Mucormycosis (zygomycosis) is the third emerging important invasive fungal infection during the past decade, it is associated with a worse outcome when compared to other invasive fungal infections such as candidiasis or aspergillosis.1-4 The increase in the incidence may be attributed to a better outcome in the survival of immunocompromised patients.5 Depending on the underlying condition, such as the withdrawal or reduction of corticosteroids, impairment of neutropenia, hematological malignancies, hematopoietic stem cell transplantation (HSCT), adequate control of glycemia in cases of diabetes, and the portal of entry, they can cause rhinocerebral, pulmonary, cutaneous, gastrointestinal or even disseminated infection.6,7 The rapid initiation of antifungal therapy is the cornerstone due to the highly difficult treatment of this destructive infection.

We report retrospective results in the present study, where we reviewed clinical characteristics, risk factors, treatment and outcome of pediatric mucormycosis, diagnosed by histopathology at our center from 2007 until 2017, a University Hospital in Southern Turkey.

ABSTRACT

Background. Mucormycosis is a fatal invasive fungal infection seen most often in patients with compromised defense mechanisms. The aim of this article was to review the data of pediatric mucor in the South of Turkey.

Methods. Twenty pediatric cases with biopsy proven mucormycosis were reported, between January 2007 through January 2017. Data were extracted from the medical charts of patients retrospectively.

Results. Underlying conditions were hematological malignancy (75%), in whom 93% had acute leukemia, aplastic anemia (15%), diabetes mellitus (5%) and other malignancies (5%). The main sites of infection were sinus (85%); alone (29.4%) or with cerebral (17.6%), and orbital involvement (17.6%). Pulmonary involvement was reported in 11 patients (55%), two of them had the alone form and nine cases were associated with nasal sinus involvement. Disseminated mucormycosis was documented in 45%. Fever and pain/swelling of organs were the most commonly encountered signs and symptoms. Treatment compromised of amphotericin B monotherapy in five patients. All patients except one received liposomal formulations (LAmB). A combination of surgery and antifungal therapy was performed in 75%. Crude survival was 55%; among 15 cases treated with a combination of surgery and antifungal therapy, survival rate was 8/15 (53%). The overall mortality rate was high in patients diagnosed with disseminated infection (100%).

Conclusions. Mucormycosis in pediatric cases requires a high index of suspicion and urgent evaluation of clinical samples. Surgical debridement should be considered when feasible. Initial medical therapy should include an amphotericin preparation with or step-down to posaconazole.

Key words: mucormycosis, zygomycosis, children, immunosuppressive, amphotericin B.

Mucormycosis in a pediatric population: a review of 20 cases from southern Turkey

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ABSTRACT

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Material and Methods

The study was conducted in a tertiary medical college hospital (Çukurova University Faculty of Medicine). Our patients were managed by a multidisciplinary healthcare team comprised of oncologists, infectious disease specialists, surgeons, pathologists, radiologists and intensivists. The study was approved by the Institutional Ethics Committee (Approval number: 04-09-2019/91).

All pediatric patients (aged 0-18) that were diagnosed histologically as mucormycosis between January 2007 through January 2017, were included in the study. All cases were proven as mucormycosis based on a histopathologic examination of a needle aspiration and/or a biopsy specimen which revealed hyphae and evidence of associated tissue damage from the nasal cavity and/or paranasal sinuses and/or palate, lung or dermis.

Histopathologic diagnosis: Mucor infections are one of the correctly detectable fungi by biopsy and they are determined as angioinvasive, broad, without septas and 90 degrees branching hyphae in tissue sections. Although routine hematoxyline-eosin tissue sections are generally sufficient some histochemical stains like PAS and GMS (Gomori’s methanamine silver) can be used, its particularly predominant appearance is necrosis. Sometimes fungal hyphaes can be few, or degraded or folded in tissue sections.

All patients underwent computed tomography (CT) or magnetic resonance imaging (MRI) scans of paranasal sinuses, orbita, craniocerebrum and lungs.

