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# ACHAIKI IATRIKI

Quarterly Official Journal of the
**Medical Society of Western Greece And Peloponnesus (IEDEP)**


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*Dear colleagues,*

In the current issue, the editorial by Papantoniou et al. assesses the strengths and limitations of the scoring systems for predicting outcomes in acute upper and lower gastrointestinal bleeding and evaluates their practical relevance in clinical settings.

The current issue features four review articles. The first, authored by Delimaris I., discusses the potential positive impact of the Mediterranean Diet in the reduction of DNA damage via the use of specific biomarkers such as 8-hydroxy-2-deoxyguanosine (8-OHdG) and F2-isoprostanes.The review by Kyriakopoulou et al. examines the complex aspects of cancer management during the COVID-19 pandemic, highlighting several factors that contributed to delays in the healthcare system's response to cancer care. The review by Patagia Bakaraki et al. offers a comprehensive understanding of how conformity influences behavior across both traditional and emerging platforms, bridging classical theories with modern applications. Finally, the review by Karakasidis E. outlines the main aspects of the diagnostic approach and treatment of tetanus in everyday clinical practice, noting that patients often seek help from various specialists. Lastly, this issue features a case report by Papantoniou et al., which evaluates the short-term biochemical response and tolerability of obeticholic acid (OCA) when added to ursodeoxycholic acid (UDCA) in patients with primary biliary cholangitis (PBC) who exhibited an inadequate response to UDCA alone.

Yours sincerely,

C. Triantos
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and Gastroenterology Faculty of Medicine,
School of Health Sciences, University of Patras
Editor-in-Chief of the journal "ACHAIKI IATRIKI"

# Scoring systems for predicting outcomes of acute upper and lower gastrointestinal bleeding. How useful are these in clinical practice?

**Konstantinos Papantoniou, Evangelia Bourdalou, Konstantinos Thomopoulos**

## INTRODUCTION

Acute gastrointestinal (GI) bleeding is a common medical emergency associated with significant morbidity and mortality. Early risk stratification is essential to guide management decisions and improve patient outcomes [1]. Over the years, several scoring systems have been developed to predict severity, the need for intervention, and mortality risk associated with acute upper and lower GI bleeding. Among these, the AIMS65, Glasgow-Blatchford Score (GBS), and Rockall score are widely used for upper GI bleeding, while the NOBLADS, Strate, and BLEED scores aim to predict severity and guide for intervention in cases of lower GI hemorrhage [2] (Table 1). Despite their widespread use, questions remain regarding their clinical applicability. This editorial examines the strengths and limitations of these scoring systems and evaluates their practical relevance in clinical settings.

### Acute nonvariceal upper gastrointestinal bleeding

Acute nonvariceal upper GI bleeding (NVUGIB) is a serious and potentially life-threatening condition, accounting for several hospital admissions each year. While many patients do not require inpatient treatment and can even be safely managed in an outpatient setting, NVUGIB continues to be associated with significant morbidity and mortality despite advances in management [3]. Therefore, early identification of patients at risk for poor outcomes is essential to ensure appropriate triage and management from the initial point of care.

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*Rockall score*

The Rockall score (RS) is a scoring system based on both clinical characteristics and endoscopic findings. Factors used for its calculation include age, the presence of shock, and patient comorbidities, as well as endoscopic identification of the bleeding source and the presence or absence of stigmata that indicate recent hemorrhage [4]. Its use in clinical practice has shown promising results in the prediction of patient outcomes, including risk of rebleeding and mortality [4,5]. However, its reliance on endoscopy makes the use of RS in everyday practice challenging. The use of a pre-endoscopic Rockall score (pRS), which only requires knowledge of patient history and hemodynamic status, is a useful tool for the identification of patients with severe NVUGIB who will require intervention for bleeding cessation [6].

*Glasgow-Blatchford score*

The Glasgow-Blatchford score (GBS) was developed to predict the need for clinical intervention in patients admitted with acute NVUGIB. The score takes into account systolic blood pressure, heart rate, the presence of melena and/or syncope and/or hepatic disease, as well as blood urea nitrogen and hemoglobin levels [7]. GBS has proven to be useful in identifying patients who are at increased risk for rebleeding, hemostatic interventions, and transfusion requirements. GBS calculation does not require endoscopic data. Its application is therefore possible at the time of hospital admission [8].

**Key words:** *Gastrointestinal bleeding; scoring systems; outcomes; prognosis; clinical practice*

**Table 1.** *Scores used as prognostic tools in patients with acute GI bleeding.*

| Score | Condition | Factors required for calculation | Main predicted outcome |
|---|---|---|---|
| Rockall | UGIB | age, shock, patient comorbidities, endoscopic identification of the bleeding source, stigmata that indicate recent hemorrhage | In-hospital mortality |
| Pre-endoscopy Rockall | UGIB | age, shock, patient comorbidities | In-hospital mortality |
| Glasgow-Blatchford | UGIB | hemoglobin, blood urea nitrogen, initial systolic blood pressure, gender, heart rate, melena, recent syncope, hepatic disease, cardiac failure | Need for intervention |
| AIMS-65 | UGIB | albumin, international normalized ratio, mental status, blood pressure, age | In-hospital mortality |
| BLEED | LGIB | on-going bleeding, systolic blood pressure, prothrombin time, mental status, unstable comorbid disease | In-hospital complications |
| Strate | LGIB | heart rate, systolic blood pressure, syncope, nontender abdominal exam, rectal bleeding in the first 4 h of evaluation, aspirin use, >2 comorbid conditions | Severe LGIB |
| NOBLADS | LGIB | non-steroidal anti-inflammatory use, no diarrhea, no abdominal tenderness, systolic blood pressure, antiplatelet use, albumin, co-morbidity score and syncope | Severe LGIB |
| OAKLAND | LGIB | age, gender, previous LGIB admission, digital rectal examination findings, heart rate, systolic blood pressure, hemoglobin | Safe discharge |

*AIMS-65*

AIMS-65 was first studied in a retrospective study of 29,222 patients with acute NVUGIB. Five factors are required for its calculation: albumin, international normalized ratio (INR), mental status, systolic blood pressure, and age. Higher scores were associated with increased in-hospital mortality, length of hospitalization, and healthcare costs ($p<0.001$) [9]. Use of this score as a prognostic factor in patients with NVUGIB is therefore reasonable, while its easy calculation makes it useful in the emergency setting.

*Comparison In clinical practice*

GBS has demonstrated superior performance and reliability compared to the RS in predicting the need for intervention and transfusion requirements. This underlines its clinical importance in the early identification of patients requiring endoscopic or surgical treatment. Current European Society of Gastrointestinal Endoscopy (ESGE) Guidelines recommend the use of the GBS for pre-endoscopy risk stratification of patients presenting with NVUGIB. Patients with GBS score of 0-1 are considered to be at a low risk for complications and can be managed as outpatients with close follow up [1]. However, less than 19% of patients have Glasgow-Blatchford score ≤1, so the majority of patients should be closely monitored in the first days following bleeding [3]. For prediction of mortality, the pre-endoscopic AIMS-65 score is preferred when compared with post-endoscopic scores. However, further studies comparing its value to GBS are required [10]. The scores mentioned above are not useful for predicting outcomes in patients with variceal UGIB. Other prognostic tools, such as Child-Pugh Turcotte and Meld scores, are useful in patients with cirrhosis and portal hypertension [6].

**Acute lower gastrointestinal bleeding**

As with UGIB, many prognostic scores have been developed for the prediction of possible adverse events and safe discharge of patients presenting with acute lower gastrointestinal bleeding (LGIB). However, their use in clinical practice remains controversial, with ongoing debate among clinicians.

*BLEED score*

The BLEED score was developed to predict in-hospital adverse events, including mortality. On-going bleeding, systolic blood pressure, prothrombin time, altered mental status and unstable comorbidities are used for its calculation [11]. Studies examining its prognostic

value in patients with LGIB show it is useful for predicting mortality, but not other outcomes, such as transfusion requirements and hemostatic therapy [2].

*Strate score*

The Strate score was developed from a study of 252 patients with LGIB. It is estimated based on patient medical history (aspirin use and co-morbidity) and clinical findings (heart rate, blood pressure, presence of syncope, non-tender abdominal examination, bleeding per rectum in the first 4 hours after presentation) [12]. Although its use initially appeared promising, external validation studies have failed to prove its reliability in predicting LGIB severity and adverse events [2,13].

*NOBLADS score*

The NOBLADS score takes into account several clinical parameters: nonsteroidal anti-inflammatory drug use, antiplatelet use, presence of diarrhea and/or abdominal tenderness and/or syncope, blood pressure, serum albumin levels and disease scores of 2 or higher [14]. Brito et al. examined the prognostic value of the score in an external validation study which included 173 patients with LGIB. They found that high NOBLADS values were significantly associated with LGIB severity ($p<0.001$) and aided recognition of patients with LGIB who will require transfusions, therapeutic intervention and longer duration of hospitalization [15].

*Oakland score*

The Oakland score was developed as a tool to predict which patients can be safely discharged after presenting with acute LGIB. It is calculated based on age, gender, previous LGIB admission, digital rectal examination findings, heart rate, systolic blood pressure and hemoglobin levels. A score lower than eight has been associated with safe outpatient management [16]. Whiteway et al. recently examined the value of the Oakland score in predicting safe discharge of 144 LGIB patients in a single-center study. They concluded that the score was useful for identifying patients who did not require intervention or hospitalization and suggested further evaluation, as scores higher than eight were also associated with favorable outcomes [17].

*Comparison in clinical practice*

Concurrent use of these scores in different studies has failed to identify a single clinical risk tool with superior predictive ability across all outcomes [16,18]. The prognostic value of tools used for patients with UGIB has also been examined in LGIB, with comparable results [2]. Almaghrabi et al. conducted a meta-analysis of nine studies comparing the Oakland, Strate, NOBLADS and BLEED scores in patients with LGIB. They concluded that the Oakland score had the best predictive value for safe discharge, severe bleeding, and transfusion requirements, while the Strate score was the most accurate in predicting the need for hemostatic intervention [19]. Current ESGE guidelines recommend the use of an Oakland score of ≤ 8 points to guide medical decisions regarding patients with acute LGIB without evidence of severe bleeding [20].

## CONCLUSIONS

The use of scoring systems aimed at predicting outcomes in patients with acute GI bleeding aids clinicians in providing improved patient care. The GBS score is currently recommended for risk stratification of patients presenting with NVUGIB, while the Oakland score can aid the identification of patients presenting with LGIB that do not require hospitalization. Despite their usefulness, these tools cannot replace clinician judgment. Further studies are required to determine which patients will mostly benefit from the use of these scores in clinical practice.

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# Investigating the Potential Positive Impact of the Mediterranean Diet in the Reduction of DNA damage: A Mini Narrative Review

**Ioannis Delimaris**


## Abstract

The Mediterranean Diet (MD) has garnered attention for its potential health benefits beyond nutritional adequacy, particularly concerning oxidative stress and DNA damage. The aim of the present study is to investigate the potential positive impact of the MD on the reduction of DNA damage through the use of specific biomarkers, such as 8-hydroxy-2-deoxyguanosine (8-OHdG) and F2-Isoprostanes. The material of the present study was gathered exclusively from Internet-based sources. The method included a comprehensive electronic literature search for studies published between 2009 and 2024 in the databases PubMed and Google Scholar, conducted from 10 August 2024 to 10 October 2024. The review of the literature revealed that adherence to MD is associated with significant reductions in biomarkers indicative of oxidative stress and DNA damage across various populations. Studies demonstrate increased levels in antioxidant markers and a decrease in DNA damage indicators linked to components of the MD, such as high-quality extra virgin olive oil and green leafy vegetables. The incorporation of coenzyme Q10 and other healthy elements further amplifies the protective effects of the MD, reinforcing its role as a robust dietary strategy for improving overall health outcomes. The findings suggest that the MD serves as an effective dietary intervention to enhance antioxidant defenses, reduce oxidative stress, and mitigate DNA damage, indicating its potential for disease prevention and management across diverse health conditions. Further research is warranted to explore its mechanisms and applications in clinical settings.


