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MODERN ASPECTS OF EPIDEMIOLOGY OF ANKYLOSING SPONDYLOARTHRITIS. REVIEW.

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Summary

Relevance. Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease of the axial skeleton and iliosacral joints, which is predominantly detected in males. AS affects people of different races and geographic areas, but there is a high disease incidence in certain populations. People suffering from AS experience not only an increased fatality rate compared to the general population, but also a high invalidity level, which leads to a large number of disabilities. Thus, the study of AS peculiarities is an urgent problem of modern medicine.

Aim: To identify the features of the AS epidemiology at the present stage.

Search strategy: A search for scientific publications was carried out in the following databases of scientific publications and specialized search engines: PubMed, Google Scholar, Web of Science, Cyberleninka. Records' number identified from databases, publicly available on the study topic, various in the design amounted to 352. 316 publications were excluded from the analysis according to the exclusion criteria. Only original publications were analyzed, including meta-analyses, systematic reviews, cohort and cross-sectional studies. The initial search depth was 7 years. 36 publications were selected. Due to the insufficient number of scientific papers and the not so significant prevalence of this disease, the group of authors decided to increase the search depth to 15 years according to the same criteria. 71 scientific papers were selected, which are presented in this literary review.

Results and conclusions: review revealed that the AS prevalence fluctuates in different world regions and depends on the frequency of the HLAB27 gene presence. Literature analysis demonstrates a tendency to increase and more frequent AS detection among the female population in recent decades. At the same time, there is a significant delay in diagnosis in women compared to men, which leads to a significant deterioration in the quality of life due to the late start of treatment.

Key words: *ankylosing spondylitis, prevalence, spondyloarthropathy, epidemiology.*

Резюме

СОВРЕМЕННЫЕ АСПЕКТЫ ЭПИДЕМИОЛОГИИ АНКИЛОЗИРУЮЩЕГО СПОНДИЛОАРТРИТА. ОБЗОР ЛИТЕРАТУРЫ.

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Актуальность. Анкилозирующий спондилоартрит (АС) является хроническим системным воспалительным заболеванием осевого скелета и илеосакральных сочленений, которое преимущественно выявляется у лиц мужского пола. АС поражает людей, относящихся к различным расам и в разных географических территориях, но отмечается высокая распространенность болезни в отдельных популяциях. У людей, страдающих АС наблюдается не только повышенный уровень смертности по сравнению с общей популяцией, но так же высокий уровень инвалидизации, что приводит к высокому уровню нетрудоспособности. Учитывая вышеизложенное, изучение особенностей течения АС является актуальной проблемой современной медицины.

Цель: выявить особенности эпидемиологии АС на современном этапе.

Стратегия поиска: Проведен поиск научных публикаций в области изучения эпидемиологии АС в следующих базах данных научных публикаций и специализированных поисковых систем: PubMed, GoogleScholar, WebofScience, Cyberleninka в количестве 352 публикации, находящихся в открытом доступе по теме исследования, различных по дизайну исследования. 316 публикаций были исключены из анализа согласно критериям исключения: краткие отчеты, описание случая и серии случаев, газетные статьи и мнение экспертов в виде коротких сообщений. Анализу

подверглись только оригинальные публикации, включающие в себя, мета-анализы, систематические обзоры, когортные и поперечные исследования. Первичная глубина поиска составила 7 лет. Было отобрано 36 публикаций. Ввиду недостаточного количества научных работ и не столь значительной распространенности данного заболевания группой авторов было решено увеличить глубину поиска до 15 лет по тем же критериям. Таким образом, было отобрано 71 научных работ, которые представлены в данном литературном обзоре.

Результаты и выводы: По результатам обзора выявлено, что распространенность АС колеблется в различных регионах мира и зависит от частоты наличия гена HLA B27. Проведенный нами анализ литературы демонстрирует тенденцию к увеличению и более частую выявляемость АС среди женского населения в последние десятилетия. При этом отмечается значительная задержка в постановке диагноза у женщин по сравнению с мужчинами, что приводит к значительному ухудшению качества жизни ввиду позднего старта лечения.

Ключевые слова: анкилозирующий спондилоартрит, распространенность, спондилоартропатии, эпидемиология.

