Bulletin of the *Transilvania* University of Braşov
Series VI: Medical Sciences • Vol. 18 (67) No. 2 – 2025
https://doi.org/10.31926/but.ms.2025.67.18.2.4

SEVERE COMPLICATIONS IN PEDIATRIC CYSTIC FIBROSIS: OVERCOMING THE CHALLENGES (CASE REPORTS)

L.L. DRACEA[1,2] A. BĂNCILĂ[2]

Abstract: *Cystic fibrosis (CF), is an autosomal recessive disorder caused by mutations in the CFTR gene, leading to atypical ion transport across epithelial cells and resulting in thick mucus accumulation. This condition significantly affects multiple organ systems, particularly the respiratory and gastrointestinal tracts, leading to infections and progressive dysfunction. The introduction of CFTR modulator therapies has dramatically improved life expectancy, now reaching approximately 50 years in high-income countries. This paper presents two CF cases from the Emergency Clinical Children's Hospital of Brașov, facing severe, life-threatening complications. One patient successfully overcame a complication related to CF, while the other experienced a significant COVID-19 complication, while presenting as a pulmonary exacerbation (PEx) of CF. The cases highlight the challenging clinical outcomes in CF and personalized approach. Intravenous antibiotic use, as piperacillin/tazobactam, one of the mainstay interventions for PEx due to its effectiveness against Pseudomonas aeruginosa, may rarely lead to severe adverse events, such as drug-induced thrombocytopenia. Furthermore, although respiratory viral infections may adversely affect pulmonary status in CF patients, emerging evidence suggests that SARS-CoV-2 infection did not severely impact this group. Paediatric inflammatory multisystem syndrome (PIMS) associated with SARS-CoV-2 infection has to be considered even in CF patients with scarce symptoms, underscoring the challenge of potential complications.*

Key words: *cystic fibrosis, complications, modulator therapy, thrombocytopenia*

1. Introduction

Cystic fibrosis, first described as a separate disease in 1938 by the pathologist Dorothy Andersen, is an autosomal recessive genetic disorder caused by mutations in the cystic fibrosis transmembrane conductance regulator

[1] Faculty of Medicine, *Transilvania* University of Braşov
[2] Clinical Emergency Children's Hospital of Brașov

(CFTR) gene, which encodes the protein that regulates the movement of chloride and sodium ions across the membranes of epithelial cells. Various organs, the respiratory system, intestine, pancreas, kidneys, sweat glands and male reproductive tract are affected. The absence or dysfunction of the protein, accumulation of mucus will lead to infections and inflammation, contributing to malnutrition and progressive pulmonary dysfunction and failure.

CFTR modulator therapy (CFTRm) is represented by the first drugs which actually treat the underlying genetic disorder, and not only the clinical symptoms, thereby changing the outcome of CF. The fatal disease of childhood in the 80's, with a life expectancy around 18 years changed in recent years, reaching 50 years in high income countries [1]. CFTRm represents a game-changing therapy and has a significant impact on outcome of lung disease, nutrition, pulmonary exacerbations, quality of life and use of medical resources for CF patients.

The paper illustrates two cases of CF patients admitted in the Clinical Emergency Children's Hospital in Brașov, who experienced critical, life-threatening complications and facing significant risk of mortality. Substantial recovery and favorable clinical outcomes were achieved despite severity.

One of the patients developed a complication linked to the preexisting severe lung status, while the second, a complication due to COVID-19 with potential severe consequences, but with no significant impact of the SARS-CoV-2 infection itself.

Carefully evaluation and personalized management may overcome even the most critical situations related to poor prognosis in CF.

2. Case report 1 (**R.G**.)

R.G., male, 7 years and 11 months old, admitted in February 2024, was diagnosed in July 2019 with cystic fibrosis heterozygous for F508del/2184insA. He was undergoing chronic treatment with pancreatic enzyme replacement therapy (PERT) (Kreon), inhaled Pulmozyme, Tobramycin, hypertonic saline 7% (Rhinorex CF), liposoluble vitamins A, D, E. Following two recent severe PEx that needed hospitalization, he was on home oxygen therapy.

