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## ABSTRACT

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## MULTIFORME EXUDATIVE ERYTHEMA AS A MANIFESTATION OF IMMUNE STRESS SYNDROME: A CLINICAL CASE

**Introduction.** Immune stress syndrome, as a manifestation of autoinfectious diseases of the oral mucosa, develops under the influence of general and local factors that can affect the tolerance of the mucosa. Violation of the barrier function of the epithelium causes inflammatory autoinfectious diseases of the oral cavity. The cause of autoinfection is the disruption of local tolerance to microorganisms of normal flora and their simultaneous activation. Potential trigger factors are necessary to start the immunological reaction of the oral mucosa. These are hypothermia, prolonged dental manipulations and other stress factors. The aim of the work is to familiarize doctors with the difficulties in diagnosing and treating immune stress syndrome, which is associated with dental manipulations.

**Materials and methods.** The article demonstrates the patient's own clinical observation and the complexity of the course of erythema multiforme exudative as a manifestation of immune stress syndrome.

**Results and discussion.** According to the results of a general blood test, blood test for IgG and IgM to herpes virus antigens type 1, 2, bacterioscopy of scrapings from the affected areas, the diagnosis of «Stevens-Johnson syndrome with predominant damage to the oral mucosa and red border of the lips» was established and complex treatment was prescribed (detoxification, anti-inflammatory, immunotherapy). Therefore, dentists need to remember about the possibility of provoking complications after long-term dental interventions. It is imperative to conduct a clinical and laboratory examination, which allows not only to verify the diagnosis, but also to substantiate an effective treatment and prevention protocol.

**Conclusions.** The authors of the article, to prevent the occurrence of the manifestation of «immune stress syndrome» in patients with a burdened psychosomatic status, proposed an algorithm for the doctor's

actions when planning dental interventions and preventive measures that the patient should perform («Landmark for the patient»).

**Keywords:** oral mucosa, immune response, diagnostics, autoinfection, stomatitis.

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## БАГАТОФОРМНА ЕКСУДАТИВНА ЕРИТЕМА ЯК ПРОЯВ СИНДРОМУ ІМУННОЇ НАПРУГИ: КЛІНІЧНИЙ ВИПАДОК

**Вступ.** Синдром імунної напруги, як прояв аутоінфекційних захворювань слизової оболонки порожнини рота розвивається під впливом загальних та місцевих факторів, здатних впливати на толерантність слизової. Порушення бар'єрної функції епітелію викликає запальні аутоінфекційні захворювання порожнини рота. Причиною аутоінфекції є зрив локальної толерантності до мікроорганізмів нормальної флори і одночасно їх активація. Для запуску імунологічної реакції слизової оболонки порожнини рота необхідні потенційні тригерні фактори. Ними є переохолодження, тривалі стоматологічні маніпуляції та інші стресові фактори. Метою роботи є ознайомлення лікарів з утрудненнями в діагностиці і лікуванні синдрому імунної напруги, який пов'язаний зі стоматологічними маніпуляціями.

**Матеріали і методи.** В статті продемонстровано власне клінічне спостереження за пацієнтом та складність перебігу багатоформної ексудативної еритеми як прояву синдрому імунної напруги.

**Результати і обговорення.** За результатами загального аналізу крові, аналізу крові на IgG та IgM до антигенів вірусу герпеса 1,2 типу, бактеріоскопії зішкрябу з ділянок ураження встановлено діагноз «Синдром Стівенса-Джонсона з переважним ураженням слизової оболонки порожнини рота та червоної кайми губ» та призначено комплексне лікування (дезінтоксикаційна, протизапальна, імунотерапія). Отже, лікарям-стоматологам необхідно пам'ятати про можливість провокації виникнення ускладнень після довготривалих стоматологічних маніпуляцій. Обов'язково проводити клініко-лабораторне обстеження, що дозволяє не тільки верифікувати діагноз, а й обґрунтувати ефективний протокол лікування і профілактики.

**Висновки.** Авторами статті для запобігання виникнення прояву «синдрому імунної напруги» у пацієнтів з обтяженим психосоматичним статусом запропоновано алгоритм дії лікаря під час планування стоматологічних втручань та профілактичні заходи, які повинен виконувати пацієнт («Пам'ятка для пацієнта»).