Түйіндеме

АНКИЛОЗДЫ СПОНДИЛОАРТРИТ ЭПИДЕМИОЛОГИЯСЫНЫҢ ЗАМАНАУИ АСПЕКТІЛЕРІ. ӘДЕБИЕТКЕ ШОЛУ.

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Өзектілігі. Анкилозды спондилоартрит (АС) - бұл осьтік қаңқа мен илеосакральды буындардың созылмалы жүйелі қабыну ауруы, ол көбіне ер адамдарда жиі анықталады. АС әртүрлі нәсілдерге және әртүрлі географиялық аймақтарға жататын адамдарда кездеседі, бірақ жекелеген популяцияларда аурудың жоғары таралуы байқалады. АС-мен ауыратын адамдарда жалпы популяциямен салыстырғанда өлім-жітім деңгейі ғана емес, сонымен қатар мүгедектік деңгейі де жоғары, бұл еңбекке жарамсыздықтың жоғары деңгейіне әкеледі. Жоғарыда айтылғандарды ескере отырып, АС ағымының ерекшеліктерін зерттеу қазіргі медицинаның өзекті мәселесі болып табылады.

Мақсаты: қазіргі кезеңде АС эпидемиологиясының ерекшеліктерін анықтау.

Іздеу стратегиясы: АС эпидемиологиясын зерттеу саласындағы ғылыми жарияланымдарды зерттеу тақырыбы бойынша ашық қолжетімді, зерттеу дизайны бойынша әртүрлі 352 басылым келесі: PubMed, Google Scholar, Web of Science, Syberleninka ғылыми жарияланымдар мен мамандандырылған іздеу жүйелерінің дерекқорларында іздеу жүргізілді. 316 басылым алып тастау критерийлеріне сәйкес: қысқаша есептер, уақиға сипаттамасы және бірқатар жағдайлар, газет мақалалары және қысқа хабарламалар түрінде сарапшылардың пікірі, талдаудан шығарылды. Мета-талдаулар, жүйелі шолулар, когорттық және көлденең зерттеулерді қамтитын түпнұсқа басылымдар ғана талданды. Іздеудің бастапқы тереңдігі 7 жыл болды. 36 басылым таңдалды. Ғылыми жұмыстардың жеткіліксіз санына және осы аурудың соншалықты көп таралмауына байланысты авторлар тобы іздеудің тереңдігін сол критерийлер бойынша 15 жылға дейін ұлғайту туралы шешім қабылдады. Осы әдеби шолуда ұсынылған 71 ғылыми жұмыс таңдалды.

Нәтижелер мен қорытындылар: әдеби шолуымыздың нәтижелері бойынша АС таралуы әлемнің әртүрлі аймақтарында бірдей еместігі және HLA b27 генінің болу жиілігіне байланысты екені анықталды. Біз жүргізген әдебиеттерді талдау соңғы онжылдықтарда әйелдер арасында АС-ның өсу тенденциясын және жиі анықталуын көрсетеді. Сонымен бірге ерлермен салыстырғанда әйелдерде диагноз қоюдың айтарлықтай кешігуі байқалады, бұл емдеудің кеш басталуына байланысты өмір сапасының айтарлықтай нашарлауына әкеледі.

Түйінді сөздер: анкилозды спондилоартрит, таралуы, спондилоартропатиялар, эпидемиология.

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Introduction

Ankylosing spondylitis (AS) is a chronic systemic inflammatory disease of the axial skeleton and iliosacral joints, which is mainly detected in males. AC affects people of different races and geographical areas, but there is a high prevalence of the disease in certain populations. Recently, significant discoveries have been noted in the epidemiology of the disease, related to a detailed study of genetic factors, differences in the course of the disease depending on gender, the impact of the disease on the quality of life. People with AS have not only an increased mortality rate compared to the general population, but also a high level of invalidity, which leads to a great quantity of disability. Considering the above, studying the features of the course of AS is an topical issue of modern medicine.

Aim: To identify the features of the epidemiology of AS at the present stage.

