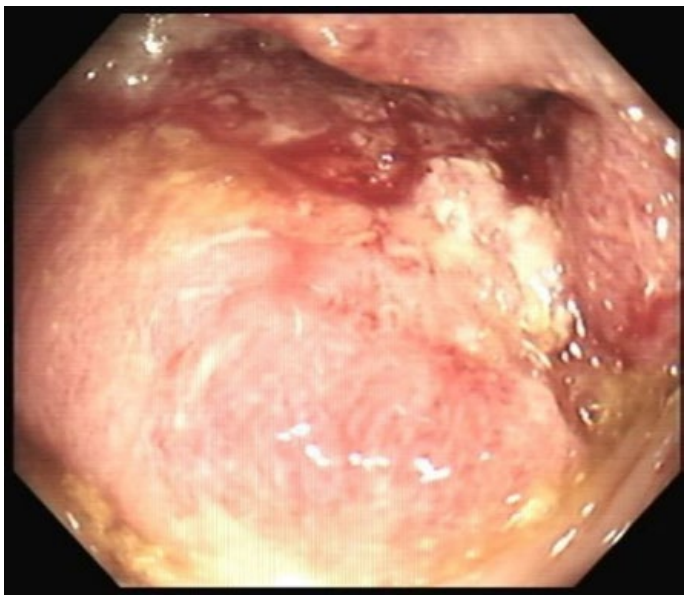

Figure 3: Direct visualisation by colonoscopy showing a fungating mass with ulceration.

Human infection cases are reported worldwide, but mostly in Asian countries.[4] Most of the reports are of sporadic cases, though outbreaks have been reported previously. In 2005, an outbreak in China resulted in 215 infected cases and 38 deaths. No person-to-person transmission was reported and all cases had direct contact with infected swine.[8]

Patients are generally healthy before infection with *S. suis*, although predisposing factors such as diabetes, alcoholism, and splenectomy have been reported.[2,4] Male sex and occupations with direct swine or pork contact are considered risk factors. In a systemic review, swine-related occupations were present in 38.1% of cases and a history of eating high-risk food in 37.3% of cases.[2] The risk is specifically high if pork is prepared in the presence of skin lesions.[9]

S. suis is a zoonotic organism that can be acquired through direct contact with swine or raw pork.[2] It can also be acquired, albeit rarely, from other animals such as dogs or cats.[10] Pork consumption is the usual method of transmission, especially high-risk foods such as fresh pig blood, or pig stomach, intestine, uterus, or tongue. This was confirmed in a case-control study that showed the presence of *S. suis*-specific DNA in a rectal swab of 6/100 confirmed cases of *S. suis* meningitis, as compared to zero detection among the 1,522 healthy control cases.[9] No stool culturing or swab was performed for the patient in this case; as a result, the method of transmission cannot be ascertained.

Not all cases, however, present with a history of contact with swine or other animals. One possibility of contracting *S. suis* infection can be through cross-contamination at places dealing with both meat and pork. A study in Thailand showed a high rate of contamination of *S. suis* in raw pork and edible pig organs sold in different areas.[11] This is further supported by this patient's history of eating meat from restaurants around the time of symptom onset.

Another possibility is suggested by several reports of *S. suis* infection with no reported history of contact to pigs or pork. One case reported a 34-year-old male presenting with meningitis caused by *S. suis* with a negative history of pig or pork contact.[12] Two other cases reported an association with cancer in patients presenting with *S. suis* infection and negative contact history: one was of metastatic oesophageal adenocarcinoma[7] and the other was of a malignancy (location not described) found during workup.[13]

This case report is the second reported case of *S. suis* infection associated with colon cancer. The previously reported case was of infective endocarditis with bacteraemia caused by *S. suis* and an iron deficiency anaemia. Colonoscopy was performed as part of the anaemia workup, which revealed colon cancer.[14] This case, however, had a positive animal contact with pigs as part of his occupation.

Based on these data, it can be concluded that *S. suis* is an occupational zoonotic infectious disease. However, in patients with no suggestive history of such high-risk contact, either directly or through cross-contamination of raw pork and meat, ruling out causes for an immunocompromised state-like malignancy is strongly advised.[7,14]

This conclusion, however, remains theoretical and is limited by several factors. First, despite the presence of *S. suis* bacteraemia with colon cancer in this case, this does not prove causation as it is unclear if the gut was the primary route of entry for the bacteraemia. Secondly, even with a negative contact history, ascertaining a true lack of exposure to pigs or pork is very difficult and, therefore, remains possible.

To the best of the authors' knowledge, this is the first report of *S. suis* infection in the United Arab Emirates and the Middle East region, and the second reported case with colon cancer association worldwide. This case should remind clinicians of the possibility of associated cancer in patients presenting with *S. suis* infection and no clear history of animal or pork contact. It should also come as a suggestion of the existence of colon cancer association with *Streptococcus* species other than *bovis*.[14,15]

LEARNING POINTS/TAKE HOME MESSAGES

- Patients presenting with *S. suis* infection may not have a positive contact history with pig or pork.

- In patients with no obvious animal or pork contact history, a diagnosis of *S. suis* infection may raise the suspicion of underlying malignancy.
- *Streptococcus* spp. other than *bovis* can be associated with colon cancer.

Ethics

Informed consent was obtained from the patient and no ethical approval was required from the institute.

References

1. Rayanakorn A et al. Risk factors for *Streptococcus suis* infection: a systematic review and meta-analysis. Sci Rep. 2018;8(1):13358.
2. Huong VT et al. Epidemiology, clinical manifestations, and outcomes of *Streptococcus suis* infection in humans. Emerg Infect Dis. 2014;20(7):1105-14.
3. Wertheim HF et al. *Streptococcus suis*: an emerging human pathogen. Clin Infect Dis. 2009;48(5):617-25.
4. Dutkiewicz J et al. *Streptococcus suis*: a reemerging pathogen associated with occupational exposure to pigs or pork products. Part I - epidemiology. Ann Agric Environ Med. 2017;24(4):683-95.
5. Sena Esteves S et al. Pig's ear: *Streptococcus suis* meningitis and its associated inner ear implications. ID Cases. 2017;10:55-7.
6. Mohapatra D et al. Chronic osteomyelitis due to *Streptococcus Suis*: first case report from India. J Glob Infect Dis. 2015;7(2):92-3.
7. Gomez-Zorrilla S et al. *Streptococcus suis* infection and malignancy in man, Spain. Emerg Infect Dis. 2014;20(6):1067-8.
8. Yu H et al. Human *Streptococcus suis* outbreak, Sichuan, China. Emerg Infect Dis. 2006;12(6):914-20.
9. Nghia HD et al. Risk factors of *Streptococcus suis* infection in Vietnam. A case-control study. PLoS One. 2011;6(3):e17604.
10. Salasia SI et al. Serotypes and putative virulence markers of *Streptococcus suis* isolates from cats and dogs. Res Vet Sci. 1994;57(2):259-61.
11. Boonyong N et al. Contamination of *Streptococcus suis* in pork and edible pig organs in central Thailand. Vet World. 2019;12(1):165-9.
12. Hidalgo A et al. Meningitis due to *Streptococcus suis* with no contact with pigs or porcine products. J Infect. 2007;55(5):478.
13. Manzin A et al. *Streptococcus suis* meningitis without history of animal contact, Italy. Emerg Infect Dis. 2008;14(12):1946-8.
14. Voutsadakis IA. *Streptococcus suis* endocarditis and colon carcinoma: a case report. Clin Colorectal Cancer. 2006;6(3):226-8.
15. Abdulamir AS et al. The association of *Streptococcus bovis/gallolyticus* with colorectal tumors: the nature and the underlying mechanisms of its etiological role. J Exp Clin Cancer Res. 2011;30:11.

Physical Activity Level and Factors Affecting Exercise Participation among Nigerian Adults with and Without Diabetes

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Abstract

Background: Diabetes presents a multifaceted challenge to health systems in Nigeria and beyond. Physical activity is a cornerstone of diabetes management but is often underutilised. Despite the positive effects of physical activity on different dimensions of health to patients with diabetes, most fail to maintain long-term adherence to physical activity programmes.

Objectives: This study aimed to determine the physical activity level and factors affecting exercise participation among patients with and without diabetes.

Methods: This was a cross-sectional study involving 400 participants recruited by convenience sampling. International Physical Activity Questionnaire (IPAQ) and Exercise Benefit and Barrier Scale (EBBS) questionnaires were used to measure physical activity and perceived benefits and barriers to exercise, respectively. The data collected were analysed using descriptive statistics of percentages and frequency, mean and standard deviation, and independent t-test. The level of significance was set at $p<0.05$.

Results: The majority of the patients with diabetes (71%) had low physical activity levels while 52% of the nondiabetic group were moderately active. There was a significant difference between physical activity levels of patients with diabetes and the nondiabetic group ($p<0.05$). Physical exertion was reported by both patients with and without diabetes as the greatest barrier to exercise participation.

