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## MENINGOCOCCAL DISEASE: CLINICAL AND EPIDEMIOLOGICAL FEATURES

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## MENINGOCOCCAL DISEASE: CLINICAL AND EPIDEMIOLOGICAL FEATURES

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(In our country a two-stage system for obtaining academic degree has been adopted, in this regard Doctor of Science is the highest research degree, in our case - D.S. in Medicine. PhD is equivalent to doctoral candidate)

### ABSTRACT

**Research objective:** to study and analyze clinical and epidemiological features of meningococcal disease at present stage.

**Material and methods.** A prospective analysis of the epidemiological, clinical and laboratory data was carried out in 118 patients with invasive meningococcal disease, who were hospitalized in the City Clinical Hospital of Infectious Diseases No.1 in Tashkent.

**Results and discussion.** The epidemiological situation of meningococcal disease in Uzbekistan is characterized by signs of the inter-epidemic period, when there is an increasing incidence of meningococcal disease in the age structure, and high proportion of patients aged 7-

14 years (17.9%) and 20-29 (39.8%). The leading serogroup among the laboratory-confirmed cases is the *N.meningitidis* serogroup A (99.1%), while currently there have been cases of disease caused by *N.meningitidis* serogroup W135 and C. The characteristic hemorrhagic rash associated with persistent hyperthermia which appeared only on the 3-4th day of the disease was a clinical feature of the generalized forms of meningococcal disease, which greatly complicated timely diagnosis. In patients who suffered from the combined form of meningococcal disease and "pure" meningitis we often observed such pathological complications as sensorineural hearing loss (3.3%), encephalopathy (11.8%), as well as the development of severe necrosis with scarring at the localization of rash.

**Conclusion.** The current epidemic situation and the clinical course of invasive forms of meningococcal disease require decisive preventive measures. Nowadays, the vaccination against meningococcal infection is one of the most important trends in reducing morbidity and mortality of meningococcal disease in children and adults.

**Key words:** meningococcal infection, meningococemia, meningitis, vaccination.

## INTRODUCTION

Meningococcal disease (MD) is a vital infection characterized by the fulminant course, severity and risk of adverse outcomes [1, 2]. MD is notable for the cyclical nature of the epidemic process with periodic outbreaks every 8-30 years, and according to the view of experts the next start of MD incidence is predicted to 2019-2025 [3, 4]. The review of the current literature [5, 9] shows that the widespread circulation of the pathogen as asymptomatic carriers, airborne transmission route, diversity of pathogen serogroup and migration flows are the basis of the periodic activation of the epidemic MD process, which requires to be solved using specific prevention measures in accordance with the WHO [3, 10].

In recent years, a great number of studies have been conducted dedicated to the atypical course of meningococcal disease [11]. Clinical polymorphism of generalized forms of meningococcal disease (GFMD), the absence of pathognomonic signs during the first hours of the disease determine the difficulty of early diagnosis, which in some cases is the cause of late hospitalization, complications and ineffectiveness of reanimation measures. However, despite severe and sometimes fulminant course of the disease, in most cases, availability of the clinical and epidemiological features of MD at the present stage allows to diagnose the disease timely, determine the correct tactics of urgent measures, thereby reducing the risk of the fatal outcomes.

## RESEARCH OBJECTIVE

The aim of the work is to study and analyze the clinical and epidemiological features of meningococcal disease in patients at the present stage.

## MATERIALS AND METHODS

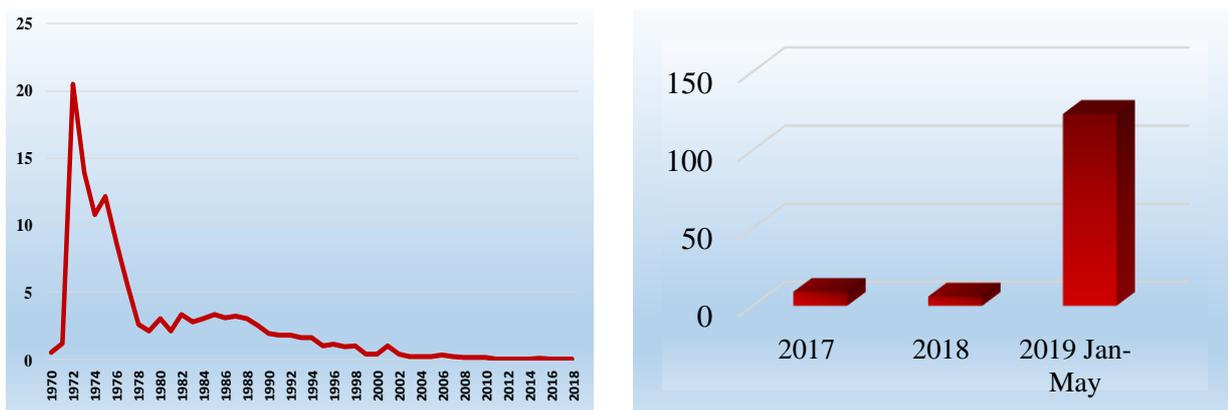
We conducted a prospective study of epidemiological, clinical and laboratory data of 118 patients with invasive form of meningococcal disease (meningococemia, meningitis), who were hospitalized at the City Clinical Hospital of Infectious Diseases No.1 in Tashkent.