Search strategy: A search for scientific publications was carried out in the following databases of scientific publications and specialized search engines: PubMed, Google Scholar, Web of Science, Cyberleninka by studying the AS epidemiology. Number of records identified from databases that are publicly available on the topic of the

study, various in the design of the study amounted to 352. After removing duplicates in the amount of 83 records, 233 publications were excluded from the analysis according to *the exclusion criteria*: summary reports, a description of the case and a series of cases, newspaper articles and expert opinions in the form of short messages. Only original publications were analyzed, including meta-analyses, systematic reviews, cohort and cross-sectional studies. The initial search depth was 7 years. Thus, 36 publications were selected. Due to the insufficient number of scientific papers and the infrequent prevalence of this disease, the group of authors decided to increase the search depth to 15 years according to the same criteria (n=611). After removing duplicate records (119 records) and applying exclusion criteria, 422 studies were excluded. Thus, 71 scientific papers were selected, which are presented in this literary review (Figure 1.). Due to the lack of publication on the prevalence of AS in the Republic of Kazakhstan and in the official statistical collection of the Ministry of Health of the Republic of Kazakhstan, data from reporting documentation in the field of healthcare of the Republic of Kazakhstan in form 12 was used for comparative analysis.

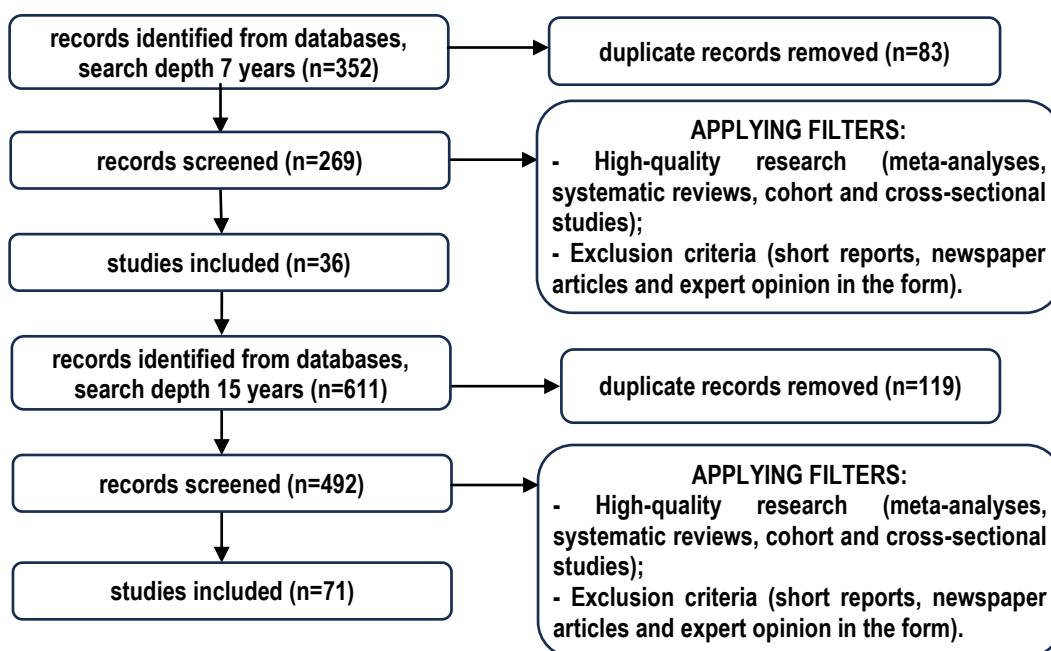


Figure 1. Algorithm of selecting publications.

Research results

Prevalence.

Ankylosing spondylitis (AS) is a rare disease with a prevalence ranging from 2 to 37 per 10,000 people [55, 65]. AS occurs in people of different races and in different geographic areas, but there is a high prevalence of the disease in certain populations, which is likely due to genetic predisposition, especially the frequency of the HLA B27 gene [6].

The highest incidence of AS is observed in a separate population of indigenous peoples of the Northern Arctic and Canada, where it reaches 60 cases per 10,000 population according to Barnabe C. and co-authors [6]. In general, in the countries of North America there is an average prevalence rate of 31.9 cases per 10,000 people,

amounting to 10.7 in the USA, and 20 cases per 10,000 people in Canada, respectively [6], [17, 18], [55].