**Key words:** *Mediterranean Diet; nutrition; DNA damage; oxidative stress; humans*

## INTRODUCTION

The Mediterranean Diet (MD) is a dietary pattern traditionally followed in countries bordering the Mediterranean Sea, characterized by high consumption of fruits, vegetables, whole grains, legumes, nuts, and olive oil, moderate intake of fish and poultry, and limited red meat and dairy products [1]. Damigou et al. (2023) [1] evaluated the adherence to MD globally, highlighting trends over time. Findings indicated moderate -though not low- adherence to MD globally. Mediterranean countries in Europe exhibited the highest adherence levels, while geographical and socioeconomic factors were found to significantly influence MD adherence worldwide. This dietary approach via MD has been associated with numerous health benefits, including reduced risks of cardiovascular diseases, type 2 diabetes, and certain cancers. Its protective role can be attributed to its rich nutrient composition, which is high in antioxidants, healthy fats, and anti-inflammatory compounds [1-4]. Biological mechanisms underlying these benefits include the modulation of lipid profiles, improvement in glycemic control, and enhancement of gut microbiota

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diversity. The anti-inflammatory properties of olive oil and omega-3 fatty acids found in fish contribute to reduced systemic inflammation. Additionally, the abundance of fiber from plant-based foods supports cardiovascular health and metabolic function. Overall, the MD promotes a holistic approach to well-being, emphasizing whole foods that synergistically support vital biological processes essential for preventing chronic diseases and optimizing health [1, 4-6].

Human DNA damage refers to alterations in the DNA structure that can disrupt genetic information.

It represents a significant health concern, as it has been linked to specific diseases, including neurodegeneration (including Alzheimer's disease and Parkinson's disease), carcinogenesis, cardiovascular diseases, diabetes, rheumatoid arthritis, chronic obstructive pulmonary disease, inflammatory bowel disease, Wilson's disease, and Huntington's disease, among others [7]. This damage can be caused by various factors, including environmental stressors like radiation, chemical exposure, and biological agents, as well as internal processes such as oxidative stress from metabolism. The consequences of DNA damage are profound, as they can result in mutations, cell death, or the initiation of oncogenic pathways, ultimately affecting an organism's overall health. To assess DNA damage, various biological methods are employed [7-9]. The 8-OHdG ELISA test, which measures 8-hydroxy-2-deoxyguanosine levels in human serum or urine, serves as a sensitive biomarker of oxidative DNA damage. Additionally, the comet assay (single-cell gel electrophoresis) analyzes DNA strand breaks in human lymphocytes, providing insights into the extent of DNA damage at the individual cell level. Both techniques highlight the correlation between DNA damage and oxidative stress, making them valuable tools in understanding the impact of environmental and lifestyle factors on human health [7, 10-14].

Some experimental studies suggest the hypothesis that the MD, rich in fruits, vegetables, whole grains, fish, and healthy fats, may reduce human DNA damage due to its high antioxidant content. Antioxidants help combat oxidative stress, a key contributor to DNA damage. Studies have indicated that adherence to this diet correlates with lower levels of oxidative markers and improved genomic stability. Additionally, the anti-inflammatory properties of the diet may further contribute to genomic protection. These findings underscore the diet's potential role in promoting overall health [15-17].

However, the experimental data on the relationship between the MD and human DNA damage is limited, revealing a gap in international literature. Currently, there is no comprehensive understanding of how this diet may influence DNA damage. Research in this area remains scarce, leaving many aspects of this potential connection unexplored.

## OBJECTIVE

The aim of this study is to investigate the potential positive impact of the MD on reducing DNA damage. This mini narrative review addresses gaps in existing literature and enhances our understanding of this dietary pattern's role in cellular health and longevity. By analyzing current research, we can better comprehend the mechanisms through which the MD may contribute to DNA repair and protection. The importance of this mini review lies in its potential to inform dietary guidelines and public health initiatives, promoting the MD as a beneficial approach for mitigating DNA damage and improving overall well-being.

## MATERIALS AND METHODS

### *Design*

A mini narrative review was performed based on a synthesis of previously published literature. The material of the present study was exclusively Internet-based. A comprehensive electronic literature search in the databases PubMed and Google Scholar was performed (from 10 August 2024 to 10 October 2024) using the following terms/key words: «Mediterranean Diet» AND «DNA damage». In addition, a search in the reference lists was carried out.

Criteria for inclusion of studies were:

- Literature written in English
- Literature published from 2009 to 2024 (15 years)
- Studies that involved original research in volunteers
- Studies that had keywords in the title and/or abstract

Criteria for exclusion of studies were:

- Reviews
- Conference papers
- Book chapters
- Books
- Short surveys
- Articles and documents written in languages other than English

### *Selection of studies*

All references obtained from the search were organized and duplicates were excluded. The titles and

abstracts were screened for content and relevance to the topic with focus on the inclusion criteria. The integral text of selected titles was read, and the reference list of selected articles was consulted in order to find out other relevant publications. Additionally, studies which failed to adequately describe the potential positive impact of the MD on reducing DNA damage were excluded.

### *Data extraction and analysis*

The essential data from each published study was extracted and synthesized. The results are presented in a brief narrative form. Seven (7) research articles were obtained and analyzed.

## Results

Urquiaga et al. (2010) [15] assessed the impact of a MD versus an Occidental diet (OD) on oxidative damage in 42 male students (20–27 years) over three months, with additional red wine (240 ml/day) during the second month. The MD enhanced plasma vitamin C, β-carotene, and total antioxidant reactivity (TAR), while OD elevated vitamin E. Wine increased plasma vitamin C, β-carotene, uric acid, TAR, and polyphenols, but reduced vitamin E. The OD group had higher 8-hydroxy-2′-deoxyguanosine (8-OHdG) and plasma nitrotyrosine levels. Overall, the MD provided better antioxidant defenses and reduced oxidative damage compared to OD.

The study of Gutierrez-Mariscal et al. (2012) [16] examined the effects of dietary fat quality on oxidative DNA damage and the role of Coenzyme Q10 (CoQ) supplementation in elderly subjects. In a crossover design with 20 participants, subjects followed three diets: MD, MD with CoQ (Med+CoQ diet), and saturated fatty acids (SFA diet) for four weeks each. The SFA diet resulted in higher postprandial 8-OHdG levels, increased p53 mRNA, and reduced Mdm2 mRNA compared to Med and Med+CoQ diets ($p < 0.05$). The Med+CoQ diet decreased cytoplasmic p53 and nuclear p-p53 (Ser20) ($p < 0.05$), suggesting it improves oxidative DNA damage.

In the randomized controlled trial of Mitjavila et al. (2013) [17], 110 women aged 55-80 with metabolic syndrome (MetS) were assigned to a low-fat diet or two MD variations (MedDiet + olive oil or nuts). Over one-year, urinary levels of F2-Isoprostane (F2-IP) decreased in all groups, with a borderline significant reduction in MedDiet groups compared to the control. Urinary 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxo-dG) also decreased in all groups, with significant reductions in the MedDiet groups ($P < 0.001$). The study concludes that the MedDiet effectively reduces oxidative damage in MetS individuals.

A study of Erdrich et al. (2015) [18], involving 20 men with diagnozed prostate cancer who followed a modified MD for three months showed significant reductions in DNA damage compared to baseline ($p = 0.013$). Notable improvements were linked to increased intake of folate ($p = 0.023$), vitamin C ($p = 0.007$), legumes ($p = 0.004$), and green tea ($p = 0.002$). Conversely, higher red meat and dairy intakes were inversely associated with DNA damage ($p = 0.003$ and $p = 0.008$).

In the study of Luisi et al. (2019) [19], the MD, enriched with 40 g/d HQ-Extra Virgin Olive Oil (HQ-EVOO), was tested on 18 overweight/obese (BMI ≥25 kg/m$^2$) and 18 normal-weight controls (BMI 18.5–24.9 kg/m$^2$) over three months. Results showed significant reductions in myeloperoxidase and 8-hydroxy-2-deoxyguanosine, markers of inflammation and oxidative stress, across both groups. In cases, pro-inflammatory cytokines decreased, while IL-10 and adiponectin levels increased.

Frugé et al. (2021) [20] in a 12-week randomized controlled crossover trial evaluated the effects of green leafy vegetables (GLV) on colonic DNA damage and colorectal cancer risk in adults (BMI > 30 kg/m$^2$) with high red meat intake. Twenty-six participants were in the immediate intervention group (IG) and 24 in the delayed intervention group (DG). During the four-week intervention, daily GLV consumption resulted in increased plasma Vitamin K1 ($p < 0.001$) and decreases in circulating 8OHdG ($p< 0.001$), fecal 8OHdG ($p< 0.001$), and TNFá ($p < 0.001$).

The study of Acevedo-León et al. (2022) [21] investigated the association between adherence to the MD and oxidative stress (OS) markers in 80 colorectal cancer (CRC) patients. Using the 14-item Mediterranean Diet Adherence Screener (MEDAS), 51.2% of patients exhibited high MD adherence. These patients showed decreased 8-oxodG levels, increased glutathione peroxidase (GPX) and HDL–cholesterol, and a trend towards a lower GSSG/GSH ratio. High MD adherence correlated with a lower tumor histological grade and reduced synchronous adenomas. The findings suggest that adherence to the MD is protective against metabolic and oxidative DNA damage in CRC patients.

## Discussion

### *Synthesis of the studies*

Several studies highlight the protective effects of the MD against oxidative stress and DNA damage across different populations. Urquiaga et al. (2010) [15] demonstrated that the MD enhances antioxidant markers such as vitamin C and total antioxidant reactivity, effectively

reducing oxidative damage compared to an Occidental diet. Gutierrez-Mariscal et al. (2012) [16] found that MD combined with Coenzyme Q10 supplementation significantly decreased DNA damage indicators in elderly subjects, while Mitjavila et al. (2013) [17] reported significant reductions in oxidative markers among metabolic syndrome patients following MD, outperforming a low-fat diet. In a pilot study by Erdrich et al. (2015) [18], men with prostate cancer benefited from changes linked to a modified MD, marked by decreased DNA damage. Similarly, Luisi et al. (2019) [19] revealed that an MD enriched with high-quality extra virgin olive oil reduced inflammation and oxidative stress in both obese and normal-weight adults. Frugé et al. (2021) [20] emphasized the benefits of green leafy vegetables in lowering oxidative DNA damage in adults at risk for colorectal cancer. Finally, Acevedo-León et al. (2022) [21] reported that adherence to the MD correlated with lower oxidative DNA damage markers and improved metabolic profiles in colorectal cancer patients. Collectively, these findings reinforce the MD's role as a robust dietary strategy for enhancing antioxidant defenses and mitigating oxidative damage across diverse populations and health conditions (Figure 1) [15-21].

The studies reviewed share a common theme of investigating the protective effects of the MD against oxidative damage, particularly in relation to DNA integrity, inflammation, and overall health outcomes in diverse populations. Across various age groups and health conditions, ranging from young volunteers to elderly subjects and colorectal cancer patients, these studies consistently demonstrate that adherence to the MD is associated with significant reductions in biomarkers indicative of oxidative stress and DNA damage, such as 8-hydroxy-2'-deoxyguanosine (8-OHdG) and F2-Isoprostanes. The incorporation of additional healthful components, such as red wine and coenzyme Q10, enhances the protective benefits of the MD, further mitigating oxidative stress [15-21]. Moreover, the studies highlight that specific dietary elements, including high-quality extra virgin olive oil and green leafy vegetables, contribute to these positive outcomes by improving antioxidant defenses and inflammatory responses. The findings reinforce the MD's role as a beneficial dietary pattern for promoting antioxidant capacity, reducing systemic inflammation, and providing a protective effect against chronic diseases and oxidative damage. Collectively, these studies underscore the potential of dietary interventions rooted in the MD to improve health outcomes through the modulation of oxidative stress pathways and support further research in dietary strategies for disease prevention and management [15-21].