Recent onset (1-2 days) of productive cough, breathing difficulty led to the hospital presentation. When admitted, a critically ill boy (20kg, 118cm tall) with severe respiratory failure, no fever, pale and suffering, pectus carinatum, frequent productive cough and frequent purulent sputum, tachypnoea, SaO2=75%, heart rate of 125beats/minute, distended but non-tender abdomen, no any digestive symptoms and clinical findings, urination normal, no neurological signs, dry skin with fingers scaling (atopic dermatitis).

Laboratory findings showed: negative RT-PCR GeneXpert for SARS-CoV-2, leukocytosis with neutrophilia, lymphopenia, respiratory acidosis, elevated C-reactive protein (12.24 mg/dL), increased fibrinogen, normal liver and renal function tests, negative panel tests for *Respiratory Syncytial Virus*, *Influenza A* and *B.* Sputum cultures were positive for *Pseudomonas aeruginosa.*

The chest X-ray revealed numerous nodular opacities distributed throughout both lung fields, extensive bronchiectasis

predominantly in the upper lobes, thickened bronchial walls with mucus impaction. (Figure 1)

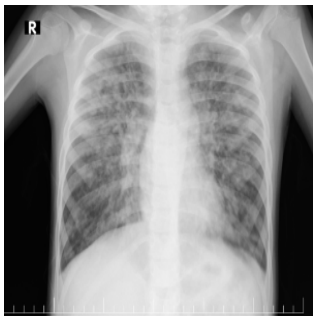

Fig. 1. Chest X-ray (addmission)

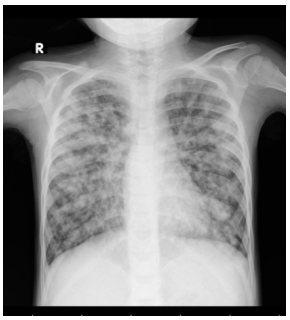

Fig. 2. Chest X-ray (day 10))

The critical state and the inability to maintain normal SaO2 levels, non-invasive mechanical ventilation using CPAP (FiO2 65%, PEEP 6cm H2O) was initiated in the Emergency Department, being followed by admission in the Intensive Care Unit (ICU) where he continued to remain critical (anxious, with tachypnea and exhausting cough, disseminated bronchial crackles), but increased SaO2 to 100% and hemodynamic stability.

CPAP was continued in the following days, along with hydro-electrolyte rebalancing and intravenous antibiotics, Meropenem and Vancomycin. Methylprednisolone, inhaled Pulmozyme, Tobramycin, Rhinorex FC, Colistin, Salbutamol (Ventolin), respiratory nursing, Kreon, Esomeprazole, probiotic, liposoluble vitamins A, D, E, antipyretics and analgesics were recommended by the CF specialist.

Cardiac examination and ultrasound showed to be normal. Normal total IgE and specific IgE for *Aspergillus fumigatus* excluded Allergic Bronchopulmonary Aspergillosis.

Despite intensive treatment, first days of hospitalization were marked by worsening with uncontrollable spasmodic cough, and severe respiratory failure that led to discontinuation of inhalation therapy (Tobramycin, Colistin, hypertonic saline solution 7%), preserving only Pulmozyme and adding intravenous Colistin to the previously mentioned antibiotic therapy.

After 10 days, due to subsequent favorable respiratory progress with maintaining normal SaO2 values using intermittent CPAP and supplemental oxygen therapy at 6 L/min via facial mask, decrease of inflammatory markers and no Chest X-ray worsening (Figure 2), the patient was transferred to the Respiratory Diseases Department, where inhaled therapy and respiratory physiotherapy were restarted.

After almost 2 weeks of hospitalization, after serious deliberation, being considered a potential „rescue therapy", with the parents' approval, CFTRm (Kaftrio, Kalydeco) was started (donation from a CF patient). It was not considered „ compassionate use", only a potential rescue therapy initiated in a severe PEx in a patient that could not be initiated on such a therapy based on the recommendations of the National

Protocol. According to the FDA, February 2024, "compassionate use" is a potential pathway for patients with possible terminal diseases to gain access to investigational medical products that "have not yet been approved or cleared by the FDA to be safe and effective for their specific use.") [10]

Change of antibiotics with intravenous Ceftazidim along Meropenem and Colistin, being mandatory after 21 days, due to the presence of mucoid *Pseudomonas aeruginosa.*

Multiple subsequent febrile episodes, a new increase in C-reactive protein levels (8.78 mg/dL), significant leukocytosis with neutrophilia, and expanding opacities on the chest X-ray (13th of March) with no pleural effusion [Figures 3, 4] were progressively noted.