The lowest prevalence is observed in Africa, where the prevalence rate ranges from 2 cases per 10,000 in Central and South Africa (sub-Saharan Africa) to 11 cases per 10,000 population in North Africa, representing an average of 7.4 across the continent [18, 55, 57, 63].

According to a systematic review of the prevalence of AS by Dean, L. E. et al., the average frequency per 10,000 people was 23.8 in Europe. At the same time, the lowest prevalence is observed in such countries as Lithuania (9.4), Denmark (6.31), Poland (7.48). [18, 43, 55, 58]. The highest prevalence of the disease in European countries is observed in Germany (32.2), Italy (37), France (43), Turkey (44) [3, 16, 33, 46, 61].

Latin America has an average prevalence of AS of 10.2 cases per 10,000 population, with epidemiological studies in Mexico, Colombia, Cuba and Venezuela ranging from 2 to 8 cases in some regions [14, 45, 51].

In Asia, the prevalence of AS is 16.7 cases per 10,000, with East Asia having the highest prevalence of 16, Southeast Asia 7, and South Asia 6 cases per 10,000 population [18, 55]. In terms of individual countries, a high prevalence rate is observed in the DPRK and is 29 cases per 10,000 population, a low prevalence level is noted in South Korea - 5.2 cases per 10,000, but one of the lowest prevalence rates of AS recorded in Japan and is 0.26 cases per 10,000 population [34, 44, 53, 69].

On the territory of CIS in the Russian Federation, there is a prevalence of 5 cases per 10,000 population according to statistics, although Erdes S. and co-authors note that extrapolation of the data that was obtained during their epidemiological study showed that the real prevalence rate is at least 10 per 10,000 people [20]. Unfortunately, no reliable sources on prevalence in other CIS countries have been found in the literature. According to official statistics, as of 2018, 3,175 patients suffering from AS have been registered in Kazakhstan, which is the prevalence rate of 1.7 people per 10,000 population [1].

Data on differences in prevalence between rural and urban populations are heterogeneous, but according to a meta-analysis by Stolwijk C. et al., conducted in 2016, the prevalence of AS in the rural region is significantly higher than among the urban population [55].

HLA B27 in epidemiology. It has been proven that AS is a genetically determined disease. [8, 24, 26, 64] Therefore, the prevalence of AS in a population depends on the frequency of occurrence of the HLA B27 gene [8]. Thus, the lowest frequency of HLA B27 (close to zero) among the world population is observed in the equatorial zone, and the highest (40%) in the Arctic and the most remote northern lands [49]. These data are consistent with data on the global prevalence of AS, with the highest incidence in a separate population of indigenous peoples of the Northern Arctic and Canada and the lowest prevalence in African countries [18, 55].

The presence of the HLA B27 gene is detected in about 85% of patients with a confirmed diagnosis of AS leads to a greater risk of developing the disease among close relatives, but also a faster diagnosis in contrast to HLA B27 negative patients [2, 4, 8, 24, 49, 50]. In relation to the clinical manifestations of the disease, HLA B27 positive patients have an earlier age of debut, a better clinical response to tumor necrosis factor inhibitors alpha, a higher risk of acute anterior uveitis, and a lower risk of psoriasis and IBD [2, 13, 30, 32, 42, 68]

Gender differences. It is believed that ankylosing spondylitis is mainly a male disease, with a male-female ratio of 3:1. However, a German study conducted among 3,000 patients belonging to the German Society of AS Patients revealed a continuous increase in the proportion of women among patients diagnosed with AS in recent decades. According to the study, the number of female patients diagnosed with AS rose from 10% in 1960 to 46% in 1990. This suggests that the predominance of men in AS may be, at least in part, a consequence of the insufficient diagnosis of AS among women in the past decades [26].

Researching the gender differences of AS, studies agree that the age of onset of the disease did not differ considerably in men and women, but women had a significantly longer delay in diagnosis [12, 25, 27, 54, 67]. The authors also note that higher activity of the disease prevails in women, while men have a more severe lesion according to X-ray examinations. At the same time, higher activity of the disease leads to a more pronounced pain syndrome and a higher dosage of drugs prescribed by NSAIDs. In the studies of Yacoub and co-authors, as well as Shahlaee and co-authors, it was noted that women have a high frequency of extra-articular manifestations, especially enthesites [27, 54].