Conclusion: Patients with diabetes in Nigeria have a low level of physical activity and are also faced with certain barriers which limit their participation in exercise programmes. Exercise barrier identification and public awareness on the health benefits of exercise and physical activity in the prevention and management of diabetes should thus be encouraged.

INTRODUCTION

Noncommunicable diseases (NCD) account for approximately 71% of all deaths globally.[1] Cardiovascular diseases, cancers, chronic respiratory diseases, and diabetes are the four most important NCD[2] and contributors to the burden of disease.[3] The prevalence of these diseases is increasing worldwide, especially in Sub-Saharan Africa (SSA).[4,5] The risk of death from an NCD is increased by unhealthy lifestyles and behaviours such as sedentary lifestyles, physical inactivity, unhealthy diets,[1] harmful alcohol and tobacco use, and high blood pressure and cholesterol.[3] Diabetes is a metabolic disorder of chronic hyperglycaemia, characterised by disturbances to carbohydrate, protein, and fat metabolism resulting from defects in the action of insulin on the target tissues.[6,7] The International Diabetes Federation (IDF) report estimated that 463 million adults are currently living with diabetes globally, and more than 19 million adults are in the African region; there are approximately 2.7 million adults with diabetes in Nigeria, which is estimated to increase to 47 million by 2045. Sixty percent of adults living with diabetes are unaware they have the condition and are therefore at high risk of developing serious diabetes-related complications. Approximately 11.3% of deaths are caused by diabetes, and 87% of all diabetes-related deaths happen in low- and middle-income countries, with an annual global expenditure of $760 billion USD,[8] and about $67.03 billion USD in SSA.[9]

Globally, pooled data from 751 population-based studies reported an increased number of adults with diabetes from 108 million (males: 4.3%; females: 5.0%) in 1980 to 422 million (males: 9.0%; females: 7.9%) in 2014.[10,11] Substantial evidence exists on the prevalence of diabetes in SSA regions; the prevalence in 2014 was 7.1%, a 129% increase since 1980.[10,12] This increase is unbalanced compared with high-income regions, is affecting younger people, and has enormous economic challenges.[13] Reports from much older literatures recorded a 2.2% prevalence rate in Nigeria,[14] 4% in Kenya,[15] and 0.7% in Tanzania.[16] In a systematic analysis report, the overall pooled prevalence of diabetes in the six geo-political zones in Nigeria was 3.0% in the North-West, 5.9% in the North-East, 3.8% in the North-Central zone, 5.5% in the South-West, 4.6% in South-East, and 9.8% in the South zone.[17] However, presently, while Nigeria reported a 3% prevalence rate, Ghana, Kenya, Tanzania, Zambia, the Democratic Republic of Congo, Gambia, and South Africa have reported rates of 1.8%, 2.2%, 3.7%, 3.4%, 6.3%, 2.0%, and 9.3%, respectively.[8,18] These observed regional differences could be caused by differences in lifestyle modifications, dietary habits, physical activity, better-resourced health systems, adiposity, genetic factors,[19,20] limited knowledge, attitude, and practice among community and policy makers in Africa. A study conducted in Nigeria comparing 40 patients with diabetes and 36 nondiabetic controls reported an insulin resistance prevalence of 87.5% in the diabetics and 27.8% in the controls.[21]

The increasing burden of diabetes has become a global epidemic, imposing an important economic burden on the already existing resource-limited health systems in SSA.[22] Awareness level in many SSA nations is low, though is higher among urban residents,[23] especially in a country like Nigeria that is faced with poor healthcare systems, superstition, poverty, low levels of education, and ignorance.[24] Some of the adults living with diabetes reside mostly in rural communities where many have superstitious beliefs about most NCD including diabetes.[25] The high economic burden and complications associated with diabetes can be mitigated if patients have appropriate awareness, knowledge, management,[26] and prompt diagnosis of the disease.

Lifestyle interventions or modifications, such as avoidance of sedentary lifestyles; regular physical activity;[27,28] reduction of unhealthy nutrition, especially diets high in sodium and calories and low in dietary fibre; moderate alcohol intake; and tobacco cessation, are important lifestyle recommendations for Type 2 diabetes mellitus management and are relevant in developing nations like Nigeria for cost effectiveness. Regular physical activity reduces high blood sugar level in people with diabetes by improving the sensitivity of skeletal muscles to insulin. According to the World Health Organization (WHO), 60–85% of people in both developed and developing countries lead sedentary lifestyles, and poor physical activity is the cause of 6% of global mortality.[29] The American Diabetes Association (ADA) recommends that each patient with diabetes should do at least 150 minutes of moderate-intensity aerobic physical activity

and at least 60 minutes of vigorous-intensity physical activity per week.[30] Barriers to physical activity are personal, social, environmental, and economic and include laziness, lack of stamina or willpower, discouragement from friends and family, fear of injury, embarrassment, weather, cost, age, sex, socio-psychological factors, time, inaccessible or inadequate facilities, transportation, distance, uneven or inappropriate surfaces, and unsupportive peers, amongst others.[13,27,31,32] Understanding what hinders physical activity for people living with diabetes is important for planning and implementing effective interventions to encourage participation in this population.[31] 'Diabetes Action Now', a collective project of the WHO and IDF, aims to stimulate and support the adoption of effective measures for surveillance, prevention, and control of diabetes, as well as to achieve a substantial increase in global awareness about diabetes and its complications.[33]

The WHO recommends prevention strategies such as imposing taxes on sugar-sweetened beverages, detailed labelling on food packaging, and the development of education and awareness campaigns to promote physical activity in the community.[8] Other measures recommended include implementing transportation policies that make it safer for people to walk and ride bicycles; legislating tobacco-free public buildings and spaces; building accessible parks, playgrounds, and community centres; and encouraging physical activity programmes in schools, communities, and health services.[29] However, this seems to be a far-fetched achievement in a country like Nigeria, where implementation of adopted policies and plans of action are not sustainable. The exercise milieu domain of the EBBS questionnaire is considered a major barrier to exercise participation from the assertion that there are few places structured for exercise and the available few are far away and are unaffordable. The interventions that are effective in one place may not be successful in another, so policies and prevention programmes must be specifically designed for each nation. There is an operational strategy to reduce physical inactivity and diabetes in Nigeria.[35] However, these are not readily available, accessible, or cost-effective. Owing to this, there is a need to fully address these barriers for effective implementation and optimal management and to invariably reduce the burden of diabetes through physical activity. Earlier studies in Nigeria on barriers to physical activity have been carried out in several patient groups such as stroke survivors,[35] but to the best of the researcher's knowledge, there is paucity of literature or evidence about the barriers to physical activity among patients with diabetes in Nigeria, hence the following research question: what are the barriers to physical activity participation among patients with diabetes in Nigeria? The authors hypothesised that there would be no significant difference between the physical activity level of those with and without diabetes.

METHODS

Study Design and Population

This was a cross-sectional study involving 400 participants (males: 243; females: 157) aged 25 years and above who were conveniently recruited from the University of Nigeria Teaching Hospital, Ituku-Ozalla, Nigeria. The hospital has an outpatient diabetes clinic once a week, as well as inpatient facilities where medical care is provided throughout the week. This outpatient clinic and the hospital was the setting for this study. The sample size was derived on the estimation that the number utilised in this study would be a representative of the total number of all patients with diabetes visiting the clinic monthly. However, this study's participants were only individuals visiting the clinic at the time of data collection and were not representative of all patients with diabetes in the area; the participants were consecutively recruited. The majority of participants were civil servants, middle-class, had at least a senior secondary education, were of Christian faith, seldomly travelled, and lived in bungalows. The patients with diabetes were on antidiabetic medication, though many were noncompliant.

The inclusion criteria included patients who had diabetes, were attending the outpatient diabetes clinic, and did not have other chronic conditions that could affect outcomes. Their medical status was obtained from their outpatient medical cards. Exclusion criteria included pregnant women and individuals with impaired cognitive functioning.

Sample Size

All consenting patients seen at the time of data collection participated in this study. The sample size was calculated thus: $n=z^2pq/L^2$; where z=1.96 for 95% confidence intervals, L=5% allowable error, and p=21.3% (q=100-p). Recruitment continued until the intended number was reached.

Procedure for Data Collection

Ethical approval was obtained prior to the commencement of the study from the ethical review committee of the University of Nigeria Teaching Hospital. Permission was obtained from the clinic's consultant. An informed consent form was signed by the participants after the study procedures had been thoroughly explained to them. Participation in this study was voluntary. Information on sociodemographic parameters (age, sex, marital status, educational level, and occupational status) was obtained. The questionnaires were researcher administered.

