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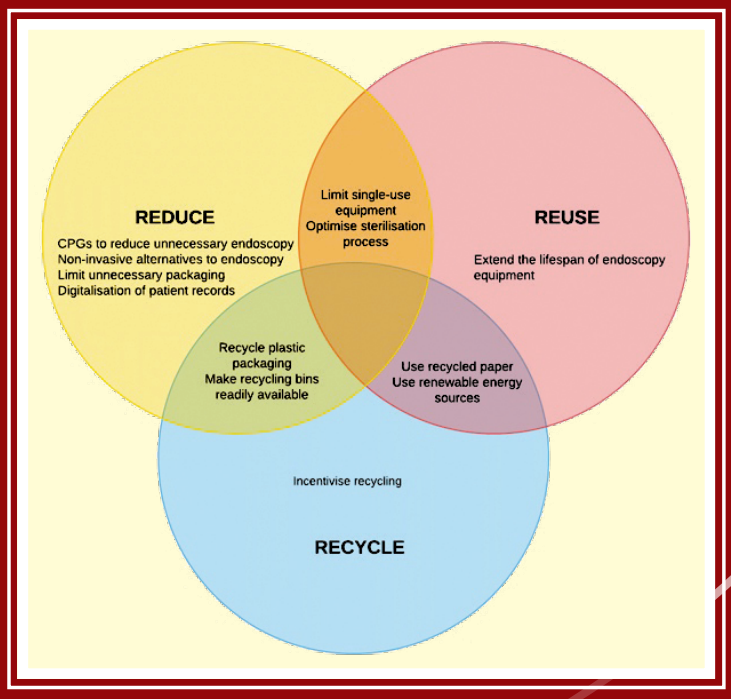

The Relationship between the 3 Rs in Sustainable Endoscopy

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CONTENTS

Dear colleagues,

In the current issue, the editorial by Cauchi et al. argues for eco-friendly measures in endoscopy and emphasies the role of healthcare providers in reducing waste. The editorial adeptly employs the three Rs (Reduce, Reuse, Recycle) framework to tackle waste management, offering practical solutions. The editorial by Milionis et al. focuses on the reverse cascade screening for paediatric familial hypercholesterolaemia (FH), which is an upcoming tool for public health. Advantages, practices, and challenges regarding FH are thoroughly discussed. Lastly, the editorial by Fousekis et al. presents the main aspects of a chronic immune-mediated cutaneous disease, dermatitis herpetiformis (DH), which constitutes an extraintestinal manifestation of celiac disease, including its diagnosis, pathogenesis, and management.

Moreover, this issue includes three review articles. The review article by Krontira et al. discusses the evolving data on the epidemiology, diagnostic approach and appropriate management of foreign body and caustic substance ingestion, based on updated guidelines published by gastroenterological and endoscopic societies. The review by Halliasos et al. provides data on the clinical presentation, diagnosis, and management of metastatic acute spinal cord compression, focusing on the importance of a multidisciplinary team approach, including spine surgeons, radiation oncologists, medical oncologists, palliative care clinicians, physiotherapists, and psychologists. Lastly, the review by Schinas et al. outlines the potential of immune modulation in the treatment of infections and the need for individualised approaches in the modern world of personalised medicine by examining some of the key strategies and immune-based therapies being developed to combat infectious diseases.

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Through the green lens: Sustainable solutions in endoscopy

Suzanne Cauchi, David Cassar, Pierre Ellul

Abstract

The global threat of climate change is becoming ever more evident over recent years with natural disasters becoming the order of the day. Reducing healthcare's carbon footprint has never been so crucial. Endoscopy is regarded as a major contributor to healthcare waste and is considered to be the third highest waste generator in hospitals. Main factors contributing to this high waste generation include the need for sterility and decontamination and the use of non-recyclable disposable items. As clinicians, we should have both vested interest and responsibility in ensuring the implementation of measures aimed at mitigating the negative effects our endoscopic practice can have on the environment, whilst ensuring patient care remains a priority. Recent guidelines, backed by a joint European consensus, aim to underline practical approaches to a more sustainable endoscopy unit. In this editorial, we highlight how these employ the three Rs; Reduce, Reuse, Recycle - as core principles in the fight to tackle waste management in this area of our practice.

Key words *Green; climate; endoscopy*

INTRODUCTION

In a world increasingly marked by the ominous shadows of climate change, the call for sustainable practices resonates louder than ever. Recent international news has been dominated by natural disasters, including forest fires across the globe and devastating floods in Italy, Spain and Greece, leading to numerous lives lost and infrastructural strains. These events are stark reminders of our collective responsibility to combat climate change at all levels.

The healthcare sector accounts for around 4.4% of total greenhouse gas, with endoscopy being a chief contributor [1]. Thus, green endoscopy has been garnering interest as it presents many opportunities in decreasing the health care carbon footprint [1,2].

In this editorial, we delve into the significance of green endoscopy, not just as a medical innovation but as a symbol of our commitment to mitigating climate change. Figure 1 outlines how the three Rs - Reduce, Reuse, Recycle will be used as the backbone of this editorial to tackle the necessary changes that need to be adopted or researched further to help achieve a healthier future.

REDUCE

Embracing the principle of 'reduce' stands as a pivotal stride towards reducing our environmental footprint and fostering efficiency.

Clinical practice guidelines [CPGs] are the first line of defence against unnecessary referrals. They help streamline patient care by offering evidence-based guidelines which not only enhance patient outcomes, but also reduce the need for multiple endoscopy visits [e.g. over surveillance], minimising patient travel costs, and alleviating the strain on departmental resources [3]. For example, the latest Baveno VII guidelines highlight how CPGs can decrease the need for oesophagogastroduo-

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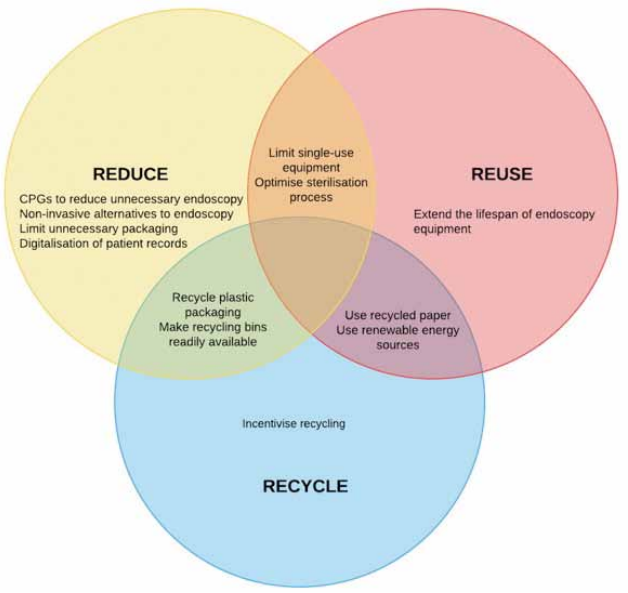

Figure 1. The Relationship between the 3 Rs in Sustainable Endoscopy.

denoscopy [OGD] [4]. Studies such as that carried out by Stefanescu et al. show how the use of non-invasive markers such as liver stiffness and platelet count can be used to assess portal hypertension in cirrhotic patients and predict the absence of oesophageal varices, avoiding so called "routine" OGDs [5].

Additionally, the use of non-invasive alternatives to endoscopy such as faecal calprotectin and intestinal bowel ultrasound as an accessory to the clinical picture minimises the need for colonoscopies [6]. Moreover, further future innovations such as the Cytosponge biomarker panel may aid in prioritising the surveillance of patients with Barrett's oesophagus, having the potential to significantly reduce the need for OGDs while improving early pre-cancerous detection [7].

When endoscopy is necessary, exercising prudence can minimise waste. The CO_2 generated for three biopsy pots has been estimated to be similar to that emitted during a two-mile drive, thus biopsies should only be taken when strictly necessary and guided by CPGs [8,9]. Advances in artificial intelligence [AI] may also reduce the need for biopsies, as has been shown in patients with Barrett's oesophagus [10]. In a pilot study by Hashimoto et al., the development of an artificial intelligence model showed promising results in its capacity to pick up on early oesophageal neoplasia in patients with Barret's oesophagus, potentially paving the way to more targeted use of biopsies [11].

In addition, to ensure efficient resource utilisation, discussions on which instruments and accessories are likely to be used prior to the procedures should be encouraged, with packaging only being opened once need is confirmed.

In patients who require sedation, careful administration of appropriate dosages is necessary to reduce waste. Furthermore, if Entonox is used for sedation, endoscopy units should make use of modern equipment which eliminates the nitrous oxide found in Entonox, thereby reducing the release of this greenhouse gas into the atmosphere [2].

The production and packaging of sterile water involves significant energy consumption. Therefore, efforts should be made to ensure that sterile water is only used when necessary. Employing smaller, recyclable containers for endoscope testing can also significantly reduce water usage.

In an attempt to prevent repeat endoscopy due to inadequate patient compliance, accessible services such as online instructional videos accessed through a QR (Quick Response) code can be invaluable [12]. These videos can provide clear guidance on bowel preparation. By enhancing patient education and support, one can reduce the chances of incomplete procedures and subsequent repeat endoscopies and their associated environmental impact whilst ultimately improving the patient experience. A digital shift may also reap its own benefits in the fight against excessive paper waste. Embracing digital technologies to store patient records and investigations facilitates seamless sharing of information between healthcare facilities, reducing paper waste, and eliminating the duplication of tests due to fragmented patient data [13].

To enhance sustainability at the endoscopy unit level, the adoption of energy-efficient lighting and motion sensors can effectively manage energy consumption. Additionally, all equipment, including computers and machines, should be powered off when not in use. Heating, ventilation, and air conditioning [HVAC] are primary energy consumers in healthcare facilities. Implementing smart HVAC practices, including turning off ventilation during non-occupancy periods, can dramatically reduce energy wastage. On a broader scale, promoting the adoption of renewable energy sources like solar panels is crucial, especially in Mediterranean regions, which receive abundant sunlight [1,2].

REUSE

In the fight for improved sustainability, the concept of "reuse" emerges as a potent catalyst for change.

In endoscopy, the advent of single-use scopes has been championed as a means to mitigate the risk of infectious transmission. However, a closer examination reveals a compelling case for reconsidering this approach in light of its significant environmental impact. Studies have shown that single-use scopes are associated with 24-47 times more CO_2 emissions than that of reusable scopes, with manufacturing accounting for over 90% of the greenhouse gas emission [14,15]. Restricting the use of these scopes to scenarios where there is a demonstrably high risk of infectious transmission, and where the standard decontamination process is not easily achievable, should be considered.

It is essential to also acknowledge that even the decontamination of reusable endoscopes for subsequent use comes at a cost, both in terms of resource consumption and energy expenditure. To address this, the decontamination process should be optimised to minimise water usage, reducing the overall energy consumption per cycle.

When it comes to PPEs, we should actively promote the availability and use of reusable options whenever feasible to curb waste generated. Safely re-using accessories or instruments used within the endoscopy suite should be further researched as this may curtail further environmental costs [16].

RECYCLE

Recycling plays a pivotal role in green endoscopy and this can be achieved not only by educating staff on waste separation but also by incentivising recycling.

Empowering endoscopy staff with a comprehensive understanding of waste management is the first step towards effective recycling. Through education and training, all members of the endoscopy team should be well-versed in differentiating between recyclable and non-recyclable materials. Recyclable items such as plastic used in the packaging of cannulas and endoscopic accessories should be properly segregated for responsible disposal. Recycling bins should be readily available and clearly labelled.

Motivating endoscopy units to embrace recycling can be incentivised through recognition and certification programs. For instance, endoscopy suites that consistently adhere to recycling practices could earn recognition such as "ACG-certified green suites" through the American College of Gastroenterology [ACG] [6]. This not only fosters a sense of achievement, but also promotes a culture of environmental responsibility within the healthcare community.

In cases where the use of paper is unavoidable, advocating for the utilisation of 100% recycled paper aligns with broader organisational sustainability goals.

GREEN HORIZONS - THE FUTURE OF SUSTAINABLE ENDOSCOPY

The quest for sustainability extends far beyond the confines of the endoscopy suite. It beckons us to reimagine the very landscape of healthcare, urging us to explore innovative strategies that not only minimise environmental impact but also enhance patient care.

The foundation of sustainability in endoscopy lies in the judicious reduction of unnecessary procedures. Embracing evidence-based guidelines and rigorous adherence to them ensures that each endoscopy is not just medically justified but also environmentally responsible. Implementing stricter triage protocols allows us to allocate endoscopic procedures to those who truly need them. Table 1 summarises some of the key sources of waste and how these can be tackled.

Assessing different aspects of the endoscopic procedure offers the possibility for further approaches to curtailing its environmental impact. The future necessitates the development and adoption of alternative pain relief methods that are less harmful to the environment.

Pivotal strategies in achieving such changes may involve the appointment of sustainability leaders within healthcare units. These individuals, often referred to as green or sustainability champions, can play a central role in driving sustainability initiatives forward. They may act as facilitators, ensuring that changes and sustainable practices are effectively communicated, implemented, and sustained within the units with an aim to establish a workplace culture that prioritises awareness of climate change and its mitigation strategies.

This approach not only enhances the dissemination of best practices but also fosters a focal point for the continuous improvement of sustainability efforts. Moreover, the Joint Advisory Group [JAG] in England now integrates sustainability into its accreditation process, while the inclusion of green champions on each unit is part of the Global Rating Scale [1]. This not only underscores the importance of sustainability within the organisational structure but also provides an added incentive to elevate sustainability practices within en-

Table 1. *Waste at the Endoscopy Unit: A Summary of Sources and Solutions.*

Problem/Source of Waste	Description	Solutions/Reduction Strategies
Excessive-Single Use Items and Failure to Recycle	Overuse of disposable materials such as gowns and caps. Irresponsible discarding of recyclable waste	Explore reusability of items e.g., endoscopes Train staff on judicious use of disposables and recycling Make recycling bins available
Energy Inefficient Equipment	Use of outdated or non-energy-efficient endoscopy equipment	Upgrade to energy-efficient equipment Implement power-saving settings when not in use e.g., energy-efficient lighting
Improper/wasteful Sterilisation Practices	Inadequate sterilisation can lead to equipment damage or need for more disposables. Beware excessive waste of water	Follow manufacturer's sterilisation guidelines Use sterile water judiciously
Excessive Paper Documentation	Reliance on paper-based record-keeping for patient data and procedures	Transition to electronic health records Encourage digital patient instructional videos and consent forms
Unnecessary Endoscopy	Performing unnecessary endoscopy generates unnecessary waste, as outlined above	Following CPGs to perform endoscopy only when indicated Use of non-invasive tests as an alternative to endoscopy where appropriate

doscopy units.

In conclusion, green endoscopy represents a pivotal shift towards eco-conscious healthcare practices, aiming to minimise waste, resource consumption, and emissions associated with endoscopic procedures. Its significance lies in limiting the environmental impact of healthcare, fostering sustainability, and ensuring that essential medical services align with the imperative of preserving our planet.

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Paediatric familial hypercholesterolaemia reverse cascade screening: A proactive approach to early recognition and treatment

Haralampos Milionis[1,3], Anastasios Serbis[2,3], Antonios Vlahos[2,3]

INTRODUCTION

Familial hypercholesterolaemia (FH) is a hereditary disorder characterised by elevated LDL-cholesterol levels from birth, posing a significant risk of atherosclerotic cardiovascular disease (ASCVD). FH is inherited in an autosomal dominant pattern, meaning that individuals with one affected parent have a 50% chance of inheriting the condition. Without proper management, FH can lead to early onset of ASCVD, emphasising the importance of early diagnosis and lifelong treatment to reduce the risk of complications [1]. Even though FH is a rather frequent disease with an estimated prevalence of 1 in 250, disease awareness in developed countries continues to be poor, and <10% of patients are diagnosed and appropriately treated [2].

In recent years, the importance of early detection and intervention for FH, especially in paediatric populations, has gained recognition. One promising strategy that has attracted substantial attention is paediatric FH reverse cascadescreening. This is a proactive approach which has the potential to revolutionise the identification and management of FH at an early age, decreasing the risk ofASCVD, improving long-term health outcomes, and ultimately saving lives.

Traditionally, efforts to detect individuals with FH were augmented with the use of the so-called cascade screening. This involves identifying and testing relatives of an index case diagnosed with FH. However, reverse cascade screening flips the conventional approach on its head by initiating the screening process in children. Rather than waiting for an adult with FH to be identified, this method aims to detect FH in children first and subsequently screen their parents and extended family members.

Paediatric Reverse Cascade Screening is considered most beneficial, and its implementation would certainly affect:

1. *Early Intervention*: One of the primary advantages of paediatric reverse cascade screening is the ability to intervene early. Identifying FH in children allows for timely medical intervention and the implementation of lifestyle modifications, which can significantly reduce the risk of cardiovascular events later in life. By intervening during childhood, we could break the vicious cycle of heart disease that often plagues families affected by FH.

Early studies have shown the effectiveness of early intervention in FH. It has been shown that early treatment of FH patients with statin therapy starting in

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Key words: *Familial hypercholesterolaemia; children, reverse cascade screening; atherosclerotic cardiovascular disease*

childhood is associated with a significantly lower risk of cardiovascular events compared to those who started treatment later in life. These findings highlight the importance of early intervention in improving long-term outcomes for individuals with FH [3].