But all researchers agree that gender differences in the clinical course of the disease require further detailed study and can certainly contribute to reducing diagnose delay and developing a more personalized approach to the diagnosis and treatment of patients with AS [12, 25, 27, 54, 67].

Age. The biggest number of people suffering from AS are in the age range of 40-50 years, followed by the age group of 50-60 years and 30-40 years [55]. Although many patients note the debut of the disease before the age of 40, which indicates an untimely diagnosis of this pathology.

Mortality structure. According to the literature, ankylosing spondylitis causes increased death rate, especially among male patients. Thus, a systematic review and meta-analysis by Chaudhary N. and co-authors showed a greatly increased risk of overall mortality in AS compared to the general population [11]. However, there was a significant growth in the standardized fatality rate in male patients, in contrast to female patients, according to the results of a study of a cohort of 677 people suffering from AS [5].

All studies agree that cardiovascular diseases are the leading cause of death [5, 11, 47]. This is indirectly confirmed by studies on the frequency of comorbid states in AS, according to which the most common concomitant diseases are hypertension, hyperlipidemia and obesity [70], which causes a large risk of myocardial infarction in the cohort of patients with AS than in the general population [31].

Oncology is in second place for the reasons of lethality; according to a systemic review and meta-analysis by Deng C. et al., in the AS group the risk of malignancy grew by 14% compared to the general population [19, 29]. Most of the oncological diseases in patients with AS are hematological malignant neoplasms, in particular multiple myeloma and lymphoma [52]. Also, a high risk of colorectal and prostate cancer was reported in a study of doctors from Taiwan [10], which was not confirmed in a American study, which, on the contrary, noted a low percentage of colorectal cancer in patients with AS compared to the general population [66]. Such discrepancies are apparently caused by racial and ethnic characteristics and need further study.

The third most frequent factor of death in the cohort of patients with AS are infectious diseases, in particular septicemia in the outcome of pneumonia [5, 47].

At the same time, there was also a boost in lethality in patients with AS, who were less likely to take non-steroidal anti-inflammatory drugs, in patients with late diagnosis of AS and in patients with high levels of CRP [5]. It is also worth noting that patients with AS due to spinal ankylosis

have a higher danger of injury even when falling to the ground from a human height and trivial injuries [52].

This, coupled with the necessity to treat severe spinal deformities, result in a higher frequency of surgical interventions, which carries a higher risk of mortality from intraoperative and postoperative complications compared to the general population [47].

Quality of life. Many authors also note that in addition to the activity of the disease and general health, there are a number of factors that require special attention and support from medical professionals. These factors significantly affect the quality of life of patients and can indirectly affect the course of the disease and the effectiveness of treatment.

Thus, according to Baysal et al., a study of 243 patients with AS identified a close relationship between the activity of the disease, the level of depression and anxiety and the quality of life of patients. According to this study, a higher level of disease activity correlated with a higher level of anxiety and a lower level of quality of life [7]. These data were also confirmed in a Chinese transverse study conducted among 103 patients with AS and 110 healthy controls [23]. In addition, the authors revealed a higher level of joint dysfunction according to the BASFI scale in the group of patients with increased anxiety. Similar data were found in other studies studying the effects of disease activity on mental health [28, 41, 62].

Moreover, in a cross-sectional study conducted among 265 patients with AS from Taiwan, higher disease activity, as assessed by the BASDAI and ASDAS disease activity scores, was significantly and independently associated with lower quality of life in all four domains of the Patient Quality of Life Questionnaire. with AS - EASI-QoL (physical function, disease activity, emotional well-being and social participation) [36].

Also, when analyzing the impact of AS on the quality of life, a correlation was identified between disease activity and decreased productivity. This, combined with increased time off work and deterioration in daily activities during free time, also leads to a decrease in quality of life [39, 62].

According to the literature, compared with the general population, patients with AS have a lower level of employment and a higher level of disability. Thus, according to the results of a study conducted by Ramonda R. and co-authors in Italy, among 770 patients surveyed, 39% noted the presence of disability, 36% reported difficulties in their professional career associated with the disease, and 21% of patients had to change their profession or quit their job altogether [48]. In a French study, among 156 participants, 35% had moderate disability and 5% had high disability according to the AS-WIS disability scale [21]. It is also worth noting the results of an international study conducted in three countries (the Netherlands, Belgium, France) over 12 years, which revealed not only a high level of disability in patients with AS at the beginning of the study, but also a dramatically growth in this level by the end of 12 years of research [9].