Research Instruments

International Physical Activity Questionnaire

Physical activity was measured using the International Physical Activity Questionnaire (IPAQ), which assesses physical activity undertaken across a comprehensive set of domains including leisure physical activity, domestic and gardening activities, work-related physical activity, and transport-related physical activity.[36] The items were structured to provide separate domain-specific scores for walking, moderate-intensity, and vigorous-intensity activity within each of the domains of work, transportation, domestic chores, gardening, and leisure time. Each activity was also weighted by its relative metabolic cost, referred to as a metabolic equivalent (MET). An average MET score was derived for each type of activity, with MET-minutes per week as the final unit of expression. According to the American College of Sports Medicine (ACSM) guidelines,[37] one MET represents the energy expenditure for an individual at rest, whereas a 10-MET activity requires 10-times the resting energy expenditure. For example, all types of walking were included and an average MET value for walking was created. The same procedure was undertaken for moderate-intensity activities and vigorous-intensity activities. Physical activity level classification was based on MET-minutes/week in three categories: high, if 7 or more days of any combination of walking or moderate or vigorous intensity activities that achieved at least 3,000 MET-minutes per week was achieved; moderate, if 5 or more days consisted of any combination of walking or moderate or vigorous intensity activities of at least 600 MET-minutes per week; and low, if a patient did not meet any of the aforementioned criteria.

Exercise Benefit and Barrier Scale questionnaire

Perceived barriers to exercise participation were assessed using the 'Barriers' component of the Exercise Benefit and Barrier Scale (EBBS) questionnaire.[38] The barrier component utilised had 14 barrier items categorised into four subscales: exercise milieu, time expenditure, physical exertion, and family discouragement.

Data Analysis

Obtained data was analysed using SPSS Version 21 (IBM, Armonk, New York, USA). Categorical descriptive variables (physical activity levels and sociodemographic profile) were analysed using descriptive statistics of percentage and frequency. Barriers to exercise participation between patients with and without diabetes were analysed in mean and standard deviation. Physical activity (in MET) between those with and without diabetes was analysed using an independent t-test. The alpha level was set at <0.05.

RESULTS

Forty-four percent of the patients with diabetes were adults aged 65 years and above. Most of the participants were male, married, civil servants, and educated to university degree level (Table 1). A total of 71% of patients with diabetes reported low physical activity levels, while 52% of the nondiabetic participants reported moderate levels of physical activity (Table 2). Physical exertion and time expenditure subscales of the barriers to exercise participation among diabetic patients had the highest and lowest mean and standard deviation values of 2.90±0.85 and 2.66±0.94, respectively. The total mean-deviation

of the exercise participation barrier was 2.78±0.88. Physical exertion and family discouragement subscales of the barriers to exercise participation among nondiabetic participants had the highest and lowest mean and standard deviation values of 2.82±1.63 and 2.68±0.80, respectively. The total mean-deviation of the exercise participation barrier was 2.75±0.83 (Table 3).

DISCUSSION

The majority of participants with diabetes in this study (71.0%) had low levels of physical activity. This may likely be because of inadequate awareness or detailed education on the benefits of physical activity in diabetes management. This result is much higher than the 31% from a previous Nigerian study conducted in the South-Western region.[39] Other SSA studies have reported 39% for a Rwandan population,[40] 25.1% for a Ghanaian population, and 54.7% for a Batswana population.[41,42] Fifty-two percent of Nepalian patients with diabetes,[27] 47% in Malaysia,[43] and 86% in Sri-Lanka[44] were mostly moderately physically active. Regular exercise improves body sensitivity to insulin and helps manage blood glucose levels. The ADA recommends that each patient with diabetes should do at least 150 minutes of moderate-intensity aerobic physical activity weekly.[30] This suggests that patients living with diabetes in this study were not within this acceptable level. However, a study involving participants from North Carolina, USA revealed that 56% of patients with diabetes reported at least 150 minutes of moderate or vigorous physical activity weekly.[45] Population size, instruments, weather, and study designs could be attributable to these differences.

Fifty-two percent of the nondiabetic participants in this study were moderately active. Similar to this finding, 58% of adults without diabetes in a USA study were physically active (moderate or vigorous activity).[46] Individuals with chronic diseases in general and diabetes in particular usually stay away from physical activity for fear of worsening their condition or triggering a hypoglycaemic crisis.[47] There was a statistically significant difference between physical activity levels using MET of patients with diabetes and nondiabetic participants. The result revealed that the patients with diabetes had a mean value of 563.73 while nondiabetic participants had a mean value 1,009.470. The mean scoring was obtained from the IPAQ: low (0–599 MET-min/week), moderate (600–2,999 MET-min/week), and high (over 3,000 MET-min/week).[48] It was surprising that the nondiabetic participants in this study were moderately physically active, as they were presumed to be apparently healthy and as such were expected to be highly active. To explain this finding, it could be that many health workers live sedentary life by virtue of the nature of their jobs, lack of time to get involved in physical activities, and an over-reliance on motorised transport to commute to work instead of walking. The lower levels of physical activity in both groups may be attributed to other factors besides failing health status; some potential barriers to exercise participation include lack of awareness about benefits; lack of national health, educational, and related policies; lack of valuing sport in society; prevailing local cultures; economic and other competing pressures; time constraints; personal motivation; lack of support from family and friends; lack of access to sport facilities; past experiences; and the lack of availability of local physical programmes.[49,50]

The results of this study on the barriers to exercise participation between participants with and without diabetes showed that both groups perceived physical exertion as the strongest barrier to exercise participation. Tiredness and fatigue have been previously reported as important factors that militate against exercise participation.[51] Evidence of findings from other SSA regions on barriers to physical activity among patients with diabetes are well researched in the literature. Lack of exercising space and no one to exercise with were the most reported barriers to physical activity in Botswana.[42] In Rwanda, poor health status, lack of motivation, and lack of awareness about the importance of physical activity were the common barriers to physical activity participation.[40] Other previous studies reported that most of the patients with diabetes were physically inactive because of lack of time and energy, and patients who reported moderate and high physical activity were those who were motivated to be healthy.[43] Lack of willpower, resources, and social support were the most frequently reported barriers in Oman.[52]

While this study utilised the barrier component of the EBBS questionnaire, these other studies used other instruments such as the 27-item Barriers to Being Active questionnaire.

Table 1: Sociodemographic characteristics of the participants.

Variables	Frequency with diabetes	Percentage (%)	Frequency without diabetes	Percentage (%)
Age (years)				
25–34	2	1.0	35	17.5
35–44	7	3.5	59	29.5
45–54	44	22.0	73	36.5
55–64	59	29.5	28	14.0
65–74	83	41.5	5	2.5
≥75	5	2.5	0	0.0
Total	200	100	200	100.0
Sex				
Male	119	54.5	124	62.0
Female	91	45.5	76	38.0
Total	200	100.0	200	100.0
Marital status				
Single	13	6.5	30	15.0
Married	101	50.5	132	66.0
Divorced	8	4	3	1.5
Widowed	57	28.5	25	12.5
Widower	21	10.5	10	5
Total	200	100.0	200	100.0
Occupation				
Unemployed	19	9.5	0	0.0
Civil servant	46	23.0	165	82.5
Private	12	6.0	0	0.0
Self employed	35	17.5	35	17.5
Retired	30	15.0	0	0.0
Farming	27	13.5	0	0.0
Stay-at-home spouse	31	15.5	0	0.0
Total	200	100.0	200	100.0
Education				
Informal	35	17.5	0	0.0
Primary	26	13.0	0	0.0
Junior secondary	6	3.0	0	0.0
Senior secondary	43	21.5	67	33.5
First degree	80	40.0	101	50.5
Postgraduate	10	5.0	32	16.0

Table 2: Descriptive and comparative statistical analysis of physical activity levels among participants with and without diabetes.

Physical activity	Frequency of people with diabetes (%)	Frequency of people without diabetes (%)	Total (%)	t value	Degrees of freedom	p value
Low	142 (71.0)	66 (33.0)	246 (61.5)	4.980	2	0.001
Moderate	47 (23.5)	104 (52.0)	113 (28.3)			
High	11 (5.5)	30 (15.0)	41 (10.0)			
Total	200 (100.0)	200 (100.0)	400 (100.0)			

Table 3: Participants' mean and standard deviation scores for domains of barriers to exercise participation among diabetic and nondiabetic participants.

Variables	Diabetic participants (mean±SD)	Nondiabetic participants (mean±SD)
Exercise milieu subscale		
1. Places for me to exercise are too far away	2.82±0.83	3.20±0.81
2. I am too embarrassed to exercise	2.98±0.78	2.38±1.04
3. It costs too much to exercise	2.90±0.79	2.63±0.77
4. Exercise facilities do not have convenient schedule for me	2.70±0.88	2.74±0.66
5. There are too few places for me to exercise	2.64±0.98	2.90±0.95
Mean	**2.81±0.85**	**2.76±0.84**
Time expenditure subscale		
6. Exercise takes too much of my time	2.68±0.92	2.76±0.84
7. Exercise takes too much time from my family responsibility	2.65±0.97	2.68±0.81
Mean	**2.66±0.94**	**2.72±0.82**
Physical exertion subscale		
8. Exercise tires me	2.87±0.86	2.64±0.78
9. I am fatigued by exercise	2.94±0.84	3.00±0.85
Mean	**2.90±0.85**	**2.82±1.63**
Family discouragement subscale		
10. My significant other(s) does not encourage exercising	2.65±0.96	2.70±0.69
11. My family members does not encourage me to exercise	2.77±0.93	2.66±0.90
Mean	**2.71±0.95**	**2.68±0.80**
Total (mean±SD)	**2.78±0.88**	**2.75±0.83**

SD: standard deviation.