### *Strengths of the studies*

The studies collectively demonstrate robust methodological strengths, particularly in their focus on the MD and its relationship with oxidative damage. Most of the research employed controlled designs, including randomized controlled trials and crossover approaches, enhancing the reliability of results by minimizing confounding variables. A diverse range of participant demographics, including young adults, the elderly, women with metabolic syndrome, and colorectal cancer patients, allows for broader applicability of findings across different populations. The use of well-defined dietary patterns and supplementation (such as coenzyme Q10 and high-quality extra virgin olive oil) helps isolate the specific effects of these interventions on oxidative

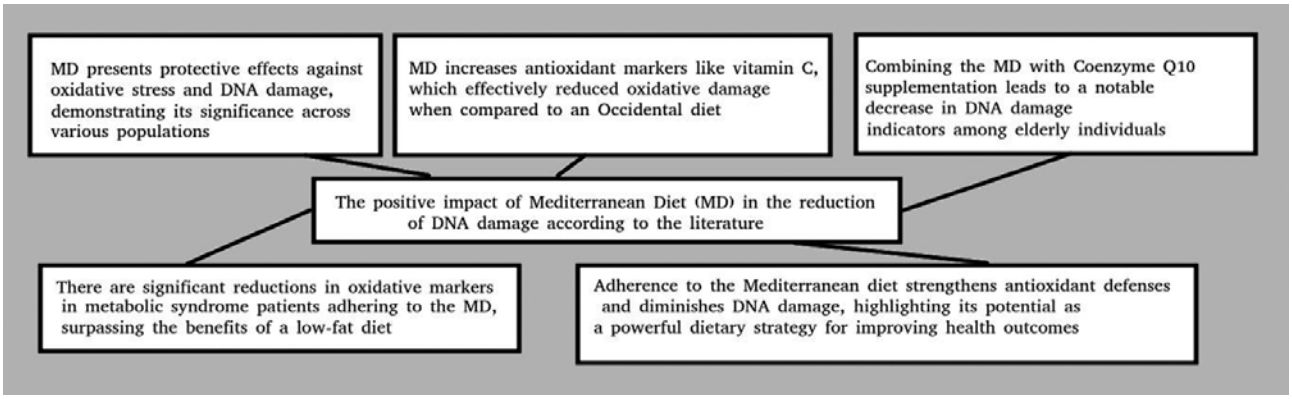


**Figure 1.** The positive impact of MD in the reduction of DNA damage according to the literature [15-21].

damage. Measurement of various biomarkers, such as 8-OHdG and estradiol, provides a comprehensive picture of oxidative stress and its implications for health. Additionally, some studies incorporate complementary assessments, such as gut microbiota analysis, which enriches the understanding of the MD's multifaceted benefits. Overall, the methodological rigor and diverse approaches utilized in these studies underscore the potential health advantages of the MD in mitigating oxidative damage and promoting better health outcomes across various populations [15-21].

### *Limitations of the studies*

The studies reviewed exhibit several limitations. Firstly, sample sizes varied, with some studies including as few as 20 participants (Erdrich et al., 2015), potentially limiting the generalizability of results [18]. The demographic homogeneity (e.g., age, gender, health status) of certain studies, such as Urquiaga et al. (2010), raises concerns about the applicability of findings to broader populations. Additionally, the short duration of interventions, typically ranging from 3 to 12 weeks, may not capture long-term effects or adaptations to dietary changes [15]. Temporal factors, such as seasonal variations in food availability, were not consistently controlled across studies, which could influence dietary composition and oxidative stress markers. Some studies relied on self-reported dietary intake, which is susceptible to recall bias (Acevedo-León et al., 2022) [21]. Additionally, cross-sectional and observational designs, like those seen in some studies (e.g., Mitjavila et al., 2013), limit causal inferences [17]. Variability in methods for measuring biomarkers of oxidative stress further complicates comparisons across studies. Lastly, the influence of confounding variables (such as lifestyle factors, physical activity, and concurrent medications) was not always accounted for, which may skew results related to dietary impacts on oxidative damage [15-21].

### *Future directions*

Future studies should focus on several key directions to deepen our understanding of the MD and its protective effects against oxidative damage. First, larger, multicenter randomized controlled trials are needed to establish the long-term impact of MD and its variations, such as those enriched with Coenzyme Q10 or high-quality olive oil, on diverse populations, including various age groups and individuals with different metabolic conditions. Second, investigations into the mechanisms underlying the effects of MD components, such as polyphenols, omega-3 fatty acids, and antioxidants, on DNA repair pathways and oxidative stress responses will provide insights into the biological processes involved. Additionally, exploring the interactions between diet and the gut microbiome will be crucial, as emerging evidence suggests that these factors may modulate inflammation and oxidative stress. Finally, research should examine the effects of dietary interventions in patients with specific conditions, such as cancer or metabolic syndrome, to tailor dietary recommendations that optimize health outcomes and reduce disease risk. These investigations will collectively enhance our understanding of the MD's role in promoting health and preventing chronic diseases through oxidative stress modulation [15-21].

## CONCLUSIONS

In conclusion, the body of research evaluating the MD highlights its significant protective effects against oxidative stress and DNA damage across diverse populations. Consistent findings from various studies demonstrate that adherence to MD correlates with reduced oxidative biomarkers, such as 8-OHdG and F2-Isoprostanes, indicating improved DNA integrity and lower inflammation levels. The inclusion of health-promoting components, such as extra virgin olive oil, green leafy vegetables, and coenzyme Q10, enhances these protective effects, further substantiating the MD's role in mitigating oxidative damage. Given the association between oxidative stress and numerous chronic diseases, these studies emphasize the MD as a beneficial dietary approach that promotes antioxidant capacity and supports overall health. The evidence advocates for dietary interventions grounded in the principles of the MD as viable strategies for disease prevention and health improvement. Future research should continue to explore the biological mechanisms underlying these protective effects and seek to establish practical guidelines for the implementation of the MD in various at-risk populations. Overall, MD emerges as a powerful tool for enhancing health outcomes, particularly in the context of oxidative stress and chronic disease management.

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# Managing cancer in the light of the COVID-19 pandemic

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**Abstract**

Since the emergence of the COVID-19 pandemic, several domains of healthcare delivery have been profoundly transformed and deprioritized in order to confront the unprecedented crisis. As with many other chronic health conditions, cancer patients have experienced to a great extent detrimental impacts on their routine management. Due to the pandemic, cancer screening programs were significantly interrupted, and treatment schedules were modified, leading to delayed diagnosis and worse outcomes overall. Furthermore, given their immunosuppressive status, cancer patients were disproportionately affected by COVID-19, resulting in increased morbidity and mortality. Scientific research, traditionally focused on oncology care, has been suspended, curtailing available treatment options and long-term development. Throughout this new era, massive efforts to mitigate adverse implications for cancer patients have deployed telemedicine to maintain universal and optimal care. In association with variations in digital literacy competencies and level of access to innovative technologies that complicate the immediate adaptation of telemedicine in oncology, considerable cancer-related health disparities have escalated and need to be addressed. The recent pandemic brought out several dysfunctions regarding the management of healthcare crisis. Thus, stakeholders should invest in preparedness plans and effective policies to confront future challenges without jeopardizing the continuum of cancer care.

**Key words:** *Cancer management; COVID-19; pandemic*

## INTRODUCTION

In December 2019, a novel coronavirus, Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-COV-2), was isolated in Wuhan, China, and was identified as the causative agent of Coronavirus Disease-2019 (COVID-19) [1]. The unprecedented worldwide spread of the virus urged the World Health Organization (WHO) to declare COVID-19 as a pandemic on March 11, 2020 [2]. Currently, the world has surmounted the global threat, but the pressure posed to healthcare and financial systems due to the COVID-19 pandemic is still apparent.

Globally, cancer –including solid tumors and hematological malignancies- is the second leading cause of mortality. As a result of the enormous "public health crisis" since the beginning of the pandemic in early 2020, many aspects of cancer care were dramatically affected, and health workers in the oncology community struggled to provide their patients with appropriate treatment in this challenging context of universal emergency concern. Over the last decades, substantial progress in oncology has been achieved through the early detection of new cases with screening and implementation

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of effective treatment modalities [3]. Unfortunately, the progress mentioned above has been endangered by the reallocation of healthcare staff and facilities. Despite all efforts to preserve resources, a detrimental impact on every aspect of cancer care remains a major concern.

Throughout the pandemic, cancer patients, by definition susceptible to infectious agents, experienced a higher risk of viral transmission and a disproportionate number of adverse outcomes including hospitalization, ventilation, and death [4]. The negative impact of the COVID-19 pandemic on oncologic patients was also reflected in the decline of cancer screening, the deceleration of cancer diagnosis rates, the increase in newly diagnosed cases at advanced stages, and the eventual rise in mortality. Hence, maintaining the cancer care continuum during the pandemic proved to be more than just a significant challenge for most oncologists, and medical societies instituted concrete recommendations to ensure best practices [5].

The present article aims to clarify the complex aspects of cancer management during the COVID-19 pandemic. Particular emphasis will be given to several factors that contributed to a "delayed" healthcare system regarding cancer management. Hopefully, patients and cancer caregivers can benefit from strategies designed to confront future challenges stemming from the recent pandemic, with a focus on preparedness from a global standpoint.

**Patients with cancer are vulnerable to COVID-19.**

Even though patients with cancer present a diverse clinical course of COVID-19 disease ranging from mild to extremely severe cases, they are indiscriminately designated as a susceptible population subgroup at increased risk of severe morbidity and mortality [4]. Apart from the immunocompromised status caused by the disease, the more significant weakening of their immune system derives from the cytotoxic treatments they receive either through chemotherapy, radiotherapy, or immunomodulatory agents. Further complexity in dealing with these patients arises due to the usually advanced age, overall impaired health status, and underlying chronic comorbidities such as diabetes, hypertension, and lung disease [6].

Significantly, a considerable confusion results from the difficulty of diagnosing COVID-19 infection in cancer patients, given that clinical signs of both diseases often overlap. To avoid underdiagnosis, reverse transcription polymerase chain reaction (PCR) and computed tomography (CT) scans are highly recommended to clarify the diagnosis among cancer patients [7].

Considering the increased risk of adverse outcomes for cancer patients, since late 2020, they have been prioritized to receive COVID-19 vaccination, including both primary and booster regimens. However, significant uncertainty remains regarding less effective immunological responses, and further clinical research is needed to establish the vaccines' efficacy among patients with cancer [8].

With the rapid spread of COVID-19, the overburdened hospitals, and frequent shortages of staff, equipment, and pharmaceutical supplies, clinicians faced ethical dilemmas regarding life support for patients infected by COVID-19 who also had a poor overall prognosis due to cancer per se. In fact, many practitioners inevitably discussed proactive palliative and end-of-life plans with patients in such difficult scenarios. Applying medical ethics in practice was paramount in delivering optimal treatment to most patients with the appropriate allocation of resources [9].

**COVID-19 and its impact on cancer screening programs**

Since 2020, national authorities worldwide have enforced restrictive measures towards interpersonal distancing to hinder the COVID-19 spread. Many cancer screening procedures have been disrupted and subsequently delaying the diagnosis of tumors that traditionally benefit from early detection, such as breast, colon, cervix, and prostate cancers [3].