Cost of illness. Considering that 1 out of every 200 people around the globe suffers from AS, this disease places a large burden on the healthcare and social economy [26].

For example, according to a study conducted in UK Cooksey et al., the total cost of AS in the UK is estimated at £19,016 per patient per year, with more than 80% of the amount associated with work-related costs [15]. A Spanish study of 578 patients found that the average annual costs per patient were 11,462,3 euros, of which 61.1% (6,999,8 euros) were allocated to direct health care costs, 5.3% (611.3 euros) to direct non-health care costs, and 33.6% (3,851,2 euros) to reduced labor productivity [40]. According to the Swedish study of 116 patients, the average annual cost per patient with AS was US \$12,365, with it noted that patients with AS had an average annual cost 3 times higher compared to the control group from the general population, and the cost of drugs was almost 10 times higher due to biological therapy. Production losses (indirect costs) accounted for more than half of total costs (53%) [56].

In a study of 257 patients in China, annual estimated costs per patient were US\$2,714.18, while indirect costs were 64.7%, with the authors noting that annual direct costs were significantly correlated with disease activity [60]. At the same time, a study of the cost of illness among the Chinese population in Hong Kong found that annual costs per patient averaged US \$9,120. The authors also note that the majority of expenses are indirect costs (62%) [71].

In a South Korean study of 191 patients with AS, the cost of the disease was US \$8,923 per year. The authors draw attention to the increase in total costs as functional severity deteriorates (class I - 5,900,7, US dollars; Class II - \$9,884; classes III and IV - \$19,308) [35].

All studies of the cost of AS disease agree that high disability of males at the most working age leads to a higher cost of AS disease due to indirect costs. Most of the indirect costs of the disease are lost productivity, early retirement, and increased days of disability [22, 37, 38, 59].

Conclusion

According to the results of our literary review, it was revealed that the prevalence of AS fluctuates in different regions of the world. Being a genetically determined disease, the prevalence of AS in the population depends on the frequency of occurrence of the HLA B27 gene. Thus, the lowest frequency of HLA B27 (close to zero) among the world's population is observed in the equatorial zone, and the highest (40%) in the Arctic and the most remote northern lands. These data are consistent with data on the global prevalence of AS, with the highest incidence in a separate population of indigenous peoples of the Northern Arctic and Canada and the lowest prevalence in African countries.

The presence of the HLA gene is B27 found in about 85% of patients with a confirmed diagnosis of AS leads to a greater risk of developing the disease among immediate family members, an earlier onset age, a better clinical response to tumor necrosis factor alpha inhibitors, and a greater risk of acute anterior uveitis. HLAs B27 negative patients have a delay in diagnosis and a lower risk of psoriasis and IBD.

By examining gender differences in AS, women have higher disease activity, delayed diagnosis, and higher rates of enthesitis. At the same time, men have a more severe lesion according to X-ray studies.

In the structure of mortality in patients with AS, mortality from cardiovascular causes leads, oncology is in second place, infectious diseases are in third place.

When analyzing the effect of AS on quality of life, a correlative relationship was found between disease activity, anxiety, depression and decreased productivity. This, combined with increased disability and deterioration of daily activities in leisure time, also leads to a decrease in quality of life.

Our analysis of the literature demonstrates a tendency to increase and more frequent detection of AS among the female population in recent decades. At the same time, there is a significant delay in diagnosis in women compared to men, which leads to a significant deterioration in the quality of life due to the late start of treatment. The results also indicate the need for diagnosis and management of patients with AS, taking into account modern gender characteristics of the course of the disease.

Furthermore, the above data indicate a significant impact of ankylosing spondylitis on both the health and socio-economic side of patients' lives. Considering the young age of morbidity, the high level of invalidity and incapacity for work among patients of this cohort, the great influence on the quality of life of the patient, the study of the features of epidemiology and the course of AS is an urgent problem of medicine.

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