The sites of infection were classified according to those utilized in the study of Roden et al.4 Accordingly, sinusitis was defined as an infection involving the paranasal sinuses; those with disease in paranasal sinuses and orbital infiltration were defined as sino-orbital infection; those with disease in the paranasal sinuses and the brain as rhinocerebral infection; those with disease in the paranasal sinuses and lungs were defined as having sinopulmonary infection; pulmonary infection was defined as infection confined to lung tissue and as deep extension when invading adjacent tissues, and dissemination was defined as two or more non-contiguous locations of Mucorales infection.

The demographic characteristics, type of underlying conditions, risk factors, the site of infection, clinical signs and symptoms of infection, radiological findings, treatments, and outcome were extracted from the medical charts of patients.

Results

The hospital pathology records identified 24 individual cases of mucormycosis in pediatric patients during 10 years. Of these, four cases were excluded from the database because they did not meet the stringent predefined inclusion criteria or the patient file could not be reached. During the study, 20 patients with proven mucormycosis (14 male, 6 female) were recorded. Demographic characteristics and clinical features are summarized in Tables I and II. The age at diagnosis ranged from 2 to 16 years (average age was 9 years) and 7 patients were aged ≤ 5 years. Two patients out of 20 were foreign (Syrian) nationals.

The patients’ underlying conditions are listed in Table II. Fifteen patients (75%) with hematological malignancy composed the largest group, in whom 93% had acute leukemia (one underwent HSCT). Three patients had aplastic anemia (2 were Fanconia anemia and one underwent HSCT). Eighteen patients were neutropenic and 8 patients were known as being on antifungal prophylaxis (5 patients with fluconazole and 3 patients with itroconazole) while 7 patients were receiving co-trimazoxole. Two patients had chronic renal failure and one patient had metabolic acidosis.

Nasal involvement was identified in a majority of the cases (17/20; 85%) patients, alone in 5/17, with cerebral involvement in 3/17, and with orbital involvement in 3/17 (Table III). Pulmonary involvement was reported in 11/20
Table I. Overview of our 20 pediatric mucormycosis cases (2007-2017).

| Number | Age/sex/year | City          | Underlying medical problem | Predisposing factor | Prophylaxis | Symptoms and signs | Co-infection | Radiological findings | Clinical form | Surgical treatment (count) | First line antifungal therapy/duration (days, mg/kg) | Survival outcome (follow-up, cause of death) |
|--------|--------------|---------------|-----------------------------|---------------------|-------------|-------------------|--------------|-----------------------|--------------|-------------------------|-----------------------------------------------|-----------------------------------------------|
| 1      | 13/F/2007    | Osmaniye      | AML (relapse)/CHB Neutropenia |         | FLU (20 days) | Facial pain, blackish necrotic debris on nose | Aspergillus | CT: sinusitis, pneumonia, pericarditis | Sino-pulmonary, tracheitis, pericarditis/deep extension/dissemination | Only biopsy | LAmB (24 days, 10mg/kg) | Died (fungal infection) |
| 2      | 3/F/2008     | Maraş         | ALL Neutropenia            |         | FLU, KO | Fever, ulcerative palate lesion | Aspergillus, Candida | CT: sinusitis, sinus wall destruction, | Sinusitis | Surgery (1) | cAmB (90 days) then POS (7 months) | Cured |
| 3      | 5/M/2008     | Gaziantep     | ALL (relapse) Neutropenia, hyperglycemia |         | ? | Fever, nasal pain, facial swelling, epistaxis, cough | - | CT: sinusitis, air crescent sign (right) | Sino-pulmonary | Surgery (1) | LAmB | Cured (transferred to another center) |
| 4      | 11/M/2008    | Adana         | AML (relapse) Neutropenia |         | ? | Fever, voice loss, chest pain | - | CT: sinusitis, pulmonary nodule, consolidation | Sino-pulmonary, tracheitis/deep extension/dissemination | Only biopsy | LAmB (31 days) | Died |
| 5      | 3/M/2008     | Urfa          | ALL (refractory) Neutropenia, cerebral mucor history |         | ? | Fever, facial pain and swelling, epistaxis, ulcerative palate lesion, cough | Pseudomonas | CT: sinusitis, sinus wall destruction, pneumonia MRI: cerebritis, leptomeningitis | Rhino-cerebral, pulmonary/dissemination | Surgery (3) | LAmB (40 days) | Died (fungal infection) |
| 6      | 8/M/2009     | Adana         | ALL (relapse) Neutropenia |         | I, KO | Fever, facial swelling | - | CT: sinusitis, pneumonia | Sino-pulmonary | Surgery (2) | LAmB (165 days, 10 mg/kg) +caspofungin, VOR, then POS | Cured (14 months) |
| 7      | 8/M/2010     | Urfa          | Neutropenia Mucor history (10 months) |         | FLU, KO | Fever, facial swelling, sepsis | - | CT: sinusitis, MRI: frontal lobe infiltration | Rhino-cerebral/dissemination | Surgery (2) | LAmB (60 days, 7 mg/kg) POS (5 months) | Died (fungal infection) |