The necessity to shift medical services to address the burden of COVID-19 and adaptations of policies to mitigate exposure, forced many cancer centers to temporarily decelerate screening programs for adults. Furthermore, out of fear of exposing themselves to the virus, people showed remarkable reluctance to attend healthcare appointments, as revealed by the increased cancellations and postponements of scheduled visits [10].

Significant declines in screening procedures have been noticed regarding invasive procedures such as colonoscopy, the cornerstone of colorectal cancer diagnosis, compared to the non-invasive mammography and Papanikolaou smear tests, tools for early detection of breast and cervical cancer, respectively [10].

It is of great interest in the context of colon cancer that many countries have adopted "neglected" alternative approaches to counteract the damage caused

by reduced surveillance colonoscopies. Integrating the fecal immunochemical test (FIT) to detect hidden blood in the stool, which can be efficiently performed even in the domestic setting, was associated with an additional colon cancer diagnosis rates [11]. Furthermore, many cancer institutions have adopted the option of computed tomography colonoscopy (CTC), a faster procedure that aligns with mandates of restricted patient-staff contact [12].

Data derived from a broad spectrum of oncology centers in different parts of the world brought to light the anticipated impacts of the curtailed screening programs, including the slower rate of precancerous lesion detection, upstaging at delayed diagnosis, increased unresectable or metastasized disease, more aggressive and complex treatment interventions, and eventually, increased mortality [13][14]. Managing advanced cancer stages at diagnosis requires more intense treatments, increasing healthcare costs. In extremely advanced cases, palliative care may be the only option instead of curative intention. Medical communities estimate that the financial burden and the workload of caregivers have been aggravated due to the surge of cancer diagnoses in the post-COVID era. Health systems' capacity has been temporarily overwhelmed and failed to meet patients' needs for optimal cancer care [15].

**Challenges of cancer treatment during the pandemic**

Delivering cancer treatment during the COVID-19 era presented unique challenges, and especially at the beginning of the pandemic, it was a subject of vigorous debate among clinical oncologists. At first, reductions in immunosuppressive treatment appeared as a sensible approach in order to protect cancer patients from contracting COVID-19 infection. On the other hand, maintaining intensive therapeutic protocols for patients with impaired immune systems in a time of uncertainty could endanger any possible benefit. In response to pragmatic needs regarding cancer treatment during the pandemic, stakeholders from medical societies published recommendations on patients' management during this complex and constantly evolving situation while assuring their safety, autonomy, and participation in the decision-making process [5].

Cancer experts, therefore, outlined three priority levels (high, medium, and low) to deliver strong guidance to patients and healthcare professionals regarding the degree of necessity for treatment. The decision-making process encompassed the tumor's aggressiveness, performance status, potential risks and benefits, and gains in terms of overall survival (OS), quality of life (QoL), and patient preferences [5]. Another critical issue to consider, while prioritizing cancer treatment and care intensity, was the epidemiological features and local Ro index (measure to estimate how many people would be infected by a single case) of the disease and the available resources [16].

Generally, all cancer patients should be provided with health education and be aware of any warning symptoms and signs of an underlying infectious process. Outpatient visits, during the COVID-19 era, were restricted to the most acceptable and safe level, mainly during the peak period of the epidemic.

It was recommended that patients requiring active treatment in the form of chemotherapy or surgery should receive timely, appropriate treatment to ensure curative outcomes. According to scientific bodies' advice and individual clinical judgment, delays in delivering treatment and elective surgeries should remain within safe time boundaries.

Furthermore, modifications to cancer treatment regimens to mitigate the risk of exposure to the virus emerged as practical, safe, and effective options. Such options included delivering extended dosing intervals of cancer, switching patients with stable disease from intravenous to oral route treatment, and considering intermittent chemotherapy for appropriate cases when scientifically justified [17].

Moreover, another critical issue was patients' mental health and psychological disorders that affected this population subgroup, leading to impaired chemotherapy adherence and a worse prognosis [18].

**Impact of the pandemic on cancer research**

Cancer researchers made substantial efforts to maintain their scientific work intact, provide innovative treatments and ensure patients' benefits during the pandemic. Scientific research projects in oncology also dealt with inevitable challenges during the pandemic due to limited or interrupted clinical trials worldwide [10].

During the COVID-19 pandemic, the imposed restrictions and measures affected the physical access of researchers to the laboratories resulting in a shortage of human staff dedicated to monitoring or enrolling new participants in clinical trials [19].

Moreover, oncology trials are, by default, extremely

demanding processes affecting patients and their families. Participation in a study requires considerable time allocation, travelling, and a meticulous record of signs and symptoms, which further inhibit patients´ recruiting, particularly in the context of a pandemic. Interestingly, a clinical trial implemented remote electronic consent (e-Consent) in order to maintain recruitment for research regarding prostate cancer patients [20]. Consistently, clinical trial stakeholders emphasized the importance of maintaining ongoing studies by reinforcing patients' safety and strengthening remote assessments via digital communication. Additionally, clear guidance was provided to prioritize Phase II and III trials but temporarily ceased the early phase ones [21].

**Use of telemedicine in oncology care during COVID-19 times**

The COVID-19 pandemic dramatically changed how healthcare was delivered worldwide, prompting healthcare providers to reframe the existing context. In a global effort to compensate for the disrupted medical services, adapting telemedicine as an alternative option rapidly began to expand worldwide. Telemedicine and teleoncology, in particular, are defined as medicine conducted remotely, a process that harnesses digital strategies to maintain the continuum of cancer care, improve cancer patients' access to treatment and reduce the travel burden [22].

Before March 2020, the use of telemedicine in oncology was limited, mostly to patients in remote areas. Additionally, telemedicine was treated with skepticism for several decades. Patients and caregivers crave detailed information about their disease, treatment plans, and interaction with their physicians, and a virtual visit might not fulfill this distinct need. However, given the new scene in healthcare delivery induced by COVID-19, many oncology societies and institutions recommended and adopted digital solutions to alleviate the multifaceted, adverse effects of the pandemic and tackle healthcare facilities towards universal coverage [22]. By definition, telemedicine is being conducted through various approaches, including phone calls, video calls, and remote patient monitoring [23].

The rapid escalation of telemedicine options during the recent pandemic highlighted its beneficial role in many aspects of cancer care. Specifically, telemedicine assures convenience, safety regarding the risk of exposure, and decreases health-related costs by reducing emergency visits and the need for travel, especially for residents in rural areas. Since most oncology institutions are usually located in big cities, telemedicine strategies to reach remote patients might also reduce geographical inequities [22].

The application of telemedicine during the recent pandemic received an enormous boost through its impact on cancer prevention, screening, and treatment. Interestingly, prevention campaigns for smoking cessation through mHealth (mobile health) are considerably effective strategies in most countries. Additionally, teleconsultation approaches to maintain cancer screening programs amid the pandemic were of paramount importance. Furthermore, medical organizations such as the European Society for Medical Oncology (ESMO) highly recommend integrating digital technology in patients' assessment regarding toxicity evaluation, dose regimens adjustment, symptoms management, and even supportive and palliative care approaches in end-stage disease [5][22].

The use of telemedicine during the SARS-CoV-2 pandemic waves promoted capacity building for many healthcare professionals through virtual training sessions focused on managing respiratory failure derived from COVID-19 infection. Remote monitoring of patients participating in clinical trials was also achieved through telemedicine [22].

It is of great interest that a considerable body of literature critically assesses and delineates patients' satisfaction with the transformed cancer care they receive. Promising results regarding telemedicine arose from a European multicenter study which enrolled 829 patients with various non-metastatic cancers and evaluated effects of remote monitoring of chemotherapy related side-effects through novel technologies. The reduction of symptom burden and enhanced health-related quality of life parameters in the intervention group favored remote monitoring systems [24]. Further evidence from published data demonstrates that virtual visits gain ground over in-person visits. Patients were satisfied and confident with the quality of care and considered telemedicine a safe and effective strategy during the epidemic [25][26]. The policy above might not fit with the diagnosis of a new cancer case that carries unique patterns of anxiety and depression and therefore demands extended in-person visits and particular psychological support [26].

Routine implementation of telemedicine policies addresses several barriers, including digital literacy and access variances. Disparities in digital literacy across

diverse demographics, including advanced age, lower socioeconomic status, and individuals of racial or ethnic minorities, build obstacles to the universal implementation of telemedicine and widen health inequalities. It has been postulated that a significant portion of the population owning digital devices like smartphones may still lack the skill to download applications for video visits or they do not even have an e-mail address at all. Furthermore, financial constraints to accessing technological devices further deteriorate the practical application of telehealth strategies. Additionally, impaired internet speed at different geographical locations may discourage patients and providers from adopting virtual visits [22].

Though inherent difficulties in navigating a relatively new model such as telemedicine are recognized, there is an urgent need to increase and maintain digital technologies beyond the recent pandemic. Prioritization of reducing telemedicine access inequities and getting acquainted with the digital world is essential for yielding optimum outcomes for cancer patients in the future.

**Proposal for cancer patient management**

The COVID-19 crisis instigated unexpected challenges to cancer care delivery. Healthcare systems, initially unprepared, were obliged to adjust their routine activities to compensate for the decline of medical services triggered by the pandemic. Consequently, a profound reorganization of oncology institutions, communities and cancer management overall, took place globally to accommodate current distinctive demands (Table 1).

At the beginning of the recent pandemic, the availability of healthcare for non-COVID-19 patients and specifically for cancer patients was significantly decreased in terms of screening, diagnosis, and treatment, especially in countries with a higher prevalence of COVID-19. The impact of haltered screening procedures and delayed diagnosis has been revealed and affected long-term mortality and survivorship [27].

Implementing vaccination programs and reducing COVID-related restrictions recently enabled oncology communities to recommence their routine activities. Interestingly, innovative strategies regarding cancer care, experimented with throughout the COVID-19 period, could serve as a blueprint for future pandemic strategies.

A fundamental principle during public health emergencies is prioritizing patients by urgency and fragility and better allocating available resources. Importantly, oncology healthcare resilience amid crisis demands preserving continuity of care and ensuring access to medical services.

In the current setting, it is imperative to promote cancer screening through increased public awareness and better health education via technology facilities. Broadcasting informational programs in mass media encourages compliance with screening programs. Moreover, supporting campaigns for preventive health

**Table 1.** *Problems and potential solutions regarding cancer patients management during the COVID-19 pandemic.*

| Problems | Potential solutions |
|---|---|
| Cancer patients´vulnerability to COVID-19 | Informational campaigns supporting intense vaccinating programs |
| | Safe hubs for cancer patients in institutions |
| Disrupted screening procedures | At home colon cancer test |
| Delayed diagnosis | Implementing less invasive procedures eg CT colonoscopy |
| Disrupted treatment protocols | Prioritization of the necessity of treatment |
| | Maintain delays within safe time boundaries |
| | Delivering extended dosing treatment, intermittent chemotherapy or switching from IV to oral route treatment when permitted |
| Limited cancer research | Prioritization of phase II and III trials |
| | Remote e- consent |
| | Remote monitoring systems |
| Digital illiteracy and access inequities | Digital education action plans |
| | Enhancing accessibility to telemedicine technologies, eg, smart phone applications, improved broadband coverage |
| Mental and psychological disorders aggravated | Telemedicine sessions to provide psychological support |

protocols to address patients' reluctance to present to oncology institutions due to fear of exposure warrants enhanced participation in screening and treatment procedures [11]. In the short term, oncology wards should designate safe cancer hubs to accommodate patients, meeting preventive and control needs.

Establishing alternative low-cost options of self-testing at home, within the patients' comfort zone, offers flexibility that ensures adherence to screening and counters impaired access to services of the underserved population [12]. Additionally, stakeholders should engineer outreach activity systems to track patients in communities and enhance their access to provided services to retain the stability of screening and diagnosis [15].

