EXPERIENCE OF IMPLEMENTATION OF ECMM EQUAL SCORES IN TREATMENT OF CHILDREN AT RISK OF INVASIVE MYCOSIS

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The ECMM EQUAL Scores tool was proposed in 2018 as a way to improve the quality of treatment of invasive mycoses and assess compliance with the diagnostic algorithm. Currently, there are no reports of its practical application in pediatrics. This study aimed to assess the prevalence of invasive mycosis in a pediatric hospital, the attributed mortality in children with invasive mycosis, and to analyze the dynamics of consumption of antifungal drugs. By design, the study was multidirectional observational, and spanned two years, with retrospective part over the period from 01.01.2022 to 31.12.2022, and prospective part — from 01.01.2023 to 31.08.2024. We used ECMM EQUAL Scores to evaluate the conformity of the fungal infection prevention measures and the empirical therapy to the established risk tier the patients were allocated to, and calculated the ATC/DDD index to measure the consumption of antifungal drugs. During the 20-month follow-up period, 78 children survived, 20 died; supervision continues. The attributed mortality rate was 25.6%. The weighted average absolute ECMM EQUAL Scores were as follows: for candidiasis — 8.4 (38%), for aspergillosis — 6.6 (24%), and for mucormycosis — 9.85 (31%). With the help of the ATC/DDD index, we assessed the dynamics of consumption of antifungal drugs in 2022 and 2023, the "before" and "after" periods. It was concluded that introduction of the ECMM tool into the invasive mycosis diagnostic routine significantly raised the number of detected cases (from 5 to 98 per year), and pushed down the attributed mortality from 60% to 25.6%. With ECMM EQUAL Scores, the NNT index was 2.9. Before introduction of the ECMM tool, in 2022, antifungal drugs were given for 30.3 DDD per 100 bed-days, after the introduction in 2023 — 54.7 DDD per 100 bed-days.

Keywords: pediatrics, mycosis, invasive, clinical trial, antifungal, mycosis risks

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ОПЫТ ВНЕДРЕНИЯ ПРОТОКОЛА У ДЕТЕЙ С РИСКОМ ИНВАЗИВНОГО МИКОЗА ECMM EQUAL SCORES

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Для улучшения качества лечения инвазивных микозов и оценки соблюдения диагностического алгоритма в 2018 г. предложен метод ECMM (EQUAL Scores). Практический опыт применения у детей в настоящее время не представлен. Целью работы было оценить распространенность инвазивного микоза в детском стационаре, атрибутивную летальность у детей с инвазивным микозом и проанализировать динамику потребления противогрибковых препаратов. Разнонаправленное наблюдательное исследование выполнено в течение двух лет: ретроспективная часть в период с 01.01.2022 по 31.12.2022 и проспективная — с 01.01.2023 по 31.08.2024. Оценку соответствия противогрибковой профилактики и эмпирической терапии инвазивного микоза установленной группе риска пациента проводили методом ECMM (EQUAL Scores), оценку потребления противогрибковых препаратов — методом ATC/DDD-анализа. За период наблюдения в течение 20 месяцев выжили 78 детей, умерли — 20, наблюдение продолжается. Атрибутивная летальность составила 25,6%. Средневзвешенная абс. оценка по методу ECMM (EQUAL Scores) для кандидоза составила 8,4 (38%), для аспергиллеза — 6,6 (24%) и для мукормикоза — 9,85 (31%) от допустимой. Изучена динамика потребления противогрибковых препаратов методом ATC/DDD-анализа за 2022 и 2023 г. «до» и «после». Сделан вывод, что внедрение метода ECMM для диагностики инвазивного микоза привело к значительному увеличению числа выявленных случаев с 5 случаев в год до 98 случаев в год со снижением атрибутивной летальности с 60% до 25,6% соответственно. Индекс NNT при использовании метода ECMM составил 2,9. До внедрения метода ECMM потребление противогрибковых препаратов в 2022 г. составляло 30,3 ЧДТ (в стандартизованной суточной дозе) на 100 койко-дней, после внедрения в 2023 г. — 54,7 ЧДТ (в стандартизованной суточной дозе) на 100 койко-дней.