The diagnosis of MD was established based on the clinical data, laboratory test abnormalities, blood culture, CSF analysis results and radiological examination. *Neisseria meningitidis* strains were isolated and identified using a standard blood culture method in all patients (118/100%). Serogroups of isolated *Neisseria meningitidis* strains were identified by latex agglutination reaction (Set Wellcogen to meningococcal disease/Wellcogen Bacterial Antigen Kit). The antibiotic susceptibility of *N. meningitidis* samples was also verified with Diffusion Tests (Mast Disc, UK).

Follow-up of patients was carried out throughout the period of their hospital stay. Clinical observation was supplemented by conventional laboratory methods survey. According to the survey results, a database was formed, and using the package Microsoft Office 2017 Professional STATISTICA 6.1 application a statistical analysis was performed.

## RESULTS

In recent years, according to official data of the Republican State Sanitary and Epidemiological Surveillance the incidence of MD in Uzbekistan maintained within 0.3 - 0.2 per 100 thousand people. The situation changed in January 2019 when there was a rapid increase in the incidence of MD, and for the period January to May 2019 123 cases of generalized forms of MD were recorded (Fig. 1). Invasive MD is characterized not only by the severity of the course, but also the possibility of high mortality rate and frequency effects of the disease with subsequent disability [12, 13]. Despite the availability of specific support-diagnostic features, advanced features of the disease course both in children and adults, possible cause of diagnostic, therapeutic and tactical errors at different stages of medical care is not excluded.

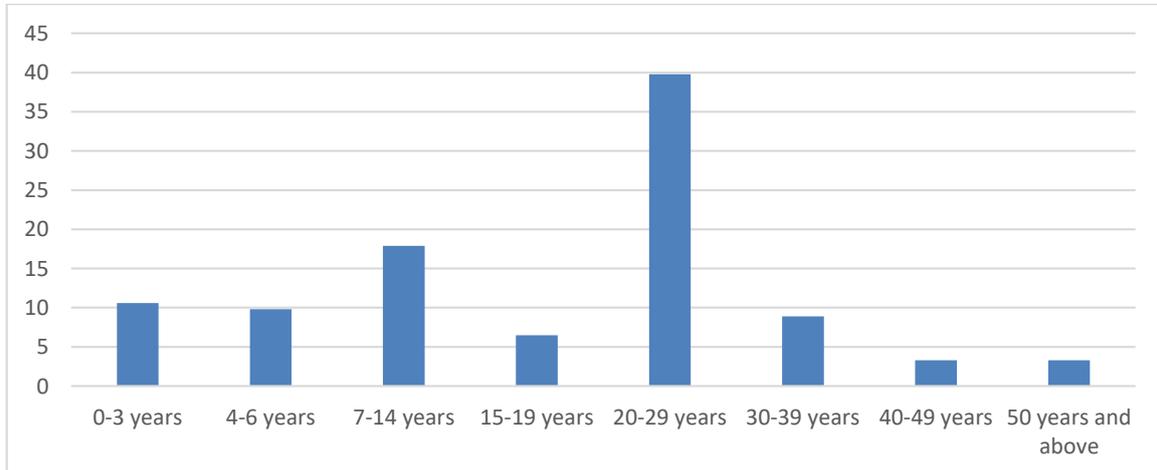


**Fig. 1. The incidence of MD in Uzbekistan in 1970 - 2019**

According to the researches of many authors, the percentage of bacteriological confirmation of the MD etiology ranges from 6% to 70% depending on the laboratory equipment. The low rate of bacteriological confirmation of the disease etiology and obtaining the result after the first day of

the studies are the causes to expand the volume of laboratory tests using rapid diagnostic methods.