There is an urgent need to optimize telemedicine beyond the recent pandemic since appropriate integration of this relatively new technology in cancer care revealed the potential to mitigate significant challenges posed by COVID-19. Full utilization of telemedicine during the pandemic and rapid adaptation from patients and physicians, in many cases, emphasized the need for proper training and primarily for equitable access to continue inroads into universal health care. While facing difficulties needed to overcome, such as variances in digital literacy and access, it seems beyond doubt that telemedicine accounts for an innovative approach to cancer care delivery in terms of cost, convenience, safety, and satisfaction [23].

Unfortunately, a considerable proportion of the population failed to achieve adequate cancer care and precautions during the recent pandemic, including self-protection from exposure, optimal screening and treatment options, advanced technology for remote assessment, and psychological support. Furthermore, the COVID-19 pandemic brought health inequalities into focus, affecting to a greater extent diverse aspects of cancer care for racial and ethnic minorities as much as aged people or those of middle and low socioeconomic status. It is critical for medical communities and national authorities to resume collaboration and accelerate efforts to strengthen public health interventions, promote health coverage and minimize inequities in the post-pandemic era.

During the pandemic, the global health community learned that most issues regarding chronic conditions, such as cancer, derived from the lack of preparedness plan. At this time of recovery and rehabilitation, with the increased likelihood of impending pandemics, healthcare systems should further invest in designing wise approaches and feasible policies to deter future "disasters" without compromising essential functions such as qualitative cancer care.

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# Social Influence and Conformity: Clinical and Digital Perspectives on Group Dynamics and Compliance

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## Abstract

Social influence and conformity are fundamental topics in social psychology, impacting individuals' decisions and behaviors within group settings. This review explores the mechanisms of social influence, emphasizing the distinction between normative and informational influence. Normative influence is based on the need for social acceptance, while informational influence stems from the desire to make correct decisions in uncertain situations. The review also examines the application of these theories in clinical and digital contexts, highlighting the significance of compliance in healthcare settings and online environments. This review aims to provide a deeper understanding of how conformity shapes behavior across traditional and emerging platforms by bridging classical theories with contemporary applications. It addresses the complexities of social influence in diverse real-world contexts, offering insights into the underlying mechanisms governing social dynamics in face-to-face and digital interactions.


**Key words:** *Social influence; conformity; group dynamics; normative compliance; informational influence*

## INTRODUCTION

Human behavior influenced by social factors is a core subject of social psychology. Social influence, the process by which individuals adapt their behaviors, thoughts, or attitudes to align with those of others, has been widely studied for its significant impact on conformity, social identity, and group dynamics [1]. Early research on social influence focused predominantly on conformity in experimental settings, such as Asch's famous experiments (1955), which demonstrated that individuals often alter their decisions to align with majority opinions. While these foundational studies offer significant insights, their limitations must also be acknowledged. For instance, Asch's experiments were conducted in controlled settings that may not fully capture the complexities of real-world group dynamics, where multiple, often competing, influences coexist. Additionally, later research has questioned whether such rigid distinctions between normative and informational influence are always applicable, particularly in more fluid, digital environments [2]. The literature reveals a lack of consensus on how these mechanisms operate outside experimental conditions, highlighting a need for further exploration in diverse, real-world contexts.

However, despite the extensive research on social influence, there remains a gap in understanding how these mechanisms operate in diverse, real-world environments, particularly in clinical and digital contexts. While classic studies provide foundational insights into social influence and conformity, contemporary research has yet to fully integrate these theories with the rapidly changing dynamics of online interaction and healthcare

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settings. This literature review seeks to address this gap by exploring the complexities of social influence within the frameworks of group dynamics and compliance, offering a comprehensive analysis of how conformity shapes behavior across both traditional and emerging platforms. By bridging the gap between classical theories and modern applications, the review aims to provide a deeper understanding of the underlying mechanisms that govern social influence, with particular attention to digital environments and healthcare-related compliance.

**Main Theme**

Social influence operates through various mechanisms that shape individual behavior in group settings. Two primary forms of social influence are normative and informational influence [3]. Normative influence occurs when individuals conform to group norms to gain approval or avoid disapproval. This type of influence is driven by the need for social acceptance and a desire to fit in with the group. It is often associated with external pressures that prompt individuals to align their public behaviors with the majority, even if privately they may hold different views.

In contrast, informational influence arises from the individual's desire to make correct decisions or hold accurate beliefs. When people are uncertain about what is right, they tend to look to others as sources of valid information, especially in ambiguous situations. This form of influence leads to genuine internal changes in beliefs or attitudes, as individuals adopt the views of others, perceiving them as credible sources of knowledge.

One of the key distinctions between these two forms of influence is the type of pressure exerted on individuals. Normative influence typically involves direct social pressure, where the individual feels explicitly or implicitly compelled to conform due to fear of rejection or social isolation. This is commonly seen in face-to-face interactions, where social cues and peer pressure play a dominant role [4].

On the other hand, informational influence can be more indirect, as it relies on the assumption that others possess more knowledge or insight. This form of influence is often observed in situations where people seek guidance from experts, authority figures, or even the majority's behavior when they are unsure. For example, in digital environments, individuals may conform to widely accepted opinions or follow trends based on the belief that the majority's choices reflect objective reality.

The distinction between direct normative pressures and indirect informational pressures highlights the multifaceted nature of social conformity. While normative pressures might lead to surface-level changes in behavior for the sake of social harmony, informational influence can result in deeper, more lasting shifts in attitudes and beliefs. Understanding this difference is crucial for interpreting how social groups operate and influence their members.

**Methodology**

This manuscript employs a narrative literature review approach to synthesize existing research on social influence and conformity. Sources were identified through a comprehensive search of peer-reviewed journals, books, and authoritative websites. The literature review focused on identifying theoretical foundations, empirical studies, and practical applications of social influence in clinical and digital environments. Key databases included PubMed, PsycINFO, and Scopus, and search terms such as "social influence,""conformity,""digital environments," and "healthcare compliance" were used. The selection criteria prioritized studies published within the last decade to ensure relevance and incorporate recent advancements in the field.

**Theoretical Foundations**

Social influence is a dynamic process that affects an individual's mental activities, emotions, and behaviors, both at the individual level and within a social context [5]. Endocentrism, a core concept in social influence, refers to the changes in behavior made by individuals to fit their responses with those of others [6]. This phenomenon is often observed when individuals modify their actions to align with group norms, even when they privately hold different beliefs.

Empirical research has demonstrated a negative relationship between intellectual independence (or ego strength) and endocentrism. Individuals with higher intellectual independence are less likely to conform to group pressures, as they are more confident in their judgments and reasoning [7]. Conversely, those who display authoritarian tendencies are more prone to endocentric behavior, as authoritarianism is linked to greater submission to group norms and authority figures. Authoritarian individuals often value order, tradition, and obedience, which can increase their susceptibility to social influence [8].

More recent studies have expanded on the concept of endocentrism, identifying two distinct forms: rational

and irrational endocentrism [9]. Rational endocentrism occurs when conformity is guided by logical reasoning, judgment, and evidence. In contrast, irrational endocentrism, or herding behavior, is driven by instinctive responses and is often influenced by the behaviors or attitudes of others without thorough reasoning. This type of behavior is particularly evident in high-pressure or uncertain situations, where individuals rely on group behavior as a form of decision-making.

In terms of compliance and conformity, there are two key motivations: normative influence and informational influence. Normative influence leads individuals to conform to gain social approval or avoid disapproval, often resulting in external compliance without genuine belief change. Informational influence, however, arises when individuals accept information from others as evidence of reality, leading to internalized belief changes based on the perceived accuracy of the information [10].

In addition, studies have shown that certain factors such as authority, scarcity, reciprocity, and social proof significantly affect people's likelihood of conforming [11]. These factors contribute to both explicit and implicit forms of influence, where individuals may comply with a direct request or subtly alter their behaviors based on cues from their environment, such as advertisements or social interactions.

Recent research also highlights the role of authoritarianism in conformity. Authoritarian individuals are more likely to conform due to their preference for order and structure. Studies have linked higher levels of authoritarianism with increased susceptibility to normative pressures, which can lead to heightened conformity, especially in hierarchical or structured environments [12].

By exploring the intricate relationship between endocentrism, intellectual independence, and authoritarianism, researchers continue to uncover the various ways in which social influence affects individual behavior. This growing body of literature helps to clarify the mechanisms that drive conformity, providing valuable insights into both individual and group dynamics.

**Clinical Applications**

The concept of majority influence provides clear examples of conformity in everyday clinical and social settings. In clinical environments, patients may conform to treatment plans or health guidelines not necessarily because they believe in their efficacy, but due to normative pressures from healthcare providers or other patients. Group therapy sessions, for instance, often involve a form of social influence where individuals align their behaviors and expressed opinions with the group consensus. Although they may privately disagree, they conform publicly to avoid standing out or disrupting group dynamics.

While these mechanisms have been extensively studied in experimental and social contexts, their relevance extends far beyond theoretical discourse. In particular, the principles of social influence play a critical role in medical contexts, where compliance with medical advice often hinges on both normative pressures and informational cues. Patients often conform to doctors' recommendations due to the perceived authority of healthcare professionals, which is an example of normative influence. In addition, informational influence can also be observed when patients adopt health behaviors based on the belief that healthcare providers are offering accurate and credible advice, leading to internalized changes in health-related behaviors. For example, in chronic disease management, patients may comply with dietary and medication recommendations, even if they initially resist, because they come to trust the medical information provided to them.

Social proof, a powerful mechanism of social influence, is frequently used in public health campaigns to promote positive health behaviors. One prominent example is the promotion of vaccinations. Public health authorities often showcase high vaccination rates to persuade hesitant individuals that getting vaccinated is the socially accepted and "correct" choice. This tactic leverages informational influence, as individuals are more likely to comply with vaccination guidelines if they believe that the majority of the population has already done so, reinforcing the idea that it is a rational and beneficial choice.

Research shows that social proof can effectively increase compliance with public health measures by influencing people's perceptions of social norms. A study demonstrated how social influence could significantly affect online health campaigns, especially when combined with likeability and social validation mechanisms. This is particularly important in the age of digital health interventions, where health-related behaviors can be influenced by online communities and social media trends [13].

Additionally, the use of authority figures in healthcare, such as doctors or public health officials, often leads to higher levels of compliance through normative

influence. People tend to follow the advice of those they perceive as experts, whether due to the potential rewards of improved health or the fear of negative consequences from non-compliance, such as illness or social disapproval. This is particularly evident in the implementation of health policies like smoking cessation programs, where compliance is often driven by the endorsement of health authorities.

In summary, social influence has profound applications in clinical settings, from individual treatment adherence to the large-scale adoption of public health interventions. By understanding the mechanisms of normative and informational influence, healthcare professionals can enhance patient compliance and design more effective public health campaigns that encourage healthy behaviors across populations.

**Future Perspectives**

As the nature of social interaction continues to evolve, particularly with the rise of digital platforms and global communication networks, the study of social influence must adapt to these changing environments. Traditional theories of informational and normative influence remain relevant but require further exploration within the context of virtual interactions, where the dynamics of conformity may differ significantly from face-to-face encounters.

One promising area of future research is the role of algorithms in shaping social influence. Digital platforms, such as social media, use algorithms to curate the content that individuals are exposed to, often reinforcing majority opinions or amplifying particular viewpoints. This creates a unique form of informational influence, where users are more likely to adopt the views, they are repeatedly exposed to, perceiving them as representative of reality. Understanding how these algorithms affect conformity and compliance behaviors could offer valuable insights into the mechanisms of digital influence.