Time expenditure and family discouragement were the least reported barriers to exercise in participants with and without diabetes, respectively. The cost of exercising, being too embarrassed to exercise, and distance to exercise facilities were highly rated as important barriers to physical activity by respondents, even when they had time or were encouraged by their families. In agreement with this study's findings, family discouragement and busy work schedules (time) were important barriers to being physically active in Nepal;[27] the United Arab Emirates;[53] Spain;[54] Denmark;[55] and North Carolina, USA.[45] Health conditions, pain, environment, lack of accessibility, and time appear to be potential barriers to physical activity among older adult populations.[56,57] The presence of these barriers could have accounted for the low levels of physical activity reported in this study.

CONCLUSIONS

This study made information available on the levels and perceived barriers of physical activity among patients with diabetes from Nigeria. There is a need to make observations in a similar population consisting of people with or without diabetes in order to detect and understand outcomes, so as to use the data from nondiabetic patients to effectively manage diabetes and the data from patients with diabetes to effectively delay disease onset. This study revealed that the majority of patients with diabetes had low physical activity level while nondiabetic participants had moderate physical activity level. However, physical exertion was reported by both patients with diabetes and nondiabetic participants as the greatest barrier to exercise participation; time expenditure and family discouragement were, respectively, the least reported barrier to exercise among participants. Recommendations are therefore that physiotherapy should be made a compulsory treatment protocols for patients with diabetes in tertiary institutions. Public awareness on the health benefits of exercise in prevention and management of diabetes should be implemented by the federal ministry of health. The federal government of Nigeria, in collaboration with state and local governments, should provide strategically placed exercise facilities for people that are willing to exercise. Physiotherapists and other health practitioners who treat patients with diabetes should always assess their physical activity level and perceived barriers to exercise. Further research involving more subjects in a very large population should be studied.

Limitations

The participants in this study were individuals visiting the clinic at the time of data collection and were not representative of all the patients with diabetes in the area. Therefore, there is limited generalisability of the findings. The cross-sectional design of this study does not allow for cause and effect inference.

References

1. World Health Organization (WHO). Non-communicable disease country profiles. 2018. Available at: https://www.who.int/nmh/publications/ncd-profiles-2018/en/. Last accessed: 4 January 2021.
2. Forouzanfar MH et al. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990-2015: a systematic analysis for the global burden of disease study. Lancet. 2016;388(10053):1659-724.
3. Farzadfar F et al. Effectiveness of diabetes and hypertension management by rural primary health-care workers (Behvarz workers) in Iran: a nationally representative observational study. Lancet. 2012;379(9810):47-54.
4. Ganu D et al. Physical disability and functional impairment resulting from Type 2 diabetes in sub-Saharan Africa: a systematic review. Afr J Diabetes Med. 2016;24(1):10-4.
5. Pastakia SD et al. Diabetes in sub-Saharan Africa- from policy to practice to progress: targeting the existing gaps for future care for diabetes. Diabetes Metab Syndr Obes. 2017;10:247-63.
6. Fattahi A et al. Physical activity and its related factors among Type 2 Diabetic patients in Hamadan. Iran J Diabetes Obes. 2014;6(2):85-92.
7. World Health Organization (WHO). Definition, diagnosis and classification of diabetes mellitus and its complications, Part 1. 1999. Available at: https://apps.who.int/iris/handle/10665/66040. Last accessed: 4 January 2021.
8. International Diabetes Federation (IDF). IDF Diabetes Atlas. 9th edition. 2019. Available at: http://www.idf.org/diabetesatlas. Last accessed: 4 January 2021.
9. Hall V et al. Diabetes in Sub-Saharan Africa 1999-2011: epidemiology and public health implications. A systematic review. BMC Public Health. 2011;11(1):11-564.
10. Non-Communicable Disease Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet.

2016;387(10027):1513-30.

11. Zhou B et al. Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4.4 million participants. Lancet. 2016;387(10027):1513-30.
12. World Health Organization (WHO). Global report on diabetes. 2016. Available at: http://apps.who.int/iris/bitstream/10665/204871/1/9789241565257 eng.pdf Last accessed: 4 January 2021.
13. Jaffar S, Gill G. The crisis of diabetes in Sub-Saharan Africa. Lancet Diabetes Endocrinol. 2017;5(8):574-5.
14. Akinkugbe OO. Non-communicable diseases in Nigeria: national survey (final report) on hypertension, coronary heart disease, diabetes mellitus, haemoglobinopathies, G6PD deficiency and anaemia. National Expert Committee on Non-communicable Diseases. Federal Ministry of Health and Social Services. Lagos, Nigeria, 1997. Available at: https://scholar.google.com/scholar?hl=en&q=+Non+communicable+diseases+in+Nigeria:+national+survey+(final+report)+on+hypertension+coronary+heart+disease+diabetes+mellitus+G6PD+deficiency+and+anaemia. Last accessed: 4 January 2021.
15. Christensen DL et al. Prevalence of glucose intolerance and associated risk factors in rural and urban populations of different ethnic groups in Kenya. Diab Res Clin Prac. 2009;84(3):303-10.
16. Ahren B, Corrigan CB. Prevalence of diabetes mellitus in north-western Tanzania. Diabetologia. 1984;26:333-6.
17. Uloko AE et al. Prevalence and risk factors for diabetes mellitus in Nigeria: a systematic review and meta-analysis. Diabetes Ther. 2018;9(3):1307-16.
18. World Bank. World development indicators. 2016. Available at: https://datacatalog.worldbank.org/dataset/world-development-indicators. Last accessed: 5 January 2021.
19. Bailey SL et al. Diabetes mellitus in Zambia and the western cape province of South Africa: prevalence, risk factors, diagnosis and management. Diabetes Res Clin Pract. 2016;118:1-11.
20. Ley SH et al. Prevention and management of Type 2 diabetes: dietary components and nutritional strategies. Lancet. 2014;383(9933):1999-2007.
21. Bakari A, Onyemelukwe G. Insulin resistance in Type 2 diabetic Nigerians. Int J Diabetes Metab. 2005;13:24-7.
22. Kibirige D et al. Understanding the manifestation of diabetes in Sub-Saharan Africa to inform therapeutic approaches and preventive strategies: a narrative review. Clin Diabetes Endocrinol. 2019;5(2):DOI:10.1186/s40842-019-0077-8.
23. Mohamed S et al. Prevalence and factors associated with pre-diabetes and diabetes mellitus in Kenya: results from a national survey. BMC Public Health. 2018;18(3):1215.
24. Adeleke OR, Ayenigbara GO. Preventing diabetes mellitus in Nigeria: effect of physical exercise, appropriate diet, and lifestyle modification. Int J Diabetes Metab. 2019;25:3-4.
25. Agofure O et al. Knowledge of dietary and medical management of Type-2 diabetes in an urban and rural community of Delta State Nigeria. Afr J Diabetes Med. 2018;26(1):12-5.
26. Odenigbo MA, Inya-Osuu J. Knowledge, attitudes and practices of people with Type-2 diabetes mellitus in a tertiary health care centre, Umuahia, Nigeria. J Diabetes Metab, 2012;3:187-91.
27. Kadariya S, Aro AR. Barriers and facilitators to physical activity among urban residents with diabetes in Nepal. PLoS ONE. 2018;13(6):e0199329.
28. Kennerly AM, Kirk A. Physical activity and sedentary behaviour of adults with Type 2 diabetes: a systematic review. Pract Diabetes. 2018;35(3):86-9.
29. World Health Organization (WHO). Global strategy on diet, physical activity and health. 2018. Available at: http://www.who.int/dietphysicalactivity/pa/en/. Last accessed: 5 January 2021.
30. American Diabetes Association (ADA). Standards of medical care in diabetes - 2016. Diabetes Care. 2016;39(Suppl 1):s27.
31. Shields N et al. Perceived barriers and facilitators to physical activity for children with disability: a systematic review. Br J Sports Med. 2012;46(14):989-97.
32. Mwaura LW et al. Effect of distance on access to health services among women with Type 2 diabetes in a rural community in Kenya. Afr J Diabetes Med. 2017;25(1):18-20.
33. Achigbu EO et al. Knowledge and impact of diabetes in patients in a tertiary clinic in southeast Nigeria. Afr J Diabetes Med. 2015;23:15-7. Available at: https://www.africanjournalofdiabetesmedicine.com/articles/8.%20AJDM-497%20(Achigbu).pdf. Last accessed: 5 January 2021.
34. World Health Organization (WHO). Diabetes country profiles. 2016. Available at: https://who.int/diabetes/country-profiles/nga_en.pdf?ua=1. Last accessed: 5 January 2021.
35. Idowu OA et al. Perceived barriers to physical activity among Nigerian stroke survivors. Pan Afr Med. 2015;21:274;DOI:10.11604/pamj.2015.21.274.6669.
36. Nolan R et al. Self-reported physical activity using the international physical activity questionnaire (IPAQ) in Australian adults with Type 2 diabetes, with and without peripheral neuropathy. Can J Diabetes. 2016;40(6):576-9.
37. American College of Sports Medicine, Guidelines for graded exercise testing and exercise prescription (1980) 2nd edition, Philadelphia: Lea & Febiger.
38. Sechrist KR et al. Development and psychometric evaluation of the exercise benefits/barriers scale. Res Nurs Health. 1987;10(6):357-65.
39. Oyewole OO et al. Physical activity among Type 2 diabetic adult Nigerians. Ann Afr Med. 2014;13(4):189-94.
40. Kabanda AM, Phillips JS. Physical activity among adults with diabetes mellitus in Rwanda. Sahara J. 2011;17(2):239-47.
41. Gatimu SM et al. Prevalence and determinants of diabetes among older adults in Ghana. BMC Public Health. 2016;16:1174.
42. Shiriyedeve S et al. Factors associated with physical activity in Type 2 diabetes mellitus patients at a public clinic in Gaborone, Botswana, in 2017. Afr J Prim Health Care Fam Med. 2019;11(1):a2036.
43. Shazwani N et al. Assessment of physical activity level among individuals with Type 2 diabetes mellitus at Cheras Health Clinic, Kuala Lumpur. Malays J Nutr. 2010;16(1):101-12.
44. Ranasinghe DC et al. Evaluation of physical activity among adults with diabetes mellitus from Sri Lanka. Int Arch Med. 2014;7:15.
45. Donahue KE et al. Identifying supports and barriers to physical activity in patients at risk for diabetes. Prev Chronic Dis. 2006;3(4):A119.
46. Morrato EH et al. Physical activity in U.S. adults with diabetes and at risk for developing diabetes. Diabetes Care. 2007;30(2):203-9.
47. Kriska AM et al. Physical activity, obesity and the incidence of Type 2 diabetes in a high-risk population. Am J Epidemiol. 2003;158(7):669-75.
48. Craig CL et al. International physical activity questionnaire: 12-country reliability and validity. Med Sci Sports Exerc. 2003;35(8):1381-95.
49. World Health Organization (WHO). "Move for health": world health day. 2002. Available at: https://www.who.int/docstore/world-health-day/2002/euro_factsheet.pdf. Last accessed: 5 January 2021.