The analysis of the age aspect of patients hospitalized with invasive MD showed that significantly higher incidence was observed in the age 20-29 years (39.8%) and 7-14 years (17.9%). As can be seen from the Figure 2, the patients were 4-6 years old - 10.6%, 0-3 years old - 9.8%, 15-19 years old - 6.5%, 30-39 years old - 8.9%, 40-49 years old - 3.3%, and 50 years and older - 3.3% of cases.



**Fig. 2. Age aspect of patients with invasive meningococcal disease (n=118)**

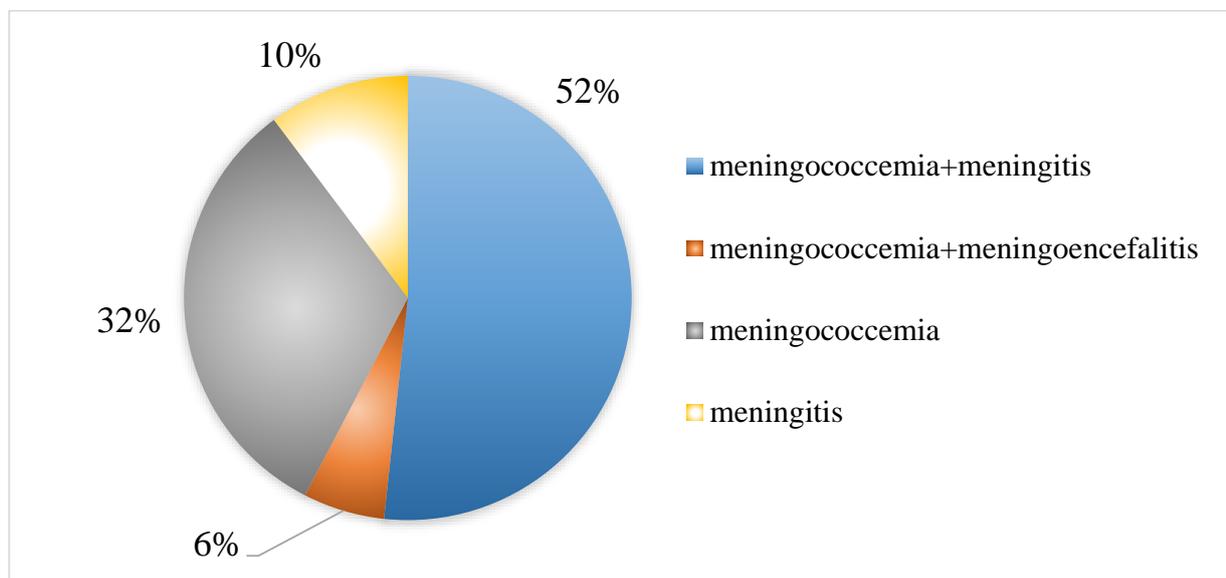
When collecting epidemiological history, it was found that 78% of the patients were residents of Tashkent city, and the rest were from various regions of the country. In over 50% of cases there was a family contact, when a family has got few children, sometimes with the parents.

The analysis of hospitalization of patients with invasive MD by months showed that more than 50% of patients were admitted in March. So, in January and February isolated cases of MD were recorded, when the patients were Uzbek citizens living in Tashkent, who had arrived the day before from the neighboring countries (Russia, etc.), sometimes already with symptoms of infection. From the end of February and in March, the number of patients increased significantly among the contact persons. Since May, there has been a decrease in the number of hospital admissions, which may be related to the rapid response of the sanitary-epidemiological service, and conduction of preventive and anti-epidemic measures, particularly identification of contacts, isolation of people with the localized form of MD (nasopharyngitis), vaccination and chemoprophylaxis of contact and risk groups.

The social and professional aspect of MD patients was presented by employees working in the construction companies, as well as schoolchildren, students, etc.

The leading clinical form of invasive MD is the combined form (68/57.6%). Thus, the combination of meningococemia with meningococcal meningitis was 61/51 in 7% of cases, meningococemia with meningococcal meningococcal meningoencephalitis 7/5 in 9% of cases recorded in all age groups. Among non-combined clinical forms

meningococemia and meningococcal disease occurred in 38/32% of cases and meningococcal meningitis in 12/10% of cases. In this case, when analyzing the current period, it should be noted that all clinical forms were evenly distributed in all age groups (Fig. 3).