2. *Enhanced Family Detection*: By focusing on children, reverse cascade screening increases the chances of identifying undiagnosed FH cases within families. Since FH is an inherited condition, there is a high probability that parents or siblings of affected children may also carry the gene mutation. Identifying and treating these cases promptly can prevent the progression of the disease and its potentially devastating consequences. Moreover, the identification of FH in children can motivate and raise awareness among their extended family members, leading to improved detection rates across generations.

Indeed, screening FH in the youth provides the potential for the identification of previously undiagnosed FH cases in parents and siblings. This approach is reportedly associated with a higher detection rate and facilitated early intervention in family members, reducing the overall burden of ASCVD within the family [4].

3. *Cost-Effectiveness*: Despite initial concerns about the cost of implementing such screening programs, reverse cascade screening has the potential to be a cost-effective strategy in the long run. Detecting FH in childhood reduces the need for expensive interventions later in life, such as coronary artery bypass grafting (CABG) surgery and/or lifelong medication. By investing in early screening and preventive measures, the economic burden of ASCVD can be significantly reduced, ultimately reducing healthcare costs. In addition, for reverse cascade screening based on biochemical rather than genetic testing, childhood is the most cost-effective period for FH screening since LDL-C levels are more reliable, reflecting predominantly the genetic predisposition and not anydietary or hormonal influences, as is the case in adulthood.

A cost-effectiveness analysis demonstrated that paediatric reverse cascade screening is a cost-effective strategy especially if it starts in children aged 1-2 years at the time of immunisation. This strategy appeared acceptable to parents and was highly cost-effective as a detection strategy for families at risk of FH [5].

4. *Public Health Impact:* Implementing paediatric reverse cascade screeningfor FH aligns with the broader public health objective of preventing ASCVD. By identifying individuals at risk and intervening early, we can reduce the overall disease burden, improve the quality of life, and potentially save lives. Moreover, as the identified individuals receive appropriate treatment and disease awareness increases, their contribution to the transmission of FH within the population diminishes, offering long-term benefits to society and future generations.

Challenges and Future Directions:

While the concept of paediatric FH reverse cascade screening holds immense potential, there are several challenges that need to be addressed to ensure itssuccessful implementation and long-term effectiveness:

1. *Access to Screening*: Ensuring equitable access to screening tests is crucial. Screening programs should be accessible to children from all socioeconomic backgrounds and geographic locations. Efforts should bemade to remove barriers such as cost, limited healthcare infrastructure,and geographical distance, to ensure that no child is left undiagnosed and untreated.
2. *Public Awareness and Education*: Raising awareness among healthcare professionals and the public about the importance of paediatric reverse cascade screening is essential. Healthcare providers should be educated about the identification and management of FH in children, and guidelines should be developed to assist them in implementing screening programs effectively. Additionally, public education campaigns can help parents and caregivers understand the significance of early disease detection in their children and themselves and encourage them to participate in screening programs.
3. *Genetic Counseling and Psychological Support*: Genetic counseling plays a vital role in FH screening programs. It provides families with valuable information about the inheritance patterns, potential risks, and available treatment options. Genetic counselors can also help individuals and families cope with the emotional and psychological aspects of living with FH, offering support and guidance throughout the screening and treatment process.
4. *Long-Term Monitoring and Follow-Up*: Continuous monitoring and follow-up are crucial for individuals identified with FH during childhood. Regular cholesterol level checks, cardiovascular risk assessment, and adherence to treatment and lifestyle modifications should be ensured. Long-term studies are needed

to assess the effectiveness and sustainability of early interventions in preventing cardiovascular events and mortality.

5. *Integration into Routine Paediatric Care*: To maximise the impact of paediatric reverse cascade screening, it should be integrated into routine paediatric care. Incorporating FH screening as part of well-child visits or school health programs can increase the reach and effectiveness of the screening programs. Collaboration between paediatricians, primary care providers, and specialists is necessary to ensure seamless implementation and follow-up care.

In this respect, EPIRUS-FH registry is a model program of reverse cascade screening for FH in children and adolescents in Northwest Greece that aims to increase public and physician awareness, strengthen the national registry of familial hypercholesterolaemia (HELLAS-FH) and constitute the core for a national FH registry in children and adolescents in Greece (NCT05825612).

CONCLUDING REMARKS

Paediatric FH reverse cascade screening holds great promise for the early identification and management of FH, potentially preventing the devastating consequences of ASCVD. By focusing on children, this proactive approach offers the potential to break the cycle of FH within families, improve long-term health outcomes, and reduce the burden on healthcare systems. However, several challenges must be addressed to ensure equitable access, raise awareness, provide necessary support, and integrate screening into routine paediatric care. By overcoming these challenges and investing in the implementation and ongoing evaluation of paediatric reverse cascade screening programs, we can take significant strides towards a future with reduced cardiovascular disease burden and improved public health outcomes.

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Celiac disease and Dermatitis herpetiformis

Fotios S. Fousekis, Konstantinos H. Katsanos

Abstract

Dermatitis herpetiformis (DH) is a chronic immune-mediated cutaneous disease and an extraintestinal manifestation of celiac disease (CD). It is triggered by gluten exposure in genetically predisposed individuals. DH presents as a pruritic rash with characteristic skin lesions, while atypical clinical manifestations are also possible. Diagnosis involves histopathology, immunofluorescence, and serological testing. DH has a lower prevalence compared to CD, with a higher incidence in men and a broad age range of onset. DH is associated with other autoimmune diseases and an increased risk of non-Hodgkin lymphoma, although a gluten-free diet may offer protective effects. The pathogenesis of DH involves genetic, immunological, and environmental factors. Treatment primarily involves lifelong adherence to a strict gluten-free diet, with dapsone as the main pharmacological therapy. Multidisciplinary management, including regular monitoring and collaboration among various specialists, is recommended. Further research is needed to explore novel treatment options and enhance understanding of the underlying mechanisms. Adherence to a gluten-free diet is essential for symptom resolution and effective disease control of DH and CD.

Key words: *Celiac disease; dermatitis herpetiformis; gluten-free diet; treatment*

INTRODUCTION

DH was first described by Louis Adolphus Duhring in 1884 and is a chronic, polymorphous, pruritic immune-mediated cutaneous disease. DH is considered as one of the most frequent and well-recognised extraintestinal manifestations of celiac disease (CD) and DH is literally referred to as a CD of skin [1]. Both CD and DH are triggered by exposure of dietary gluten in genetically predisposed individuals [2] and both diseases are associated with similar pathogenetic mechanisms.

DH typically presents as a pruritic rash consisting of herpetiform papulovesicular lesions that progress to blisters, erosions, excoriations, and hyperpigmentation on the external surfaces of the body. It mainly affects the elbows, lower limbs (such as the anterior thigh and knee), buttocks, and sacral region, while involvement of the shoulders and scalp is less common. Atypical clinical presentations of DH can include palmar purpura, chronic urticaria, prurigo pigmentosa-like lesions, and pseudovasculitis [3]. Additionally, DH can also affect the oral mucosa, causing aphthous stomatitis [4].

DIAGNOSIS

A diagnosis of CD requires a combination of villous atrophy and lymphocytic infiltration in duodenal biopsies, as well as the detection of celiac-specific antibodies in the serum. Classical symptoms of CD include diarrhoea, abdominal pain, weight loss, anaemia, and flatulence. However, patients with DH, despite having coexisting CD, typically experience milder gastrointestinal symptoms, with signs of malabsorption being rare [5]. While 70% of DH patients exhibit villous atrophy, the remaining patients may have mucosal inflammation indicative of early-stage CD. Importantly, the presence of villous atrophy at the time of DH diagnosis does not affect the clinical recovery of patients on a gluten-free diet [6].

The diagnosis of DH is based on specific findings from direct immunofluorescence and histopathology of skin biopsies, along with the clinical presentation

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and CD diagnosis. Histopathological examination of an erythematous papule typically reveals neutrophilic microabscesses within the dermal papillae, while a vesicle biopsy shows a subepidermal blister [7]. However, these histopathologic findings alone do not allow for differentiation from other autoimmune diseases, such as linear IgA disease, bullous pemphigoid, anti-laminin-1 pemphigoid, or the inflammatory form of epidermolysis bullosa acquisita. The detection of granular IgA either in the dermal papillae or along the dermo-epidermal junction in direct immunofluorescence is considered the gold standard for diagnosis of DH and helps to differential diagnosis between DH and other cutaneous autoimmune diseases [8]. IgA deposition in DH can occur in both involved and uninvolved skin, as well as the oral mucosa. In contrast, CD patients without DH do not show cutaneous IgA deposition. Epidermal transglutaminase (eTG) has been identified as the primary autoantigen target in DH, and the measurement of serum IgA eTG antibodies can effectively distinguish DH from other dermatological conditions [9]. Furthermore, IgA eTG antibodies persist for a longer period in DH patients compared to IgA anti-TG (tissue TG) antibodies in CD patients on a gluten-free diet [10].

EPIDEMIOLOGY

DH is considered a rare disease, and its prevalence varies among countries. The reported prevalence ranges from 1:1,000,000 new cases per year to 59: 100,000 new cases per year [11]. In comparison, the prevalence of CD is higher, affecting approximately 1% of the population, although it also varies geographically. In Europe and North America, CD is diagnosed more frequently, with a prevalence of up to 2% in Finland. Asian countries generally have a lower prevalence of CD. DH can manifest at any age, but the most common age for diagnosis is between 30 and 40 years [12]. However, it is worth noting that DH has been diagnosed in infants as young as 8 months old [13]. Men are more commonly affected by DH, with a male-to-female frequency ratio of approximately 2:1. In contrast, CD appears to occur more frequently in women, with a ratio of approximately 2:1 [14].

ASSOCIATED DISEASES

Several autoimmune diseases have been associated with DH, including rheumatoid arthritis, systemic lupus erythematosus, myasthenia gravis, Sjogren syndrome, autoimmune thyroiditis and sarcoidosis. However, the prevalence of autoimmune disorders in patients with DH is similar to patients with CD only [15]. Additionally, patients with DH may have a higher risk of non-Hodgkin lymphoma, particularly enteropathy-associated T cell lymphoma, but a gluten-free diet may protect against the development of lymphoma [16].

PATHOGENESIS

The pathogenesis of DH is multifactorial and involves a combination of genetic factors, immunological mechanisms, and environmental factors. There is a genetic predisposition with an association to human leukocyte antigens (HLA) DQ2 and DQ8, indicating a potential role of the immune system in the aetiopathogenesis. The closest association is observed with HLA-DQ2 (a combination of the DQA10501 and DQB102 alleles) and DQ8 (a combination of the DQA103 and DQB10302 alleles), present in approximately 85% and 15% of the patients, respectively. Furthermore, patients with DH appear to have a genetic predisposition to developing the condition. A follow-up study on CD and DH revealed that around 20% of patients had affected first-degree relatives, resulting in a prevalence rate of 5.5% among relatives. The annual incidence of CD and DH was found to be 15 times higher compared to the general population [17].

MANAGEMENT

DH and CD are primarily treated with a lifelong gluten-free diet (GFD). Adhering strictly to GFD leads to the resolution of skin and bowel symptoms associated with these conditions. However, in some cases, additional medications such as dapsone, sulfonamides, or steroids may be used temporarily to control symptoms until the diet alone is sufficient. A multidisciplinary approach involving dermatologists, gastroenterologists, dieticians, and other specialists is recommended for managing DH and CD, as it allows for regular assessment of diet adherence, treatment response, side effects, and potential complications [18].

Gluten-free diet

Adherence to a strict GFD is crucial for managing DH. Patients should avoid foods containing gluten, including cereals such as wheat, barley, rye, and malt. Gluten-free foods such as rice, maize, potatoes, and vegetables are safe to consume. Oats can be consumed if they are pure and uncontaminated with gluten. However, most store-bought oat products are typically contaminated,

so they should be avoided. Studies have shown that strict adherence to the GFD reduces the need for medication, improves well-being, and has a protective effect against lymphoma [19].

Dapsone

Dapsone is the primary drug used to treat DH. It has anti-inflammatory and antibacterial properties and provides quick relief from symptoms. Dosing of dapsone may vary, but most patients can be managed with 100-200 mg daily. Hemolysis and methemoglobinaemia are potential side-effects, particularly in individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency. G6PD screening is recommended before starting treatment. Regular monitoring of complete blood count, reticulocyte count, liver and renal function is necessary. Other sulfonamides may be used if dapsone is not tolerated or ineffective [19].

Other medications

In some cases, alternative medications such as methotrexate, colchicine, cyclosporine, heparin, and rituximab may be considered, if GFD and sulfonamides are inadequate. However, more research is needed to evaluate their effectiveness. Biologics targeting IL-1, IL-17, and IL-36 show promise as potential future therapies [20].

Overall, strict adherence to a GFD is essential for managing DH and CD. Dapsone is the mainstay of treatment for DH, with sulfonamides and other medications used as alternatives. Regular monitoring and a multidisciplinary approach are important for assessing treatment response, managing side effects, and addressing complications. Future research is needed to explore additional treatment options and novel therapeutic targets.

CONCLUSION

DH is a chronic immune-mediated cutaneous disease and one of the extraintestinal manifestations of CD. Both conditions are triggered by gluten exposure in genetically susceptible individuals. DH presents as a pruritic rash and can have atypical clinical manifestations. Diagnosis involves a combination of histopathology, immunofluorescence, and serological testing. DH has a lower prevalence compared to CD and can manifest at any age, with a higher incidence in men. Associated autoimmune diseases and an increased risk of non-Hodgkin lymphoma have been observed in DH patients. Pathogenesis involves genetic and immunological factors, and a gluten-free diet is the primary treatment. Dapsone is commonly used to manage DH, with alternative medications considered for refractory cases. Adherence to a gluten-free diet is crucial for symptom resolution and disease control. Close monitoring and a multidisciplinary approach are recommended for effective management of DH and CD. Further research is needed to explore new treatment options and understand the underlying mechanisms of the diseases.

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Foreign body and caustic substance ingestion

Sofia Krontira*, Petros Mantzios*, Konstantinos Thomopoulos, Christos Konstantakis

Abstract

Ingestion of foreign bodies or caustic substances constitutes an emergent diagnostic and therapeutic challenge, with potentially high morbidity and mortality. Identification of the ingested agent and determination of intention are of paramount importance, as they dictate the appropriate treatment and forecast the overall outcome. Both situations require high levels of suspicion by the treating physician, early recognition and implementation of emergency treatment protocols in order to optimize patient outcomes. A multidisciplinary approach is often required.

Key words: *Foreign body ingestion; food bolus; caustic ingestion; corrosive agents; acid; alkali; endoscopy; computed tomography; esophageal strictures; surgical management*

INTRODUCTION

Injuries of the upper GI (gastrointestinal tract) include, among others, the ingestion of foreign bodies and corrosive agents. Although relatively uncommon, these conditions are associated with potentially high morbidity and mortality.

The ingestion of foreign bodies is confronted in everyday clinical practice, particularly in paediatric patients [1,2]. In the adult population, on which this current review aims to focus, ingestion is usually associated with accidental food bolus impaction, sometimes in the presence of underlying anatomical abnormalities or motility disorders [3]. While the vast majority of ingested objects cross the gastrointestinal tract without complications, endoscopic intervention may be required in up to 20% of cases [4-6]. Treatment selection depends both on the location of impaction and characteristics of the foreign body, including size, shape and material [7].

The ingestion of corrosive chemicals still represents a major issue in developed countries, despite the implementation of educational programs and preventive measures by western governments [8-10]. In developing countries, its occurrence is still increasing [11-13]. Epidemiological data are scarce and the phaenomenon is widely underreported. Therefore, management of these cases remains a challenge [14]. In adults, the consumption of corrosive agents is usually intentional and associated with extensive damage and long-term complications. On the contrary, children tend to ingest caustic chemicals with exploratory intention and present with mild injuries.

This review aims to outline the evolving data on the epidemiology, diagnostic approach and appropriate management of these conditions, based on updated guidelines published by gastroenterological and endoscopic societies. For the purpose of this manuscript, two separate MEDLINE and PUBMED searches from 1975-2022 were performed to evaluate relevant articles, with priority to high quality publications of the last five years.

FOREIGN BODY INGESTION AND FOOD BOLUS IMPACTION

Epidemiology

Foreign body ingestion constitutes a gastroenterological emergency, accounting for almost 5% of all ur-

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gent endoscopies undertaken. More than 100.000 cases per year are reported in the US [2,14,15]. As expected, epidemiological data differ across age groups. In the paediatric population ingestion is more common and almost exclusively accidental/exploratory (98%), with coins being the objects most frequently encountered (66%), followed by toys, magnets and batteries [1,2,16]. On the other hand, food bolus impaction remains the primary cause in adult patients, while true foreign body ingestion is more commonly observed in the presence of psychiatric disorders, impaired mental status, intoxication or for secondary gain in incarcerated patients [3,17]. Edentulous condition and use of prosthetic dentures is another risk factor in elderly patients [3,20].