50. World Health Organization (WHO). Non-communicable disease prevention and health promotion. 2003. Available. https://www.who.int/mip/2003/progress/en/nmhmip2003.pdf. Last accessed: 5 January 2021.
51. Dalibalta S, Davison G. Perceived exercise benefits and barriers of a mixed student population in the United Arab Emirates. Int J Sci Res Innov Tech. 2016;3(2):115-39.
52. Alghafri T et al. Perceived barriers to leisure time physical activity in adults with Type 2 diabetes attending primary healthcare in Oman: a cross-sectional survey. BMJ Open. 2017;7(11):e016946.
53. Al-Kaabi J et al. Physical activity and reported barriers to activity among Type 2 diabetic patients in the United Arab Emirates. Rev Diabet Stud. 2009;6(4):271-8.
Nicolas Lopez J et al. Barriers to physical activity in people with diabetes residing in Spain. Atena J Public Health. 2020;2:3.
54. Lidegaard LP et al. Barriers to and motivators for physical activity among people with Type 2 diabetes: patients' perspectives. Diabet Med. 2016;33(12):1677-85.
55. Schuler PB et al. Barriers and motivations to exercise in older African American and European American women. Calif J Health Promot. 2006;4(3):128-34.
56. Schutzer KA, Graves BS. Barriers and motivations to exercise in older adults. Prev Med. 2004;39(5):1056-61.

Identifying Early Extraperitoneal High-Volume Urine Leak Post Kidney Transplantation

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Abstract

Transplant clinicians need to be watchful of several potential surgical complications in the early post-transplant period, including haemorrhage, extraperitoneal urine leak, and lymphocele. While haemorrhage and extraperitoneal urine leak usually present in the early post kidney transplant period, lymphoceles usually present 2–6 weeks after transplantation. While the colour and volume of the drained fluid can give some indication of the problem, is not enough evidence for a confident urine leak diagnosis. Further investigations, such as serum biochemical parameter analysis of the drained fluid and ultrasonography, help to identify the true cause. This paper discusses how to identify high-volume extraperitoneal urine leaks in the early post kidney transplant period and considers the differential diagnoses. Different ureteroneocystostomy procedures, including the Lich–Grégoir, Politano–Leadbetter, and U-stitch techniques, are discussed and compared regarding complication rates (especially urine leak and haematuria). The authors also address the management of low- and high-volume extraperitoneal urine leak, the follow-up needed, and the impact of urine leak on graft and patient survival, length of hospital stay, and rate of hospital readmission.

INTRODUCTION

The first few days after kidney transplantation are the most critical in determining the fate of the graft and the recipient. The clinical team is extremely vigilant in monitoring parameters that could indicate graft dysfunction, graft rejection, delayed graft function, post-operative complications, drug levels (especially tacrolimus or cyclosporine level), infection, and the general wellbeing of the kidney transplant recipient (KTR) and donor. Urine leak is an early post-operative complication after kidney transplantation and occurs in 1.2–8.9% of these operations. Low-volume leaks may subside with conservative management and provided there is no distal obstruction. If not resolved, or if it is large-volume urine leak, surgical exploration and

correction may be needed. This article discusses the identification of extraperitoneal urinary leak in a KTR in the post-operative period, as well as the clinical clues that help to rule out the differential diagnoses.

URETEROVESICAL ANASTOMOSIS AND A COMPARISON OF ASSOCIATED COMPLICATIONS

Many different techniques are used to achieve ureterovesical anastomosis in kidney transplantation.[1,2] The most popular methods include the Lich–Grégoir, Politano-Leadbetter, and U-stitch techniques.[2-5] Meta-analyses performed by Alberts et al.[2] showed that the Lich–Grégoir technique is significantly associated with a lower incidence of urinary leakage compared to the Politano-Leadbetter technique. The analyses also showed significantly fewer incidences of haematuria with the Lich–Grégoir method than both the Politano-Leadbetter and U-stitch techniques, regardless of ureteral stenting. The investigators concluded that the Lich-Grégoir technique results in fewer urological complications than the other two ureterovesical anastomosis procedures.[2] Whichever technique is used, in order to prevent reflux during voiding, the ureterovesical anastomosis must be tension-free and protected by at least a 1 cm submucosal tunnel.[1]

UROLOGICAL COMPLICATIONS DURING THE POST-OPERATIVE PERIOD IN KIDNEY TRANSPLANT RECIPIENTS

The most common surgical urology complications include urine leakage, ureteral obstruction, and lymphocele (fluid collection between the urinary bladder and the kidney allograft).[6] The rates of urological complications range from 2.5% to 30.0% of all recipients.[6] In cases of urine leak, the patient may have a fever, pain over the graft, and fluid leakage from the wound.[1] Routine prophylactic intraoperative stenting of the ureter in kidney transplant recipients mitigates the effects of ureteric complications but does not reduce the incidence of these complications. The stents are generally well tolerated, but when longer stents are used (stent length: ≥20 cm), or if used for longer periods (>6 weeks), they may result in stent-related complications including infection, migration, and encrustation.[7] The initial step in urine leak management is to maximally decompress the urinary system. This is achieved by inserting a urethral catheter, as well as performing a nephrostomy or placing an antegrade ureteric stent. The drain is left *in situ*. If this technique fails, or if large-volume extravasation occurs, surgical exploration to reimplant the transplant ureter becomes necessary.[8]

Other urological complications include:[9,10]

- Complications caused by the length of the transplanted ureter. A long ureter is liable to kinking and obstruction as a result of ischaemia because the vascularity of the transplant ureter depends on renal vessels supplying through periureteric tissue, unlike the native ureter which has a segmental blood supply. A short ureter may not be appropriate for achieving tension-free anastomosis.
- Atrophic bladder or dysfunctional bladder in the recipient may result in bladder perforation or anastomotic dehiscence.[11]
- Proximal calyceal leak may occur because of lower pole artery complications (thrombosed, ligated, not reconstructed).[12-14]
- Damage to the ureter during dissection may result in ureteric ischaemia, necrosis, and distal leak.[15,16]

Urological complications in the post-operative period can be identified by the drained fluid's colour (clear, haemorrhagic, or purulent) and odour (uriniferous or foul).[17] If there is a delayed graft function, a urinary leak can be detected only after the urine output increases.[18]