ALL: acute lymphoblastic leukemia, AML: acute myeloid leukemia, cAmB: conventional amphotericin B, CHB: chronic hepatitis B, CRF: chronic renal failure, CT: computerized tomography, FAA: Fanconi aplastic anemia, FLU: fluconazole, HSCT: hematopoietic stem cell transplantation, I: itraconazole, KO: co-trimoxazole, LAmB: liposomal amphotericin B formulation, MRI: magnetic resonance imaging, PNET: primitive neuroectodermal tumor, POS: posaconazole, V: voriconazole.
| Number | Age/sex/year City | Underlying medical problem | Predisposing factor | Prophylaxis | Symptoms and signs | Co-infection | Radiological findings | Clinical form | Surgical treatment (count) | First line antifungal therapy/duration (days, mg/kg) | Survival outcome (follow-up, cause of death) |
|--------|-------------------|---------------------------|--------------------|-------------|-------------------|--------------|-----------------------|--------------|----------------------------|-----------------------------------------------|-------------------------------------------|
| 8      | 5/M/2010 Hatay    | ALL (induction) Neutropenia |                    | FLU         | Fever, facial swelling, oral blackish necrotic debris, ulcerative palate lesion | -            | CT: sinusitis, sinus wall destruction | Sinusitis     | Surgery (2)                | LAmB (163 days) POS (52 months)                  | Cured                                    |
| 9      | 12/M/2012 Osmaniye | ALL (induction) Neutropenia |                    | -           | Fever, blackish necrotic debris in nose, ulcerative palate lesion | -            | CT: sinusitis, sinus wall destruction | Sinusitis     | Only biopsy                | LAmB (34 days) then itraconazole               | Cured                                    |
| 10     | 2/M/2013 Urfa     | ALL-HSCT Neutropenia       |                    | FLU, KO     | Fever, cutaneous lesion | -            | Ultrasound: cutaneous abscess extension | Cutaneous/deep cutaneous abscess extension | Surgery (1) | LAmB (22 days)              | Cured                                    |
| 11     | 7/F/2013 Antakya  | FAA and CRF Neutropenia, metabolic acidosis | | KO | Fever, epistaxis, sepsis, periorbital swelling, sepsis | -            | CT: sinusitis, periorbital cellulitis, hepatic calcification | Sino-orbital/dissemination | Surgery (1) | LAmB (29 days) +VOR        | Died (fungal infection)                        |
| 12     | 16/M/2014 Urfa    | PNET (metastatic) Neutropenia | | I | Fever, mucositis, throat ache, nasal congestion, headache, diarrhea | -            | CT: pansinusitis, air crescent sign (multiple, bilateral) | Sinusitis | Surgery (1) | LAmB (21 days) POS (5 months)            | Cured                                    |
| 13     | 15/M/2014 Osmaniye | AML (relapse) Neutropenia | | I | Fever, epistaxis | Aspergillus | CT: pansinusitis, air crescent sign (multiple, bilateral) | Sino-pulmonary/dissemination | Surgery (1) | LAmB (28 days)              | Died (fungal infection)                        |
| 14     | 11/F/2014 Hatay   | ALL (induction) Neutropenia | | - | Facial swelling, palate lesion | Candida | CT: pansinusitis | Sinusitis | Surgery (1) | LAmB (60 days) POS          | Cured                                    |