Gastroenterologists should be aware that food bolus impaction, in 45–75% of cases, occurs in the context of pre-existing oesophageal abnormalities, such as peptic strictures or oesophageal rings [3,4,7]. Achalasia and other motility disorders may also be present. Interestingly, food bolus impaction is rarely a presenting symptom of oesophageal malignancies [3,4]. Eosinophilic oesophagitis is another emerging recognised risk factor (33–40%), characterised by infiltration of the oesophageal mucosa by eosinophils, causing nonspecific symptoms and long term, non-reversible narrowing [3,7]. The diagnosis is confirmed through biopsy. Therefore, current guidelines emphasise the need of histologic evaluation in all patients with suspicious endoscopic findings in order to recognise underlying pathology and prevent symptom recurrence [3,4,6,14].

Initial evaluation

Patient history is the initial and often defining step in the diagnostic approach. Patient symptomatology at first presentation may differ between cases, depending on the type of the foreign body and the degree of obstruction. Usually, there is a clear correlation between time of ingestion and onset of symptoms. For non-communicative patients and children, a reliable history depends on relatives who witnessed the incident. Information on patient comorbidities and the characteristics of the foreign body (size, shape and material) will assist in treatment planning.

Patients may present with acute chest pain and dysphagia or odynophagia, nausea and vomiting. The presence of blood-stained saliva is an alarming feature, suggestive of possible laceration. Retrosternal discomfort is common; however, the area of discomfort is not helpful in determining the exact site of impaction, because of pain radiation [15]. Respiratory distress or wheezing are usually indicative of upper airway obstruction or tracheal compression by oesophageal oedema. Hypersalivation (inability to manage secretions) is suggestive of complete oesophageal obstruction and warrants prompt management. Vital signs, airway status and hemodynamic stability should always be assessed at baseline. Other causes of thoracic pain need to be excluded through biochemical work-up and 12-lead ECG. Areas of anatomic narrowing located above the ligament of Treitz, such as the upper and lower oesophageal sphincter, the aortic notch and the left main stem bronchus are associated with higher impaction risk. After successful food bolus removal some patients experience a persistent subjective feeling mimicking dysphagia for some time (usually up to 24 hours). Patients need to be reassured and followed-up accordingly [3,6].

Clinical signs of oesophageal perforation include fever, edema in the neck and chest area and subcutaneous crepitus. Sharp pointed objects may cause peritonitis by piercing through the GI tract, especially in areas with acute angulation (10). Abdominal guarding, reduced bowel sounds and systemic inflammation symptoms are common in such cases [16]. Surgical intervention is the treatment of choice.

Radiographic evaluation, using biplane radiographs may be helpful in case of ingested radiopaque bodies. Neck, chest and abdomen radiographs can help reveal the exact number and configuration of ingested items and assess for complications by revealing the presence of free air in the mediastinum or under the diaphragm, or lung aspiration. However, their usefulness is limited when concerning radiolucent foreign objects and (non-bony) food bolus content. A classification of commonly encountered items, according to radiodensity, is provided in Table 1.

ESGE and ASGE guidelines propose the use of computed tomography imaging (CT), especially when high index of suspicion for complications exists, in difficult cases (i.e., above the upper oesophageal sphincter / throat – ENT region) [3,18,20]. CT scan, with its superior diagnostic accuracy (70–100%) and ability for 3D reconstruction, provides detailed information on the location and size of foreign bodies and confirms the nature and extent of complications (i.e. abscess, aortoesophageal fistula formation), and therefore is recommended in cases of suspected perforation [3,18-20].

Notably, guidelines recommend strongly against the use of contrast-enhanced radiographic imaging,

Table 1. *Classifications of foreign bodies according to their radiodensity.*

Foreign bodies-objects usually identified in plain or biplanar radiographs (radiopaque)	• Most true foreign bodies (ie batteries-magnets-coins-nonfood content) • Large steak bones
Foreign bodies-objects unlikely to be identified in radiographs (radiolucent)	• Food bolus • Fish and chicken bones • Wood • Plastic • Glass objects • Thin metal objects • Aluminum fragments

using oral mediums (barium, gastrografin). These agents compromise direct visualisation by the endoscopist and are associated with risk of pulmonary oedema if aspirated [3,14,18,20].

Conservative management

Each case of ingestion is unique and presents a different challenge. Up to 90% of ingested foreign bodies will cross the GI tract uneventfully, without requiring further intervention [3,20]. As such, a "watch-and-wait" approach should be chosen for asymptomatic ingestion of blunt, short (<5-6 cm length) and narrow (<2.5 cm diameter) objects (batteries and magnets are excluded). ESGE also recommends conservative management in cases of "body packing" (intentional hiding of packaged, illegal narcotic substances in a person's GI system) in order to avoid accidental leakage and subsequent systemic toxicity. In this way, 95% of parcels will be expelled automatically. Inpatient observation and use of PEG laxatives has been implemented, causing bowel irrigation and facilitating quicker passage. If symptoms of obstruction or toxicity present, or when parcels fail to progress beyond 48 hours, surgical referral is necessary [3,7].

Endoscopic management

In the subset of patients that will not benefit from conservative management, endoscopic treatment is usually undertaken. Flexible endoscopes are considered the primary option, providing excellent diagnostic accuracy (even in the absence of imaging findings) and concurrent management. Oesophagogastroduodenoscopy (EGD) is usually performed under conscious sedation in adults. Endotracheal intubation might be needed in cases of high aspiration risk or poor cooperation, like children, patients with a full stomach or select cases of oesophageal impaction [3,20]. The reported success rate exceeds 95%. ESGE and ASGE guidelines also recommend the use of special equipment, including an overtube or a protective hood, placed over the endoscopic device to prevent mucosal injury during retrieval of sharp objects, while reducing the incidence of aspiration and facilitating foreign body extraction [3,20,21].

The role of rigid endoscopy (RE) in the current ASGE guidelines is complementary to flexible endoscopy (FE). Interestingly, this procedure is not included in the 2016 ESGE guidelines. ENT physicians are accustomed to the use of the rigid oesophagoscopes with excellent results in removal of foreign bodies lodged in the upper oesophagus and hypopharynx, proximally to the upper oesophageal sphincter. Navigation/manipulation of the upper oesophagus with RE appears to be more effective in the hands of experienced users compared with FE. Interestingly, a large meta-analysis conducted by Ferrari et al in 2018 reported no statistically significant difference between RE and FE in terms of foreign object removal success rates and frequency of complications [21].

A wide range of retrieval devices is available and selection depends on the ability and experience of the endoscopist, as well as the size, shape and location of the foreign object. Retrieval forceps of various configurations (alligator forceps being the most commonly used), standard biopsy forceps, retrieval nets (usually indicated for small blunt object or en bloc food bolus removal) and the widely available and economic polypectomy snares have all been used. Endoscopic baskets, such as the Dormia basket, are ideal for removing round and slippery objects. Before intervention, endoscopists are encouraged to rehearse grabbing an object similar to the one ingested, in order to choose the device best suited to the task, thus reducing procedure time and endoscopy related risks [3,6,20].

Food boluses remain the most common foreign bodies in the adult population. The endoscopist usually implements the "gentle push" technique, using the flexible endoscope to apply pressure on the central part of the bolus and advance it past the gastroesophageal junction and into the stomach. Larger boluses might need to be fragmented before the procedure is completed. Since undiagnosed anatomical disorders are often present, guidelines advise against over exerting pressure blindly especially when met with resistance.

In such instances, an attempt to by-pass the bolus, or an en bloc or piecemeal removal is performed, using either a polypectomy snare or a retrieval basket and net [3,20,22]. If eosinophilic oesophagitis is suspected, biopsy specimens should be obtained, even in the presence of a macroscopically normal oesophagus. In the presence of strictures or rings, dilation may be performed concurrently or after a monthly period of proton pump inhibitor administration [3,6]. Figure 1 shows food bolus impacted in the lower oesophagus of a 52-year-old male.

Timing of endoscopic intervention is one of the most critical factors determining the eventual outcome. According to current ESGE and ASGE guidelines, procedures are classified time-wise as **emergent** (performed within 6 hours of patient presentation), **urgent** (performed in the first 24 hours) or **nonurgent** (performed electively within 48-72 hours). Overall, removal of a foreign object impacted in the oesophagus is recommended within 24 hours, even when only partial lumen obstruction has occurred [3,20].

Emergent endoscopic retrieval is recommended in cases of sharp pointed objects in the oesophagus, or when symptoms of complete oesophageal occlusion are present (i.e., drooling/inability to swallow fluids). Timely treatment reduces the risk of aspiration and perforation in these patients, as prolonged oesophageal impaction has been linked with increased incidence of complications. Furthermore, batteries and magnets ingestion warrant emergent retrieval, despite their blunt shape.

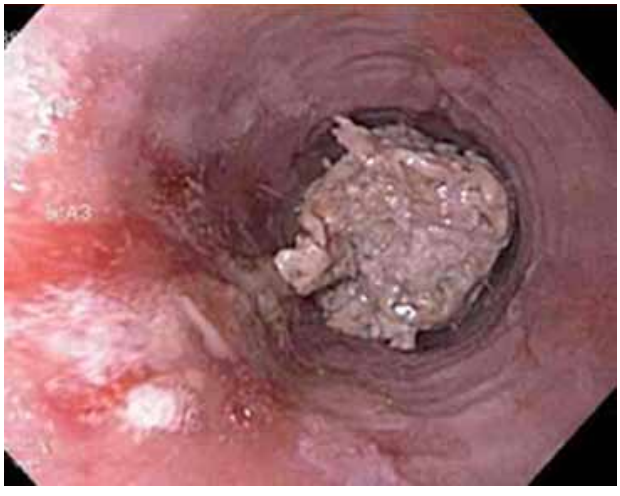

Figure 1. Food bolus impacted in the lower oesophagus of a 52-year-old male. Biopsies were obtained after removal, to identify any underlying pathology.

Button batteries, when impacted in the narrower areas of the oesophagus may cause serious injury or even necrosis, due to electrical damage, pressure ischaemia and leakage of alkaline substances resulting in caustic injury. Cylindrical batteries are encountered more rarely and appear to be less dangerous, as they often move into the stomach, from where they can be removed even after 24 hours. Magnet ingestion in the upper GI tract must also be treated endoscopically within six hours, especially when concomitant ingestion of other magnets or metal objects is suspected, as the development of attraction between them might lead to incomplete or complete bowel obstruction, volvulus, pressure-induced ischaemia and perforation [3,6,20]. An algorithm summarising the proposed intervention timing and strategies in cases of foreign body ingestion is presented in Figure 2.

Pharmaceutical management with intravenous administration of glucagon has been used. Glucagon facilitates bolus passage into the stomach by acting as a smooth muscle relaxant. However, its efficacy is decreased in the context of underlying anatomic abnormalities and should not delay endoscopic intervention, which remains the treatment of choice [3,6,7,20,22].

Complications

Following initial management, patients with foreign body ingestion or food bolus impaction might be either admitted for further monitoring, or discharged and instructed as outpatients. In most cases, complications arise before endoscopic extraction and not as its result. Oesophageal perforation is the most common and severe complication. Following endoscopic extraction, perforations might be managed conservatively, although endoscopic treatment is indicated if recognised early. Surgical intervention will be required in rare cases. Hospitalisation is deemed appropriate after a technically challenging removal or in cases of failed endoscopic retrieval, especially when concerning sharp objects or batteries. Daily radiographic assessment is useful to monitor passing of the foreign body. Once into the colon, foreign body expulsion usually proceeds without problems and colonoscopy is rarely required [3,6,15].

CAUSTIC INGESTION

Epidemiology

Caustic ingestion refers to the consumption of a chemical substance that results in tissue injury on direct physical contact. These chemicals include a wide

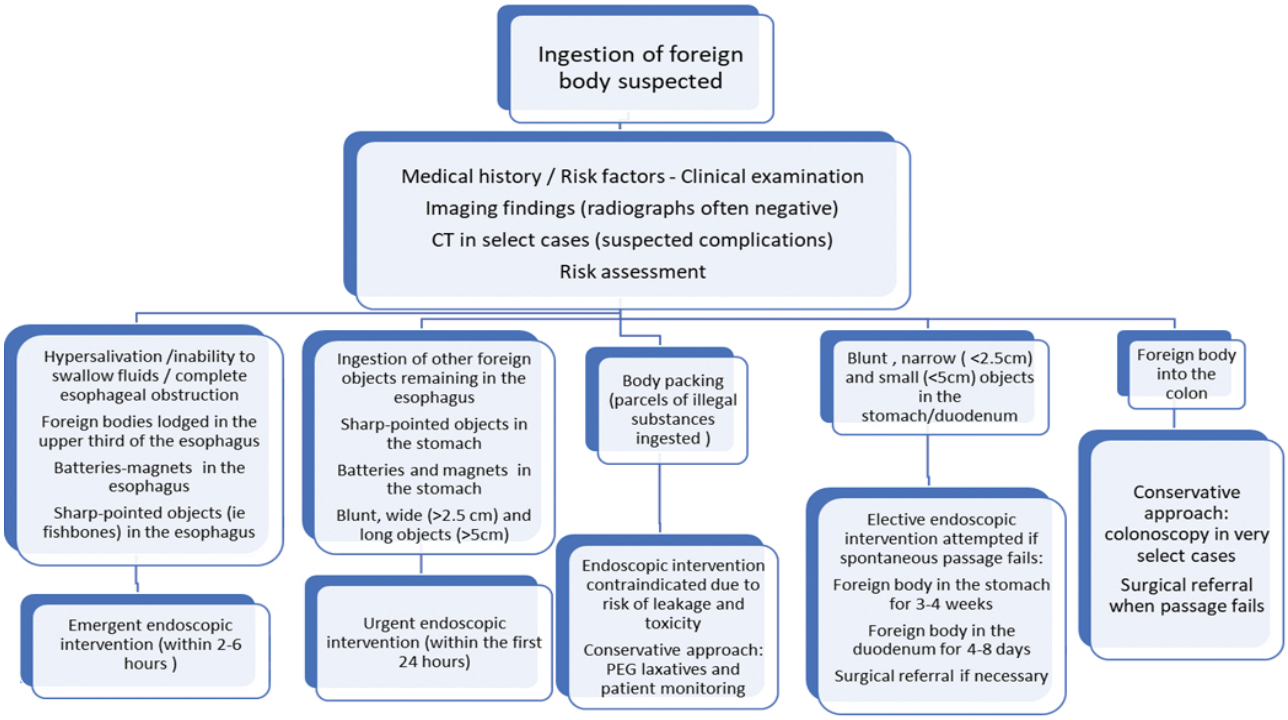

Figure 2. Proposed algorithm for foreign body ingestion management based on the latest ESGE and ASGE guidelines.

range of agents for domestic and industrial use, in the form of household cleaners, anti-rust agents, bleach, deodorants, batteries etc. [12,13]. Table 2 summarises the most common caustic substances encountered [13,26]. Frequently, the term corrosive is used as a synonym of caustic, although the first implies degradation, which is not always the case with caustic ingestion [13]. Nevertheless, in this review the two terms will be used interchangeably, for facilitation reasons.

According to the 2021 annual report of the American Association of Poison Control Center, there were nearly 50.000 cases of exposure to chemicals (acids: 7.325, alkalis: 3.471) and approximately 189.000 cases of household cleaning substances exposures. A significant number of these cases occurred by ingestion. The same report stated that in 2020 and 2021, household cleaning substances were the second most frequently consumed chemicals, both in adults and children [23].

Among the most common substances ingested in western countries, alkalis account for 79% of the total [8,12]. On the contrary, acid ingestion is more common in Asian regions like Iran, where hydrochloric acid is the most frequent cause of intentional ingestion [8]. The distinction between acids and alkalis is based on the pH (Potential of Hydrogen) of the corrosive agent.

Children aged five years or less represent the major-

Table 2. *Common caustic substances and their commercial application.*

Chemical substance	Commercial Application
Acids	
Hydrochloric acid	Metal and toilet bowl cleaners, solvents, anti-rust compounds
Sulfuric acid	Drain cleaners, batteries, metal plating
Acetic acid	Photographic stop bath, permanent wave neutralisers
Phosphoric acid	Toilet cleaners, anti-rust compounds
Oxalic acid	Household bleach, metal polish, disinfectants, furniture refinisher
Formic acid, formaldehyde	Deodorants, plastic menders
Alkalis	
Potassium hydroxide or sodium hydroxide (lye)	Oven cleaner, soaps, hair products
Ammonia/Ammonium hydroxide	Household cleaners (glass cleaners, floor stripes, wax removers)
Sodium hypochlorite	Cleansers, bleaches, swimming pool chlorinator

ity of cases worldwide (80%) and the remaining 20% is attributed to adolescents and adults [8,24]. Most minors consume unintentionally corrosive agents and have mild injuries. On the contrary, adults usually consume caustic chemicals in an attempt to commit suicide and present with more severe corrosive injuries. Most adult cases can be linked to psychiatric disorders, thus the evaluation of individuals by psychiatrists, should be an integral part of management [14,25].

Pathophysiology

Alkalis and acids produce tissue injury by different mechanisms. Alkalis tend to penetrate tissue by saponifying fats. The resultant injury is called liquefaction necrosis and is responsible for the formation of a gelatinous membrane which allows deep penetration and excessive damage to the mucosa. The injury extends rapidly through the wall of the oesophagus, towards the mediastinum, until tissue fluids buffer the alkalis. In the stomach the neutralisation of alkalis by gastric acid may limit the extent of injury. With that being said, consumption of a large volume and / or a high concentration alkaline solution, is expected to produce significant gastric injury [12,25,27-29].

