

Clinical and economic estimation of children's pharmacotherapy with meningococcal infections in Ukraine

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Abstract

A comprehensive study for assessment the appointments rationality for children with meningococcal infectious (MI) in Ukraine in real clinical practice has been conducted. The doctor's appointment sheets from 184 inpatients medical cards have been processed by the integral ABC / VEN / frequency analysis. In average, children were in the hospital (14±7) bed-days, they were granted 2908 appointments of 191 drugs by the INN. It has been established that medicine for MI etiotropic therapy took the third place in the appointments frequency. At the same time, the ABC / VEN-analysis results revealed a rational approach to pharmacotherapy. The total treatment cost was estimated at USD 25,173.59 (for one child – USD 136.81). Since currently in Ukraine inpatient children treatment is mainly provided by parents, further medical prescriptions improvement is needed in order to increase the efficiency and minimize the children MI therapy cost.

Keywords

ABC-analysis, children, frequency analysis, meningococcal disease, VEN-analysis

Introduction

Meningococcal infection (MI) continues to be a public health problem (Cabellos et al. 2019). It is caused by *Neisseria meningitidis* and characterized by clinical polymorphism with nasopharyngitis and simple carriage to generalized forms – meningitis and meningococemia (Vaz 2017). MI is potentially fatal and should always be considered as an emergency medical aid. Taking into the account the global and rapid spread of MI in the human population, high mortality, WHO attributed this disease to a group of especially dangerous infections and constantly monitors morbidity (WHO 2017). Usually, MI is represented by meningitis, septicemia, or a combination of them. Among 12 recognized serogroups, six (A, B, C,

W, X, and Y) may cause a worldwide epidemic of MI with a mortality rate from 0 to 20%. In Europe and North America, serogroups B, C and Y are wide spread (Jafri et al. 2013; Borrow et al. 2017).

A heavy burden of MI lies in Sub-Saharan Africa regions, known as the meningitis belt, stretching from Senegal in the west to Ethiopia in the east (Nadel 2012). According to the Report on the Epidemiological Surveillance of Controlled Bacterial Infections ECDC (2018), in 2016 30 EU / EEA countries reported 3,280 confirmed MI incidents. In general, the incidence of MI in the EU / EEA countries decreased from 0.95 per 100,000 in 2008 to 0.6 per 100,000 in 2016. The highest incidence rates were re-

gistered in Lithuania, Ireland, and the United Kingdom (ECDC 2018). In Bulgaria, the incidence rate was 0.17 per 100,000 in 2016, with a prevalence of male sex (66.67%) among those registered in the year. Frequency of invasive meningococcal infection was highest in children under 1 year – 3.05% (2 incidents) and 1–4 years – 1.86% (5 incidents) (Kurchatova et al. 2016).

In Ukraine, there is an increase tendency of the incidence in recent years: 0.63 per 100,000 in 2016 and 0.7 – in 2017. The mortality rate for meningococemia among children ranged from 15% to 17.5%, and in some areas – up to 50%. Therefore, in Ukraine, in the structure of mortality of children with infectious diseases under the age of 14, 20.3% goes on the MI (2012) (<https://phc.org.ua>).

Rapid detection of meningococcal disease and aggressive early treatment have a primary importance for reducing mortality. Treatment of patients with MI is conducted taking into account the clinical form and severity of the disease. In Ukraine, the protocol for the treatment of meningococemia in children is regulated by the order of the Ministry of Healthcare of Ukraine № 737. According to this, the treatment of patients, in addition to antibiotic therapy, includes infusion therapy, treatment of DICs syndrome, sympathomimetic and inotropic hemodynamics, corticosteroids, diet therapy (Order of the Ministry of Health of Ukraine № 737 of 12.10.2009). The NICE directive (The National Institute for Health and Care Excellence of the United Kingdom) recommends the introduction of benzylpenicillin at the pre-hospital stage for adults and children over 10 years at a dose of 1.2 g / day, from 1 to 9 years – 600 mg, and up to 1 year – 300 mg. However, the administration of antibiotics should not delay the hospitalization of the patient. The most economical is the use of ceftriaxone (once a day). However, according to the NICE data, as well as the Scottish Intercollegiate Guidelines Network (SIGN), it is recommended not to use ceftriaxone with calcium-containing substances and during 48 hours after use, and if necessary to replace ceftriaxone with cefotaxime (NICE 2010).

The current economic conditions determine the increase in demand for pharmacoeconomic studies as arguments for decision-making in health care. In Ukraine such practice is being mastered and first of all they should relate to potentially life-threatening diseases, for example MI. Therefore, the selected topics are actual at the present time.

The aim of the work

To carry out a comprehensive assessment of the appointments rationality for children with MI according to the Ukrainian protocol for children meningococemia treatment.