**Fig. 3. The structure of clinical forms of meningococcal disease**

When analyzing clinical features of invasive forms, it was found that typical classical variant of the disease was observed in 100% of patients. Acute onset, characterized by temperature rising to 39,5-40°C during the first hours of the disease, and hyperthermia were resistant to the antipyretics; even in case of defervescence for 1-2°C, it again began to rise after a while. Hyperthermia in children was accompanied by a change in the child's behavior, ahypnosis, severe psychomotor agitation (10.6%), and most often it occurred in the first year of infants' life. However, in most cases, patients were observed with hypersomnia and weakness, which in 100% of cases was noted in children under 3 years old. In 64% of patients at initial stages of the disease vomiting appeared, which in some cases has been repeated. From the first hours of the disease most patients (72.8%) had hypersensitivity to all kinds of stimuli; in children it was presented by sensitivity to light and any touches. Besides, an inconsolable crying was also the clinical feature of the intoxication process in patients under 3 years. Severe headache of a diffuse-bursting nature, aggravated by a change in body position was recorded in 61.0% of cases, significantly more often in older patients. Loss of consciousness was noted in 11.0% of patients. As a result of dehydration therapy, after 2-3 days the headache decreased, and on the 4-5th day of the disease it stopped.

The pathognomonic symptom of meningococemia and combined invasive MD forms was a hemorrhagic necrotic rash in a star-shaped form. In patients under our observation the rash appeared on the first day of the disease (96.6 %), more often - in 12 hours from the disease onset. On the 2nd day the rash developed more intensively. The early occurrence of rash (first 5–8 hours) was specific for

severe hypertoxic forms of MD, and was mainly observed in children under 3 years old (5/4.2%), and only in 2.2 % - in children aged 4–7 years. The rash was characterized by star-shaped hemorrhagic-necrotic and spotty-papular eruptions. Its localization involved all parts of the body, but most often it was observed on the lower limbs and lower torso (83/70, 3%). In cases of invasive MD associated with 2-3 grade toxic shock syndrome (TSS), rash mainly localized on the area of face and upper body, and then spread to the limbs. Spotted-papular nature of rash was specific for elder patients. This fact complicated the work of ambulance doctors and physicians to diagnose MD at the prehospital stage. Only on the 3-4th day of the disease against the background of fever we observed classical hemorrhagic necrotic rash associated with simultaneous development of toxic shock syndrome that considerably complicated the timely diagnosis.

As mentioned above, the most frequent early complication of invasive MD was the toxic shock syndrome (TSS), occurred in more than 50% of patients. In 72 patients under our observation (61.0%), we noted manifestations of TSS. Grade 1 TSS (46/63,8%) was predominant, grade 2 TSS was less frequently registered (20/27,7%), while grade 3 TSS was observed in 6 (8.3%) patients.

Meningococcal meningitis was observed in 10.2% of patients, and was characterized by acute onset, fever, intoxication, severe headache, hyperesthesia, vomiting that didn't bring relief, as well as positive meningeal symptoms (stiff neck, Brudzinski's and Kernig signs), purulent nature of the cerebrospinal fluid.

The analysis of fatal outcomes due to the invasive MD showed that the most important risk factor for the adverse outcome was the age of the patient (children under one year), as well as late health seeking behavior. It was revealed that in most cases (63/53,3%) patients sought medical advice in the first 12 hours from the disease onset; in 55/46, 7% - on the 2nd day of the disease. However, the analysis of admitting time showed that 52% of patients were hospitalized at the first call, 36% - at the time of the second emergency call, and 12% of patients were hospitalized after repeated calls and examinations by an ambulance or a physician.

Outcomes of invasive MD observed in patients were characterized by the development of severe residual impairments, which could worsen the quality of life, as well as lead to disability. Most often patients were observed with hypertensive-hydrocephalic syndrome, severe headache of diffuse nature, periodic dizziness, amnesia, impaired concentration, and fatigue. Moreover, sensorineural hearing loss (3.3%), fronto-cerebellar ataxia (5%), residual encephalopathy (11.8%), symptomatic epilepsy (3.3%) were noted. Those patients were managed at dispensary and were regularly visited by a neurologist. In severe forms of meningococemia, deep necrosis developed, which formed further scarring of the skin and subsequently required plastic surgery [14].