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| Number | Age/sex/year | City | Underlying medical problem | Predisposing factor | Prophylaxis | Symptoms and signs | Co-infection | Radiological findings | Clinical form | Surgical treatment (count) | Survival outcome (follow-up, cause of death) |
|--------|--------------|------|-----------------------------|---------------------|-------------|-------------------|--------------|----------------------|--------------|---------------------------|-----------------------------------------------|
| 15     | 5/F/2014     | Adana| ALL (induction) Neutropenia | KO                  | Fever, cough | -                 | -            | CT: air crescent sign (left) | Pulmonary    | Surgery (lobectomy) LAmB (75 days) + VOR POS (2 years) | Cured                                    |
| 16     | 11/M/2015    | Adana| FAA-HSCT (1.5 years ago) and CRF | -                   | Cough        | -                 | -            | CT: air crescent sign (right) | Pulmonary    | Surgery (lobectomy) LAmB | Cured (transferred to another center) |
| 17     | 16/F/2016    | Adana| Diabetes mellitus Hyperglycemia | -                   | -            | Pain of tooth and nose, nasal congestion, facial swelling, headache, vomiting | -            | CT: sinusitis, MR: frontal lobe abscess (1 cm) | Rhino-cerebral | Only biopsy LAmB (44 days) POS (43 day) | Cured                                    |
| 18     | 16/M/2016    | Elazığ| Non-Hodgkin lymphoma (relapse) Neutropenia | KO                  | Fever, facial swelling, sepsis Aspergillus, Candida | -           | -            | CT: pansinusitis, periorbital cellulitis, pulmonary nodule and effusion | Sino-orbital, pulmonary, dissemination | Surgery (2) LAmB (15 day) + VOR | Died (fungal infection) |
| 19     | 5/M/2016     | Syrian| ALL (relapse) Neutropenia    | -                   | Fever, facial swelling | -            | -            | CT: pansinusitis, periorbital cellulitis, pulmonary nodules (bilateral) | Sino-orbital, pulmonary/dissemination | Surgery (4) LAmB (60 days) / caspofungin (when LAmB not available) | Died (fungal infection) |
| 20     | 107/M/2016   | Syrian| Aplastic anemia Neutropenia, hepatitis | -                   | Fever, facial and periorbital swelling, ulcerative palate lesion, tooth pain, sepsis | -            | -            | CT: pansinusitis, sinus wall destruction, tonsillar abscess, air crescent sign (right) | Sino-pulmonary, tonsillar abscess/ dissemination | Only biopsy LAmB / caspofungin (when LAmB not available) (105 days) | Died (fungal infection) |

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In 9/20 (45%) patients. There were unusual presentations, including 2 patients with parotitis and hepatitis.
Mucormycosis in Pediatric Population

In several studies, mucormycosis was reported primarily in males (65%). In case reports from Turkey, mucormycosis was reported to have a higher rate of occurrence in males (85%). Although Pan et al., in 63 children diagnosed with mucormycosis, reported the rate of girls as higher, in our study, the majority of children (85%) were male. In our series, the majority of children (85%) were older than 5 years, with a mortality of 78%.

### Table III. Distribution of the sites of involvement.

| Involvement | Sinusitis (%) [case no] | Dissemination (%) (case no) | Sex (M/F) | Malignancy | Aplastic anemia | Diabetes mellitus | Surgery | Mortality |
|-------------|-------------------------|----------------------------|-----------|------------|----------------|------------------|---------|-----------|
| Alone       | 5 (25%)                 |                            | 3/2       | 5          | -              | -                | 4       | 0         |
| Orbital     | 3 (15%)                 |                            | 2 (10%)   | 2          | 1              | -                | 3       | 3         |
| Cerebral    | 3 (15%)                 |                            | 2 (10%)   | 2          | -              | -                | 1       |           |
| Pulmonary   | 9 (45%)                 | 2 (10%)                    | 7 (35%)   | 9          | 2              | -                | 8       | 8         |
| Cutaneous   | -                       | 1 (5%)                     | -         | 1/-        | -              | -                | -       |           |
| Total       | 17 (85%)                | 3 (15%)                    | 9 (45%)   | 14/6       | 16 (80%)       | 3 (15%)          | 15 (75%)| 9 (45%)   |

*: tracheitis, †: tonsillar abscess, #: case 5 had cerebral and pulmonary involvement; case 18 had orbital and pulmonary involvement.