Additionally, the study of social identity in online settings is increasingly relevant. In digital communities, individuals can simultaneously belong to multiple social groups, some of which may have competing norms and values. This creates mixed-identity dynamics, where individuals must navigate the expectations of different groups. Future research could examine how social identity theory applies in virtual spaces, particularly how individuals reconcile conflicting group pressures and how this affects their behavior in both online and offline environments.

Another important direction for research is the interdisciplinary approach to social influence, integrating findings from neuroscience, psychology, and sociology. Advances in neuroscience offer new ways to study the cognitive mechanisms underlying conformity, such as how the brain processes social rewards or the neural correlates of group conformity. By combining these insights with sociological models of group behavior and psychological theories of influence, researchers can develop a more comprehensive understanding of how social influence operates across different contexts.

Furthermore, the increasing prevalence of online communities and the shift towards virtual interaction offer a rich field for studying the long-term effects of social influence. Digital platforms facilitate both majority and minority influence, often simultaneously, and allow for rapid shifts in public opinion. Exploring the long-term consequences of these digital interactions, particularly in terms of sustained behavior change and belief formation, could have significant implications for areas such as public health, political activism, and consumer behavior.

Lastly, the rule of reciprocity, one of the most powerful social forces, remains underexplored in the context of digital environments. In online spaces, where individuals exchange information, support, and even validation through actions like "liking" or "sharing," the mechanisms of reciprocity may operate differently than in face-to-face interactions. Future studies could explore how digital reciprocity influences conformity and compliance, particularly in cases where individuals feel socially obligated to align with the norms of their virtual communities.

In conclusion, as technology continues to reshape the way we interact, the study of social influence must also evolve. By integrating interdisciplinary approaches and focusing on the unique dynamics of digital platforms, future research can provide deeper insights into the processes that drive conformity, compliance, and group dynamics in the modern world.

**DISCUSSION**

The process of social influence is multifaceted, with various outcomes depending on the context and the individuals involved. Group consensus often serves as a foundation for decision-making, leading individuals to believe that their judgments are more accurate when they align with the group. This consensus provides a sense of social acceptance and helps individuals main-

tain a positive self-image by avoiding being perceived as deviant or stubborn.

In recent years, the rise of digital media has significantly altered the landscape of social influence. Online communities and social networks have become powerful platforms where normative and informational influence operate at an accelerated pace. Digital platforms enable individuals to connect with larger, more diverse groups, where social norms are quickly established and disseminated. The instantaneous nature of online interactions facilitates rapid conformity, as people are exposed to real-time feedback from peers, influencers, and larger audiences.

On social media, individuals often conform to perceived majority opinions or trending topics to avoid social isolation or criticism. This phenomenon is particularly evident in the behavior of "likes" or "shares," where users align with popular opinions to gain social validation. The informational influence in online environments is also heightened because individuals perceive opinions shared by influencers or large groups as more credible, leading to internalized belief changes. This process has been observed in movements related to public health, political activism, and even consumer behavior, where social proof and authority are leveraged to shape public opinion.

Furthermore, the dynamics of mixed-identity groups, where minority and majority identities coexist, present unique challenges to conformity. Research has shown that majority groups tend to provoke public compliance, while minority groups are more likely to influence private acceptance. In a mixed-identity group, individuals may publicly conform to the majority's opinions to avoid conflict or negative identification, while privately agreeing with the minority's stance. This dual pressure creates a complex dynamic where individuals must navigate both external social norms and internal beliefs.

Minority influence is often more impactful in terms of long-term attitude changes, as individuals exposed to minority viewpoints tend to reflect more deeply on their beliefs. Conversely, majority influence typically results in surface-level behavior changes aimed at maintaining social harmony. For instance, in political discussions, an individual might publicly express support for the dominant political party in their community, even if they privately disagree. This behavior underscores the power of normative influence in mixed-identity groups.

The digital environment amplifies these dynamics, as individuals are frequently exposed to both majority and minority opinions simultaneously. Online platforms, where anonymity and reduced accountability are possible, can foster dissident behavior where individuals express minority opinions more freely. However, in more visible settings, such as social media profiles linked to personal identities, individuals may still conform publicly to majority norms while harboring different private views.

The influence of digital media on social conformity continues to evolve, with important implications for understanding group dynamics in virtual settings. Future research should explore how compliance techniques and social validation mechanisms, such as "likes" or "comments," impact conformity in these environments. Additionally, studies could examine the role of algorithms in shaping exposure to majority and minority opinions, as well as their potential to reinforce social conformity or encourage diversity of thought.

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# Tetanus: A disease that should not be overlooked

Efstathios Karakasidis

**Abstract**

Tetanus is a bacterial disease caused by *Clostridium tetani*. It has become preventable and is rare in recent decades due to vaccination and advances in medical care. Tetanus presents with neurological symptoms and lacks a specific cure, apart from treatment according to the presenting symptoms. The purpose of this narrative review is to raise physicians' awareness about tetanus as early treatment is highly important for survival and to review the epidemiology, pathophysiology, symptoms, and treatment options of tetanus.

**Key words:** *Tetanus; spasms; internal medicine*

## INTRODUCTION

Tetanus is a non-communicable disease caused by the gram-positive anaerobic bacterium *Clostridium tetani* which is mainly found in soil [1,2], as well as in the feces of some mammals such as horses, cows, sheep, rats, and pigs [3,4]. It is transmitted to humans via minor wounds. However, in a substantial percentage varying between 20% and 50% no obvious site of entry is recognized [1,2]. The incidence of this disease varies worldwide, and it is more prevalent in developing countries, especially in the farming community [5,6], and reaches mortality rates up to 100% if left untreated [7]. In this narrative review, we aimed to summarize the epidemiology, basic pathophysiological features, and treatment options for tetanus.

## MATERIALS AND METHODS

This literature review aims to highlight the main aspects of the diagnostic approach and treatment of tetanus in the everyday clinical practice of clinicians, as in most cases the patients seek help from different specialists. A non-systematic approach was employed, searching the Medline and Scopus databases from July 2024 to August 2024 for relevant articles. The primary keywords used included: "tetanus", "symptoms", "clinical presentations", "epidemiology", "treatment" and "pathophysiology", while Boolean operators ("AND", "OR") were also used. The existing literature has been reviewed, including original articles, reviews, meta-analyses, and case reports. Only full-text accessible articles published in English were included while articles in other languages were excluded. By screening the references of included articles using the snowball method, additional articles were retrieved. From these, we selected the most representative and high-impact articles for inclusion.

### Epidemiology

The spores of *C. tetani* can remain viable for several months due to their resistance to high temperatures and stability under ambient oxygen tension. Common antiseptics such as ethanol, phenol, and formalin are ineffective in their elimination, whereas iodine or hydrogen peroxide are effective ways to eradicate them [4]. Autoclaving at 120°C for 15 min is another effective method [3]. The incubation period of tetanus varies from one day to several months, with most cases occurring within eight days of exposure. The closer the

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site of spot entry of spores is to the central nervous system the shorter the incubation period tends to be [6]. Several factors such as urbanization, agricultural activities, especially in summer that enable direct exposure to soil due to light dressing, environmental factors (humidity and temperature), and socioeconomic factors, such as poverty, poor hygiene, and lack of health services, significantly influence tetanus incidence [8,9]. People over 60 years old are at high risk for tetanus, given that vaccine-induced antibody titers decline over time and because they might have been born before vaccination programs. However, cases of both generalized [10-14] and localized [15] tetanus have been reported in patients with adequate anti-tetanus antibodies who have been vaccinated. Although complete vaccination does not seem to guarantee immunity, it is associated with better clinical outcomes [16]. In addition to advanced age, diabetes, immunosuppression, and intravenous drug use are well-known risk factors for tetanus [1,2].

In 2019, 73,662 cases of tetanus and 34,684 related deaths were reported, with most of them occurring in low- and middle-income countries. In contrast, tetanus is rare in high-income countries [17,18,19]. Interestingly, 50% of all tetanus cases reported in 2019 in high-income countries involved people over 70 years old [19]. The majority of cases and deaths during both the neonatal and non-neonatal periods occurred in South Asia and Sub-Saharan Africa [19,20]. A meta-analysis revealed that the fatality rate of tetanus in Africa is 43.2%, indicating that the sociodemographic index is inversely associated with tetanus incidence and mortality [6,19]. Epidemiological studies have shown that neonatal tetanus has contributed significantly to global tetanus cases. In 1990, 370,885 out of 615,728 (60.24%) cases of tetanus occurred in the neonatal period, while in 2019 27,171 out of 73,662 (36.89%) cases were neonatal [19].

Over the last three decades, mortality due to tetanus has declined dramatically. In 1990, tetanus was the 41$^{st}$ cause of death and in 2021, it dropped to the 113$^{th}$ [21]. In 1990, there were 275,381 confirmed deaths due to tetanus which declined to 62,866 and 34,684 in 2010 and 2019, respectively [17]. Kyu et al reported a significant decline in both neonatal and non-neonatal tetanus deaths between 1990 and 2015, with neonatal deaths decreasing by 90% and non-neonatal deaths by 81% [20]. An important finding is that neonatal tetanus accounts for a substantial proportion of tetanus-related deaths. In 2010, 57% of the deaths (35,580/62,866) and in 2015, 35% (19,937/56,743) occurred during the neonatal period [17,20]. This high percentage of neonatal tetanus cases and deaths can be attributed to the inability of health systems to provide immunization and sterile conditions during and after birth [20]. The difference in tetanus mortality rates between low- and high-income countries of 54.3% and 35% respectively, as well as the decline in deaths, can be attributed to immigration of populations from rural to urban areas that resulted in decreased exposure to tetanus spores, widespread vaccination of children, adults, pregnant women and women of reproductive age. Better living conditions, differences in medical staff and knowledge and early treatment have also played a significant role. In addition, societal factors such as religious tenets, cultural beliefs and traditional healers may act as barriers to immunization and effective wound care [1,5,6,22]. In 2023, 84% of infants worldwide received three doses of diphtheria-tetanus-pertussis (DTP)- containing vaccine [23]. The differences in medical practice include improvements in wound care, the administration of tetanus immune globulin, ICU facilities, closer monitoring, and pharmacological interventions, and improvements in hygienic delivery practices and umbilical cord care [1,19]. Importantly, the disruption of vaccination programs such as natural disasters or conflicts can affect the incidence of tetanus both in the short term due to hygiene conditions and in the long term as people are more vulnerable to future infections [2].

**Pathophysiology**

*C. tetani* spores are introduced into the human body through a wound and, under favorable anaerobic conditions [4], convert to a vegetative form [10]. After autolysis, the bacteria produce [24] two toxins called tetanospasmin and tetanolysin and a protein called collagenase. Tetanospasmin, also known as tetanus toxin, is encoded on a plasmid and consists of a heavy chain that is responsible for binding and entrance to neurons and a light chain that mediates the inhibition of presynaptic neurotransmitter release [10]. This toxin cannot cross the blood-brain barrier [14]. Collagenase affects bacterial growth and toxin production [10,26], while the role of tetanolysin in the pathogenesis of tetanus remains unclear [10].

Tetanospasmin enters the motor neuron axon terminal via endocytosis at the neuromuscular junction. It

is then transported retroaxonally to the spinal cord and brainstem, where it binds to nerve terminals, thereby affecting all parts of the body beyond the initial site of infection [7,24,26]. Then, it is transcytosed into inhibitory interneurons [24], and cleaves a protein called vesicle-associated membrane protein 2 (VAMP2) also referred to as synaptobrevin 2 [27], thereby inhibiting the release of Gamma-aminobutyric acid (GABA) and glycine and resulting in sympathetic overactivity and spasticity [7,24,26,28]. The toxin affects both motor and sensory nerves, but it does not impair mental status, as patients remain conscious [26,28].