Materials and methods

Retrospective analysis of medical appointments was carried out with the help of 184 cards of inpatients –

children with meningococcal infection on the basis of 6 health care facilities of Ivano-Frankivsk, Ternopil, Vinnytsia, Kyiv, Kharkiv and Odessa oblasts for 2009–2016. A comprehensive assessment of the actual financial costs of pharmacotherapy was carried out by ranking the costs of pharmacotherapy (ABC analysis), ranking of prescribed medicines by their degree of importance (VEN-analysis). The ABC analysis involves the distribution of drugs from the highest to the lowest cost, depending on their proportion in the indicator of general drug use. It shows on which drugs money are mainly wasted to: A group – a group of drugs on which is spent 80% of all money (prescribed value), B group – 15%, and C group – 5% (Vorobiov 2008). The ABC analysis of the consumed pharmacotherapy cost was conducted with retail prices, calculated by multiplying the drugs average wholesale selling price by a margin rate 1.25, taking into account 7% of VAT as of September 1, 2018, according to the resource of the «Software complex «Apteka»» (1 USD = 28.20 UAH).

A formal approach was used during conducting VEN analysis (WHO 2003, Vorobiov 2008). Distributing drugs to groups V – «Vital», E – «Essential» and N – «Non-essential» was carried out in accordance with the Protocol for treatment of meningococemia in children (Order of the Ministry of Health of Ukraine № 737 of 12.10.2009).

Results

According to medical cards it has been studied the socio-demographic characteristics of sick children. Statistical analysis of the sample showed that the proportion of sick boys amounted to 50.5% of the total number of children. Accordingly, the proportion of sick girls is 49.5% (Table 1). Consequently, the most dangerous MI is for children aged 1–4, as it is accompanied by difficult course and complications. For the most part sick children were urban residents (56%). In the structure of meningococcal infection among generalized forms, 40.2% have meningococcal disease, 11.4% meningitis, and 48.4% – combination of them. In the first place among the complications is the toxic shock syndrome (TSS), the second is the disseminated intravascular coagulation (DIC), the third is the arthritis.

Table 1. Demographic characteristic of children with meningococcal disease.

Gender distribution	
Male	50.5%
Female	49.5%
Distribution by residence area	
City	56%
Village	44%
Distribution of children by age	
>1 year	32.6%
1–4 years	40.2%
5–9 years	16.3%
10–14 years	3.8%
15–17 years	7.1%

The next stage of the study was a frequency analysis. Totally, 2908 appointments were made to patients (15.8 appointments per one sick child). The children were in the hospital on average (14.0±7) bed-days. Table 2 shows the top 10 INN for usage frequency.

Thus, leaders of appointments were sodium chloride, which is used for infusion therapy and as a solvent; ceftriaxon as an antibacterial agent for etiotropic MI therapy, it is recommended by both the Ukrainian protocol and international standards. Distribution of drugs according to the ATC classification showed that the largest share of all names of medicines covered the funds of groups J “Anti-infectives for systemic use” (21.6%) and A “Alimentary tract and metabolism” (21.4%) (Figure 1).

The next stage of the research was the conduction of ABC analysis. Group A included drugs, which accounted for 79.3% of the total, and amounted to USD 19 964.5 on September 2018. There were 19 INN (9.9% from the total assortment). B group included 33 INN (17.3%), the value of which amounted to USD 3 751.2 (14.9% of the total cost). In group C there are 139 INN (72.8%) with the cost of USD 1 457.87 (5.8%). The total cost of treatment con-

sumed by 184 patients was USD 25 173.59 (USD 136.81 / per patient).

For VEN classification Protocol for treatment of meningococemia in children in Ukraine was used in current study. V group included drugs which used only for etiotropic therapy and are presented in Protocol: ceftriaxone, cefotaxime, benzylpenicillin, ampicillin, levomitsetin succinate and aminoglycosides (amikacin, netilmicin). Glucocorticoids, antibiotics and other drugs presence in protocol are forming E group. The remaining drugs belong to N group. According to the results of the VEN analysis, the largest number of drugs (64.4% of the total assortment) is secondary and the ratio between the number of drugs in the groups V: E: N in the percentage was 4.2:31.4:64.4. The share of expenditures for medicines with N status is 23.4%, which determines the need for further search of ways to reduce costs for secondary drugs. The results of complex clinical and economic analysis are presented in Table 3.

Table 2. TOP-10 INN by the frequency of appointments for the treatment of children with meningococcal disease.

No	INN	Absolute number of appointments	Share in totality of appointments, %	Share of inpatients, which took medicine, %
1.	Sodium chloride	160	5.50	87
2.	Ascorbic acid	126	4.33	68.5
3.	Ceftriaxone	121	4.16	65.8
4.	Probiotics	114	3.92	62.0
5.	Electrolytes in combination with other drugs	113	3.89	61.4
6.	Furosemide	112	3.85	60.9
7.	Dexamethasone	100	3.44	54.3
8.	Supplements	86	2.96	46.7
9.	Heparin	85	2.92	46.2
10.	Coccarboxylase	84	2.89	45.6

Table 3. Results of the complex ABC/VEN – analysis of children therapy with MI for the A group.