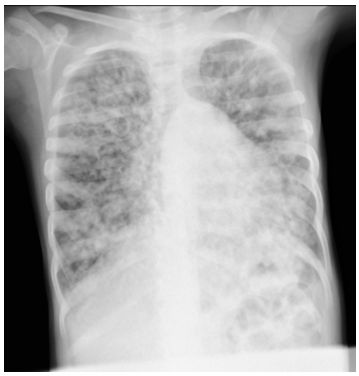

Fig. 3. Chest X-ray (13th of March)

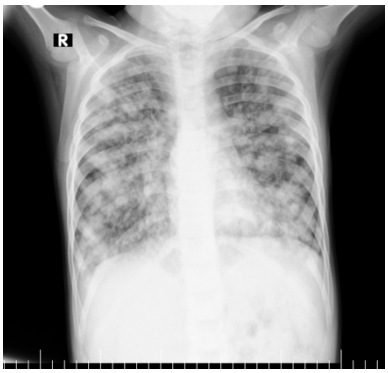

Fig. 4. Chest X-ray (16th of February)

Piperacillin-Tazobactam and amikacin followed the former combination of antibiotics after 21 days since admission.

Upon the initiation of CFTRm, the patient's respiratory status has gradually improved, with reduction of cough frequency, decrease of sputum., better oxygenation and reduction in pCO2 levels.

After one month of admission, the patient presented minimal hemoptysis following a coughing episode. Thrombocytopenia was noted, initially not significant, aggravated in the following days (8,000/µL). Every 12h intravenous tranexamic acid was administered along with a compatible platelet transfusion. A complete blood count (regenerative anemia) and immunologic evaluation (normal) was recommended to rule out other medical diagnosis vs. a potential side effect of medication.

Thrombocytopenia was regarded as a potential side effect of medication administration, with no clear relationship with CFTRm or Piperacillin-Tazobactam (administered for 9 days). Minimal thrombocytopenia was reported in clinical trials with CFTRm, but for safety reasons, treatment was initially interrupted. Due to worsening of thrombocytopenia, Piperacillin-Tazobactam was also stopped. After these interventions no more active hemorrhages were noted, a few petechiae were observed on the chest, abdomen, and oral mucosa, therefore intravenous immunoglobulin therapy and two platelet transfusions were initiated.

Progressive normalization of platelet counts followed.

Stopping CFTRm for 2 days increased the frequency of productive cough and sputum. As the platelet count progressively increased with no further external bleeding, CFTRm was reintroduced, with daily monitoring of hemogram parameters. Reduction of cough and sputum followed and thrombocytopenia did not recur. Clinical respiratory status and chest X ray improved as well. After 33 days of iv antibiotics, oral Ciprofloxacin started.

Piperacillin-Tazobactam induced thrombocytopenia, confirmed by different literature reports, probably also related by the first-time administration of the antibiotic in this particular patient was considered.

As CFTRm may lead to cataracts, the patient underwent an ophthalmologic evaluation that showed normal.

Normalization of blood tests, no inflammatory markers, mild anemia, normal renal and liver function and attenuation of the lung opacities followed.

Lung function was severely affected with very low FEV1 (0.75l, 29% predicted), and FVC (0.75l, 45% predicted), demonstrating severe obstructive lung disease and mixt ventilatory dysfunction. The patient remained oxygen dependent when discharged and several months afterwards. CFTRm continued and in the following months improved nutrition, lung disease, even need for oxygen.

Despite severe lung disease with a life-threatening PEx that posed serious medical challenges, CFTRm therapy proved to be a game- changer in end-stage lung disease illustrating remarkable efficacy. This subtle, progressive and significant recovery reveals the transformative potential of today's targeted therapies.

Drug-induced severe thrombocytopenia, even extremely rare, promptly recognized, a complication of Piperacilin-Tazobactam therapy, was successfully managed.

3. Case report 2 (D.V.)

D.V., a 16-year and 3-month-old male patient, homozygous delta F508 cystic fibrosis, with moderate/severe lung disease since 2018, presented with spasmodic cough, fever (a maximum value of 38.6°C), odynophagia, 3 days before admission.

He was undergoing chronic treatment with digestive enzymes (Kreon), Dornaze alpha (Pulmozyme), Tobramycin, hypertonic saline solution 7% (Rhinorex FC), Azithromycin. liposoluble vitamins A, D, E, ursodeoxycholic acid.