Ключевые слова: педиатрия, микоз, инвазивный, клиническое исследование, противогрибковый, риски микоза

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Invasive mycoses account for a significant part of complications and deaths in patients with malignant neoplasms and impaired immunity in the background, or in cases of allogeneic hematopoietic stem cell transplantation (HSCT) [1].

No invasive mycoses management clinical recommendations have been published in Russia. Moreover, not every medical institution can verify an invasive mycosis diagnosis and establish its etiology [2, 3]. "Crawling" antifungal therapy is the

prescription of antifungal drugs that are not recommended for empirical antifungal therapy to patients who have not went through the complete diagnostic algorithm and thus have the lesion loci unidentified and the etiology unclear [4]. In patients with suspected invasive mycosis, such treatment regimen increases the risk of adverse reactions and drug interactions due overprescription of antifungal medications. Ultimately, crawling antifungal therapy may prolong inpatient stay, adversely affect the outcome of treatment of the underlying disease, and decrease the survival rate of patients [1, 3].

In 2018, European Confederation of Medical Mycology (ECMM) developed EQUAL Scores, a tool enabling systematic approach to diagnosing and improving the quality of treatment of patients with invasive mycoses. According to multicenter studies, introduction of this tool into protocols designed for adults helped raise the rate of invasive mycoses survival in this population [5-7]. As for children, there are currently no reports describing the use of ECMM EQUAL Scores in their treatment. Optimized amounts of antifungal drugs prescribed is one of the indicators of successful application of the principles of adequate diagnosing. Earlier, optimization of consumption of antibiotics confirmed this statement [8]. The degree of optimization of prescription of antifungal drugs can be one of the indicators in the dynamic assessment of the effectiveness of ECMM EQUAL Scores [1–3]. This study was organized to investigate applicability of ECMM EQUAL Scores in pediatrics, where the tool has not been used before.

The purpose of this study was to assess the prevalence of invasive mycosis in patients of a multidisciplinary pediatric hospital, determine the attributed mortality in this group, and analyze the dynamics of consumption of antifungal drugs against the background of adoption of ECMM EQUAL Scores as a tool to assess/categorize the risk of invasive mycosis in patients.

METHODS

Protocol of the study

The observational multidirectional study consists of retrospective and prospective parts. The retrospective component included patients of both sexes, aged from one month to 18 years, diagnosed with invasive mycosis, treated from 01.01.2022 to 31.12.2022. The prospective component includes 130 patients aged from one month to 18 years, diagnosed with invasive mycosis, treated from 01.01.2023 to 31.12.2025. Inclusion criteria: invasive mycosis diagnosed as per the CDC criteria. Non-inclusion criteria: terminal failure of organs and systems as competing with the infection for the main diagnosis or condition. Exclusion criteria: foster care; previous/concomitant therapy is not relevant for inclusion in the study. The diagnosis of invasive mycosis should be established under the CDC guidelines, with at least one host factor meeting the clinical and radiological criteria. The medical histories of inpatients diagnosed with invasive mycosis were analyzed in KIS EMIAS, a consolidated medical information system, and ECMM EQUAL Scores enabled assessment of the adequacy of treatment and invasive mycosis control to the diagnosis. The diagnosing methods were microbiological and microscopy examinations of liquid and dense substrates (tissue and fluid samples), including calcofluor white staining that allows detecting septic and unseptated mycelium. All patients had various organs, including those in the chest, scanned with high-resolution computed tomography, since typical signs of invasive pulmonary mycosis are often lacking, and even atypical pulmonary infiltrates may indicate presence of this disease [4]. To diagnose aspergillosis, we tested biological fluids for galactomannan antigen (GalMAg-ELISA).

All patients diagnosed with invasive mycosis underwent a genetic study that employed iPLEX Pro PGx panel (Agena Bioscience, USA) 68 SNP/INDEL. VeriDose® Core Panel allows detecting of the relevant variants in the genes *ABCB1, APOE, CYP1A2, CYP2B6, CYP2C19, CYP2D6, CYP3A4, CYP3A5, PNPLA5, SLCO1B1, SULI4A1*, which can potentially affect drug metabolism. In addition, using real-time allele-specific PCR, we sought for clinically significant variants of the *TPMT, ATIC*, and *SLC19A1* genes in patients.