**Clinical presentation**

There are four forms of tetanus: 1) generalized 2) neonatal 3) local and 4) cephalic [7]. The symptoms of tetanus differ among generalized, local, and cephalic. Trismus is frequently the initial symptom in all forms of tetanus because cranial nerves have a high affinity for tetanospasmin and toxin is rapidly delivered to the brainstem and spinal cord due to their close anatomical connection [7,26]. Cephalic tetanus, while quite rare, can be associated with head lesions or chronic otitis media and presents with cranial nerve palsy 1 to 2 days after infection [2,29]. Local tetanus is associated with low toxin load and in 2 out of 3 cases evolves into generalized tetanus because tetanus neurotoxin continues being produced and released for days resulting in a general distribution [26]. Generalized tetanus is the classic form of the disease and accounts for more than 80% of cases. It gradually begins approximately 3 to 21 days after the infection, with symptoms typically worsening over a week [29].

The first symptom of tetanus is flaccid paralysis with the craniofacial muscles first affected followed by the trunk and finally, the limbs, which are less severely affected [3,7,10]. Spasms can be triggered by a stimulus (auditory, tactile, or visual) and can affect all muscle groups. The typical symptoms of tetanus apart from trismus are opisthotonus and risus sardonicus. Tetanus toxin can affect both the pharyngeal and laryngeal muscles causing dysphagia, aspiration, and respiratory failure as well as abdominal rigidity [2,7]. Tetanospasmin inhibits the release of neurotransmitters in the spinal cord, brainstem, and thoracic sympathetic ganglia thereby affecting the inhibition of adrenal release of catecholamines resulting in excitability of the sympathetic nervous system due to increased levels of noradrenaline and adrenaline in the blood circulation [2,26,30]. As a result, the patient suffers from autonomic dysfunction in the second week after the onset of symptoms. The symptoms include hypertension, tachycardia, and sweating that follow symptoms of the motor system. Notably, rapid fluctuations in blood pressure as well as bradycardia can occur thereby complicating the management of the patient [2,7,30]. Although in the past the majority of deaths were attributed to respiratory insufficiency due to the act of tetanus toxin, currently because of advancements in intensive care most patients with tetanus pass away due to autonomic dysfunction [2,7]. Apart from the motor nerves, tetanus toxin also affects the sensory nerves causing altered sensations, such as pain and allodynia [7]. Other unusual symptoms are diplopia, nystagmus, and vertigo that result from neuronal inactivation [7]. Because of the severe muscle spasms, the patients can suffer from fractures of the spinal or long bones, tendon avulsion, hyperpyrexia, pneumonia, pulmonary emboli, and rhabdomyolysis that can cause acute kidney injury [3-5]. All these complications contribute to the high fatality observed in severe tetanus cases.

Predictors that negatively affect the outcome of the patients are an incubation period of less than seven days, an interval between the first symptom and the first muscle spasm of less than 48 hours, age over 60 years, physical status, the presence of sepsis and severe autonomic dysfunction [2,3,6,26]. Other factors that significantly affect survival are lower wound debridement, the presence of abdominal rigidity and aspiration pneumonia, the need for high sedation, severe tetanus requiring neuromuscular blockade, and mechanical ventilation [3, 6].

**Diagnosis - Differential diagnosis**

Tetanus should be suspected in a patient with a history of antecedent tetanus-prone injury, especially if medical help was not sought and a history of inadequate immunization for tetanus is present. However, other diseases should be excluded (Table 1).

There is no specific laboratory test for the diagnosis of tetanus which is based on clinical suspicion and manifestations. Anti-tetanus antibody levels cannot be used for tetanus diagnosis but they can be used to consider the likelihood of diagnosis with a level up to 0,1 IU by standard ELISA can be protective and therefore the likelihood of tetanus can be considered unlike, but the diagnosis cannot be excluded [1,2].

**Table 1.** *Differential diagnosis of tetanus.*

| |
|---|
| Stroke |
| Hypocalcemia |
| Oropharyngeal and mandibular pathologies |
| Botulism |
| Epileptic seizures |
| Drug-induced dystonia |
| Malignant neuroleptic syndrome |
| Stiff-man syndrome |
| Strychnine poisoning |
| Meningoencephalitis |
| Subarachnoid hemorrhage |
| Alkalemia |
| Intracranial lesions |
| Drug withdrawal |
| Psychiatric disorders (conversion reactions) |
| Acute abdomen |

## Treatment

The severity of the disease is assessed by the Ablett score (Table 2). The Ablett score ranges from 1 to 4, with grades 1 and 2 indicating that mechanical ventilation may not be needed while grades 3 and 4 require mechanical ventilation [31,32].

The first step of treatment in a patient with suspected tetanus infection is to place them in a room without light or noise that may provoke spasms. Additionally, proper cleaning and debridement of necrotic tissue must be performed to reduce the bacterial load and prevent bacterial growth [4,29]. Benzodiazepines such as diazepam, midazolam, and lorazepam should be administered to control muscle spasms and induce sedation and anxiolysis [5,10,29]. The most popular option of these drugs is diazepam, which is inexpensive and available in many resource-limited settings where tetanus is a significant public health problem [5]. The dosing of this drug should be adjusted according to the patient's clinical response due to its potential toxicity. There is a risk of inducing metabolic acidosis due to preservative propylene glycol [5], withdrawal symptoms (aggressive behavior and noncooperation), and venous thrombosis that can complicate the treatment of the patient [25]. Tolerance to benzodiazepines is frequently observed, and propofol can be used as an alternative drug to induce sedation [5,10,33]. This drug is a GABA-A agonist with sedative, anxiolytic, anti-inflammatory, and anticonvulsant properties [34–36] that has a rapid onset of action and short half-life (30-60 min after infusion) [34]. Administration should be performed with caution, as propofol can induce the severe propofol infusion syndrome. This syndrome is characterized by high anion gap metabolic acidosis, rhabdomyolysis, hyperkalemia, acute kidney injury, hypotension, and bradycardia. Other adverse effects of propofol include pancreatitis and hypertriglyceridemia [34-37].

**Table 2.** *Ablett classification of tetanus severity.*

| Grade | Clinical features |
|---|---|
| 1 | Mild: Mild trismus, general spasticity, no respiratory compromise, no spasm, no dysphagia |
| 2 | Moderate: Moderate trismus, rigidity, short spasms, mild dysphagia, moderate respiratory involvement, respiratory rate 30 breaths/min |
| 3 | Severe: Severe trismus, generalized rigidity, prolonged spasms, severe dysphagia, apneic spells, pulse >120 beats/min, respiratory rate > 40 breaths/min |
| 4 | Very severe: Grade 3 with autonomic dysfunction |

For the treatment of tetanus, antibiotics are also used to prevent the generation of tetanospasmin through the killing of bacilli. The antibiotics used are metronidazole 500 mg intravenously every 6-8 h for 7-10 days or alternatively penicillin G 2–4 million units intravenously every 4–6 h [10,29]. Metronidazole is preferred over penicillin because penicillin produces a non-competitive voltage-dependent inhibition of GABA-A receptors obtunding postsynaptic inhibitory potentials that can potentiate the action of tetanospasmin and can induce seizures [25,38]. Another drug that is commonly used for the treatment of tetanus is magnesium sulfate which is administered intravenously. It is a calcium antagonist causing vasodilation, presynaptic neuromuscular blockade, and prevention of catecholamine release helping in controlling the spasms and autonomic dysfunction [2,9,29]. Its administration is not associated with a lower need for mechanical ventilation [39] or changes in mortality in patients with tetanus [40], but it does reduce the need for other drugs to control muscle spasms and cardiovascular instability [39]. However, the administration of magnesium can have some adverse effects such as loss of the patellar reflex, hypocalcemia, excessive

sedation, hypotension, and muscle weakness resulting even in respiratory failure [9,40]. To deal with the spasms also neuromuscular blockers such as pipecuronium, vecuronium, and pancuronium can be used [5]. In case spasms cannot be controlled with the administration of the aforementioned drugs, intrathecal baclofen can be administered [5,41]. Baclofen is a GABA-B receptor agonist that cannot cross the blood-brain barrier, so it is administered intrathecally [41,42]. Its adverse effects include drowsiness, weakness, dizziness, nausea, confusion, and hypotension. Its dosage should be decreased gradually as its sudden cessation might induce severe withdrawal symptoms such as excessive spasticity, fever, and malignant syndrome. On the other hand, overdose may result in coma which is reversible with flumazelin administration [41,42].

For the treatment of autonomic dysfunction β blockers, clonidine, and morphine are used because of their sedative effects. Morphine sulfate maintains cardiac stability, decreasing blood pressure and heart rate without deleterious effects on cardiac performance. It replaces endogenous opioids and reduces reflex sympathetic activity and histamine release [43]. In the past, propranolol was used but nowadays it is not recommended because it can cause hypotension and sudden death [29,43]. It is replaced by labetalol that has a dual effect on α- and β- receptors, and esmolol, which has a short time of duration and whose effects in blood pressure and heart rate are reversible [43].

Furthermore, human tetanus immune globulin (TIG) should be administered intramuscularly into either the deltoid muscle or the lateral thigh muscle. TIG acts by binding unbound tetanus toxin, thereby preventing disease progression [29,44]. Studies have shown that there is no benefit from the intrathecal administration of tetanus immunoglobulin. When human tetanus immunoglobulin is unavailable, equine antitoxin can be used at doses of 1500–3000 IU intramuscularly or intravenously [10]. Potential advantages of human TIG include its longer half-life and fewer hypersensitivity reactions than equine antitoxin in which hypersensitivity reactions are observed in 20% of cases in which it is administered [33,44]. Recovery from tetanus does not confer immunity and as a result, all patients should be given three doses of tetanus and diphtheria toxoid at least two weeks apart, immediately upon diagnosis [10]. Contraindications for the administration of tetanus toxoid vaccination are fever or acute infection at the time of vaccination request, a history of an allergic reaction to a previously given tetanus vaccine/booster, and hypersensitivity to any element of the vaccine, including the thimerosal component [44]. The pharmacological choices for the treatment of tetanus are summarized in Table 3.

Due to muscle spasms, autonomic dysfunction, pyrexia, and critical illness, patients have high nutritional

**Table 3.** *Pharmacological treatment of tetanus.*

| Mechanism | Class of medication | Drugs |
|---|---|---|
| Muscle spasms control | Benzodiazepines | Diazepam, Midazolam, Lorazepam |
| | GABA-B receptor agonist | Baclofen (Intrathecal) |
| | Neuromuscular blockers | Pipecuronium, Vecuronium, Pancuronium |
| | Calcium antagonist | Magnesium sulfate |
| Autonomic dysfunction management | Beta-blockers | Labetalol, Esmolol |
| | Calcium antagonist | Magnesium sulfate |
| | Others | Morphine, Clonidine |
| Prevention of disease progression | Antibiotics | Metronidazole, Penicillin G |
| | Immunizing agents | TIG, equine antitoxin |
| Sedation and anxiolysis | GABA-A agonist | Propofol |
| | Benzodiazepines | Diazepam, Midazolam, Lorazepam |
| Anti-inflammatory and anticonvulsant properties | GABA-A agonist | Propofol |

**Abbreviations:** GABA, Gamma-aminobutyric acid; TIG, Tetanus Immune Globulin

needs. Early nutritional support and adequate fluid resuscitation are therefore essential [4,25]. The preferred route of administration is enteral feeding, necessitating the placement of a nasogastric tube [4,25]. Central venous nutrition is necessary if severe abdominal spasms or ileus are present [4].

Notably, in most cases, patients with tetanus should be admitted to the intensive care unit as it is easier to manage complications of both the disease mainly that of the airways and the drugs administered [10]. Nakajima et al examined the treatment course of 499 patients with tetanus in Japan. They reported that half of the patients required mechanical ventilation, with the majority of them (80.6%) needing it in the first three days after admission and 77.5 % undergoing tracheostomy. They pointed out that despite the low mortality rate the patients required either a long hospital stay or nursing care in facilities other than their homes [8]. Deep sedation and paralysis with artificial ventilation in an ICU have its drawbacks. The patient may require prolonged periods of intubation and ventilation, increasing vulnerability to ventilator-associated pneumonia, tracheal stenosis, difficulty in weaning and adult respiratory distress syndrome, paralytic ileus, weight loss, atelectasis, deep vein thrombosis, and pressure sores [5,25].