The process of liquefaction necrosis lasts three to four days and results in vascular thrombosis and mucosal inflammation, excessive sloughing and formation of ulcers [30]. It is worth mentioning that the ingestion of ammonia, an alkali caustic agent, apart from the cited process above, leads to superficial haemorrhage of the stomach, 24 to 48 hours after the ingestion and requires strong suspicion from the treating physician [24].

In contrast, acids are responsible for the denaturation of proteins which results in coagulative necrosis. During this process, the consolidation of the connective tissue leads to the formation of oesophageal eschars which lessens tissue penetration and decreases the extent of injury. Despite this property, acid agents can cause severe injuries and death. As it passes through the stomach, the irritation of pylorus leads to pylorospasm and stagnation of the acid agent which results in injuries of the antrum and explains the sparing of duodenum in some cases [12,28,29].

Following caustic ingestion, either acid or alkali, the repair of the damaged tissue will start at approximately the end of the second week and the recovery will be completed by the sixth week. Around the third week, scars will start to form, a process that could last for several months and often advances to the formation of strictures. Figure 3 demonstrates the pathophysiological path following caustic ingestion.

A heavily scarred oesophagus demonstrates dysmotility problems that could lead to gastro-oesophageal reflux (GER) [31]. GER seems to further contribute to the formation of strictures and further decrease response to endoscopic dilation therapy [12].

Determinants of severity

The severity and extent of tissue injury after corrosive ingestion depends on multiple factors. The most important ones are the pH of the agent and the intent behind the ingestion. Other factors that should be considered are the physical form of the ingested agent (liquid, solid), the amount and concentration of the substance that is being consumed, the duration of contact with the tissue and the duration of time between consumption and medical treatment [33]. It is well established that pH values of <2 or >12 are considered as strong acids and alkalis respectively and translate into severe tissue injury. Acids tend to require longer contact time than alkalis in order to penetrate the tissue, so they ''prefer" the gastric mucosa from the oesophageal wall [11].

In case of massive ingestion of a highly concentrated agent, both acids and alkalis produce severe damage with excessive necrosis. The amount of ingestion is commonly linked to the intention behind the consumption [9]. Adults consume massive amounts of highly concentrated substances and delay to seek professional help with suicidal intent. On the contrary, children usually ingest small amounts with exploratory intent and usually spit them [34-38]. In conclusion, the intention behind the caustic ingestion and the pH of the substance seems to be the main risk factors and the main predictors of poor outcome [8].

Clinical presentation

The clinical signs and symptoms after corrosive ingestion vary widely depending on the location of the injury. The eyes, skin, airway, oesophagus, and stomach are the organs most likely involved. The injury may extend to adjacent tissues such as duodenum, jejunum, colon, pancreas, gallbladder but that is not frequently observed. The immediate and most frequently observed symptoms include pain, swelling of the tongue and mouth, dyspnea, dysphagia, hypersalivation, drooling, vomiting and self-limited hemorrhage in most cases [8]. Symptoms such as hoarseness, stridor and cough are indicative of epi-

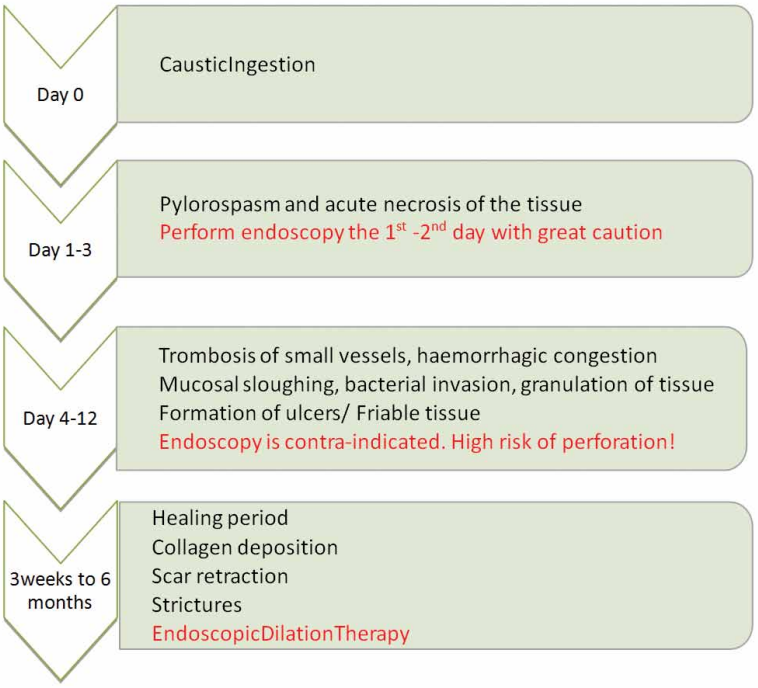

Figure 3. The Pathophysiological Path After Caustic Ingestion.

glottic involvement, which could lead to respiratory failure, an indication for intubation. If oesophageal impairment is present dysphagia and odynophagia would most likely appear. Epigastric pain and bleeding are suggestive of gastric involvement. It is worth mentioning that symptoms do not correlate with the severity and extent of damage. The absence of pain and oral lesions does not rule out the possibility of severe oesophageal damage [12,24].

Complications

Among the short-term complications are oesophageal or gastric perforations. They can occur at any time, but usually present the first two to three weeks after the ingestion. Subcutaneous emphysema, retrosternal pain and haemodynamic instability should prompt a thorough evaluation for perforation. It is accompanied with high mortality as it could extend to mediastinum, causing mediastinitis, sepsis and subsequently death. Presence of gastric perforation will cause epigastric pain, rebound tenderness and signs of peritonitis. A sudden deterioration of a previously stable patient should prompt an emergency evaluation for perforation.

The delayed complications include the formation of strictures, fistulas with adjacent organs (aortoenteric fistulas, tracheoesophageal fistula), bleeding and oesophageal squamous cell carcinoma. By far the most common complication is the formation of strictures in the oesophageal lumen or at the pyloric antrum, usually 3 months to 1 year after the caustic ingestion. Corrosive strictures of the oesophagus are commonly multiple, long, irregular and have long stabilisation delays. Symptoms related to oesophageal strictures are substernal pain, dysphagia and odynophagia. Gastric strictures are rare because of the large diameter of the stomach, but the formation of strictures at the area of the gastric antrum is responsible for gastric outlet obstruction syndrome, which causes early satiety, post- prandial nausea, vomiting and weight loss. Collectively, stricture formation is a disabling and resource consuming issue, which affects the quality of life [12,29,39].

Bleeding is an unusual late sequela after corrosive ingestion. In most cases, it is a single, self-limiting event, although severe haemorrhage has been reported. The formation of fistulas with adjacent organs is a very rare phaenomenon (its occurrence is less than 3%) but the mortality rates are very high when aortoenteric fistulas are present. They can occur at any time after ingestion [24,40]. Lastly, patients after caustic ingestion, demonstrate a 1000-to-2000-fold increase in the incidence of oesophageal carcinoma, but this risk may be overestimated [25,29,42]. Nevertheless, it is prudent to implement endoscopic surveillance. A surveillance protocol dictating endoscopy at 2–3-year intervals,

starting 20 years after the caustic ingestion has been proposed [29,42].

Diagnosis

Laboratory tests

At the emergency department a complete blood count and full biochemical screening tests with measurement of electrolytes, creatinine, liver tests, CRP (C-reactive protein), pH, serum lactate, blood alcohol level and β-HCG, in young women, should be performed. Blood test results are not directly correlated to the severity of damage and normal values cannot rule out significant oesophageal or gastric damages [12,42]. However, monitoring the pattern of change of blood test values contributes to a patient's management protocol, with severe acidosis, elevated WBC and CRP, deranged liver tests, thrombocytopenia and renal failure suggesting severe damage [11,14,24,42]. It is worth highlighting that specific agents are known to cause severe electrolyte disturbances (hypocalcaemia: phosphoric, hydrofluoric acids/ hyponatraemia: strong alkalis and acids/ hypokalaemia,etc.), which could further deteriorate a patient's outcome [14].

Risk stratification

For decades, endoscopy has been the main tool in the evaluation algorithms. The main drawback is its inability to accurately predict depth of necrosis, which could result in unnecessary or delayed surgery. Recently, in 2019, the role of CT imaging for risk stratification of caustic ingestions by the World Society of Emergency Surgery consensus (WSES) conference was also proposed as an alternative [14].

Endoscopic evaluation

Flexible endoscopy when used should not be delayed. It should be performed ideally in the first 3-48 hours to reduce the danger of endoscopy-associated complications (i.e. perforation) and to avoid misinterpretation due to mucosal changes. The Zargar classification is the most widely used grading system [45]. The endoscopic classification of corrosive injuries along with their prognosis is summarised in table 3 [46]. The extent of oesophageal damage on endoscopy is a predictor of complications, with a nine-fold increase in mortality and morbidity for every increased grade [42]. Generally, patients with endoscopic grade 3b or more, will need emergency surgery, whereas patients with grade 3a or less could be managed non operatively [14]. Endoscopy remains the main diagnostic and therapeutic tool for oesophageal or gastric strictures.

Endoscopic ultrasound (EUS) has been used to evaluate the extent of damage of the oesophageal muscular layers and consequently, it could predict the formation of strictures. However, it failed to outperform conventional endoscopy in predicting early or late complications. For now, there is no place in guidelines for EUS but further research is needed [43-44].

Imaging evaluation

A plain chest radiograph in the upright position is the initial test in most patients, but demonstrates low sensitivity and specificity. When disclosing free air in the abdomen it should prompt for further evaluation [43-44].

CT, much like endoscopy, should also be performed as soon as possible, preferably in the first 3-6 hours following caustic ingestion. CT of the neck, thorax and abdomen can accurately evaluate the extent of injury, predict patients in need of surgical treatment and forecast the early/late consequences [14]. The radiological classification based on CT findings is demonstrated in Table 4 [25]. According to this three-fold grading system, the absolute absence of enhancement of the organ's wall after the injection of an intravenous iodine-based contrast agent is indicative of transmural necrosis and should prompt for emergency treatment [24].

Table 3. *Endoscopic classification of corrosive injuries and Prognosis.*

Grade	Appearance	Prognosis
0	Normal	Complete recovery
1	Edema and hyperaemia of mucosa	Complete recovery
2a	Superficial localised ulcerations, friability, blisters	Low probability of stricture formation
2b	Circumferential, deep ulcers	High risk of stricture, low risk of perforation
3a	Multiple ulceration with scattered areas of necrosis	High risk of stricture, medium risk of perforation
3b	Extensive necrosis	High risk of strictures and perforation
4	Perforation	High mortality and morbidity

Table 4. *Radiological classification of caustic injuries based on CT findings.*

GRADE	CT appearance	Correlation with endoscopy
Grade 1	Normal appear	Low grade (0-2a)
Grade 2	Wall edema, inflammation of the surrounding tissues, post-contrast wall enhancement **No transmural necrosis**	More severe endoscopic burns (2b-3b)
Grade 3	Transmural necrosis (no enhancement of wall post-contrast)	High grade (3b)

The choice between endoscopy or/and CT should be based on local availability and expertise. There is no clear consensus. Although both modalities are widely available, there is considerably greater experience with endoscopy. CT evaluation is based on bowel ischaemia protocols and although results can be reproduced by outside expert centers, it requires radiologists that are familiarised with this protocol. Endoscopy is useful in cases that CT cannot be performed or is contraindicated (CT is unavailable, patient history of allergic reaction to iodine-based contrast agents, inconclusive results and children) [14]. CT offers the advantage of being less invasive and thus it can be utilised better in patients with more severe clinical presentation, especially when there is a strong suspicion of perforation. An individualised approach is advised [12,14,24].

Management

Initial approach should align with the Acute Life Support (ATLS) guidelines for burn injuries. This includes securing the airway, administering pain relief medicine and establishing haemodynamic stabilisation with intravenous fluid resuscitation. The Poison Control Center should be contacted as soon as possible to evaluate the toxicity of the agent and guide treatment. Following caustic ingestion, the most life-threatening event is loss of the airway due to oedema and direct impairment of the larynx. The threshold for placement of a definitive airway should be low in the presence of symptoms suggestive of airway obstruction (stridor, inability to control secretions, hoarseness, loss of consciousness, etc.). It is preferable to use a guided fiberoptic laryngoscope over blind intubation to avoid further injuries to the upper airway. It is of paramount importance to prevent vomiting and repeated passings of the caustic agent through the oesophagus in order to minimise damage. The patient should be placed in a 45-degree position and receive antiemetic medicines, such as metoclopramide. The insertion of a nasogastric tube is not recommended because it could result in further damage, by leading to gagging and vomiting, further exposing the oesophagus to the corrosive agent. Moreover, it is contradicted to administer pH neutralisation agents because they lead to exothermic reactions, contributing to more injury [25]. Administration of milk or charcoal has never been proven and is not advised [12]. The use of PPIs or H2-blockers is advised [25,32].

The use of corticosteroids is controversial. Most studies failed to show a benefit of prolonged administration of a high dose of a corticosteroid, so their use is contradicted unless the patient demonstrates symptoms of upper airway involvement [12,24-25,42]. However, Usta and colleagues support the administration of a 3-day course of methylprednisolone, as it seems to limit the formation of strictures, in children's population, after alkaline ingestion [47]. Based on the above, a short-term administration of steroids, to patients with alkaline grade 2b on the endoscopic classification, could be beneficial but more research is required [13]. Use of antibiotics is not routinely recommended unless indicated (i.e., infection) [25,42].

After initial evaluation, most patients (70%-90%) will be deemed eligible for non-operative treatment. If the following values are present: grade I on CT, consumption of a small amount, low concentration of the agent and the patient is able to control saliva/ no symptoms of airway obstruction, it is safe to discharge the patient after a brief observational time. In all other cases, fasting is mandatory and the patient should be closely observed for at least 48 hours after the ingestion [14].

Most patients with grade 3 on CT classification, or grade 3b on endoscopic classification, especially those with clinical signs of perforation/peritonitis and haemodynamic instability, should be treated with emergency surgery. Laparotomy remains the standard approach and transhiatal stripping oesophagectomy with total gastrectomy is the most commonly used procedure. All organs that show transmural necrosis should be resected at the emergency surgery. Signs and symptoms suggesting ongoing necrosis should prompt an evaluation with a second CT and maybe additional surgery [14,25].

Management of strictures

The most common late sequelae after corrosive ingestion, is the appearance of strictures. Endoscopy (dilations) remains the first-line of non-operative treatment and the upfront tool for the evaluation of symptomatic patients. It should be avoided in the first 5-15 days after caustic ingestion because the tissue is friable during the healing period and perforation could occur easily [29,42]. Both balloon dilators and bougies have been used, with no clear advantage of each method over the other. Usually multiple sessions (3-5) will be required in order to successfully create sufficient luminal conduit. The intervals between sessions vary from 1 week to 3 weeks. The use of stenting for oesophageal dilation is still being researched and more data are required in order to determine the optimal time and the type of stent most suitable [14]. After 5-7 failed attempts, reconstruction surgery of the oesophagus should be considered.

CONCLUSION

In conclusion, although foreign body ingestion and food bolus impaction are frequently encountered and are usually self-resolved conditions, their management requires a multidisciplinary approach by a team consisting of gastroenterologists, otorhinolaryngologists, surgeons and radiologists, in order to diagnostically confront complications and achieve the optimal therapeutic result. Oesophageal involvement, especially of the upper third, constitutes a true endoscopic emergency. Flexible endoscopy is the treatment of choice in these cases, with excellent safety and efficacy. Gastroenterological societies' guidelines recommend the establishment of secondary re-evaluation in all patients, aiming to recognise latent pathologic conditions and prevent symptom recurrence.

Consumption of corrosive agents remains a significant public health problem, with increasing numbers in developing countries. Despite the high morbidity and mortality, it is widely unreported, a factor that hinders the formation of guidelines. As caustic agents can be found in an enormous amount of household products, the main future directions should focus on prevention of injury with safe packaging regulations and educational programs. CT and endoscopy are the cornerstones of the emergency evaluation after caustic ingestion. An individualised approach based on the severity of the case and the local expertise is necessary. Endoscopic dilation is the upfront non-operative treatment of strictures, which are the most commonly observed late consequence. Surgery is recommended in all patients who demonstrate transmural necrosis and in cases that endoscopic dilation fails to establish sufficient oesophageal patency.

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Management of patients with metastatic acute spinal cord compression - A diagnostic and therapeutic approach

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Abstract

Metastatic acute spinal cord compression (MASCC) is a serious complication in oncologic patients, causing a remarkable impingement in the patient's quality of life. Symptoms at presentation include sensory loss, pain, sphincter dysfunction and paralysis. It is an emergency that necessitates prompt diagnosis and immediate intervention from a multidisciplinary team to maintain neurological function and enhance the functional outcome given the risk of permanent injury. Imaging modalities such as contrast-enhanced Magnetic Resonance Imaging (MRI) and/or Computerised Tomography (CT) are of paramount importance for establishing the diagnosis. Ambulatory status at presentation is an important prognostic factor in these patients. The goals of treatment are preservation of ambulation, neurological function and pain management. Rapid initiation of steroids followed by surgical decompression in selected patients, and radiation therapy (RT) are the main therapeutic approaches. Additionally, chemotherapy in specific tumour types, bisphosphonates and supportive care measures promote quality of life, alleviate symptoms, and prevent additional complications.