His medical history was marked by other relatives with CF (brother, first degree cousin, other deceased 2 siblings), deceased father with pulmonary embolism. He is known to be allergic to Ceftazidime, has kidney and gallbladder stones.

Clinical examination revealed no fever, congested pharynx, hypertrophic tonsils, spasmodic cough, bilateral rhonchi, SaO2=96%, no dyspnea or retractions, normal heart sounds, no abdominal tenderness, normal urine output, absence of neurological clinical signs.

The complete blood count showed no significant changes, although inflammation was significantly present (C-reactive protein = 20 mg/dl). Over time, a progressive decrease in C-reactive protein levels was noted, ultimately leading to normalization.

Elevated hepatic transaminases indicated

moderate hepatocytolysis syndrome, with normalization of these values upon repeated testing. The urinary sediment revealed no significant abnormalities. SARS-CoV-2 Ig G were positive.

Nasal and pharyngeal swabs were negative, as was the urine culture. Given the presence of a pronounced inflammatory syndrome without an identification of an infectious source, pediatric multisystem inflammatory syndrome (PIMS) associated with SARS-CoV-2 was suspected, prompting the measurement of cardiac inflammatory markers, significantly increased: NT-pro BNP: 1159 pg/ml, CK-MB: 122 U/L, increased D dimer.

Intravenous methylprednisolone was initiated in doses recommended by international protocols, cardiology assessment was performed, revealing myocardial distress, with dilation of the right coronary artery, Z-score >4. Aspirin therapy was recommended. These evaluations confirmed the diagnosis of PIMS.

Further cardiology assessment after the first week, revealed favorable progression of the coronary artery dilation, with decrease in dimensions in the following two weeks from admission, showing recalibration to 3.5 mm and a Z-score of 1.4 mm. Another follow-up was recommended in one month. NT-pro BNP and CK-MB levels had a declining trend.

Bilateral moderate bronchiectasis with mucus impaction was observed on the chest X-ray.

Abdominal ultrasound revealed moderately enlarged, homogeneous liver; micro gallbladder with 3-4 mm hyperechoic images; common bile duct and portal vein were normal. The pancreas was smaller in size, hyperechoic and heterogeneous. Both kidneys were in normal position and size, with 4-5 mm hyperechoic images and mild renal pelvic dilation on the left side.

Along intravenous hydro-electrolyte rebalancing during the first days of admission, antibiotic therapy with Amikacin, Imipenem-Cilastatin, probiotic, Colobreathe inhaler, ursodeoxycholic acid, hypertonic saline solution 7% (Rhinorex CF), liposoluble vitamins A, D, E, digestive enzymes and aspirin 75 mg orally once a day were administered for two weeks.

Upon discharge, the patient was afebrile, hemodynamically stable with no respiratory symptoms, good appetite and responsiveness.

Cardiology follow up was recommended to monitor dilation of coronary artery following PIMS. After a month, cardiac outcome was excellent with normalization of coronary artery indexes, confirming literature data, with excellent outcome even after serious PIMS in children and adolescents.

4. Discussions

Complications in severely ill CF patients are frequent, and treatment associated complications, as well. Interventions in clinical borderline situations must be judged according patients' status, known risks and evaluation of short-term outcomes. CFTRm has been proved to be life saving for some severely ill patients but may pose risks as well. The first illustrated case was on the edge of severe complications resulting from severe thrombocytopenia due to possible adverse reaction from two categories of medication. To rule out which one is the culprit is not easy for the clinician, much more when no specific tests are available.

It is known that frequent administration of antibiotics in CF patients is associated with possible side effects, sensitization, and even more severe complications such as renal failure, hearing loss, etc.