**Ключові слова:** слизова оболонка порожнини рота, імунна відповідь, діагностика, аутоінфекція, стоматит.

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## ABBREVIATIONS

MEE – multiform exudative erythema  
WHO – World Health Organization  
ECG – electrocardiogram  
ESR – erythrocyte sedimentation rate  
PCR – polymerase chain reaction

## INTRODUCTION

Due to the deterioration of environmental conditions, psycho-emotional and somatic state of patients in recent years, the number of infectious-allergic, toxic-allergic and herpetic lesions of the oral mucosa with an atypical or complicated clinical picture has significantly increased. After long-term dental manipulations, vesiculobullous or vesiculoerosive lesions of the oral mucosa occur, which the authors patented as a «stress syndrome», which is more often associated with persistent herpetic infection [1, 2, 3].

Also, immune stress syndrome, as a manifestation of autoinfectious diseases of the oral mucosa, develops under the influence of general and local factors that can affect the tolerance of the mucosa, including during extensive dental interventions [4, 5].

The oral mucosa is a place of intense immune activity, where a wide variety of immune cells are found, providing the first line of defense against pathogenic organisms. The phenomenon of immunological tolerance is a state of immune tolerance to an antigen that enters the body orally [6].

The ecological system of the oral cavity balances between the immune response and tolerance to antigens. The nature of the immune response is determined by quantitative characteristics, that is, the intensity of the action of a particular factor [7].

Due to its topographic location, the oral mucosa is the first to be attacked by various pathogens, primarily infectious antigens [8]. The complex of innate and acquired factors of the immune system is a powerful barrier to the penetration of microbes, viruses, toxins, and carcinogens. Violation of the barrier function of the oral epithelium causes inflammatory autoinfectious diseases of the oral cavity. The cause of autoinfection is the disruption of local tolerance to microorganisms of the normal flora and their simultaneous activation.

The ability of the organism to maintain the stability of the microecology of a certain biological niche, including the oral cavity, is realized by the colonization resistance system, and the ability of colonization resistance to resist the formation of an infectious process is anti-infectious resistance [9]. Important in the formation of colonization resistance belongs to resident microflora, epithelial cells of the mucous membrane and their receptors, complementary adhesins of bacteria that form the microbiocenosis of a particular biotope [10].

Understanding the causes of pathological processes is closely related to the mandatory consideration of the role of the organism in causing the disease. The same factor can be pathogenic for one organism and not cause pathological changes in another. Pathogens do not just act on the organism, but their peculiar interaction occurs. When a disease occurs, the properties of the factor and the entire organism are important. It is believed that the cause of the disease is necessarily related to the characteristics of the human body and any external factor can be pathogenic if it can cause a pathological reaction in this organism. Clarification of the cause-and-effect relationships between somatic and psychological factors and the patient's personality in somatic diseases, including dental ones, is called the psychosomatic approach [11].

It is undeniable that the high level of chronic psycho-emotional stress in society, associated with information overload and the pace of modern life, affects the occurrence of dental diseases, in particular diseases of the oral cavity and internal human pathology [12].

The war in Ukraine only increases the severity and course of emotional stress in a person and causes such negative social psychological reactions as anxiety and fear, which can also lead to post-traumatic stress disorder, depression [13]. It has been established that the severity of clinical manifestations and the degree of metabolic disorders in patients with diseases of oral mucosa correlate with the individual typological features of nervous regulation. According to the research of scientists of the school of Professor L.M. Tarasenko, stressor damage to cells is non-specific. The mechanism of stressor damage to the tissues of the oral cavity is characterized by high sensitivity to neurohumoral factors. Moreover, the typological features of the organism play a significant role [14].

Potential trigger factors are necessary to launch an immunological reaction in autoinfectious diseases of the oral mucosa. These can be hypothermia, stress factors, prolonged dental manipulations, etc.