The results of the study of *N.meningitidis* serogroup strains isolated by patients with invasive MD showed that since the period of increased disease incidence, the leading serogroup among laboratory confirmed cases was the serogroup *N.meningitidis* A (99.1%), and in one case - *N.meningitidis* W135 (0.9%) (Fig. 4).

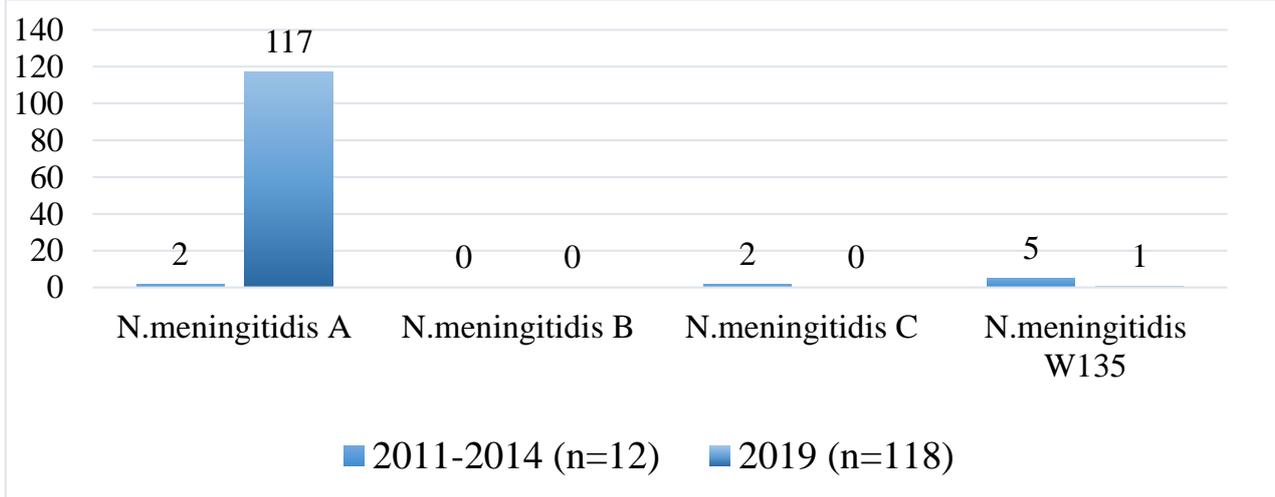


Fig. 4. Serogroups of *N. meningitidis*, isolated from patients with MD

Comparative characteristics of the serogroups of isolated *N. meningitidis* in the period 2011 to 2019 is shown in Fig. 4.

It should be remembered that the etiologic diagnosis with serogroup identification of *N.meningitidis* is the integral part of meningococcal disease surveillance, which provides informed prevention of meningococcal disease, including vaccination [15].

## CONCLUSION

Summarizing the above stated, we can conclude that the general circulation of the causative agent of meningococcal infection in carriers, the airborne transmission route of infection, the variety of serogroups of the pathogen and migration flows are the basis for the periodic activation of the epidemic process of MB. This problem requires resolving on specific prevention of MD in Uzbekistan. Issues of timely diagnosis, principles of etiotropic and pathogenetic treatment of various clinical forms of MD, as well as specific prevention remain relevant and require development in the system of epidemiological surveillance of meningococcal infection.

## Highlights

1. The epidemiological situation of meningococcal disease in Uzbekistan is characterized by signs of the interepidemic period.
2. The increase in MD incidence was observed in the age aspect: patients aged 7-14 years (17.9%) and patients aged 20-29 (39.8%).
3. The leading serogroup among the laboratory-confirmed cases is *N.meningitidis* serogroup A (99.1%); recently there have been cases of disease caused by *N.meningitidis* serogroups W135 and C.
4. The observed clinical forms of invasive MD, with characteristic hemorrhagic rash associated with persistent hyperthermia, developing on the 3-4th day of the

disease. It was considered as a feature of the clinic of invasive forms of MD, significantly complicating the timely diagnosis.

5. Patients who suffered from the combined form of MD and the "pure" meningitis often were observed with such pathological complications as sensorineural hearing loss (3.3%), residual encephalopathy (11.8%), as well as the development of severe necrosis with scarring at the rash localization.
6. The use of polyvalent conjugate vaccines against meningococcal disease in potential risk groups will reduce the MD incidence and mortality among children and adults.

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