Piperacillin is a beta-lactam antibiotic commonly administered in combination with the beta-lactamase inhibitor tazobactam. This combination results in the broadest-spectrum antibiotic within the beta-lactam class, with efficacy against a range of gram-negative bacteria, including *Pseudomonas spp,* a bacterium that frequently colonizes or chronically infects the respiratory tract of CF patients. It's clinical use is primarily reserved for hospital-acquired or nosocomial infections. One notable adverse effect of this drug is myelosuppression, particularly neutropenia. However, drug-induced thrombocytopenia (DIT) associated with beta-lactam antibiotics, particularly piperacillin/tazobactam (P/T), is documented, yet an exceedingly rare adverse effect. [2]

In a retrospective study published in 1999 on 38 cystic fibrosis patients from Children's University Hospital, Leipzig, Germany with chronic pulmonary infection with *Paeruginosa* and treated with piperacillin/tazobactam, one of them developing DIT thrombocytopenia and neutropenia. A normal blood cells count was recorded 4 days after discontinuation of P/T. [3]

Furthermore, in a systematic review published in 2020 in the Journal of Clinical Pharmacy regarding hematologic side effects induced by P/T, P/T thrombocytopenia was identified in 13,02% of the patients. [4]

P/T is among the most frequently utilized antibiotics in clinical practice, particularly for hospital-acquired or nosocomial infections and specifically in CF patients with chronic pulmonary infection with *Paeruginosa.* Although rare, drug-induced thrombocytopenia associated with P/T is a potential adverse effect that clinicians should be aware of and suspicion of DIT should be considered when a patient undergoing P/T treatment develops thrombocytopenia.

On a different note, regarding case 2, that developed PIMS after a nonsignificant previous SARS-CoV-2 infection documented by positive Ig G antibodies, the diagnosis has to be suspected even in CF patients with clinical and laboratory markers for this syndrome.

It is also known that while viral respiratory infections generally more severely impact CF patients when compared to general population, a limited number of studies suggest that SARS-CoV-2 does not lead to severe infections in individuals with CF. This may be due to intrinsic specific immune reactions at the level of bronchial epithelial cells. This finding was unexpected, given that comorbidities, such as preexisting lung disease, may be linked with poorer outcomes in SARS-CoV-2 infections. It has been suggested that it may be a causative relationship with variations and expression of the ACE and ACE2 genes, which are crucial for SARS-CoV-2 infection, and which may be associated with a reduced severity of the infection. [5]

Regarding the issue of complications of SARS-CoV-2 infection, which emerged after the initial wave of the COVID-19 pandemic, there was no doubt that some clusters of children presented with unusual multisystem inflammatory manifestations. The clinical syndromes displayed variability, with manifestations like toxic shock, Kawasaki disease, or

undifferentiated inflammatory traits, and were frequently associated with current or previous COVID-19 infection. [6] In a 2022 retrospective study conducted by Lods Medical University, Poland, the dilation of the coronary arteries was found in 22,8% of the patients. [7] Undoubtedly, although most children typically experienced mild or asymptomatic SARS-CoV-2 infection, the post-infectious complications can lead among others (long COVID) also to Pediatric Inflammatory Multisystem Syndrome, which may pose to life-threatening risk. [8]

PIMS illness is often distinguished by persistent fever, laboratory markers of inflammation, and evidence of single or multiorgan dysfunction. It may overlap with Kawasaki syndrome (conjunctival and mucosal injection, rash, swelling of the hands and feet, coronary artery dilation) or toxic shock syndrome (erythroderma, renal involvement, and hypotension). Cardiac manifestations, such as ventricular dysfunction, coronary artery dilation and aneurysms, arrhythmia, and conduction abnormalities may be common.

PIMS can be severe in a limited number of cases and cardiac involvement is usual in male adolescents. This complication needs an accurate diagnosis with the collaboration of a pediatric cardiologist to initiate proper treatment and monitor the outcome. More so, coronary artery dilatation is a significant finding in PIMS with a reported incidence of 20-45% of cases. There is a predilection for the left coronary artery and recent studies suggest that anomalies are not solely the result of inflammation but may be associated also with other immunological mechanisms. A small percentage of children that developed enlargement of coronary arteries have been proven to associate anatomic anomalies. Timely diagnosis is mandatory to start anti-inflammatory treatment with methylprednisolone. Literature showed that most patients had good outcomes when followed up after one year from diagnosis.

The case we presented has been regularly followed up and cardiac involvement solved with no need for prolonged treatment for PIMS.

5. **Conclusions**

Cystic fibrosis is a challenging disease. The multisystemic involvement, chronic pulmonary infection, can be managed with complex interventions and medication that frequently may represent an added challenge for the clinician. The new era with use of CFTRm even in severely ill patients led to life-changing outcomes. CFTRm can represent a risk for adverse reactions and treatment has to be carefully monitored. Adverse reactions from antibiotics are common and must be individually managed. Severe adverse reactions are rare but have to be anticipated by an experimented clinician. The choice of treatment for severely ill CF patients is always difficult, and clinical judgment must be specifically tailored according to short and long-term perspectives.