Key words: *Spinal cord compression; imaging; neurosurgery; radiotherapy; chemotherapy; corticosteroids; rehabilitation.*

INTRODUCTION

Metastatic acute spinal cord compression (MASCC) is a devastating demonstration of a metastatic cancer lesion displacing and compressing the spinal cord or cauda equina within the spinal canal [1]. Most patients with MASCC (80%) have a history of cancer diagnosis, while in up to 20% of them, the diagnosis of a primary cancer is absent at the time of presentation [2]. Non-Hodgkin lymphoma, multiple myeloma, lung, prostate, breast cancer and cancer of unknown primary tumour (CUPT) are the most frequent malignancies causing MASCC [2–6]. Although approximately 30% of all oncologic patients develop metastases in the spine, about 10-20% of them develop spinal cord compression [7]. In total, 5% to 10% of all cancer patients experience spinal cord compression during the natural history of their disease [4,8]. Data from the USA show that the incidence is approximately 20,000 new cases and the median age at the time of diagnosis is 65 years [9,10].

Although MASCC potentially may implicate any portion of the spinal cord, it is more frequently located in the thoracic, lumbosacral, and cervical segments of the spine [11]. Thoracic and cervical spine are usually involved by breast cancer and lung metastases, while the lumbosacral spine is targeted by pelvic tumours, colon cancer and prostate cancer [12].

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Extradural (or epidural) metastatic lesions are caused by direct extension from a metastasis in the body of a vertebra [8]. The culprit of the epidural compression is soft tissue in 75% of the cases and in the remaining 25%, compression is caused by collapsed bony fragments [13]. In approximately 5% of cases of all MASCCs, intradural (but extramedullary) metastases are caused by tumour cell migration via the circulatory movement of the cerebrospinal fluid [5,11]. Rarely, metastases from breast, lung and renal cancer are intramedullary [7].

Two major mechanisms seem to contribute to the development of neurological damage secondary to compression: At an early stage, tumour extension into epidural space causes compression of the Batson venous plexus which in turn increases vascular permeability with subsequent development of venous congestion, vasogenic oedema and demyelination. Recovery from neurological damage is still reversible if the compression is relieved. However, if compression is sustained, secondary vascular injury causes increased pressure on small arterioles, occlusion of these vessels and finally infarction of the cord structure, at which time the damage is irreversible with loss of neurological function [11,14,15].

The majority of MASCC patients die within the first year following diagnosis [9]. Morbidity from MASCC is associated with increased susceptibility to infections and thromboembolic events, which in turn reduce the survival [7]. A meta-analysis of 38 studies of MASCC paraplegic patients demonstrated one-year survival rates of 12-58%, with median survival between 2.4 and 30 months [16].

In this review, we provide evidence-based data on the clinical presentation, diagnosis, and management of MASCC. We emphasise the importance of a multidisciplinary team approach, including spine surgeons, radiation oncologists, medical oncologists, palliative care clinicians, physiotherapists, and psychologists.

CLINICAL PRESENTATION

Although the initiation of symptoms in this group of patients gradually spans over several days or even weeks, most of the times symptoms progress expeditiously, ranging from a few hours to a few days.

Mechanical, local or radicular pain is by far the primal and most constant symptom in almost 95% of all MASCC cases [6]. It originates from the direct compression of the spinal cord and/or the nerve roots from the metastatic lesion. It is of paramount importance to take into consideration the fact that if the compression progresses slowly, isolated pain may be the only tangible symptom without neurological manifestations present at that time. Localisation of the pain is dependent on the segment of the spinal cord affected. High intensity back pain reaching the level of 8-9/10 in the Visual Analogue Scale, aggravated by any movement or light physical activity, is suggestive of spinal instability [14,17]. The irritation or direct compression of nerve roots is responsible for radicular pain. It is distributed to the dermatome of the involved nerve root and is typically quantified as constant in duration (i.e., sciatic nerve pain). This type of pain is increased by straining and as such, a useful differential diagnosis tool is the application of straining maneuvers i.e., Valsalva, that intensify radicular pain [18].

Motor impairment is the second most frequent symptom [19,20]. Damage of the upper or lower motor neuron is manifested with classical neurological symptoms such as limb weakness, difficulty in walking, Babinski sign, hand coordination difficulty, brisk reflexes, and balance issues [21].

Furthermore, sensory loss is also typical. For example, loss of temperature and/or pain sensation, reflex loss, or radicular sensory loss, correlates reliably with the level of compression [5]. For cervical and thoracic epidural MASCCs, flexion of the patient's neck elicits a pathognomonic abrupt sensation of electric shock running along the portions of the spine (Lhermitte's sign).

Commonly occurring as a delayed symptom, is the development of autonomic dysfunction and loss of voluntary sphincteric control which causes bladder and/or bowel dysfunction (i.e., urinary bladder and/or fecal incontinence or retention) and is associated with a poorer prognosis [22].

An interesting although rare clinical variant of MASCC is the cauda equina syndrome. In adults, the spinal cord ends at the lower end of the L1 vertebra or at the upper end of L2 vertebra. Epidural metastases below that level manifest with flaccid paraparesis of feet and toes, absent ankle reflexes, impaired hip abduction and extension, saddle paresthesia and sphincter dysfunction [23].

DIAGNOSIS

The phrase ''time is the essence'' fully applies in MASCC patients, regarding the diagnosis and treatment. Any delays can have dreadful implications on the ambulatory status and sphincter functions of the patient, leading eventually to deterioration in the quality of life and consequently reduced survival. Delays in obtaining the diagnosis are due to either the absence

of recognition of the symptoms by the patient himself or the erroneous attribution by the attending physician of the referred symptoms to other pathologic entities.

Appropriate imaging modalities are essential for establishing the diagnostic hypothesis of MASCC, localising the level of spinal cord or cauda equina compression, quantifying the degree of compression and planning the treatment of MASCC [18].

The gold standard imaging study is gadolinium-DTPA contrast enhanced MRI with a sensitivity of 93% and a specificity of 98% [4]. In order not to misdiagnose MASCC present in multiple levels of the spinal cord, or metastases affecting non-symptomatic vertebrae, sagittal T1 and T2-weighted sequences, as well as Diffusion-Weighted images (DWi) of the entire spine should be obtained [24,25].

Complementary to the MRI, is CT scan with 3D-plane reconstruction which assesses spinal cord stability and assists the surgical planning (i.e., vertebroplasty, kyphoplasty or spinal surgery) [4]. It is nevertheless an option in cases where absolute contraindications performing MRI are present or MRI is inadequate. Even though CT scans permit superior depiction of bone tissue involvement within the spinal canal, myelography on the other hand is a time-consuming, labor intensive, more expensive and invasive procedure.

Another diagnostic modality to obtain first line images is plain X-ray. Its role before any treatment is to reveal dislocation of bony fragments from compression or pathologic fractures and areas of vertebral erosion, whereas its post-surgery function is to evaluate the structural integrity of the instrumentation as well as spinal alignment [2,7].

Additional imaging studies encompass positron emission tomography (PET) combined with CT and bone scan (99mTc-MDP). Both techniques are helpful in detecting vertebral metastases but remain inferior to MRI regarding the involvement of neural tissue and accurately localising the metastatic lesion [2].

TREATMENT

Therapeutic goals of MASCC are firstly, to conserve or recover the ambulatory status, and secondly the preservation or improvement of neurological function and analgesia. Treatment is largely palliative and only seldomly, in patients with MASCCs as the only site of disease (e.g., patients with renal cell cancer and no other systemic metastases), the intention of treatment is curative [26]. The processes of diagnosis and treatment should be closely associated and start and proceed hand in hand, as early intervention undoubtedly correlates with an improved outcome [27].

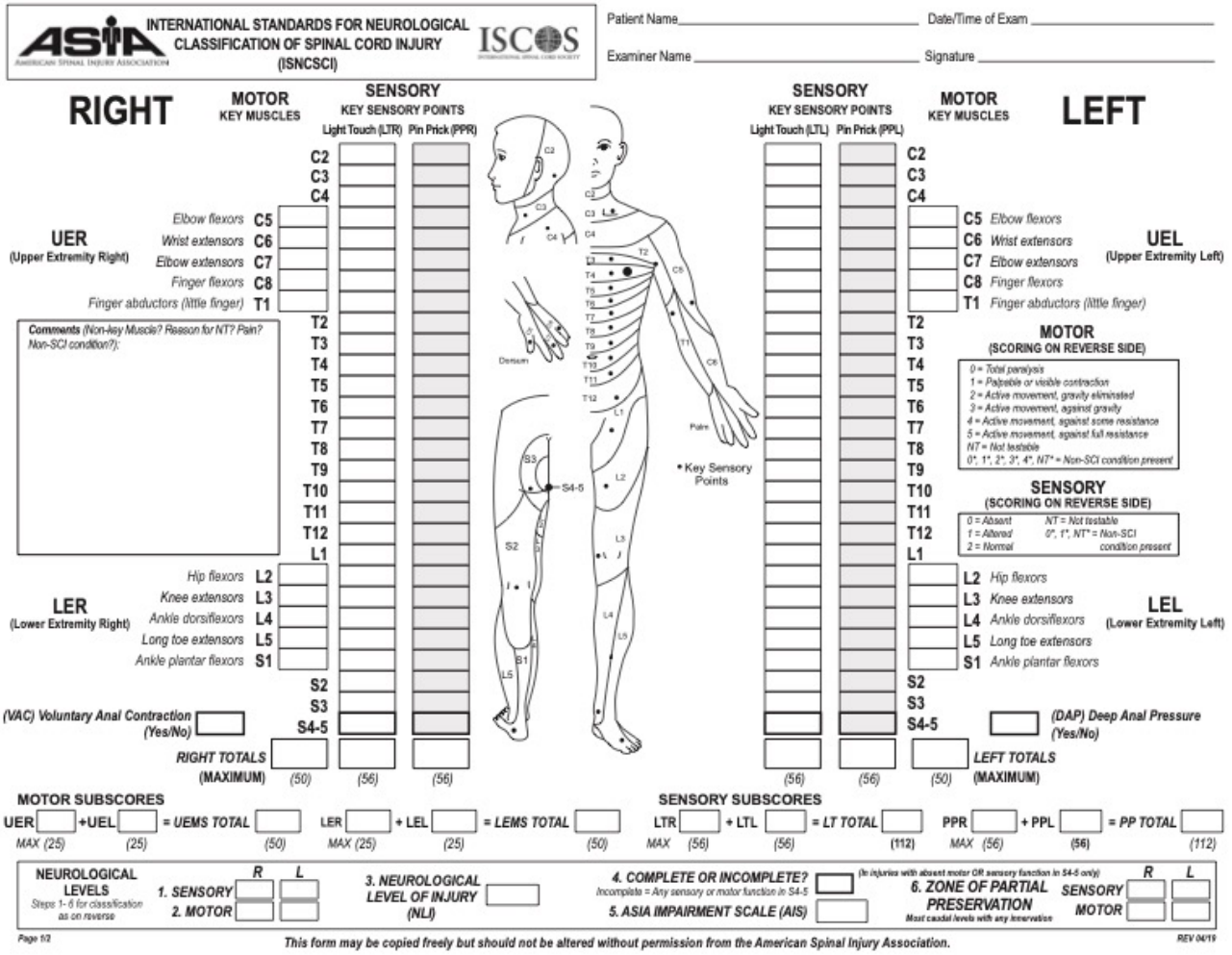
Surgery

To prevent unnecessary surgical morbidity, major surgical interventions should be considered for patients with a life expectancy of at least 3 months [28]. Various research groups have published scoring tools for the preoperative evaluation of a prognosis of a patient with a metastatic spinal tumour. Among these are the Tokuhashi score, the Spinal Instability Neoplastic Score (SINS) and the International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI), commonly referred to as the ASIA Exam.

The Tokuhashi score is a prognostic scoring system for spinal metastases. This system dates back in 1989. A revised version was published in 2005 [29]. The Spinal Instability Neoplastic Score (SINS) identifies patients who may benefit from surgical consultation or intervention. It also acts as a prognostic tool for surgical decision making [30]. The ASIA Exam, was developed by the American Spinal Injury Association (ASIA) as a universal classification tool for spinal cord injuries based on a standardised sensory and motor assessment, with the most recent revision published in 2019 (Figure 1) [31,32].

The classical surgical approach for MASCC patients is the posterior decompressive laminectomy, which is associated with an increased rate of complications, such as spinal instability and wound infections to mention but a few [33]. Later, development of new anterior and lateral approaches widened the indications and enabled better access to the lesion site, circumferential decompression of the spinal cord as well as intraoperative reconstruction of the spine.

Several non-randomised surgical trials reported promising results with these novel surgical approaches. A meta-analysis of various cohort studies suggested better outcomes in patients who received surgery followed by radiotherapy [8]. This meta-analysis determined that patients who had undergone surgery had 1.3 times higher probability to be ambulatory post-surgery and two times more likely to recover ambulatory function than patients who had received radiation as monotherapy. Altogether, ambulatory success rates for surgical treatment were 85% and for radiation therapy 64%. The efficacy of direct decompressive surgery was assessed in a randomised multi-institutional trial [15]. This was



Under permission: American Spinal Injury Association: International Standards for Neurological Classification of Spinal Cord Injury, revised 2019; Richmond, VA.

Figure 1. The ASIA exam.

the first randomised trial demonstrating the advantage of decompressive surgery followed by postoperative radiation over radiation alone. The primary endpoint was the ability to walk after treatment. All patients received high-dose dexamethasone. Both treatment groups received 30 Gy of radiation in 10 fractions. In the surgical group, more patients were able to walk after treatment (84% vs 57%; p = 0.001). Additionally, surgical patients retained the ability to walk longer (median 122 vs 13 days; p = 0.003) and regained the ability to walk more frequently than did those in the radiotherapy group alone (62% vs 19%; p = 0.01). Moreover, surgical treatment lowered the demand for corticosteroids and opioids and was correlated with lower 30-day morbidity than the radiotherapy-only group. Potential complications of surgery involve cerebrospinal fluid leak, thromboembolic disease, wound infection, vasogenic oedema, respiratory complications [34].

Modern surgical techniques allowing circumferential decompression of the spinal cord with synchronous stabilization and reconstruction techniques can be classified in five types: anterolateral transthoracic endoscopic approach usually through the pleural space, anterior transcavitary approach (retroperitoneal or transthoracic), posterolateral approach (lateral gutter: laminectomy plus removal of pedicle, transpedicular, costo-transversectomy, pedicle sparing transfacet approach), posterior approach (midline laminectomy) and lateral extra cavitary approach [33,35].

In patients with an anterior, anterior paraspinal,

unilateral epidural tumour or vertebral body lesion in the lumbar and/or thoracic region, the most appropriate technique is the anterior transcavitary (retroperitoneal or transthoracic), delivering direct access to the vertebral body. When maximal circumferential decompression is necessary, the technique could be combined with a posterior or posterolateral approach. On the other hand, always in the context of metastatic lesions located in the lumbar or thoracic region, when there are contraindications for an anterior transcavitary approach or in cases of multilevel disease, major spinal deformity, circumferential compression of the spinal cord, diffuse bone involvement, the posterolateral approach is to be preferred to the anterior counterpart. Stabilization and reconstruction techniques consist of the use of expandable titanium cages, Steinmann pins, autologous bone graft and a synthetic resin produced from the polymerization of methyl methacrylate namely polymethylmethacrylate (PMMA) [35].

More advanced surgical techniques are currently developed that provide optimal decompression to the spinal cord. This is the case of the separation surgery, in which only a portion of the tumour is removed, creating a margin surrounding the spinal cord for the subsequent application of radiotherapy [36,37]. When the risk of massive intraoperative hemorrhage (such as in tumours with rich vascularisation e.g., leiomyosarcoma, hepatocellular carcinoma, renal cell carcinoma), surpasses the benefit of decompression, an efficient and safe technique to contain blood loss is the use of a minimally invasive image-guided procedure called trans arterial chemoembolisation [38,39].

In cases of malignant fractures, other minimally invasive image-guided treatment options include percutaneous kyphoplasty and percutaneous vertebroplasty [40–42]. In percutaneous vertebroplasty polymethylmethacrylate is directly injected into the vertebral body. This stabilises the fracture and relieves pain and disability. Kyphoplasty differs from vertebroplasty by adding an important additional step which is the placement of an expandable balloon to create a cavity which reduces kyphosis, restores vertebral body height and aligns the spinal canal and then injection of PMMA follows. Although the use of these minimally invasive procedures in epidural MASCCs is considered a relative contraindication, in poor surgical candidates the combination of radiation therapy along with the previously mentioned percutaneous techniques can considerably alleviate pain.

Radiation therapy

Palliative RT as a monotherapy is a treatment of choice for patients with an expected survival of 6 months or less. In this patient population surgical procedures should be avoided [37,43,44].