Signs and Symptoms

Varied symptoms can occur as a result of kidney transplant, including local (graft pain and tenderness, and local swelling over the graft)[10] and systemic (fever, tachycardia, hypotension, and tachypnoea).[10] Signs may be masked because of immunosuppression and analgesics. A high index of suspicion is warranted in a patient with high drain output.[10,19,20]

Investigations

The following investigations are helpful in evaluating extraperitoneal urine leak post

kidney transplantation, and to rule out differential diagnoses:

- Compare drain creatinine and potassium levels with serum creatinine and potassium levels.[21-23]
- Use ultrasonography to identify and define the perinephric collection and dilatation of the pelvicalyceal system.[18]
- Doppler ultrasonography can be used to identify defects in perfusion.[18]
- CT or MRI scans are a useful tool to identify and define the perinephric collection and pelvicalyceal dilatation.[18]
- An intravenous pyelogram may be helpful to identify location of the leak.[18]
- Focal tracer scintigraphy uses mercaptoacetyltriglycine or technetium 99 to identify the location of the leak. This technique is not useful if there is delayed graft function or ureteral stasis.[24,25]
- Retrograde cystography helps clinicians to look for urinary bladder dehiscence.[24,25]
- Antegrade pyelogram testing through a nephrostomy may accurately identify the location of the leak. This can be done in delayed graft function scenarios too. Pelvicalyceal dilatation makes it easier to do this procedure.[26]

Identifying Extraperitoneal Urine Leak Post Kidney Transplantation

A high volume of clear drain fluid may indicate the possibility of extraperitoneal urine leak. Ultrasonography, CT scan or MRI, and fluid biochemistry further aid diagnosis. If drain fluid creatinine and potassium values are not dissimilar from the serum values, then the possibilities of lymphocele or seroma are higher. However, if they are significantly higher than the serum values, or are values that are incompatible with life, then it is a urine leak or urinoma. Urinoma will easily be picked up on an ultrasound scan or nuclear scan (Figure 1). Antegrade pyelogram, cystogram, or scintigraphy may be required to identify the cause and to localise the leak.[27]

DIFFERENTIAL DIAGNOSIS AND CLINICAL REASONING

Haemorrhage

If the drain is haemorrhagic, with accompanying factors like tachycardia, anaemia, local swelling over the graft, or if bleeding is a possibility, ultrasonography, CT scan, or MRI may be used to identify haematoma, necessitating an emergency re-exploration.[22,28,29] Haemorrhage is not a common complication after kidney transplantation. If it occurs, it is usually from the vessels in the graft hilum that are not ligated, or from small, severed retroperitoneal vessels. There are some recipient- and therapy-related risk factors that can predispose recipients to the risk of haemorrhage. These risk factors include recipient obesity, use of antiplatelet agents, and anticoagulation.[10]

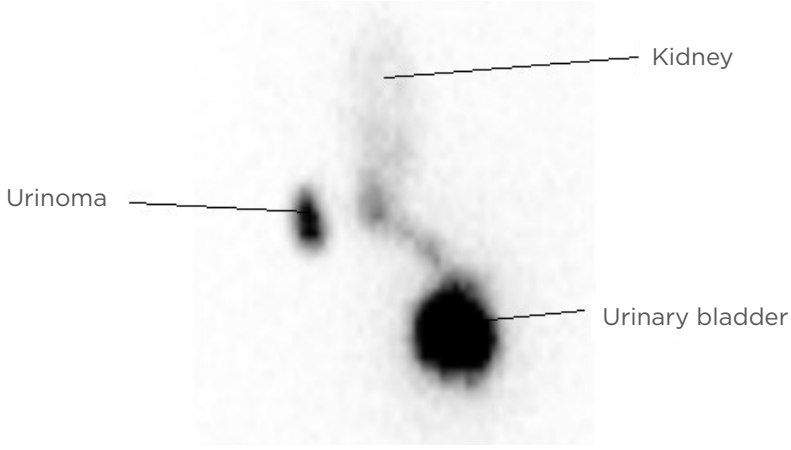


Figure 1: Urinoma, as seen in focal tracer scintigraphy using mercaptoacetyltriglycine.

Serial measurement of haematocrit may show a falling haematocrit level. The patient may develop hypotension, tachycardia, and pain in the flank or lower quadrant. Surgical exploration is usually not required because bleeding usually stops spontaneously. However, if the patient needs pure red blood cell transfusion repeatedly, or if there is haemodynamic instability or compression of the kidney by haematoma, surgical re-exploration may be required.[1]

Urinary Fistula

Urinary fistula occurs in 2–5% of kidney transplantations, and may lead to significant morbidity, graft loss, and mortality;[30,31] there is an 8% risk of mortality associated with urinary fistula.[30] Ureteral ischaemia and necrosis and technical problems associated with the transplant procedure are important causes of urinary fistula development.[30] The risk factors associated with development of urinary fistula include younger recipient age (aged <10 years), uretero-ureteric anastomosis, use of high-dose steroids in immunosuppression, number of renal arteries, and bladder problems.[30] Early intervention helps to prevent graft loss and reduces mortality.[30] Urinary fistulas may be managed by different techniques including ureteral ligature and nephrostomy, ureteroureterostomy, pyeloureterostomy, ureteroneocystostomy, percutaneous nephrostomy and ureteral stenting, and prolonged vesical drainage.[30,31]

Perinephric Abscess

Perinephric abscesses are uncommon complications post kidney transplantation. They usually present in the early post-transplant period (in the first few week's post-transplant). The causes include pyelonephritis, infection of lymphocele, haematoma, or urinoma.[32] If the drained fluid is purulent, with accompanying symptoms and signs (fever, swelling, and tenderness over the graft), ultrasonography, CT scan, or MRI may aid the diagnosis of perinephric abscess. Aspiration of the collection and performing microscopy and culture of the aspirate may further help the diagnosis.[28,29]

Lymphocele and Seroma

A collection of lymph in the perigraft area is called a lymphocele. Lymphoceles occur in 1-20% of kidney transplant operations.[33] Lymphocele may occur from as early as 2 weeks to as late as 5 years post-transplant.[33] Usually they are small and asymptomatic, and such lymphoceles require no intervention.[33] Lymphoceles may present with features of compression symptoms including retention of urine, decreased urine output, elevated serum creatinine, thrombosis of iliac vein, and limb oedema.[33] It is believed that lymphocele formation occurs because of technical failures to seal perivascular lymphatic channels incised during surgical exposure of the iliac vessels, or because of lymph leakage from the hilum of the allograft itself. Investigators have also found an association between sirolimus use and occurrence of lymphoceles and seromas.[34]

In lymphocele and seroma, the drainage fluid is clear. Ultrasonography, CT scan, or MRI, and fluid biochemistry further aid diagnosis. If drain fluid creatinine and potassium values are not much different from the serum values, then the possibilities of lymphocele or seroma are higher.[28,29] Treatment options include aspiration (nearly 100% chances of recurrence), percutaneous drainage (50% success rate), drainage by laparoscopic method, or open marsupialisation.[33] Laparoscopic drainage of the lymphocele is the method of choice for the treatment of post-transplant lymphocele. However, open drainage is preferred over laparoscopic technique in patients with wound complications. Open drainage is also preferred over laparoscopic technique in patients with a small lymphocele adjacent to vital renal structures, which increases the risk of vessel or ureter injury.[35] If the lymphocele is lateral to the renal allograft, laparoscopic drainage is usually difficult.[36] Continuous drainage may be used together with the application of sclerosants like povidone iodine, fibrin glue, and doxycycline, tetracycline, ethanol, bleomycin.[33,36] Periureteral fibrosis is a risk if sclerosing agents are used.[36]

Urine Leak and Urinoma

Urine leak is an early post-operative complication after kidney transplantation and occurs in 1.2–8.9% of cases.[33] Urine leaks post kidney transplantation may manifest as free fluid (urine ascites), extravasation in local tissues, or may be encapsulated (urinoma).[37]

Different clinical presentations of urine leak

The different clinical presentations could be early extraperitoneal high-volume leak; early extraperitoneal small leak, defined by a persistent low urine output through drains, associated with low urine output, graft site swelling, and pain (imaging with contrast may help identify urinoma); late leak (1–2 weeks after kidney transplant), which may be caused by ureter necrosis or early removal of double J stent (<3–6 weeks); and intra-abdominal leak, which presents with an acute abdomen.[18,38]

Evidence-based management plan in extraperitoneal urine leak

Low-volume leak at the anastomotic site can be managed conservatively by performing maximum decompression.[39,40] Antegrade pyelogram to identify the site of the leak is helpful. Placing a Foley catheter and ureteral stent performing a nephrostomy are the techniques used for decompression.[39,41] Once the urine leak stops, the Foley catheter and nephrostomy tube can be removed; however, the ureteral stent is only removed after a period of 4–6 weeks.[41] After conservative management, the patient is carefully followed-up.[39] If the fluid collections become infected, or cause ureteral obstruction and extrinsic compression on the ureter, then urgent percutaneous drainage is required.[39,41] Surgical re-exploration and reimplanting the transplant ureter becomes necessary if conservative measures for stopping low-volume urine leak fail, or if there is a high-volume drain.[8,39-43]