Permanent orthodontic equipment (bracket systems, appliances) affects the conditions for self-cleaning and complicates the individual hygiene of the patient's oral cavity. The hygienic condition of the oral cavity in the presence of a bracket system deteriorates due to various structural elements of the appliances, which serve as retention points for the accumulation of microbial

biofilm. This leads to high microbial contamination of the surface of the teeth and orthodontic appliances, changes the composition of the microbiome, increases the number of opportunistic microorganisms and causes dysbacteriosis [15]. Orthodontic treatment also leads to changes in homeostasis, activation of the inflammatory process in the periodontal tissues, mucous membrane and increases the susceptibility of teeth to caries, which is associated with the presence of a stressful situation in the oral cavity. The chewing function and physical condition of the dento-maxillary system change, and the quality of life of patients undergoing orthodontic treatment decreases [16].

A characteristic feature of the group of diseases of the mucous membrane of the mouth and lips is an acute onset with pronounced clinical manifestations both in the oral cavity (polymorphism of rashes), and a general reaction of the human body with signs of intoxication (malaise, fever), which complicates the diagnosis. A typical example of such a pathology is moderate and severe forms of exudative erythema multiforme - (ICD-11:13DA01.13), Stevens-Johnson syndrome, herpetic infection (ICD-11:13 DA01.3) [17, 18, 19, 20, 21].

Typical manifestations of MEE are quite characteristic and are diagnosed almost without difficulty: acute onset, fever, deterioration of the general condition with damage to the skin, red border and mucous membrane of the oral cavity with polymorphism - spotty-papular lesions, erosions, cracks, bloody crusts, etc. In Stevens-Johnson syndrome, the patient's condition is more severe: these symptoms are accompanied by lesions of other mucous membranes (eyes, genitals), etc.

In herpes infection, vesicular rashes on the mucous membrane or skin are also typically observed, with subsequent evolution into erosion and crusts. Changes in the general condition are determined by the clinical form of the disease (acute or exacerbation of the chronic course, severity, etc.).

Moreover, the above diseases have a similar clinical picture, require systemic analysis and deep understanding for adequate diagnosis, selection of individual complex treatment, and, most importantly, prognosis and prevention.

The purpose of the work is to familiarize doctors with the difficulties in the diagnosing and treatment of immune stress syndrome, which is associated with dental manipulations.

#### **MATERIAL AND METHODS**

During the examination of the patient, general, ethical, moral and legal requirements were observed that do not contradict the International Recommendations of the Helsinki Declaration of Human Rights, the Council of Europe Convention on Human Rights and

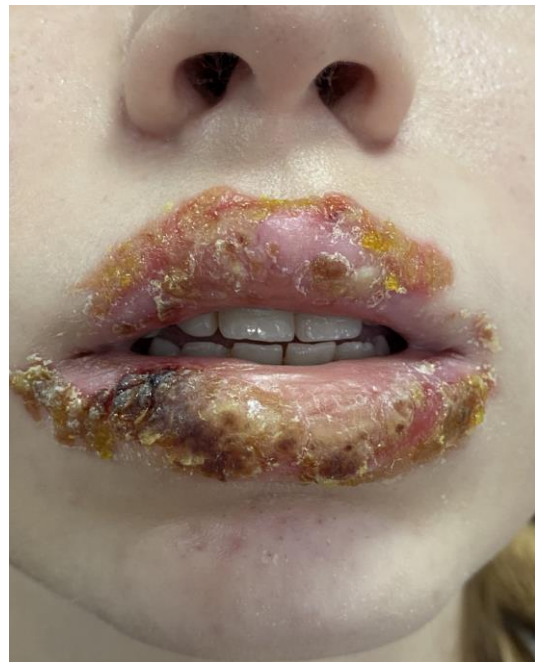
Biomedicine (1977), the relevant provisions of the WHO and the laws of Ukraine (Minutes of the meeting of the Biomedical Ethics Commission of the Poltava State Medical University No. 201 dated 01/27/2022) [22].

On 07/09/23, patient B., born in 2002, an internally displaced person from Kharkiv, applied to the clinic of the Department of Therapeutic Dentistry for a consultation with complaints of general malaise, fever, pain and rashes on the lips and in the oral cavity, inability to eat, etc. Symptoms of the disease appeared a few days ago. Initially, spots and vesicles appeared on the lips, the temperature rose to 37.5°C (04/09/23). On the eve of the rashes (2 days ago), she visited an orthodontist, where they replaced the arch wire on the braces system for an hour.