Throughout the study, up to 31.12.2025, we shall monitor patients to register possible ineffectiveness of therapy, development of adverse reactions, and deaths. Registration of an adverse reaction includes assessment of the severity of manifestations, the cause, and association with the antifungal drug.

It is planned to gather a control group of 30 patients with oncological or oncohematological diseases but not diagnosed with invasive mycosis; in this group, we shall also look for the polymorphisms of candidate genes. The subsequent analysis of the associations between such polymorphisms and ineffectiveness of antimycotic therapy, development of adverse reactions, and fatalities will be based on the results of this genetic study.

The comprehensive observational study was conducted at the Pediatric Oncology, Onco-Hematology and Hematopoietic Stem Cell Transplantation (HSCT) Department of Morozovskaya Children's City Clinical Hospital; it lasted two years, including the retrospective analysis part from 01.01.2022 to 31.12.2022, and the prospective analysis part 01.01.2023 to 31.08.2024. In both parts, we used ECMM EQUAL Scores to assess the adequacy of antifungal preventive measures and empirical invasive mycosis therapy to the established risk tiers. DDD analysis enabled assessment of the dynamics of antifungal drug consumption over the 12 months of 2022 and 2023. The effort to improve the invasive mycosis diagnostic methods included development of internal protocols and algorithms approved by the management order (Fig. 1). To diagnose aspergillosis, we looked for galactomannan antigen in biological fluids. In addition, microscopic examination of biological fluids with calcofluor white staining was introduced [8–10].

A patient was diagnosed with invasive mycosis if there were factors affecting the host and clinical and radiological criteria were met [12–14]. The criteria confirming the presence of invasive mycosis include at least one positive result returned by the following studies: microscopic, histopathological, cytopathological, microbiological, serological, or genetic, followed by verification of the fungal agent [15–17]. We stratified the patients into the invasive mycoses development risk tiers based on host factors for mycelial and yeast invasive mycoses:

– grade 4 neutropenia (< 0.5×10^9 neutrophils for >10 days);
– hematological tumors;
– recipient of allo-HSCT or a solid organ transplant;
– over three weeks of taking glucocorticosteroids (GCS) at an average minimum dose of 0.3 mg/kg/day (prednisone equivalent);
– treatment with T-cell immunosuppressants within the last 90 days;
– treatment with B-cell immunosuppressants (only for mycelial invasive mycoses);
– hereditary severe immunodeficiency (chronic granulomatous disease or severe combined immunodeficiency, deficiency of signaling protein and activating transcription factor 3);
– acute graft-versus-host disease (grade III or IV) with intestinal, lung, or liver damage, resistant to first-line therapy with GCS [3, 8, 11].

Table. ECMM EQUAL Scores assessment criteria

Invasive mycoses assessment criteria (98 patients)	Candidiasis (n = 98)	Aspergillosis (n = 98)	Mucormycosis (n = 98)
	Maximum ECMM EQUAL Scores values, points		
Patient's risk tier Radiological studies Platings Microscopy, preferably using optical brighteners Molecular diagnostics Histology Galactomannan test (aspergillosis identification)	10	15	18
TREATMENT Drug therapy (administration of an etiotropic antifungal drug without or after prior mould prophylaxis) Surgical treatment (removal of affected tissues according to indications)	10	5	8
FOLLOW-UP Radiological examination of the lesion locus (dynamical registration) Blood plating	2	7	6
Total	22	27	32

Using ECMM EQUAL Scores, we quantified the quality of diagnosis and treatment of invasive mycosis of various types based on medical records of inpatients. Table gives the quality assessment criteria and maximum scores for each section.

There is evidence of candidemia having the mortality rate of up to 40% in the adult population despite antifungal therapy. In case of *Candida*, the overall mortality rate varies significantly depending on the species; it averages at 7.7% for *C. albicans*, 23.7% for *C. glabrata*, 7.7% for *C. parapsilosis*, and 63.6% for *C. tropicalis* [18]. As for the paediatric population, there is currently no general mortality rate data describing cases of candidemia and other types of mycosis. In this study, at the time of introduction of the ECMM algorithms, the attributed mortality was 25.6%

We analyzed (ATC/DDD approach) the consumption of antifungal drugs in 2022 and 2023.