The most important predictive factor of RT outcome is the neurological status of the patient before irradiation, followed by the Karnofsky score, the duration of neurological symptoms, the interval between initial tumour diagnosis and MASCC, the extent of compression of the thecal sac and the histology of the primary tumour [45,46].

The standard treatment procedure of MASCCs for several years has been the combined action of radiation and steroids. Numerous prescription modalities have been used in clinical practice, without establishing superiority of any regimen over the others. The fractionation schedule, total and daily dose are yet subject of debate.

Typical conventional radiation treatment plans comprise total doses of 20 Gy in 5 fractions for the short course (offered to patients with shorter life expectancies), to 30 Gy in 10 fractions for the longer courses in those with less extensive disease [33].

Treatment is usually delivered with a single posterior field for the thoracic, lumbar, or sacral spine or two opposed lateral fields for the cervical spine.

The radiation field includes the involved spinal segment plus one level above and below this region [45]. Rades et al. investigated patients with MASCCs, treated with RT by short-courses i.e., one fraction of 8 Gy in 1 day, or 5 fractions of 4 Gy in 1 week, versus patients who underwent longer-courses of RT i.e., 20 fractions of 2 Gy in 4 weeks or 15 fractions of 2.5 Gy in 3 weeks or 10 fractions of 3 Gy in 2 weeks [47]. Similar outcomes were reported between all cohorts in terms of motor function improvement and ambulatory rates after treatment. A palliative treatment of a single dose of 8 Gy in 1 fraction is a rational approach for patients with a shorter life expectancy. On the other hand, longer courses i.e., 30 Gy in 10 fractions or 40 Gy in 20 fractions, should be reserved for patients with longer survival [36,37].

Recent technological advances have enabled the implementation of unconventional modalities such as three-dimensional conformal radiation therapy (3D-CRT), stereotactic body radiosurgery/radiotherapy (SBRS or SBRT), intensity-modulated radiation therapy-(IMRT), intraoperative radiation therapy (IORT) in the treatment of MASCC [48]. The rationale behind these advanced techniques of delivering radiation therapy

is to maximise the dose to the neoplastic lesion (one or a few large fractions of 8 to 30 Gy per fraction under imaging guidance), while at the same time avoiding the surrounding normal cells with the goal to improve outcome while minimise morbidity [45,49].

Adverse events related to radiation therapy depend on the irradiated normal tissues and include bone marrow suppression, gastrointestinal toxicity, mucositis and even radiation-induced myelopathy which can become a chronic side-effect [5,17].

Recurrences in the irradiation field are especially important because up to 25% of patients already treated with RT, develop recurrent disease. The use of re-irradiation to the spine for recurrent MASCCs is recommended only if the risk of radiation myelopathy is low and the interval between RT courses exceeds 6 months [50,51]. Radiobiological data offer formulas for calculating this risk. SBRS has been applied to the setting of recurrence [45,52]. Nevertheless, the recommendations of the American Society for Radiation Oncology (ASTRO) are that patients with poor performance status should not be managed with SBRT [53]. Until recently, there is not enough evidence to support the superiority of SBRS over conventional fractionated radiation or decompressive surgery in this group of patients [54].

In the context of postoperative adjuvant treatment, radiation therapy can start 7 to 14 days after surgery using the default standard scheme of 30 Gy in 10 fractions in two weeks [5,15,55]. In patients with a good prognosis submitted to surgical treatment, highly conformal re-irradiation techniques must be considered to permit not only sufficient dose to the tumour, but also to spare the surrounding normal neural structures.

Key factors in deciding whether to pursue surgery before RT include spinal stability, presence of neurologic deficits, and patient prognosis [3]. Tables 2 and 3 summarise the general indications for surgery and radiation therapy, respectively.

Currently, the available literature supports the use of pre-irradiation surgical decompression in eligible surgical cancer patients with MASCCs [56]. Consequently, it is of extraordinary importance for each treatment modality (radiation alone vs surgical decompression followed by radiotherapy) to adequately select candidate patients to optimise the outcome and avoid unnecessary morbidity. For patients who meet surgical criteria, radiation therapy has an adjuvant role. Nonetheless, in patients unfit for surgery or where surgery would be inappropriate, radiotherapy should be the primary treatment [56].

Table 1. *Key points of MASCC.*

MASCC is an oncological emergency
Providers of clinical services and patients at high risk should be aware of the signs and symptoms of MASCC and how to respond if such an acute situation develops
Upon first signs/symptoms of MASCC, patient should be placed in bed rest, immediate onset of steroid treatment and urgent magnetic resonance imaging (MRI) within 24 hours.
Spinal pain in an oncologic patient is the commonest symptom suggestive of metastasis, requiring for MRI within 1 week from its onset
There should be a network of services (multidisciplinary management) for MASCC patients beginning from rehabilitative care during acute hospitalisation and transitioning out of the acute care setting to psychosocial support to promote the quality of life of the patient and his loved ones

Table 2. *Common indications of surgery in MASCC.*

Mechanical instability of the vertebral column
Life expectancy ≥6 months
Unsuccessful application of radiation therapy (e.g. evolution of neurological deficits during radiotherapy)
or in cases of a recurrence when re-irradiation is not an option
or in cases of radiation-resistant tumours (e.g. renal cell carcinoma, sarcoma, melanoma etc..)
Cancer of unknown primary tumour (CUPT) (no histological diagnosis available)
Fulminant progression of neurological signs and/or symptoms
When the origin of the spinal cord compression is primarily mechanical (i.e. from posteriorly dislocated bone fragments, or from a deformed spinal column)
Metastatic lesion extending beyond the vertebral canal and into the paravertebral space

Systemic Therapy

In chemo-sensitive tumours (e.g., leukaemia, germ cell tumours, neuroblastoma, lymphomas), chemotherapy, either in combination with other treatments or as the primary modality, may have a role in the treatment of MASCCs [57–60]. The predominant advantage of using chemotherapy as the primary treatment of MASCCs in patients with chemo-sensitive tumours is the possibility to provide concurrent therapy to other possible foci of systemic disease as well as avoiding

Table 3. *Common indications of radiation therapy as primary treatment in MASCC.*

Patient unfit for surgery (high or very high surgical risk) or patient does not wish surgery as a primary treatment option
Life expectancy < 6 months
Radiosensitive tumours in a patient not fulfilling surgical indications (e.g. multiple myeloma, lymphoma, prostate, breast, seminoma, neuroblastoma)
Metastatic lesions compressing spinal cord in multiple levels
Complete neurological deficit established for > 24–48 hours
Asymptomatic spinal cord compression (i.e. finding of an imaging exam)

probable complications of surgery. In asymptomatic or with minimal symptoms MASCCs patients with lymphoma, chemotherapy as a neoadjuvant therapy is an attractive alternative reserving radiotherapy for patients non-responding to chemotherapeutic agents.

Currently, there is strong evidence that targeted therapy prolongs the survival of cancer patients with metastatic disease. Tyrosine kinase inhibitors (TKIs) have improved the median progressive-free survival and the treatment response rates of patients with anaplastic lymphoma kinase mutations or in tumours expressing epidermal growth factor receptor (EGFR) [61,62]. Moreover, immunotherapies are an additional therapeutic tool in a wide range of malignancies regarded as highly immunogenic [63–66].

Steroids

Corticosteroids are indicated for the initial treatment of MASCC. Loading intravenous (i.v.) dose is followed by a maintenance i.v. or per os dose. There is consensus that combination of steroids with RT is superior to RT alone [67]. Steroids have a beneficial effect in pain control and have direct cytotoxic effects on leukaemias and lymphomas [17,45]. An improvement of motor function following initiation of steroids is a positive prognostic factor, because it is associated with additional motor function recovery after definitive treatment [68]. Moreover, corticosteroids reduce spinal cord vasogenic oedema, thus protecting from the secondary complication of reduced arterial flow and subsequent ischaemia, infarction, and irreversible injury [45].

Steroid effectiveness is better exploited when administered immediately (i.e., ideally within 12-hours of symptom onset) once the diagnosis of MASCC is confirmed. Following definitive therapy with RT or surgery, a tapering schedule should be implemented to reduce the incidence of side effects. The optimal duration of steroid therapy is subject of debate. Toxicity from steroids has been demonstrated when usage exceeds 21 days and becomes more prominent at 40-days following initiation [67].

Numerous clinical trials have studied the role and dose of steroids [68–70]. Sorensen et al. performed a randomised single-blind trial, comparing two groups: one group with no steroid treatment and the other group that received a short course (13 days in total) of high-dose dexamethasone (96 mg iv loading dose, followed by 24 mg per os every six hours for three days and a ten-day tapering). The results demonstrated that 81% of patients in the corticosteroid group were ambulatory at three months vs 63% of patients in the non-steroid group ($p = 0.0460$), resulting in better functional outcome [68]. Extra caution should be applied to avoid using steroids in younger patients or in cases of undiagnosed primary cancer until a suitable diagnostic histological specimen is obtained, especially when malignant thymoma or lymphoma is suspected.

Supportive care and rehabilitation

Supportive therapy is a generic term under the umbrella of which are hosted physical therapy, management of bowel and/or bladder incontinence, prophylaxis of thromboembolic disease, adequate analgesia, access to specialist rehabilitation and finally psychological as well as social support.

Probably, pain management is the objective with the highest priority during the treatment pathway, due to its obvious and solid correlation, not only with the ability of patients to undergo rehabilitation but also with the quality of life. The potential aetiologies of pain are numerous, especially if surgery is performed. There are two principal types of pain and often occur in combination. Neuropathic pain (e.g., preexisting chemotherapy-related peripheral neuropathy, post-radiation or post-surgical fibrosis, radiculopathy from tumour invasion or from compression ab extrinseco), defined as "pain caused by a lesion or disease affecting the somatosensory system" [71,72]. It is the result of direct damage to the nervous system from a tumour or a metastatic lesion or from cancer treatment. It is estimated that 20% of cancer pain cases is purely neuropathic in origin. Neuropathic pain is typically chronic, and it manifests as recurrent, painful episodes or persisting continuously. Its consequences are

spontaneous pain, increased pain sensitivity and loss of function. Nociceptive pain, on the other hand, (e.g., infection, postsurgical pain, failure of stabilisation, bone pain), is defined as "pain that arises from activation of nociceptors due to threatened or actual damage to non-neural tissue". In contrast to neuropathic pain, in nociceptive pain, the somatosensory nervous system is functionally normal. Most of the times though, pain is mixed in nature thus neuropathic plus nociceptive components. Accurate diagnosis is of utmost importance for the choice of the best treatment scheme [73]. Steroids are effective in ameliorating inflammation, oedema and consequently pain, but the use of nonsteroidal anti-inflammatory drugs (NSAIDs) and, more commonly, opiate, non-opiate or opioids medication are often required. These are administered per os, as transdermal therapeutic systems (TTS), as epidural or intrathecal pumps or as intravenous patient-controlled analgesia (PCA) for breakthrough pain. Use of specific molecules (e.g., pregabalin) for neuropathic pain found in medications (e.g., anxiolytics, tricyclic antidepressants, anticonvulsants) has also proven beneficial. Possible side-effects are cardiac arrhythmias, orthostatic hypotension, sedation and anticholinergic effects. As mentioned earlier, if NSAIDs and/or corticosteroids are used, gastric protection with PPIs should also be introduced. Nonpharmacologic therapies include transcutaneous electrical nerve stimulation (TENS), acupuncture, acupressure, cognitive therapies, psychology sessions, massage, yoga, assist devices (e.g. spinal braces), which can also help with pain control [74].

Stretching splints, passive stretching exercises and medications (e.g., benzodiazepines, baclofen, tizanidine) could be used to address a common complication of upper motor neuron lesion which is spasticity.

Decreased intestinal motility and constipation is another frequent symptom of multifactorial origin e.g., a side effect from the use of analgesics, decreased physical activity, autonomic dysfunction (i.e. upper motor neuron lesions that cause sphincter hyperreflexia and retention). Treatment is conservative with combined use of stool softeners and oral osmotic laxatives (e.g. polyethylene glycol). Oral colonic stimulants of peristalsis (e.g. senna) are also used to promote normal bowel movements and avoid exacerbation of pain secondary to Valsalva maneuvers. Patients with more severe constipation may require lactulose, enema, or suppository. On the other hand, lesions of the lower motor neuron cause fecal incontinence. Bulk forming agents (e.g. psyllium) or manual evacuation schedules are used.

Intermittent catheterisation and anticholinergic agents can be implemented for upper motor neuron lesions which cause external sphincter hyperreflexia and urinary retention, whereas indwelling catheters and bladder retraining can be applied for lower motor neuron bladder patterns manifesting with sphincter flaccidity and incontinence.

Cancer patients have a 4-to-7-fold higher risk of venous thromboembolism (VTE) (Deep Venous Thrombosis-DVT and Pulmonary Embolism-PE), compared to healthy individuals [75]. If no contraindications are present, application of graduated elastic compression stockings, physiotherapy with leg exercises, and use of prophylaxis with anticoagulants (i.e., Direct Oral AntiCoagulants-DOACs, Low-Molecular-Weight Heparins -LMWHs) are recommended [75]. The duration of thromboprophylactic treatment is based on the presence of ongoing risk factors, comorbidities, overall clinical condition and return to mobility. Many of the patients with MASCC, because of their low performance status and decreased mobility due to accompanying risk factors (e.g. impaired state of consciousness, pain, pathological fractures, cachexia), are confined in bed and consequently, should be nursed in bed. Spinal precautions (e.g. postural braces) ensuring the stability of the vertebral column and management of decubitus ulcers, are equally important goals of patient's treatment [76].

CONCLUSIONS AND FUTURE DIRECTIONS

MASCC is a relatively frequent oncological emergency. Optimal management requires close cooperation from a multidisciplinary team consisting of radiologists, oncologists, neurosurgeons, nurses and physiotherapists for an immediate and accurate diagnosis, the implementation of the most effective treatment, management of complications and comorbidities. Because of the urgency of such a situation in high-risk patients, clinicians should be aware of the signs, symptoms and how to address them in case of development. Initial surgical decompression in eligible surgical candidates with MASCCs has a prominent role in the treatment. In patients unfit for surgery or where surgery would be inappropriate, radiation therapy should be the primary treatment. Evolution of minimally invasive surgical techniques and application of modern radiation therapy techniques should be further explored. Chemotherapy seems to play a role in carefully selected patients with tumours sensitive to pharmacologic agents, especially in combination with other treatments. Bisphosphonates have demonstrated a role in the reduction of

the number of skeletal complications, metastatic bone pain, treatment of hypercalcaemia and improvement of quality of life. Steroids have a beneficial role in oedema and pain control improving the clinical outcome. Finally, supportive therapies of care and rehabilitation through a network-led service for the delivery of services are of great significance to promoting the quality of life of patients with MASCC.

Future research on this clinical entity should focus on two main pathways: First, to develop diagnostic algorithms leading physicians to the proper selection of appropriate imaging techniques and second, to apply guidelines which can be used by the multidisciplinary team for the careful choice of the suitable treatment modality. Bearing always in mind that the therapeutic goal for this group of patients is to improve or maintain the quality of life in these patients.

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Immunomodulation in Infectious Diseases; A review of current applications and future directions

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Abstract

Infectious diseases are a major global health issue, particularly at a time when resistance to antibiotics is increasing. Viewing infections as a consequence of immune system dysfunction, immunomodulation offers an alternative approach that shifts the focus to the host. Among the immunomodulation strategies, vaccines and adjuvants aim to shape the patient's immunity to prevent the severity of the infection, whereas immunomodulating peptides, based on derivatives from the immune system, exert both immunoregulatory and antibacterial activity. Hematopoietic growth factors regulate the production of blood cells, while cytokines specifically modulate the immune response against a particular pathogen, exhibiting both enhancing and anti-inflammatory properties. Monoclonal antibodies exert a dual action, as in addition to targeting a specific antigen, they prevent excessive anti-inflammatory activity. At the molecular level, factors acting through TLR receptors regulate the immune response against microbial pathogens, whereas immune checkpoint inhibitors remove the inhibition of the immune system, allowing for a targeted response. CAR-T cells are another approach, where specially engineered T cells target pathogens with greater precision. The present review seeks to highlight immunomodulation as a potential adjunctive therapy for infectious diseases and emphasizes the need for further personalization of antimicrobial treatment strategies. In line with this, we also discuss documented cases of infections, such as COVID-19, malaria, and sepsis, where immunomodulation strategies have been effectively utilized.

Key words: *Immunomodulation; infectious diseases; immunomodulatory strategies; sepsis; Covid-19*

INTRODUCTION

Infectious diseases constantly threaten global health, with emerging pathogens often posing challenges to humanity. For many years, traditional approaches to fighting these diseases have mainly focused on the use of antimicrobial agents to either kill or directly inhibit pathogen growth. However, increasing antibiotic resistance, in conjunction with the limitations faced in the development of new antibiotics, has shifted the focus of attention to the direction of immune modulatory therapies, since in one sense infectious diseases, can be considered as immunological disorders. Immunomodulatory-based treatments focus on the hosts' reaction rather than on the pathogen itself. Either natural or synthetic and further divided into three categories,

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i.e., immunoadjuvants, immunosuppressants, and immunostimulants, immunomodulators assert their action either by mitigating the immune response and, thereby, limiting the auto-inflammatory damage or by enhancing its defensive capabilities through adaptive immune system stimulation [1].