Preventive measures: importance of the golden triangle

Urine leak usually occurs because of technical errors in the ureteroneocystostomy technique, the method of graft ureter implantation in the recipient's urinary bladder, or because of the transplanted ureter's compromised vascularity, which is caused by vessel damage during the harvest of the donor kidney.[41] Presence of multiple renal arteries is also a risk factor for development of urological complications post kidney transplantation.[41] During harvesting of the donor kidney, gentle handling of the ureter at the time of ureteral dissection is crucial to prevent urine leak post kidney transplantation. An adequate periurethral tissue in the 'golden triangle' must be carefully preserved:[43,44,45-48] the 'golden triangle' is bound by the lower border of the junction between the renal vein and the inferior vena cava on the right, lower pole of the kidney on the left and the gonadal vein.[43,44] Important factors that help to prevent major urological complications include delicate dissection of the ureter during donor nephrectomy to preserve adventitia; fat and blood supply of the ureter; short ureter length; and fixation of the adventitia, fat, and blood supply of the ureter to the bladder wall to prevent kinking or twisting.[49]

Outcome of extraperitoneal urine leak: short-term and long-term effects on graft function and survival

Surgical complications can cause graft loss post kidney transplantation.[1] Several studies have shown that urological complications post kidney transplant may lead to prolonged hospitalisation and reduced graft survival (see Table 1). Buggs et al.[50] conducted a retrospective cohort study of consecutive adult kidney transplant recipients and identified 36 cases of urine leak out of 1,308 cases. These investigators found that the patients with urine leak had a statistically significant longer length of hospital stay, more readmissions, more delayed graft function, and lower rates of graft survival.[50] In another observational cross-sectional study of 3,102 kidney transplant patients, Carvalho et al.[51] found that surgical complications occurred in 527 (17.0%) patients and urinary complications in 184 (5.9%). The most common complications observed were ureteral obstruction (in 85 patients; 2.7%) and urinary fistula (in 72 patients; 2.3%). They observed that surgical complications after kidney transplants lead to prolonged hospitalisation and decreased graft survival.[51] Though most of the studies show similar results, some have also shown conflicting results (see Table 1).[50-54]

CONCLUSION

Different ureteroneocystostomy techniques, including the Lich-Grégoir, Politano–Leadbetter, and U-stitch techniques, have an impact on development of urine leak. The Lich-Grégoir technique has a significantly lower incidence of urinary leakage compared to the Politano–Leadbetter procedure.

Table 1: Impact of urological complications post kidney transplant on duration of hospitalisation and graft survival.

Study	Total number of patients	Number of patients with urological complications	Investigators' observations
Buggs et al.,[50] 2019	1,308	36 (2.75%), urine leak	Prolonged hospitalisation, more readmissions, increased rate of delayed graft function, and lower rates of graft survival.
Carvalho et al.,[51] 2019	3,102	184 (5.93%), urinary complications	Prolonged hospitalisation and decreased graft survival.
van Roijen et al.,[52] 2001	695	42 (6.04%), required revision of vesicoureteral anastomoses	No effect on long-term graft survival by a surgically treated urological complication within 1-year post transplantation.
Pillot et al.,[53] 2012	200	49 (24.50%), 66 surgical complications in 49 patients, with the majority being urological complications	Increased incidence of delayed graft function and graft rejection episodes among patients with surgical complications. No impact on patient or graft survival.
Kaskarelis et al.,[54] 2008	21	21 (9 with urinary leak, 6 with ureteric obstruction, and 6 with obstruction preceded by leak)	No impact on patient and graft survival.

Technical errors in ureteroneocystostomy techniques or compromised vascularity of the transplanted ureter, caused by damage of the vessels during harvesting the donor kidney, are usually responsible for urine leak. Presence of multiple renal arteries is also a risk factor for development of urological complications post kidney transplantation.

A high index of suspicion is needed to identify the complications as the symptoms and signs may be masked because of the immunosuppressive drugs and the analgesics used. The colour of the drained fluid (haemorrhagic, clear, or purulent) and odour (uriniferous or foul) may indicate the development of a urological complication. If drain fluid is clear and the creatinine and potassium values are not much different from the serum values, then the possibilities of lymphocele or seroma are higher. If drain fluid is clear and drain fluid creatinine and potassium values are significantly higher than the serum values, then it is a urine leak or urinoma. Ultrasonography, CT, or MRI may help to arrive at a diagnosis. Doppler ultrasonography, contrast pyelogram, focal tracer scintigraphy using mercaptoacetyltriglycine or technetium 99, and retrograde cystography may be useful.

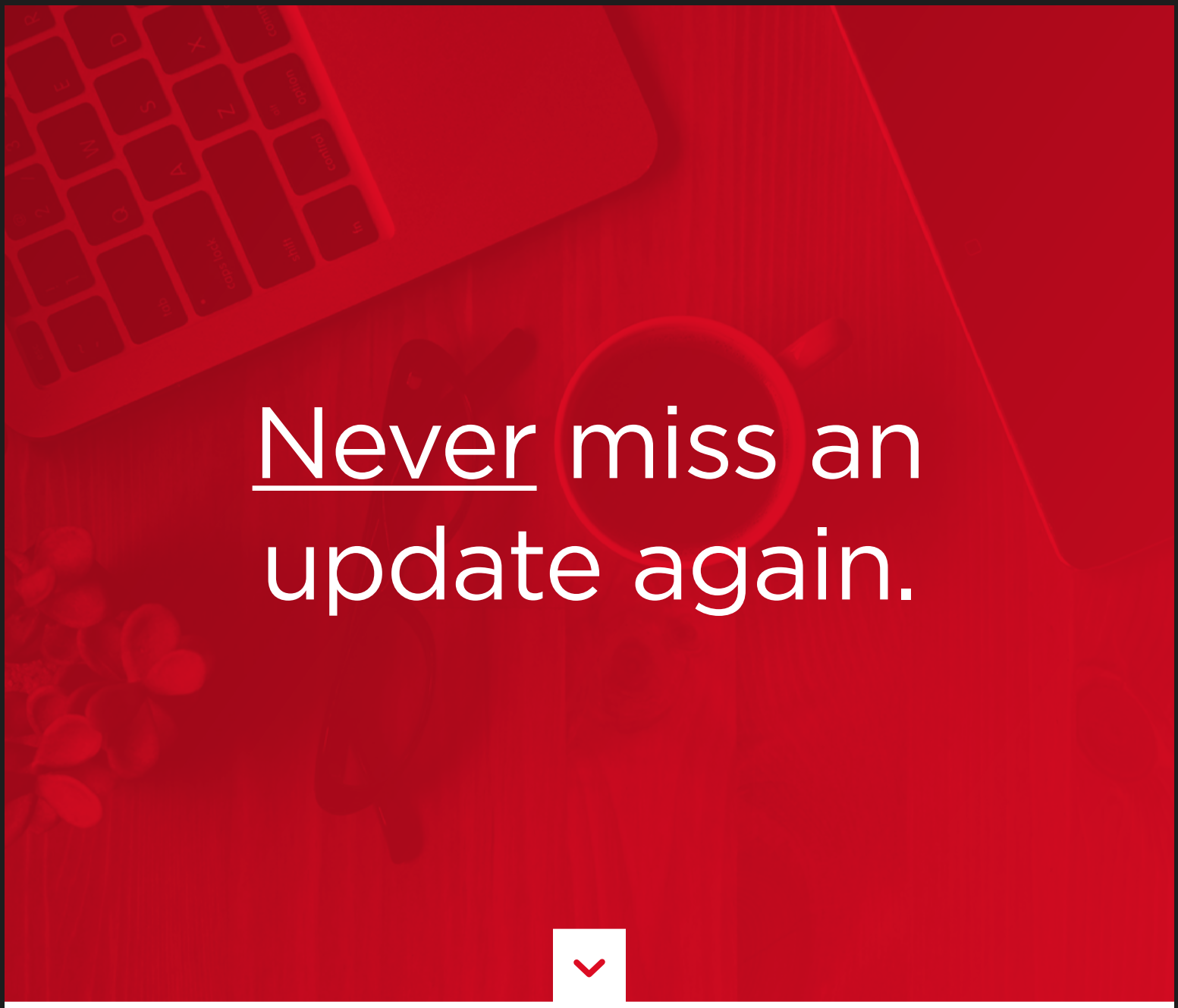
Extraperitoneal low-volume urine leak may be managed conservatively. Conservative management includes Foley catheterisation, nephrostomy, and placement of an antegrade ureteric stent. If conservative management fails, or if there is extraperitoneal high-volume leak, then surgical exploration and correction may become necessary. The ischaemic or necrosed part of the ureter needs to be removed, followed by reimplantation of the ureter. Development of urine leak may be associated with significant longer length of hospital stay, more readmissions, more delayed graft function, and lower rates of graft survival. If conservative management is used to manage the urine leak, prolonged follow-up may be necessary.