Figure 1 gives the principles of diagnosis of invasive mycoses under this protocol.

Statistical procedures

The IBM SPSS Statistics v26 software package (IBM, USA) was used for statistical processing of the research results.

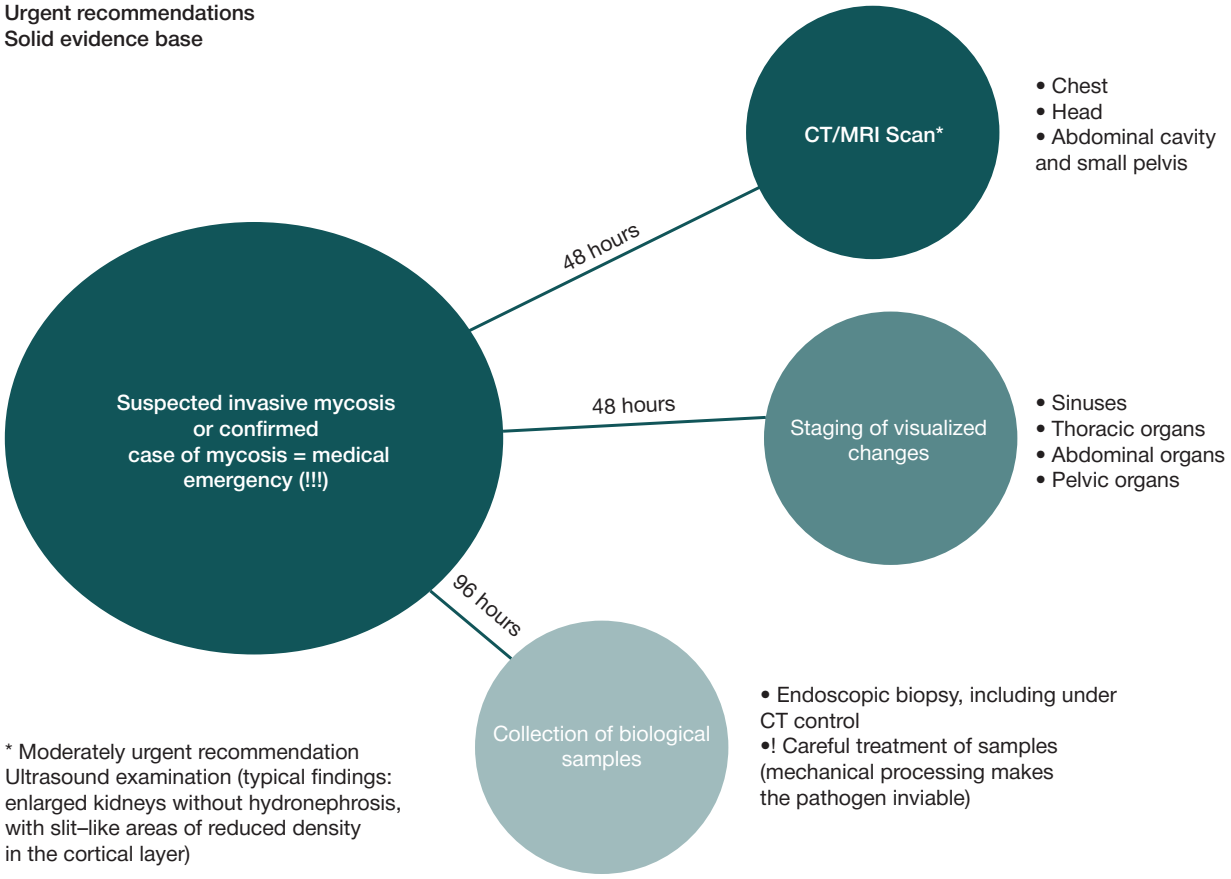

Fig. 1. Invasive mycoses diagnosing algorithm. Adapted from: Duane R. Hospenthal et al., 2023 [3]