The introduction of corticosteroids in the treatment protocols of sepsis dates back to the mid-twentieth century [2]. The potential of immune-based therapies as sustainable, long-term solutions to the global burden of infectious diseases has been evident ever since. However, limitations in terms of technology and pharmacology may have stalled investment and attention in the field. The COVID-19 pandemic renewed interest in terms of therapy for immune modulation, owing to the widespread research on the discovery and use of novel immunoregulatory therapies to tackle disease severity and prevent adverse outcomes in Sars-CoV-2-related pneumonia [3]. Breakthrough use of immunomodulatory agents such as Tocilizumab - a monoclonal antibody that targets and binds to the interleukin-6 (IL-6) receptor- and Baricitinib -Janus kinase (JAK) inhibitor- for COVID-19 has ascertained their clinical value and significance.

The concept of immune modulation in the treatment of infections has been widely explored. However, a "one size fits all" approach is, by definition, flawed when taking into account the variability of pathogens and the particularities of the hosts' reactions. Multiple pathogens, including bacteria, viruses, and fungi, have been proven to cause immune system checkpoint inhibition through numerous mechanisms, thereby leading to an exaggerated or diminished immune response from the host's side [4,5]. For instance, cytomegalovirus (CMV), directly encode proteins that are homologs of immune checkpoint ligands which inhibit T-cell activation, helping the virus to evade the immune response [6]. Similarly, hepatitis B and C viruses induce the expression of PD-L1 [7], a checkpoint ligand, on the surface of infected cells, which, when binding to PD-1 on T cells, suppresses their activation and thus allows the virus to proliferate unchecked.

Moreover, immune adaptations, ranging from total immune paralysis to markedly severe systemic inflammation, are commonly encountered in cases of infection. It becomes evident that many parameters need to be addressed when it comes to personalized clinical decision-making and individualization of clinical care in infection. Living and practicing in the modern world of personalized medicine brings a whole new meaning to the matter.

This review aims to further emphasize the potential of immune modulation in the treatment of infections and the need for individualized approaches in the modern world of personalized medicine by examining some of the key strategies and immune-based therapies being developed to combat infectious diseases.

IMMUNOMODULATORY STRATEGIES IN INFECTIOUS DISEASES

Vaccines

Vaccines play a crucial role in modulating the immune system by providing a safe and controlled exposure to antigens, allowing the immune system to generate a robust, specific, and long-lasting response. Through this exposure, vaccines stimulate the production of memory B and T cells, providing long-term protection against subsequent infections [8,9]. Evidence has shown that, vaccination affects some innate immunity cells apart from adaptive immunity. Vaccines indirectly enhance the innate immune response by regulating an epigenetic reprogramming of innate immune cells such as monocytes, macrophages, and NK cells. This process, also known as 'Trained Immunity,' acts in favor of reducing the possibility of reinfection in a non-lymphocyte-inducing manner [10]. Vaccines can also help reduce symptoms' severity and duration by boosting the immune response. This can be particularly beneficial in individuals with weakened immune systems or those at a higher risk of severe disease. Vaccines are, therefore, not only an effective preventive measure against infectious diseases but also an essential tool for immunomodulation. Attempts to combat the susceptibility and severity of SARS-CoV2, as well as, respiratory infections in the elderly by administering the BCG vaccine are examples of novel approaches to vaccines that provide an immunomodulatory platform against infections [11,12].

Historically, adjuvants are substances utilized to enhance the strength of an adaptive response elicited by a vaccine, as measured by metrics such as antibody titer or protective efficacy. Hence, a secondary function of adjuvants, as equally important, has lately emerged: the ability to steer the nature of the adaptive response towards the most optimal forms of immunity tailored to each pathogen. Presently, adjuvants utilized in human vaccines are designed to bolster primarily humoral immunity. However, in various stages of clinical or preclini-

cal testing, many new adjuvants are aimed at amplifying specific T-cell responses and fostering the multifarious immune reactions necessary to counteract complex diseases such as HIV or malaria [13].

Immunomodulatory peptides

Immunomodulatory peptides, such as, thymosin alpha 1, and vasoactive intestinal peptide (VIP) [14], are compounds being explored as a potential treatment for preventing and treating infections. These compounds are based on natural peptides produced by the innate immune system and are typically enriched with cationic and hydrophobic amino acids. They have diverse mechanisms of action, including the direct killing of bacterial pathogens and modulation of the host's immune system. For example, the peptide thymosin alpha 1 has been shown to enhance immune responses, particularly T-cell responses, and has been proposed as an adjuvant to various infections and cancers [15]. Other peptides, referred to as host defense peptides (HDPs), such as the antimicrobial peptide LL-37 [16], have been developed for their bilateral immunomodulatory properties and protective activity against bacterial pathogens, such as suppressing proinflammatory chemokines in reaction to bacterial lipopolysaccharides and lipoteichoic acids or enhancing the production of chemokines, angiogenesis promotion, and wound healing [17]. These are under consideration for preventing infections in immunosuppressed patients undergoing cancer chemotherapy. Synthetic peptides, such as cyclic di-GMP [18], are also being used as components of vaccine adjuvants to stimulate adaptive immunity and antibody production. Bacteriocins, a diverse class of bacterially produced antimicrobial peptides, such as nisin [19] and pediocin [20], are also being explored for their potential to prevent and treat bacterial infections as well as for their immunomodulatory properties [21]. Inducing the expression of endogenous peptides, such as interleukins, is another approach under investigation and may be a cheaper alternative to the administration of synthetic peptides. Overall, immunomodulatory peptides show promise as a potential immunomodulatory treatment. However, further research and clinical trials are needed to fully understand their mechanisms of action and efficacy in preventing and treating infections.

Cytokines and hematopoietic growth factors

Cytokines and hematopoietic growth factors serve as chemical messengers to regulate blood cell production and immune responses. Their versatility and low concentration efficacy make them highly effective as immunomodulatory treatments. For instance, the growth factors G-CSF and GM-CSF have been utilized for several years to prevent infections in patients suffering from neutropenia [22,23]. These growth factors stimulate the production of neutrophils and other leukocytes in patients with congenital abnormalities in neutrophil production and immunosuppressed patients undergoing cancer chemotherapy or bone marrow transplantation [24]. The administration of these growth factors consistently reduces the incidence of infections and the duration of hospitalization in these patient groups.

Interleukins (ILs) and tumor necrosis factors (TNFs) are among the most well-studied cytokines and have been the subject of numerous clinical trials. These signaling molecules are pivotal in directing immune responses towards a particular pathogen and regulating the magnitude and duration of these responses. For example, Interferons (IFNs) have been used as therapeutic agents for decades in treating viral infections and certain cancers. Type-I interferons are major mediators of antiviral immune response and are utilized in patients with chronic hepatitis B and C viral infections.[25] Interferon-alpha (IFN-α) has been approved for the treatment of hepatitis B and C, as well as for certain types of leukemia. At the same time, Interferon-beta (IFN-β) has been used to treat multiple sclerosis [26]. TNF-α blocking agents such as etanercept and infliximab have been approved for the treatment of rheumatoid arthritis, Crohn's disease, and other chronic inflammatory conditions [27].

Similarly, several cytokines that can stimulate T-cell functions and immunity against intracellular pathogens are being investigated in patients with tuberculosis, with promising results of IFN-γ administration observed so far. IL-7, which instructs standard B and T lymphocyte development, has shown promise in stimulating T cell expansion and improving T cell function in HIV-infected patients [28]. Further clinical trials for IL-7 and other cytokines with the potential to stimulate T-cell functions are ongoing.

Monoclonal Antibodies

Monoclonal and polyclonal antibodies (Abs) have been utilized as a form of immunomodulatory therapy in various medical fields, particularly in the treatment of inflammatory diseases and cancer. Monoclonal abs (mabs) can bind directly to pathogenic antigens, neutralizing the pathogen and blocking its ability to cause

harm. Additionally, mabs can target immune mediators, such as cytokines and chemokines, that regulate the host response to infection. By targeting these mediators, they can modulate the intensity of the immune response and prevent excessive auto-inflammatory damage, which can cause harm to the host. This dual mode of action makes mabs highly versatile immunomodulators that can be used to treat various infectious diseases, including viral infections, bacterial infections, and toxin-mediated diseases [29].

In the field of infectious diseases, immunoglobulin replacement therapy, which involves administering polyvalent IgG, is used in patients with agammaglobulinemia and other congenital disorders of B cell function and constitutes the most effective therapeutic strategy for avoiding recurrent infections in these patients [30]. Due to the recognized risks of systemic inflammation, their use to stimulate immune response has yet to be attempted in an active infection. Currently, the application of mabs for the prevention and treatment of infectious diseases includes the neutralizing antibody against the F protein of respiratory syncytial virus (RSV), known as Palivizumab, which is approved for the prevention of respiratory disease in infants and immunocompromised adults [31], the fully humanized mab that targets the toxin B of *Clostridium* , Bezlotoxumab, acknowledged for its use against *C. difficile* recurrence [32] and the SARS-CoV2 spike-targeting monoclonal antibody, tixagevimab /cilgavimab, that was recently developed to combat the pandemic and has shown promising results, especially in immunocompromised populations.

The numerous successful applications of mabs in other medical fields highlight their potential as an up-and-coming class of agents for the modulation of immune responses.

TLR targeting

Immunomodulatory agents acting through TLRs are attracting interest for use in immunotherapy and are being exploited as adjuvants to trigger humoral and cell-mediated immune responses. The discovery of TLRs, NOD-like receptors, and RIG-like receptors has revolutionized the field of molecular mechanisms mediating pathogen recognition by the innate immune system, leading to the identification of many new drug targets. TLRs that interrelate with microbial molecules are crucial in activating innate immunity and shaping adaptive immunity [33]. TLR agonists are being explored for the stimulation of immune responses in chronic viral infections. Most clinical trials involving TLRs ligands evaluate them primarily as adjuvants, with double the number of trials investigating TLRs ligands as adjuvants compared to those considering them as drugs. The Food and Drug Administration has approved TLR ligands, such as MPLA and imiquimod, to be used as adjuvants in various vaccine formulations and as drugs to cure viral diseases [34]. The advances in our understanding of the innate immune system hold promise for creating more effective vaccine adjuvants, with new formulations targeting different innate immune system receptors currently in development [35].

Immune checkpoint inhibitors

Another promising approach to immunomodulation is immune checkpoint inhibitors, designed to block the inhibitory signals that regulate the immune response and prevent excessive activation of immune cells. In a variety of chronic infectious diseases such as malaria, HIV, HCV and HBV infection, where upregulation of immune checkpoint receptors such as CTLA-4 and PD-1 has been described, drug administration has not yet been most potent. Blockade of these pathways may thus serve as an additional approach in tackling drug efficacy issues or eliminating viral reservoirs. Table 1 summarizes the available clinical trial data on the efficacy and safety of such compounds in the management of chronic viral infections. Moreover, in the case of infections where highly effective vaccines have not yet been discovered, immune checkpoint inhibitors may help prevent the blockade of the immune system and thus ensure an efficient immune response against infectious pathogens [36].

CYTOTOXIC T LYMPHOCYTE-ASSOCIATED ANTIGEN 4 (CTLA-4)-TARGETED AGENTS

CTLA-4, the first recognized immune checkpoint inhibitor, is important in regulating T-cell priming during antigen presentation [37]. It further transmits an inhibitory signal that results in the downregulation of the immune response [38]. Mabs that bind with high affinity to CTLA-4 and conclusively inhibit its action have been widely used to treat melanoma and do not seem to correlate with susceptibility to infections if used as the only immunotherapy [39].

PROGRAMMED DEATH (PD)-1 AND PD-1 LIGAND 1 (PD-L1)-TARGETED AGENTS.

PD-1 is considered an inhibitory immune factor of

Table 1. *Clinical trials assessing the efficacy and/or safety of Immune Checkpoint Inhibitors in the treatment of chronic viral infections.*

Clinical trial number (NCTID)	Study	Infection or disease	Target Inhibitory protein	Agent	Study design/ Number of participants/patient population	Clinical Outcomes	Safety Outcomes
NCT03239899	PD-1 Inhibition to Determine CNS Reservoir of HIV-Infection	HIV	PD-1	Pembrolizumab	12 patients with HIV-1 infection receive a one-time dose of 200mg pembrolizumab with a baseline study period of 3 weeks, a one-day treatment phase, and a 6-month post treatment phase.	No results posted	No results posted
NCT03787095	Safety and Immunotherapeutic Activity of an Anti-PD-1 Antibody (Cemiplimab) in HIV-1-infected Participants on Suppressive cART	HIV	PD-1	Cemiplimab	Experimental: Cohort 1: Cemiplimab 4 Participants received 0.3 mg/kg of cemiplimab, administered at Day 0 and Week 6 for a total of two infusions. Comparator: Cohort 1: Placebo 1 Participant received placebo, administered at Day 0 and Week 6 for a total of two infusions.		One participant revealed hyperthyroidism on routine safety labs at 4 weeks after 1st infusion. Per protocol for possible irAEs, 2nd infusion was held; one week later repeat labs confirmed thyroiditis judged probably related to study drug. One participant, had asymptomatic Grade 3 AST and ALT elevations 2 weeks after 1st infusion, resolved 35 later without intervention. Transaminase enzyme elevation pattern (AST=ALT) and slow resolution were deemed inconsistent with acute alcohol toxicity and therefore were judged possibly related to study drug. Two participants received both infusions without report of adverse events or laboratory abnormalities.

T-cells in the peripheral tissues, expressed in various immune system cells. Through binding to its ligand PD-L1, which is also found in the microenvironment of tumors, PD-1 suppresses the CD8 T cells' activity [38]. The use of agents targeting PD-1 and PD-L1 does not increase susceptibility to infections on its own [40];

Table 1. *Clinical trials assessing the efficacy and/or safety of Immune Checkpoint Inhibitors in the treatment of chronic viral infections (continued).*

Clinical trial number (NCTID)	Study	Infection or disease	Target Inhibitory protein	Agent	Study design/ Number of participants/patient population	Clinical Outcomes	Safety Outcomes
NCT03354936	Assess the safety of the use of immune checkpoint inhibitors in HIV infected patients	HIV	IMC	Nivolumab Pembrolizumab	50 HIV Infected Patients with Cancer Treated by immune checkpoint inhibitors will be recruited. Blood samples will be collected to constitute cell bank, plasma bank, serum bank, DNA bank in order to meet the objectives of this substudy and possibly for complementary research	No results posted	No results posted
NCT03367754	A Single Dose of Pembrolizumab in HIV-Infected People	HIV	PD-1	Pembrolizumab	Participants will either receive a single dose of 200mg (iv infusion) of pembrolizumab or a single dose (iv infusion) of placebo	No results posted	no results posted
NCT03407105	An open-label, multiple ascending dose study of the anti-CTLA-4 antibody ipilimumab in viremic HIV patients	HIV	CTLA-4	Ipilimumab	24 participants received 2 or 4 doses of ipilimumab (0.1, 1, 3, or 5 mg/kg) every 28 days.	Two participants (8.3%), one each in the 0.1- and 1-mg/kg dose groups, had a decrease from baseline HIV-1 RNA of 0.85 and 1.36 log10 copies/mL. Fourteen participants (58.3%) had an increase from baseline HIV-1 RNA (mean, 0.87 log10 copies/mL; range, 0.59–1.29). Of these 14 participants, all but 1 were in the higher ipilimumab dose groups (3 or 5 mg/kg). No pattern was noted regarding change from baseline in CD4 or CD8 T cells	No serious adverse events (AEs) or dose-limiting toxicities were reported; one participant discontinued ipilimumab for an AE of grade 2 facial palsy. Twenty participants (83.3%) had ≥1 AE; all but 1 were grade 1 or 2. Eight participants (33.3%) had potentially immune-related AEs (7 had grade 1 diarrhea not requiring corticosteroids; 1 who had diarrhea also had transient antinuclear antibody positivity; 1 had grade 2 facial palsy requiring corticosteroids).

Table 1. *Clinical trials assessing the efficacy and/or safety of Immune Checkpoint Inhibitors in the treatment of chronic viral infections (continued).*

Clinical trial number (NCTID)	Study	Infection or disease	Target Inhibitory protein	Agent	Study design/ Number of participants/patient population	Clinical Outcomes	Safety Outcomes
NCT03899428	Immune Checkpoint Therapy vs Target Therapy in Reducing Serum HBsAg Levels in Patients with HBsAg+ Advanced Stage HCC	HBV	PD-L1	Durvalumab Sorafenib Lenvatinib Regorafenib Cabozantinib (Tyrosine kinase inhibitors)	The participants will receive durvalumab 1500 mg Q4W (iv infusion) or tyrosine kinase inhibitors, including sorafenib, lenvatinib, regorafenib, or cabozantinib, daily	No results posted	No results posted
NCT00703469	A Study of MDX-1106 to Treat Patients with Hepatitis C Infection (MDX1106-02)	HCV	PD-1	BMS-936558 (MDX-1106) – a fully human anti-PD-1 monoclonal immunoglobulin-G4 that blocks ligand binding	Interferon-alfa treatment-experienced patients (n=42) were randomized 5:1 to receive a single infusion of BMS-936558 (0.03, 0.1, 0.3, 1.0, 3.0 mg/kg [n=5 each] or 10 mg/kg [n=10]) or of placebo (n=7). An additional 12 HCV treatment-naïve patients were randomized to receive 10 mg/kg BMS-936558 (n=10) or placebo (n=2).	Five patients who received BMS-936558 (0.1 [n=1] or 10 mg/kg) and one placebo patient achieved the primary study endpoint of a reduction in HCV RNA ≥0.5 log10 IU/mL on at least 2 consecutive visits; 3 (10 mg/kg) achieved a >4 log10 reduction. Two patients (10 mg/kg) achieved HCV RNA below the lower limit of quantitation (25 IU/mL), one of whom (a prior null-responder) remained RNA-undetectable 1 year post-study.	One patient (10 mg/kg) experienced an asymptomatic grade 4 ALT elevation coincident with the onset of a 4-log viral load reduction. Six patients exhibited immune-related adverse events of mild-to-moderate intensity, including two cases of hyperthyroidism consistent with autoimmune thyroiditis.

however, their immune-related adverse event potential may necessitate immunosuppressive therapy, resulting in opportunistic infections. In addition, there have been reports of latent TB reactivating with their use [41].