## CONCLUSIONS

Tetanus is caused by the bacterium *Clostridium tetani* and mainly presents with neurological symptoms. Despite being a more common disease in developing countries, tetanus cases still occur in developed countries. Therefore, clinicians should remain vigilant, as prevention and early diagnosis are critical to improving disease course and outcomes.

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CASE REPORT ACHAIKI IATRIKI | 2025; 44(3):151–154

# Short-term therapeutic response to obeticholic acid in patients with primary biliary cholangitis: A case series from the University General Hospital of Patras

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## Abstract

**Introduction:** Obeticholic acid (OCA) is a synthetic derivative of chenodeoxycholic acid that has been approved for the treatment of patients with primary biliary cholangitis (PBC), particularly those with an inadequate response to ursodeoxycholic acid (UDCA). This case series presents the early biochemical response and tolerability of OCA in two patients with PBC followed at our hospital.

**Materials and Methods**: A prospective observational follow-up was conducted on two female patients with PBC receiving treatment with OCA in addition to UDCA at the University Hospital of Patras. Data was recorded and analyzed regarding patients' status before treatment, any previous treatment received, as well as patients' therapeutic response in the first six months of treatment.

**Results**: The patients had no findings of advanced liver disease on liver elastography and were asymptomatic at treatment initiation. Both patients had elevated alkaline phosphatase (ALP) levels, while one patient also exhibited increased aspartate aminotransferase (AST), alanine aminotransferase (ALT) and gamma-glutamyl transferase (γ-GT). Patients were re-evaluated within six months of the onset of treatment. Biochemical response with reduced ALP and γ-GT levels was observed in both patients. One patient reported mild nocturnal pruritus after OCA initiation; however, treatment was not discontinued.

**Conclusions**: The combination therapy of UDCA and OCA in these patients with PBC contributed to the improvement of liver biochemical markers while no significant complications occurred within six months of treatment onset.

**Key words:** *Obeticholic acid; ursodeoxycholic acid; primary biliary cholangitis; clinical benefits*

## INTRODUCTION

Primary biliary cholangitis (PBC), previously known as primary biliary cirrhosis, is a chronic cholestatic liver condition characterized by autoimmune destruction of intrahepatic bile duct epithelial cells, prompting the onset of cholestasis which may ultimately result in hepatic fibrosis, cirrhosis, and decompensated liver disease. Typical symptoms include pruritus and fatigue, with jaundice and abdominal pain being less common. Several patients may remain asymptomatic for years before symptoms arise [1]. Serological positivity for antimitochondrial antibodies (AMA) is a hallmark for PBC

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diagnosis when combined with abnormal serum liver tests. In AMA negative patients, the diagnosis of PBC can be made based on positive PBC specific antinuclear antibodies (ANA) detected by immunofluorescence (nuclear dots or perinuclear rims) or ELISA (sp100, gp210) results. Liver biopsy is not required for the diagnosis of PBC and is reserved for patients without PBC-specific antibodies or when comorbidities, such as autoimmune hepatitis (AIH) or metabolic dysfunction-associated steatohepatitis (MASH), are suspected [2].

First-line treatment for PBC is ursodeoxycholic acid (UDCA), regardless of the disease stage. UDCA treatment has been reliably shown to improve biochemical markers, slow histologic progression, delay the appearance of esophageal varices, and enhance transplant-free survival in patients with PBC, while also being well tolerated [3]. However, many patients show an incomplete response to UDCA monotherapy and require combined therapy with second-line medications. Obeticholic acid (OCA) is a synthetic derivative of chenodeoxycholic acid which was approved for the treatment of patients with PBC in 2016. Although OCA is generally well tolerated, patients may experience side effects such as pruritus. Contraindications of OCA use include advanced cirrhosis, portal hypertension and a history of liver decompensation [4]. However, clinician experience with OCA prescription for PBC remains limited.

## CASE SERIES

This case series includes a prospective follow-up of patients with PBC receiving treatment with OCA at the University Hospital of Patras. Patient data were collected and analyzed, including baseline status, prior treatments, and therapeutic response within the first six months of OCA therapy. OCA treatment was initiated in two patients with PBC. Both were females, aged 48 and 58 years respectively, and were receiving treatment with UDCA after being diagnosed with PBC. Results from liver elastography showed no evidence of advanced liver disease in either patient. Both were under treatment with statins due to dyslipidemia and calcium due to osteoporosis, with no other serious comorbidities. Both patients were asymptomatic, with elevated alkaline phosphatase (ALP) and gamma-glutamyl transferase (γ-GT) levels. Additionally, one patient also had elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT) levels (Table 1). ALP ≥ 1.67 × upper normal limit (ULN) is a threshold commonly used for the definition of inadequate response to UDCA, and patients who do not achieve this target after 12 months of therapy can be considered for second-line treatments of PBC [5]. Both patients exhibited ALP>1.67 ULN after treatment with 750mg UDCA for six years and 1000mg for 1.5 year, respectively. Both patients were prescribed OCA treatment 5mg once a day along with UDCA and were re-evaluated six months after OCA onset.

Biochemical response was observed in both patients after six months of treatment, with a reduction in both ALP and γGT levels. ALP was reduced to <1.67 ULN in both patients. One patient reported mild nocturnal pruritus two months after treatment initiation, but the side effect was not severe enough to require treatment discontinuation. No other clinical or laboratory side effects were observed during patient follow-up.

## DISCUSSION

This prospective observational study evaluated the therapeutic response of two patients with PBC who received OCA. Over a six-month period, both patients demonstrated significant improvements in liver bio-

**Table 1.** *Liver biochemistry markers of patients before and six months after OCA initiation.*

| | Normal lab values | Patient 1 before OCA initiation | Patient 1 six months after OCA initiation | Patient 2 before OCA initiation | Patient 2 six months after OCA initiation |
|---|---|---|---|---|---|
| **Total bilirubin (mg/dl)** | 0,1-1,3 | 0,37 | - | 1,14 | 0,75 |
| **AST (U/L)** | 5-40 | 24 | 28 | 61 | 59 |
| **ALT (U/L)** | 5-40 | 68 | 32 | 75 | 79 |
| **GGT (U/L)** | 10-50 | 65 | 39 | 104 | 56 |
| **ALP (U/L)** | 34-104 | 186 | 134 | 349 | 150 |

**Abbreviations:** OCA, obeticholicacid; mg/dl, milligramsperdeciliter; AST, aspartateaminotransferase; U/L, units/liter; ALT, alanineaminotransferase; GGT, Gamma-glutamylTransferase; ALP, alkalinephosphatase.

chemical markers, especially the cholestatic enzymes. These findings support the growing body of evidence suggesting that OCA is an effective treatment option for PBC, particularly in patients with an incomplete response to UDCA, which remains the first-line therapy for PBC.

The efficacy of OCA in treating PBC has been well-established through multiple studies. Reduction of ALP levels is important, as it is a key marker of cholestasis and disease progression in PBC. Nevens et al. found that OCA significantly reduced ALP levels compared to placebo in patients with PBC, including those who had an inadequate response to UDCA [6]. Results from the phase 2 trial by Kowdley et al. showed improved ALP levels in patients who received long term OCA monotherapy, as well as reduction of other liver enzymes, bilirubin and immunoglobulin M (IgM) [7]. Reduction of cholestatic enzymes with OCA treatment could be attributed to improved transport of bile acids from the bloodstream into the bile. Kjærgaard et al. tested the effect of OCA treatment on the bile acid transport capacity of the liver, using PET scan. OCA treatment reduced the duration that potentially harmful bile acids remained in the liver by 30% [8]. In this case series, patients similarly showed a reduction in ALP levels after six months of OCA therapy, along with improvements in other liver biochemistry markers, including AST, ALT and γ-GT.

Bowlus et al. evaluated both biochemistry and liver biopsy reports in PBC patients receiving OCA over a three-year follow up period. They observed sustained reductions in ALP, ductal injury, liver fibrosis, and hepatic inflammation with long-term OCA therapy. These results further reinforced OCA's role in improving both biochemical and histological endpoints in PBC patients [9]. Although the present case series did not evaluate histological changes, the biochemical improvements observed in the patients after six months of OCA therapy support its potential for long-term benefits in slowing disease progression and improving liver health.

While OCA is generally well-tolerated, some patients experience side effects, most notably pruritus. In the Nevens et al. trial, pruritus was a common side effect in patients receiving OCA, though it was usually mild to moderate in severity and manageable in most cases [6]. The safety profile of OCA was also evaluated by Bowlus et al., who found that OCA was well-tolerated over extended periods, with no new safety concern identified [9]. This suggests that treatment with OCA is suitable for prolonged use, making it an option for long-term management of PBC. The present case series reported mild nocturnal pruritus in one of the patients, with no other significant complications. Notably, pruritus did not lead to treatment discontinuation, indicating that it is often a manageable adverse event.

UDCA remains the standard of treatment for PBC; however, many patients do not achieve adequate disease control with UDCA alone. This has led to the investigation of combination therapies, including UDCA and OCA. This combination was studied by D'Amato et al., who observed significant reduction in ALP, ALT and bilirubin levels in one third of patients after 12 months of UDCA and OCA combination therapy, especially in those not diagnosed with cirrhosis before OCA initiation [10]. Similarly, the present case series showed a biochemical response in both patients who were receiving UDCA before starting OCA, underlining the added benefit of OCA for those patients not fully controlled with UDCA alone.

Results from the recent randomized, placebo-controlled COBALT trial demonstrated that OCA added to UDCA led to a higher rate of biochemical response in PBC patients, particularly those with incomplete responses to UDCA, thus confirming the synergistic effect over UDCA monotherapy. However, failure of the study to provide clear long-term clinical benefits of OCA treatment compared to placebo has raised concerns that these benefits might not outweigh potential risks [11]. In the recent HEROES trial, patients who received OCA treatment showed a significantly reduced incidence of decompensated liver disease, need for liver transplantation and mortality; however, the mean follow-up period was less than two years [12]. Other studies examining long-term effects of OCA treatment in PBC patients are currently lacking. Despite the limitations of the COBALT trial and real-world data supporting the use of OCA in patients unresponsive or intolerant to UDCA, the EMA recommended revoking market authorization of OCA for patients with PBC [13]. At that time, OCA was the only available second-line therapy for PBC patients, and its unavailability in the EU posed a concern for both clinicians and UDCA non-responders, especially those who improved with OCA treatment or awaited treatment initiation. However, the recent conditional approval of two new agents, Seladelpar and Elafibranor, as second-line treatment for PBC patients, has provided new alternatives for these patients [14, 15].

## CONCLUSIONS

The results of this case series support the growing real-world body of evidence indicating that OCA is an

effective treatment for improving liver biochemistry in PBC patients, particularly when combined with UDCA. The observed reductions in ALP and liver enzymes, six months after the onset of treatment, are consistent with findings from larger clinical trials. Although the study's small sample size and short follow-up period limit the conclusions that can be drawn, the findings suggest that OCA offers significant clinical benefit in managing PBC, especially in patients who are not fully responsive to UDCA monotherapy. Recent data from clinical trials have not confirmed long term clinical benefits of OCA therapy in PBC. Larger, long-term real-world follow-up studies are needed in order to determine whether the biochemical improvements seen with OCA treatment translate into meaningful clinical outcomes, as well as which patients might mostly benefit from UDCA and OCA combination therapy, and who might require different treatment options.

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