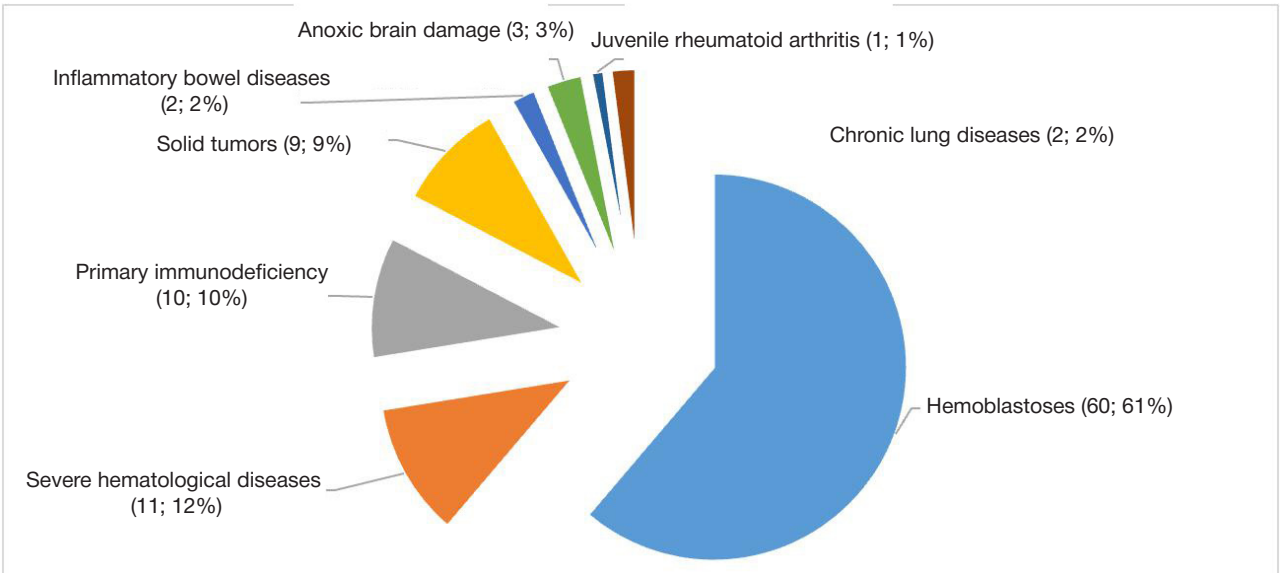

Fig. 2. Characteristics of the main diseases in patients diagnosed with invasive mycosis

RESULTS

In 2022, invasive mycosis was diagnosed in five children aged one month to 18 years (three boys and two girls), mean age of 7.6 years. Of them, two children are being treated against invasive aspergillosis, and three children have died (two with invasive mucormycosis and one with aspergillosis). The diagnosis of invasive mycosis was established in accordance with the CDC criteria. All patients included in the retrospective analysis had host factors characteristic of mycelial and yeast invasive mycosis: two of them underwent allogeneic HSCT in the first year without T-cell immunity restoration, and three children suffered from oncohematological diseases and had long-term neutropenia, receiving high doses of steroids.

From 01.01.2023 to 31.08.2024, the diagnosis of invasive mycosis was established in 98 patients (56 boys and 42 girls) aged from one month to 18 years, mean age of 12.4 years (13.0 years). Of them, 36 patients underwent allogeneic HSCT transplantation in the first year without T-cell immunity restoration; they also took steroids or several immunosuppressive drugs. 45 patients suffered from long neutropenia, and 17 were taking high doses of steroids. During the 20-month follow-up period, 78 children survived, 20 patients died; supervision continues. The attributed mortality rate was 25.6%. In one case involving a prevented fatality, the effectiveness of preventive intake of antifungal drugs was assessed using the EQUAL Scores and the NNT (number needed to treat) calculator, as described in [19].