She notes a seasonal allergy to ragweed, characterized by itching eyes, nasal congestion, etc. As prescribed by her family doctor, she takes loratadine and instills dexamethasone solution in her eyes.

After the rashes appeared, she independently lubricated her lips with retinol, but her condition did not improve. She consulted a dermatologist, who prescribed antiallergic drugs and referred her to a dentist.

On objective examination: general condition of the patient is moderate, facial skin is pale. Lips are swollen, hyperemic, the eroded surface of the red border of the upper and lower lips with the transition to the skin is completely covered with yellowish-brown crusts (Fig. 1). Palpation of the lips is sharply painful. The submandibular lymph nodes are enlarged to the size of a



**Figure 1 – Initial examination of patient B., the condition of the red border of the lips**

bean, painful, not fused with tissues. The mucous membrane of the cheeks is swollen with whitish layers over the entire surface, which are not removed by scraping (Fig. 2, 3). The tongue, hard and soft palate, floor of the mouth are without pathological changes. No rashes were found on the skin of the extremities, trunk and other mucous membranes.

It was impossible to examine the dentition during the first visit. During the observation: the oral cavity was sanitized, the bite was transverse, a bracket system was fixed on the upper and lower jaws.

For diagnosis, a laboratory examination was prescribed: a general blood test, a blood test for IgG and IgM to herpes virus antigens type 1, 2, a bacterioscopic examination of a scraping from the affected areas.

During a microscopic examination from 09/07/2023, staphylococcal microflora was detected, leukocytes - 3-5 in the field of view. A preliminary diagnosis was made: «Multiform exudative erythema, infectious-allergic form». Treatment was prescribed: applications to the affected areas with a methacyl-anesthetic mixture before meals; alternate with treatment with hydrocortisone and Levomekol ointments. The next day (09/08/23) the patient came to continue treatment, but without the results of the laboratory examination. The condition is previous. After approval, she was referred for hospitalization to the allergy department of the Municipal Enterprise «Poltava Regional Clinical Hospital named after M.V. Sklifosovsky of the Poltava Regional Council».



**Figure 2, 3 - Initial examination of patient B., condition of the oral mucosa**

We present data from the hospital medical record of the patient. Laboratory test data: general blood test from 08.09.23 – leukocytes  $10.9 \times 10^9/l$  and ESR 21 mm/h; biochemical blood test from 12.09 – indicators within the age norm; ECG – normal; enzyme immunoassay from 13.09 – IgG to antigens of toxocara, ascaris, opisthorchiasis – negative; IgA, IgM, IgG to antigens of giardia – negative, antibodies to IgM and IgG to syphilis from 14.09 – negative. The allergist diagnosed «Stevens-Johnson syndrome with predominant lesion of the oral mucosa and red border of the lips». Treatment was carried out: Reosorbilact, sodium chloride solution, Dexamethasone, Acyclovir, Furosemide, Suprastin, Virolex, Ringer's solution.

On 15.09.23, the patient was discharged from the hospital with improved condition. Recommended: outpatient care by an allergist, family doctor, hypoallergenic lifestyle, hypoallergenic diet.

Recommended: blood test for immunoglobulins M and G to herpes virus type 1,2, with positive results, perform PCR for herpes virus type 1,2 (quantitative). With a positive result, add Valavir 500 mg, Overin 250 mg according to the scheme in accordance with clinical protocols. Contraindicated: hypothermia, physical and emotional stress, contact with allergens, herbal medicine.

#### DISCUSSION OF A CLINICAL CASE

There are more and more publications on the development of microbial diseases of the oral mucosa caused by immune stress syndrome, including herpetic lesions and those caused by opportunistic microflora [23, 24].

The results of microbiological studies of scrapings from the oral cavity in patients with autoinfectious diseases of the oral cavity showed an increase in gram-positive diplococci by 2.7 times, streptococci and gram-

positive bacilli by 2 times, staphylococci by 3 times, gram-negative cocci that form clusters by 2.25 times and gram-negative diplococci by 2.3 times [24].

Patients of dental clinics represent an extremely heterogeneous group in composition, and it is not always possible to detect pathognomonic changes in systemic immunity, therefore, the indicators of immunity of the oral mucosa acquire a decisive role [10].