CAR T CELLS

Chimeric Antigen Receptor (CAR) T cells are created by modifying a patient's own T cells in vitro so that they express a CAR on their surface. CARs are artificial receptors that consist of a targeting component connected to a spacer, which is then attached to a transmembrane domain and an intracellular signaling domain [42]. The production of CAR T cells is a strategy of creating more specialized and effective T cells to successfully eradicate targets such as neoplastic cells, specifically hematologic malignancies. They may also conduct an important role in some cases of infections, especially when adaptive and innate immune cells lack in frequency, thus in efficacy to be used in immunotherapy. Such cases include viral diseases like HIV, HBV, HCV, and fungal infections. Through their chimeric antigen receptor, these redirected T cells can avoid the escape mechanisms of bacteria, viruses, and fungi and effectively attach to their target since they do not require MHC presentation and HLA restriction [43]. Although targeting specific pathogens can provide greater precision and reduce the risk of affecting non-target organisms, avoiding off-target effects, pathogen escape mechanisms, and reservoirs remain significant challenges.

The most proposed application of CAR T cells therapy

in the field of infectious diseases is HIV-infection. CAR T cells can recognize and eliminate HIV-infected cells independently of the major histocompatibility complex (MHC) [44, 45] and can generate functional memory T cells for rapid response to reinfection [46]. Two main approaches for designing anti-HIV CAR constructs are based on CD4 receptors [47] or broadly neutralizing antibodies [bNAbs) [48]. While CD4 receptor-based CARs have shown limitations [49], bNAb-based CARs hold potential due to their ability to target HIV envelope glycoprotein and deactivate various HIV strains [50]. Furthermore, the HIV-specific CD8+ cytotoxic T lymphocyte (CTL) response plays a crucial role in host immunity against HIV infection [51]. Therefore, designing CD8+ T cells with a CAR that can recognize HIV antigens may be an important aspect of future therapies.

Early clinical trials have shown the potential of CD4-CAR T cell therapy in extending T cell survival and reducing HIV burden [47,52]. Ongoing and recently completed clinical trials are evaluating the safety and efficacy of CAR T cell therapy in HIV-positive patients under cART treatment, using different CAR designs such as bNAb-based CARs [53] and CD4-CARs (Clinical Trial NCT03617198) modified for HIV resistance.

However, several limitations have been identified, such as challenges in achieving sufficient expansion [47,54], susceptibility of CAR T cells to HIV infection [55], off-target effects [56,57] and toxicity mainly referring to severe cytokine release syndrome and neurologic toxicity [58,59].

NK CELLS

Natural killer (NK) cells are important mediators of the body's innate immune system and are primarily involved in defending against viral infections. The release of interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α) by activated NK cells not only facilitates the killing of target cells but also triggers an inflammatory response, highlighting their immunomodulatory capabilities [60]. Nonetheless, the development of immunomodulatory treatments targeting NK cells implicates various other mechanisms including the direct cytotoxic activity against target cells, the ability to mediate cell killing through antibody-dependent processes and the interaction with dendritic cells [61]. Moreover, another significant mechanism involving NK cells is the memory response. Some subsets of NK cells, often termed 'memory NK cells', are capable of generating a robust and enhanced response to antigens they have previously encountered. This aspect of NK cell functionality allows for a more rapid and potent immune response upon re-exposure to the same antigen, thereby playing a crucial role in immunological memory, traditionally thought to be exclusive to adaptive immunity.

Two crucial elements must align for NK cells to identify and neutralize target cells: the absence of inhibitory signals and the presence of activating signals. This intricate process involves a variety of receptors, each capable of recognizing distinct molecular markers on target cells. These receptors relay either activating or inhibitory signals, thus determining the course of NK cell response. When activated, NK cells undertake several defensive strategies such as releasing cytotoxic granules, expressing death-inducing ligands, and secreting Th1-type cytokines or chemokines [61]. Specific activating receptors like NKp30, NKp44, and NKp46 have been identified and linked to viral infections such as influenza virus [62, 63] and human cytomegalovirus [64], while the interaction between activating killer Ig-like receptors (KIR) and human leukocyte antigen (HLA) molecules is associated with the progression or control of viral infections, including HIV.

In fact, considerable evidence exists to investigate the potential use of NK cells in HIV-infection. Boosting the activity of NK cells, which have shown a protective role during HIV-1 infection, could help eliminate viral reservoirs and prevent infection. In particular, NK cells exhibit natural cytotoxicity and antibody-dependent cellular cytotoxicity (ADCC), which can control cell-associated virus and block cell-to-cell transmission [65]. Preclinical studies have evaluated the administration of molecules like IL-15 to promote NK cell activation and proliferation [66]. The administration of IL-15 is considered as part of the "kick and kill" strategy, aiming to induce viral replication in latently infected cells while boosting NK cell activity to eliminate them in combination with antiretroviral therapy [67]. However, further evaluation is required to determine if this induced NK cell phenotype can be effective in controlling HIV infection [65].

Overall, the extensive and multifaceted mechanisms deployed by NK cells, along with their involvement in antigen-targeting specificity and immune memory, illustrate their profound potential in orchestrating immune responses. This potential notably distinguishes NK cells from other forms of immunomodulatory therapy, such as T-cell targeting agents. Given their distinct attributes, NK cells have become a primary focus in immunological research, underscoring their immense potential in advancing therapeutic immunomodulatory strategies.

Building on this understanding of the unique and powerful capabilities of NK cells, we propose a research protocol that seeks to further explore their immunomodulatory capabilities. This protocol, titled "Development of Memory-Like NK Cells for Vaccine Strategies Based on Cellular Immunity," is inspired by a previous clinical trial that evaluated the efficacy of memory-like NK cells against leukemia cell lines [68] and demonstrated the enhanced responses of memory-like NK cells against myeloid leukemia.

Our proposal aims to extend this understanding by investigating the potential of these cells in the development of new vaccine strategies based on cellular rather than adaptive immunity. Specifically, this protocol will involve the in-vitro development of memory-like NK cells, followed by an evaluation of their cytotoxic response and IFN-γ production. The ultimate goal is to assess whether this response may provide sufficient coverage during early infection, possibly employing animal models in future studies in order to determine safety and efficacy. It is our hope that this study will contribute to the growing body of knowledge on NK cells and their potential applications in immunotherapy, and ultimately lead to the development of more effective vaccine strategies.

Table 2 delineates a proposed research protocol for the investigation of memory-like natural killer (NK) cells in the development of new vaccine strategies and outlines the steps from the initial objective of developing memory-like NK cells in vitro through the evaluation of their cytotoxic response and IFN-γ production, to the assessment of their potential in new vaccine strategies. Furthermore, the table also acknowledges potential limitations and analyses the expected outcomes of the proposed research

EXPLORING APPLICATIONS OF IMMUNOMODULATORY STRATEGIES IN INFECTIOUS DISEASES

Many cases of infectious diseases have been studied to understand the immune-modulatory mechanisms,

Table 2. *Research Protocol Outline for the Development of Memory-Like NK Cells for Vaccine Strategies.*

I. Purpose & Aim	• To elucidate the capacity of memory-like natural killer (NK) cells to bolster vaccine efficacy via cellular immunity. • Potentiate robust cytotoxic responses and IFN-γ secretion during early pathogenic invasion.
II. Objectives	1. To develop memory-like NK cells in vitro and confirm their memory status using phenotypic and functional assays. 2. To evaluate the cytotoxic response and IFN-γ production of these cells against standard pathogenic models. 3. To assess the potential of memory-like NK cells in enhancing vaccine strategies, particularly as an adjuvant.
III. Methodology	• *NK Cell Isolation:* Utilize density gradient centrifugation or magnetic-activated cell sorting to extract NK cells from peripheral blood mononuclear cells. • *NK Cell Pre-activation:* Incubate with interleukins (IL-12, IL-15, IL-18) to induce a memory phenotype. • *Differentiation and Proliferation Monitoring:* Employ flow cytometry to track expression of activation and memory markers and cell division. • *Functional Assays:* Conduct LDH release assays for cytotoxicity and ELISA for IFN-γ quantification to evaluate effector functions.
IV. Evaluation in Animal Models	Inject memory-like NK cells into in vivo models, appraise immunological performance → track immune response kinetics through serum and tissue analysis → measure protective efficacy, and observe for physiological or behavioral changes.
V. Potential Limitations	Variability in individual NK cell responses, affecting reproducibility and predictability of outcomes, and the complexity of extrapolating in vitro findings to in vivo contexts, requiring validation in multiple animal models and human trials.
VI. Expected Outcomes	Establish a new paradigm in vaccine development leveraging memory-like NK cells, potentially leading to a paradigm shift in prophylaxis and therapeutic management of infectious diseases.

Note: This table outlines the key stages of the research, including the development, evaluation, and assessment of memory-like NK cells, potential limitations of the study, and the expected outcomes.

which are activated during infection, in an effort to update the existing strategies and treatments with the latest scientific knowledge in the field of immune activation. We hereby present an example of 3 cases, that of malaria (parasitic disease), sepsis (mostly attributed to bacteria) and COVID-19 (viral infection) that immunomodulatory regimens have found room for implementation. Of note, this is more of a proof-of-concept rather than an exhaustive list, thus not all relevant applications are included e.g tuberculosis.

A. Malaria

Malaria is a potentially life-threatening parasitic disease caused by infection with *Plasmodium* protozoa, that still afflicts the global health community due to its high morbidity and mortality. Many studies have been conducted to uncover an appropriate treatment, based on host-mediated immunopathology to reduce the severe manifestations and the mortality rates of the disease. In this setting, the complexity of the life cycle of *Plasmodium* is a predominant cause of difficulty in developing protective strategies such as an efficient malaria vaccine. In severe malaria, an intense proliferation of immune cells (i.e., macrophages, neutrophils, and effector T cells) and increased production of proinflammatory cytokines, such as TNF, IFN-g, IL-6, and IL-1b [69], has been described. Experimental malaria models demonstrate the innate, cellular, and humoral immune responses that IFN-γ and TH1 cells orchestrated during the *Plasmodium* blood stages. Patients with acute-phase infection were found to express PD1 on CD4+ and CD8+ T-cells, and CTLA4, OX40, glucocorticoid-induced TNFR-related protein (GITR), and CD69 on CD4+ cells, suggesting a role for regulatory T (T_{reg}) cells in suppressing immunity to malaria and also highlighting the feasible contribution of immune checkpoint blockade to more prolonged vaccine efficacy, prevention of reinfection, fewer complications, better immune response and survival rates [36].

Other cytokines, such as TGF-β and IL-10, have been identified as important anti–inflammatory immunomodulators, that help to limit inflammation and pathology during the course of disease [70]. The anti-inflammatory effects, including inhibition of proinflammatory cytokine expression of corticosteroids (dexamethasone) and the use of intravenous immunoglobulin, were the first immunomodulation strategies that had an impact on cerebral Malaria. Despite the promising reports from anti-TNF models [71], the trials with monoclonal antibody B-C7, pentoxifylline, and thalidomide in cerebral malaria have controversial clinical outcomes [72]. Recent reviews highlighted some promising new therapies, including arginine and inhaled NO to increase NO concentrations, and peroxisome proliferator-activated receptor (PPARγ) agonists, such as rosiglitazone, which can modify CD36 transcription and TLR2-dependent innate inflammatory immune responses and suppression of genes involved in proinflammatory cytokine secretion, as potential agents to adjunctive immunomodulatory strategies in the management of severe malaria [72]. In conclusion, the complexity of the undergoing pathways of the immune response to *Plasmodium* spp leaves the field open for further research into the immunomodulatory therapies in Malaria.

B. COVID-19

The COVID-19 pandemic provided an excellent opportunity to test efficacy of immunomodulation in the acute treatment of infectious diseases. Given SARS-CoV2 unique pattern of immune dysregulation [73], immunomodulation has proven crucial in controlling and preventing the severity of COVID-19 disease. In critically ill patients with COVID-19 pneumonia, a cytokine storm or cytokine release syndrome (CRS) is accountable for multiple organ failure and disease progression [74,75]. Anakinra, tocilizumab, baricitinib, and anti-SARS-CoV-2 mAb (tixagevimab-cilgavimab) represent the most widely used (currently) and approved for the management of severe COVID-19 disease, immunomodulatory factors.

Anakinra, an Interleukin-1 (IL-1) receptor antagonist, constitutes an important therapeutic tool in COVID-19 management, as confirmed by the SAVE-MORE double-blinded randomized clinical trial [76,77]. SARS-COV-2 enters the epithelial cells through the ACE receptor and consequently releases cytokines such as IL-1β, leading to hyperinflammation, cytokine storm, and tissue damage [78].

Tocilizumab is a recombinant humanized monoclonal IgG1 antibody against the interleukin-6 (IL-6) receptor. The central role of IL-6 in the progress of inflammation and, thus, in cytokine storm, hyperinflammation, and acute respiratory distress (ARDS) in patients with severe COVID-19 pneumonia is confirmed by various studies. Tocilizumab seems to reduce mortality in hospitalized adults with severe or critical COVID-19 that meet the WHO severity criteria [79], and its use in combination with corticosteroids is indicated for these patients [80].

Baricitinib is an orally administered JAK inhibitor, that interrupts the multiple cytokine pathways implicated in COVID-19 immunopathology. It also acts via reported antiviral activity by blocking viral cell entry and suppressing type I interferon-driven angiotensin-converting-enzyme-2 upregulation [81]. Combined with remdesivir, it shortens the time to recovery in COVID-19 hospitalized patients and reduces mortality when added to corticosteroids [82,83]. Clinical data on baricitinib›s use in COVID-19 are lacking, and evidence of its anti-inflammatory effects mainly derives from rheumatoid arthritis clinical trial programs [30].

Several anti-SARS-CoV-2 mAb products directed against the SARS-CoV-2 spike protein have been evaluated to treat COVID-19, with tixagevimab-cilgavimab, a monoclonal antibody combination, being the one currently still in use. Its use for pre-exposure prophylaxis was, until recently, the only option for individuals (including pregnant people) with moderate to severe immunosuppression or for those who cannot receive a recommended series of COVID-19 vaccine because of a severe adverse reaction to the vaccines or their components [84].

C. Sepsis

Sepsis, a potentially fatal complication caused by an abnormal response to an infection, is a wide-ranging and complicated condition. Patients on the one side of the septic spectrum experience hyperinflammation as a result of the overproduction of proinflammatory cytokines [85], predominantly interleukin-1β, which can potentially cause pancytopenia, liver failure, and disseminated intravascular coagulation [86]. On the other extreme of the spectrum, we find patients that may become "immunoparalyzed", meaning that their immune system may not be capable of mounting a sufficient response, hence; constituting them vulnerable to secondary infections and resulting in increased hospitalization and fatality rates. This manifestation of sepsis is defined by reduced expression of human leukocyte antigen-DR on circulating monocytes coupled with lymphopenia [87,88]. However, a rise in T regulatory cells and a decrease in B cell markers has also been described in some patients [89]. Pilot trials have shown that immunoparalysis can be restored by administering recombinant human interferon-γ [90].

The timing of intervention in immunotherapies is vital for determining their efficacy; therefore, individualized diagnosis and pattern recognition analysis are required to determine the optimum approach. Identification of the clinical phenotype is essential for directing the administration of immunomodulatory therapies for such complex disorders. Immunomodulatory medications will likely become more effective for treating infections in general, leading to improved outcomes and survival rates, as the value of clinical phenotypic recognition becomes more widely acknowledged [91].

CONCLUSION

Immunomodulation can present an effective complement to traditional antimicrobial treatments for infectious illnesses. Immunomodulators can either minimize auto-inflammatory damage or boost the host's defenses by targeting the immune response. A personalized treatment approach along with a clinically-driven insight into the timing of intervention are essential for optimizing outcomes. In the modern age of personalized medicine, recognizing the unique characteristics of each individual's immune response may allow for tailored immunomodulatory therapies, enabling more effective control and/or treatment of infectious diseases. Future research should focus on developing these customized solutions and improving our understanding of the complex interplay between infections, hosts, and immune responses, which will ultimately result in more effective treatment plans for our patients.

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3. Systematic Reviews and Meta-analyses
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5. Letters to the Editor
6. Case Reports

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