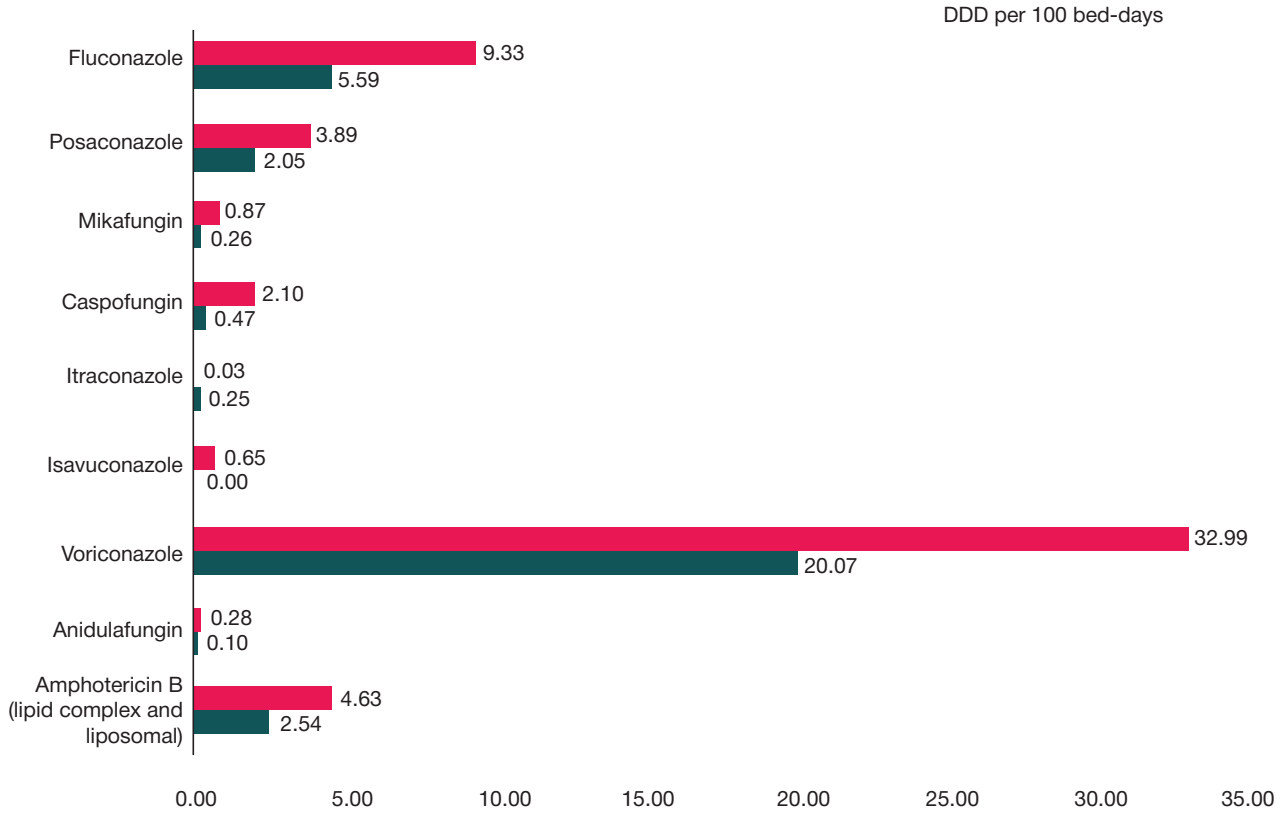

Fig. 3. Dynamics of consumption of antifungal drugs before and after introduction of the ECMM EQUAL Scores tool in 2022–2023

The median ECMM EQUAL Scores value for invasive candidiasis was 8.4 points, which is equivalent to 38% of the maximum. For invasive aspergillosis, this value was 6.6 points (24% of the maximum), and for invasive mucormycosis — 9.85 points, which is 31% of the maximum. Figure 2 presents the distribution of patients by main diseases.

Invasive mycosis was diagnosed in accordance with criteria 1–6 of the standard invasive mycosis case definition [3]. In real practice, the process of diagnosing potential invasive mycosis with clarification of its localization and etiology in a patient exhibiting host factors begins almost simultaneously with empirical and preventive (diagnostic) antifungal therapy, so the key aspects that can be improved in this context are the current diagnostic algorithms, which should be standardized, and administration of antifungal drugs, which can be rationalized. These changes will play an important role in ousting ineffective approaches, including the irrational practice of crawling antifungal therapy.