SARS-CoV-2 infection and its complications posed diagnosis and treatment problems for many patients, including those less affected by the infection itself, as CF patients. Even in those with nonsignificant symptoms, PIMS must be regarded as a potential severe complication with need of thoughtful evaluation and observation. Timely and accurate diagnosis is mandatory, mostly in those patients with cardiac involvement.

Results of careful observation and intervention can be rewarding even in the most severe of patients, that are more at risk for complications that challenge the clinician.

Acknowledgment

Approval was obtained from families and hospital Ethics Committee.

References

1. Bierlaagh MC, Muilwijk D, Beekman, J.M. *et al.* A new era for people with cystic fibrosis. *Eur J Pediatr* 2021; 180: 2731–2739. https://doi.org/10.1007/s00431-021-04168-y
2. Atalaia Barbacena H, Soares R, Lopes, I, Monteiro P. Drug Induced Immune Thrombocytopenia Associated with Piperacillin/Tazobactam: A Clinical Challenge. *International Journal of Medical Case Reports and* M*edical Research.* 2013; 10.61148/2994-6905/IJMCRMR/042.
3. Reichardt P, Handrick W, Linke A, Schille R, Kiess W. Leukocytopenia, thrombocytopenia and fever related to piperacillin/tazobactam treatment--a retrospective analysis in 38 children with cystic fibrosis. *Infection.* 1999 Nov-Dec; 27(6):355-6. doi: 10.1007/s150100050042. PMID: 10624596.
4. Wang, Q, He Z, Wu X. *et al.* Hematologic adverse effects induced by piperacillin–tazobactam: a systematic review of case reports. *Int J Clin Pharm.* 2020; **42**: 1026–1035. https://doi.org/10.1007/s11096-020-01071-8
5. Stanton BA, Hampton TH, Ashare A. SARS-CoV-2 (COVID-19) and cystic fibrosis. *Am J Physiol Lung Cell Mol Physiol.* 2020 Sep 1; 319(3):L408-L415. doi: 10.1152/ajplung.00225.2020. Epub 2020 Jul 15. PMID: 32668165; PMCID: PMC7518058.
6. Schlapbach LJ, Andre MC, Grazioli S, Schöbi N, Ritz N, Aebi C, Agyeman P, Albisetti M, Bailey DGN, Berger C, Blanchard-Rohner G, Bressieux-Degueldre S, Hofer M, L'Huillier AG, Marston M, Meyer Sauteur PM, Pachlopnik Schmid J, Perez MH, Rogdo B, Trück J, Woerner A, Wütz D, Zimmermann P, Levin M, Whittaker E, Rimensberger PC; PIMS-TS working group of the Interest Group for Pediatric Neonatal Intensive Care (IGPNI) of the Swiss Society of Intensive Care and the Pediatric Infectious Diseases Group Switzerland (PIGS). Best Practice Recommendations for the Diagnosis and Management of Children with Pediatric Inflammatory Multisystem Syndrome Temporally Associated with SARS-CoV-2 (PIMS-TS; Multisystem Inflammatory Syndrome in Children, MIS-C) in Switzerland. *Front Pediatr.* 2021 May 26; 9:667507. doi: 10.3389/fped.2021.667507. PMID: 34123970; PMCID: PMC8187755.
7. Stasiak A, Kędziora P, Kierzkowska B, Niewiadomska-Jarosik K, Perdas E, Smolewska E. Changes in the cardiovascular system in children with pediatric multisystem inflammatory syndrome temporally associated with COVID-19 - A single center experience. *Int J Cardiol.* 2022 Aug 15; 361:126-133. doi: 10.1016/j.ijcard.2022.05.030. Epub 2022 May 14. PMID: 35577166; PMCID: PMC9106401.

8. Lacina L, Bŕabek J, Fingerhutová Sˇ, Zeman J, Smetana K. Jr. Pediatric inflammatory multisystem syndrome (PIMS) - potential role for cytokines such is IL-6. *Physiol. Res*. 2021; 70: 153–159. https://doi.org/10.33549/physiolres.934673.
9. Commissioner, O. of the *U.S.* Food and Drug Administration. Available at: https://www.fda.gov/ (Accessed: 19 September 2024).