The resistance of the oral mucosa is particularly influenced by general and local factors («danger signals» according to N.V. Gasiuk). The general factors include stress, acute respiratory viral infections, hypothermia, physical exertion, deficient conditions, unbalanced nutrition, bad habits. The local factors include decayed teeth, poor hygiene, periodontal disease, trauma to the oral cavity, occlusion pathology, orthopedic structures. General and local «danger signals» in combination can affect the resistance of the mucosa and change it during extensive dental interventions (professional hygiene, tooth extraction, long-term endodontic treatment, tooth restorations, etc.). In our opinion, the installation of a brace system and orthodontic treatment of the patient can also be attributed to this group of causes of the disease, and all the above causes an intensive microbial load on the oral mucosa and leads to an immune reaction.

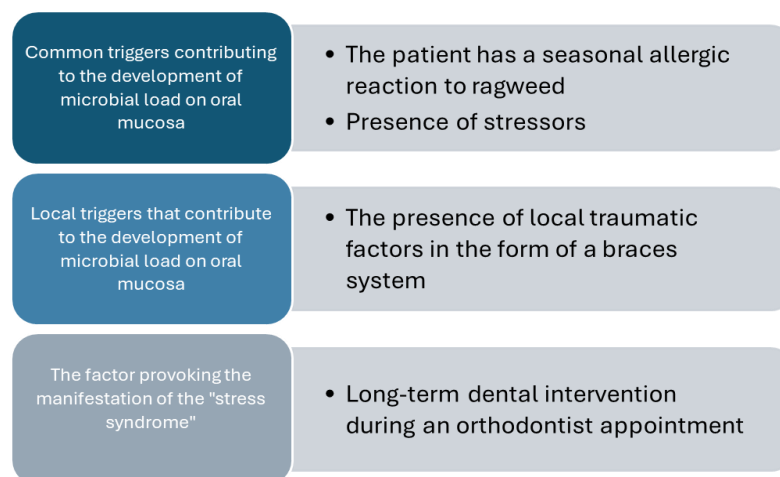
In view of the above, let us analyze the given clinical case. Local status, allergic pathology in the anamnesis and many staphylococcal microflora allowed us to make a preliminary diagnosis of «Multiform exudative erythema, infectious-allergic form». However, the question arises – why are there no typical rashes on the skin with severe intoxication of the body? Perhaps this is due to the constant intake of antihistamines, or the preliminary diagnosis is incorrect, and this is a «syndrome of immune stress» of a herpetic

nature that developed after of dental interventions? However, in literary sources, the authors cite only vesicular rashes on the oral mucosa after long-term dental restorations. In the above case, the clinical manifestations are more pronounced, which can be interpreted as MEE, which arose against the background of sensitization of the body under the influence of a persistent viral or bacterial infection. The results of laboratory tests performed in the hospital indicate the presence of an acute inflammatory reaction. However, the diagnosis made in the allergy department «Stevens-Johnson syndrome with predominant involvement of the oral mucosa and red border of the lips» also does not correspond to the typical clinical picture described in the literature [17, 18, 19, 21].

Unfortunately, blood tests for immunoglobulins G and M and for herpes virus types 1,2 or PCR diagnostics were not performed in the hospital. That is, herpes virus infection as the cause of the disease was not excluded, and accordingly, the diagnosis is not final. This is also indicated by the hospital treatment, where antiviral drugs were used simultaneously with detoxification therapy. Therefore, the allergist is also not completely sure of the diagnosis and therefore prescribed additional examinations for herpes virus infection, including PCR. A week after discharge from the hospital, we spoke with the patient, emphasizing the need for additional immunological testing, but the patient refused.

The etiological factors of this clinical case are presented in the form of a flowchart (Fig. 4).

To prevent the occurrence of the manifestation of «immune stress syndrome» in patients with a burdened psychosomatic status, we offer an algorithm for the doctor's actions when planning dental interventions and preventive measures that the patient should take («Landmark for the patient») (Fig. 5, 6).