References

1. Humar A, Matas AJ. Surgical complications after kidney transplantation. Semin Dial. 2005;18(6):505-10.
2. Alberts VP et al. Ureterovesical anastomotic techniques for kidney transplantation: a systematic review and meta-analysis. Transpl Int. 2014;27(6):593-605.
3. Sinh TN, Chuan HK. Modified Lich-Grégoir technique in renal transplantation by assisted peroperative transvesical cystoscopy: 2327. Transplantation. 2012;94(10S):921.
4. Lee RS et al. Ureteral complications in renal transplantation: a comparison of the Lich-Grégoir versus the Taguchi technique. Transplant Proc. 2007;39(5):1461-4.
5. Friedersdorff F et al. The ureter in the kidney transplant setting: ureteroneocystostomy surgical options, double-J stent considerations and management of related complications. Curr Urol Rep. 2020;21(3).
6. Haberal M et al. Surgical complications after kidney transplantation. Exp Clin Transplant. 2016;14(6):587-95.
7. Wilson CH et al. Routine intraoperative ureteric stenting for kidney transplant recipients. Cochrane Database Syst Rev. 2013;6:DOI:10.1002/14651858.CD004925.pub3.
8. Veeratterapillay R et al. Management of urine leak following renal transplantation: an evidence-based approach. J Urol Nephrol. 2018;4(1):1-5.
9. Nie ZL et al. Treatment of urinary fistula after kidney transplantation. Transplant Proc. 2009;41:1624-6.
10. Ramirez CGB, "Kidney transplantation: surgical complications", Ramirez C, McCauley J (eds), Contemporary Kidney Transplantation (2018). Springer: Berlin, Germany. DOI:10.1007/978-3-319-14779-6_15-1.
11. Mishra SK et al. Kidney transplantation in abnormal bladder. Indian J Urol. 2007;23:299-304.
12. Leong KG et al. Renal transplant ultrasound: the nephrologist's perspective. Australas J Ultrasound Med. 2015;18(4):134-42.
13. Kolofousi C et al. Ultrasonographic features of kidney transplants and their complications: an imaging review. ISRN Radiol. 2012;2013:480862.
14. Gunawansa N et al. Post-transplant urinary leak; the perennial 'Achilles heel' in renal transplant surgery. 2018;11(2):2-4.
15. Fernando MH et al. Complete necrosis of graft ureter following renal transplant in a patient with primary antiphospholipid syndrome: a case report. Clin Case Rep. 2018;6(7):1330-3.
16. Ogawa Y et al. Posttransplant urine leakage with extensive ureteral stricture corrected by pyelopyelostomy: a challenging case. JOJ Uro Nephrol. 2019;6(3):555690.
17. Cassini MF et al., "Surgical complications of renal transplantation, surgical complications of renal transplantation", Ortiz J, Andre J (eds), Understanding the Complexities of Kidney Transplantation (2011). IntechOpen: London, UK. DOI:10.5772/16767.
18. Mohanka R et al. Practical approach to urine leak after kidney transplant. J Egypt Soc Nephrol Transplant. 2019;19:24-9.
19. Patri P et al. Vaccines for kidney transplant recipients: efficacy considerations and recommendations. Br J Renal Med. 2019;24(1):21-7.
20. Chitralli DK et al. IgA vasculitis in a patient on dialysis. Asian J Res Nephrol. 2020;3(1):17-23.
21. Mah TJ et al. Ureteric complications in recipients of kidneys from donation after circulatory death donors. Clin Transplant. 2017;31(4):DOI:10.1111/ctr.12912.
22. Sui W et al. Timing and predictors of early urologic and infectious complications after renal transplant: an analysis of a New York statewide database. Exp Clin Transplant. 2018;16:665-70.
23. Flores-Gama F et al. Determination of creatinine in drained liquid. Urinary leak or lymphocele? Cir Cir. 2010;78:327-32.
24. Son H et al. Extraperitoneal urine leak after renal transplantation: the role of radionuclide imaging and the value of accompanying SPECT/CT - a case report. BMC Med Imaging. 2010;10:23.
25. Dirlik A et al. Diagnosis of urinary leakage in renal transplant patients: ultrasonographic, clinical and scintigraphic findings. J Turk Soc Nephrol. 2001;10(4):239-43.
26. Kumar S et al. Ureteral obstruction following renal transplantation: causes, diagnosis and management. Br J Radiol. 2014;87:20140169.
27. Hamouda M et al. Urine leak after kidney transplant: a review of the literature. Exp Clin Transplant. 2018;16(1):90-5.
28. Singer J et al., "The transplant operation and its surgical complications", Danovitch GM (ed), Handbook of kidney transplantation (2005) 5th edition. Lippincott Williams & Wilkins: Philadelphia, Pennsylvania, USA, pp.193-212.
29. Shoskes D, Jiménez JA, "Urological complications after kidney transplantation", Morris PJ, Knechtle SJ (eds), Kidney transplantation: principles and practice (2013) 7th edition. Saunders: Oxford, UK, pp.464-71.
30. Mazzucchi E et al. Primary reconstruction is a good option in the treatment of urinary fistula after kidney transplantation. Int Braz J Urol. 2006;32(4):398-404.
31. Batagello C et al. Ligation of the native ureter for treatment of urinary fistula in kidney transplantation: is it safe? Abstract C222. 2015 American Transplant Congress, 4 May, 2015.
32. Alshamsi I et al. Perinephric transplant fluid collection approach and management. Saudi J Kidney Dis Transpl. 2019;30:564-70.
33. Sabnis RB et al. The development and current status of minimally invasive surgery to manage urological complications after renal transplantation. Indian J Urol. 2016;32(3):186-91.
34. Valente JF et al. Comparison of sirolimus vs. mycophenolate mofetil on surgical complications and wound healing in adult kidney transplantation. Am J Transplant. 2003;3(9):1128-34.
35. Fuller TF et al. Management of lymphoceles after renal transplantation: laparoscopic versus open drainage. J Urol. 2003;169(6):2022-5.
36. Duty BD, Barry JM. Diagnosis and management of ureteral complications following renal transplantation. Asian J Urol. 2015;2(4):202-7.
37. Ginanni B et al. Urine leaks and urinomas: causes, diagnosis and imaging features. Poster C-1087. ECR 2011, 3-7 March, 2011.
38. Kamaraj K et al. Post-operative surgical complications after kidney transplantation – a nephrologist's perspective. J Renal Transplant Sci. 2019;2(2):99-108.
39. Chughtai SA et al. Urine leak following kidney transplantation: an evidence-based management plan. J Clin Exp Nephrol. 2018;3(3):14.
40. Elsayed S. Early urological complications post kidney transplant. Urol Nephrol Open Access J. 2020;8(1):1-4.
41. Sujeet P. Current insights on urinary leak in renal transplantation. Exp Tech Urol Nephrol. 2020;3(1).
42. Buresley S et al. Postrenal transplantation urologic complications. Transplant Proc.

2008;40:2345-6.

43. Buttigieg J et al. Early urological complications after kidney transplantation: an overview. World J Transplantation. 2018;8(5):142-9.
44. Gopalakrishnan G. Surgical aspects of renal transplantation: contributions to solutions for complex problems. Saudi J Kidney Dis Transpl. 2002;13:451-9.
45. Indu KN et al. Is early removal of prophylactic ureteric stents beneficial in live donor renal transplantation?. Indian J Nephrol. 2012;22:275-9.
46. Arvind NK, Kumar A. Laparoscopic live donor nephrectomy: an indian perspective. Indian J Urol. 2002;19:29-37.
47. Dinckan A et al. Early and late urological complications corrected surgically following renal transplantation. Transplant Int. 2007;20(8):702-7.
48. Breda A et al. EAU Guidelines on male infertility. 2018. Available at: https://uroweb.org/wp-content/uploads/EAU-Guidelines-on-Male-Infertility-2018-large-text.pdf. Last accessed: 17 November 2020.
49. Davari HR et al. Urological complications in 980 consecutive patients with renal transplantation. Int J Urol. 2006;13(10):1271-5.
50. Buggs J et al. Repair of ureteral leaks post-kidney transplantation. Am Surg. 2019;85(8):e380-2.
51. Carvalho JA et al. Surgical complications in kidney transplantation: an overview of a Portuguese reference center. Transplant Proc. 2019;51(5):1590-6.
52. van Roijen JH et al. Long-term graft survival after urological complications of 695 kidney transplantations. J Urol. 2001;165(6, Part 1):1884-7.
53. Pillot P et al. Risk factors for surgical complications after renal transplantation and impact on patient and graft survival. Transplant Proc. 2012;44(9):2803-8.
54. Kaskarelis I et al. Ureteral complications in renal transplant recipients successfully treated with interventional radiology. Transplant Proc. 2008;40(9):3170-2.



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