No	Drugs	Consumption, USD	VEN
1	Meropenem	4883,1	E
2	Ceftriaxone	2323,1	V
3	Heparin	2064,1	E
4	Vancomycin	1889,3	V
5	Probiotics	1349,9	N
6	Electrolytes in combination with other drugs	1304,5	E
7	Cefotaxime	997,7	V
8	Benzylpenicillin	893,3	V
9	Immunoglobulins	787,7	N
10	Furosemide	787,7	E
11	Amikacin	432,7	V
12	Mannitol	365,9	N
13	Fluconazole	347,6	N
14	Sodium chloride	327,3	E
15	Methylprednisolone	272,9	E
16	Potassium chloride	246,8	E
17	Hydrocortisone	246,7	E
18	Ceftazidime	223,3	E
19	Lysine	221,0	N

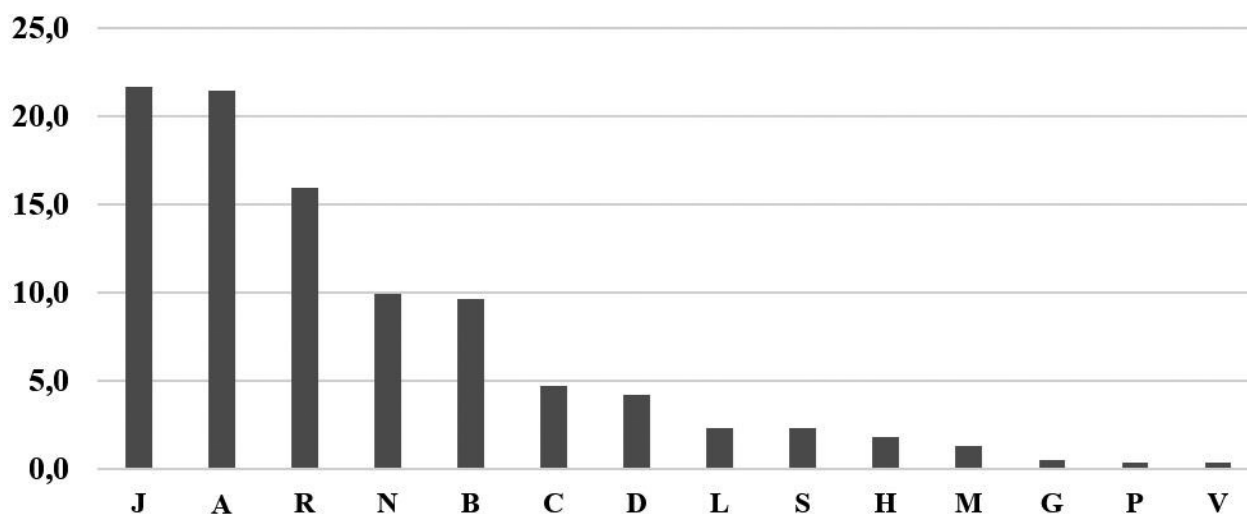


Figure 1. Distribution of prescribed medicines by ATC-classification groups.

Discussion

It has been processed 184 medical cards of inpatients with MI, which have received treatment in 6 hospitals of different regions of Ukraine. The analysis found that the MI was mostly characteristic of children aged 1–4 years (40.2%), who live more often in urban areas (56%). For underage patients 2908 appointments were made of 191 medicines for the INN.

It has been estimated the present state of pharmaceutical provision of children with MI with retrospective methods of clinical and economic analysis. The results of the frequency analysis showed that by ATC-classification medicines from the groups J “Antiinfectives for systemic use” (21.6%) and A “Alimentary tract and metabolism” (21.4%) were dominating, and the leaders of appointments were sodium chloride, ascorbic acid and ceftriaxone. Simultaneously, the results of real clinical practice analysis in Ukraine revealed the prevalence of cephalosporins, namely ceftriaxone in the doctors' prescriptions. The use of ceftriaxone or cefotaxim is advisable in the treatment of patients with MI according to Zalmanovici TA et al and National Collaborating Center for Women's and Children's Health publications, and that is showed in the results of this research.

The total cost of consumed treatment amounted to an average USD 136.8 per 1 patient. In researches of Italian

scientists (Bozzola et al. 2019), the cost of treatment for children with meningococcal meningitis was 26 to 9329 EUR per patient. According to the ABC / VEN-analysis, a rational approach to pharmacotherapy has been identified, since group A includes classes V and E recommended by the Clinical Protocol. However, by the number of appointments, 64.4% are occupied by secondary drugs of class N, the cost of which totaled 23.4% of the funds, which requires an urgent revision.

Conclusions

Comparison of the results of ABC-, VEN- and frequency analysis have shown that in general funds are spent for pharmacotherapy of MI patients in the clinics of 6 Ukrainian oblasts and it could be considered as rational and economically effective. At the same time, the distribution of consumed drugs by classes of rationality revealed a high proportion of secondary drugs in pharmacotherapy for children with MI. The results of real clinical pediatric practice of treatment of children with MI show the need for its further optimization both in relation to evidence-based therapy and pharmacoconomics, as in modern conditions of reforming health care it is fully provided by the parents' cost.

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