**Figure 4 - Etiological factors of this clinical case**

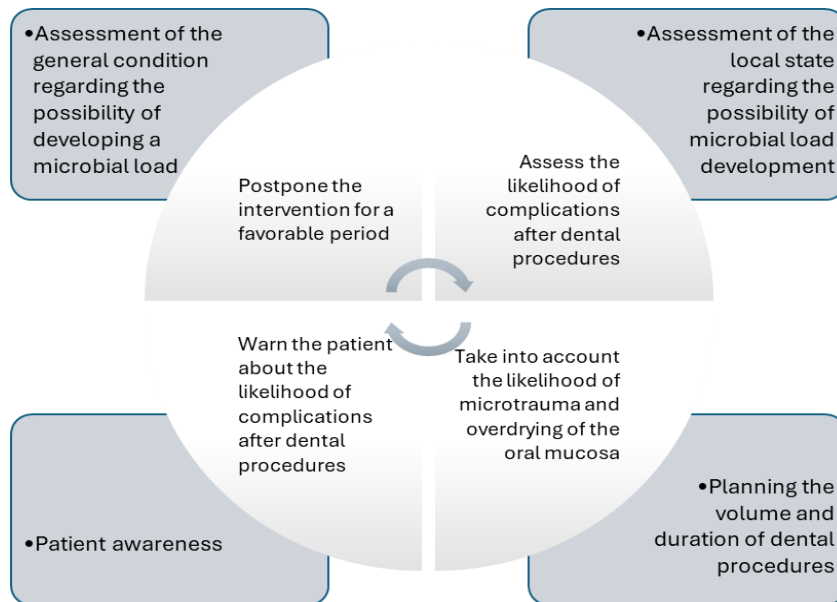


Figure 5 - Algorithm of doctor's actions when planning dental interventions

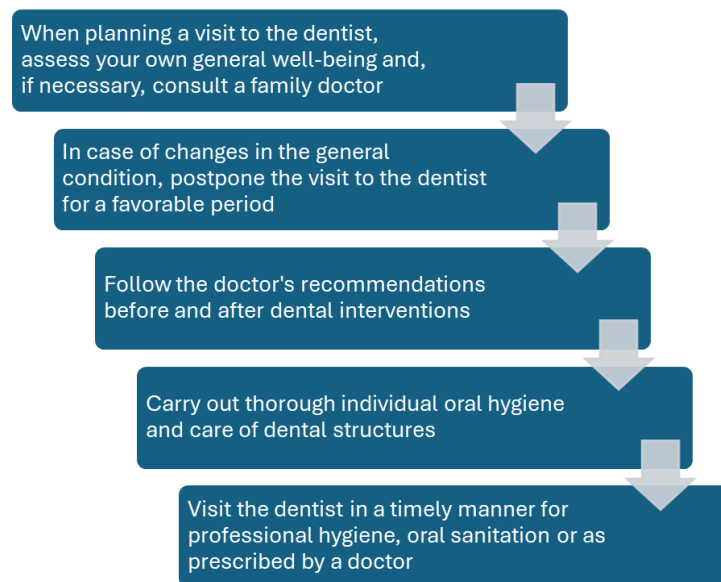


Figure 6 - Preventive measures to prevent immune stress syndrome ("Landmark for the patient")

**CONCLUSIONS**

Therefore, the success of establishing a final diagnosis depends on the completeness of the history taking, the results of a thorough examination, patient observation during treatment, and the subsequent correction of the previously established diagnostic conclusion. The presented clinical case confirms the statement: «Diagnosis is not a static concept, but a

dynamic one». It is worth noting that dentists need to remember about the possibility of provoking complications after long-term dental interventions and insist on conducting a mandatory clinical and laboratory examination, which allows not only to verify the diagnosis, but also to substantiate an effective treatment and prevention protocol.

**PROSPECTS FOR FUTURE RESEARCH**

Prospects for further research include the accumulation of clinical materials on the manifestations of stress syndrome at a dental appointment, generalization of diagnostic and treatment methods, and writing a scientific review article.

**AUTHOR CONTRIBUTIONS**

Ніколішин А.К. - концептуалізація, адміністрування проєкту, рецензування та редагування;  
 Котелевська Н.В. - методологія, ресурси, збір даних, аналіз та інтерпретація результатів, написання;  
 Ніколішина Е.В. - візуалізація та дизайн дослідження, програмне забезпечення, підготовка рукопису.

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None.

**CONFLICT OF INTEREST**

The authors declare no conflict of interest.

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