In 2022, voriconazole was the most consumed antifungal drug (20.07 DDD per 100 bed-days) (Figure 3). It was followed by fluconazole (4.59 DDD per 100 bed-days), amphotericin B liposome and lipid complex (2.54 DDD per 100 bed-days), posaconazole (2.05 DDD per bed-days), caspofungin (0.47 DDD per 100 bed-days), and anidulafungin (0.10 DDD per 100 bed-days).

In 2023, after the introduction of the ECMM EQUAL Scores tool, voriconazole consumption remained dominant (32.9 DDD per 100 bed-days), followed by fluconazole (9.33 DDD per 100 bed-days), amphotericin B (liposomal and lipid complex) (4.63 DDD per 100 bed-days), posaconazole (3.89 DDD per 100 bed-days), caspofungin (2.10 DDD per 100 bed-days), isavuconazole (0.65 DDD per 100 bed-days), and micafungin (0.28 DDD per 100 bed-days).

DISCUSSION

The retrospective part of this study has shown that before adoption of the ECMM EQUAL Scores tool, the frequency of inappropriate use of antifungal drugs in the context of crawling therapy was 78%. After the said adoption, this figure decreased to 32%, but overall consumption of the antifungal drugs has grown significantly: in 2022, the total use was 30.3 DDD per 100 bed-days, and in 2023, after introduction of ECMM EQUAL Scores, this value increased to 54.7 therapy days per 100 bed-days. The growth of consumption of antifungal drugs may be associated with improvements in the fungal infections diagnosing routines or changes in clinical practice that boosted preventive use of antifungal drugs.

While crawling therapy became less common, the total consumption of antifungal drugs increased 1.8 times compared to 2022, because they were prescribed for preventive purposes. The number of children who could benefit from the ECMM EQUAL Scores in the context of prevention of one fatality by invasive mycosis was 2.9 (NNT), therefore, this study shows that the tool is effective and should be considered for use in paediatric clinical practice.

Study limitations

There are no voriconazole and posaconazole concentrations monitoring reagents registered in the Russian Federation, which disallows realizing the full potential of the ECMM EQUAL Scores tool. Despite this, the results of the study conducted under these conditions remain significant.

CONCLUSIONS

The prevalence of invasive mycosis in 2023–2024, within the scope of this study, was 1.5 cases per 100,000 hospitalized patients. Introduction of the ECMM EQUAL Scores tool into invasive mycosis diagnosing routines significantly increased the number of detected cases (from 5 to 98 patients from 01.01.2023 to 31.08.2024), and decreased the attributed mortality from 60% to 25.6%. The NNT index of 2.9 indicates that approximately three patients must be treated using the ECMM tool to prevent one death from invasive mycosis. In the adult population, the total candidemia mortality is 40%, but for the pediatric population, there is no data on the invasive mycoses mortality rate. After adoption of the ECMM EQUAL Scores tool, the use of antifungal drugs increased from 30.3 DDD per 100 bed-days in 2022 to 54.7 DDD per 100 bed-days in 2023. Thus, the tool boosted consumption of antifungal drugs by 80% within a year. Diagnosis and treatment of invasive mycoses in children are based on the same principles as in adults. This study has shown that ECMM EQUAL Scores significantly increases the effectiveness of invasive mycoses diagnosing in children. We have observed an improvement in the detection of invasive mycoses, which, in turn, allows a more accurate adherence to the current clinical guidelines. Although introduction of the ECMM EQUAL Scores tool decreased the number of crawling therapy cases from 78% in 2022 to 32% in 2023, this practice remains quite common. The analysis of consumption of antifungal drugs (ATC/DDD) before and after adoption of this tool revealed that approximately half of the hospitalized patients required antifungal drugs for prevention and therapy. In this study, we have shown the effectiveness of the ECMM EQUAL Scores for children: to prevent one fatal case of invasive mycosis, it was necessary to preventively give apply antifungal drugs to 3 patients (NNT index of 2.9). Thus, the ECMM EQUAL Scores tool should be recommended for wider application in paediatric clinical practice.

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