### Discussion

Mucormycosis is a life-threatening fungal infection characterized by a highly aggressive (angirotropic) progression that occurs mostly in immunocompromised patients. Data concerning patient sex, age at onset of disease, symptoms and signs, radiological findings, and treatment modalities were analyzed retrospectively, and a 10-year period was considered. To our knowledge, there have been a limited number of reports from the Turkish pediatric population diagnosed with mucormycosis. Therefore, our report is a large case series.

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For older infants and children, Francis et al. has recently reported that hematologic malignancy is a significant risk factor, as is being a hematopoietic stem cell transplant or solid organ transplant recipient, these were followed by diabetes. Kömür et al. conducted a retrospective study evaluating 51 cases of mucormycosis in our city in adult patients and reported that malignancy was the most common co-morbidity affecting 59% of the subjects, followed by diabetes. In our series of 20 pediatric mucormycosis cases, the most prominent identified underlying conditions were hematological malignancies, especially acute leukemia (70%), and this was followed by aplastic anemia (15%). In patients with prolonged neutropenia, aggressive evaluation should be performed in case of fever. The majority of patients in our series had neutropenia (90%). Fever was observed in almost every neutropenic case. Although, we have a well working transplantation unit, only two (10%) of our pediatric mucor patients were transplant patients; the distribution of infection is different from the literature. In our experience, the mucor infection occurred in four patients in the early stage of chemotherapy, during induction, and that contrasts with the data in the literature of pediatric mucor cases in which this was reported to occur later on during chemotherapy. Seven of the ALL cases were either relapsed or refractory and clinically unwell. In our study, in only one of 20 cases, the patient had uncontrolled diabetes mellitus.

Seasonal variation in atmospheric concentration of fungal spores has been documented for some molds in several geographical locations. As reported in India and in Middle East countries such as Iran, events are reproduced in August and in tropical and subtropical sea-sons when spores are most intense in the air. It is necessary to evaluate the contribution of this climate zone and the seasonal weather conditions we have in our city. The fact that our region is moist might be an effective risk factor for disease development.

The authors’ prior and most recent experience with hematological malignancy patients suggests that mucormycosis is most likely in cases when the patient has been receiving Aspergillus-active antifungal (especially voriconazole) prophylaxis. Although in our series, 8/20 patients who had received antifungal prophylaxis with fluconazole or itraconazole, did not have Mucorales activity.

For Mucorales the portals of entry in the human body are the respiratory tract through inhalation of fungal spores. In most series, such as the studies of Chakrabarti et al. and Roden et al., rhino-orbito-cerebral mucormycosis was reported as the most frequent clinical manifestation and this can quickly progress to disseminated form with disastrous consequences if not diagnosed and treated early. This is consistent with the global trend, the most commonly identified condition was sinus involvement (75%) alone in 5/20 and with concomitant involvement in 12/20 in our study, followed by the pulmonary form, have been found to be the most prevalent in our study. Pulmonary mucormycosis has been reported at a frequency between 44-64% in children. Although rhinoorbitocerebral sinus disease is mostly common in diabetic patients, pulmonary disease predominates in pediatric patients with malignancy and hematopoietic cell transplantations (75%). We detected that eleven cases (55%) had pulmonary involvement (9/11 had added involvement of other forms). Seven (7/11, 78%) with pulmonary involvement occurred as the disseminated form. From a recent review of Francis et al. the dissemination form of the disease occurs in 32% to 38% of pediatric cases, which was 45% in our cases, higher than the literature. The patients with a single in-volvement form had a better outcome than those with dissemination.

Histopathologic examination of clinical specimens and culture are recommended for the diagnosis of mucormycosis. Although tissues frequently are not available for biopsy, because of thrombocytopenia or hemodynamic instability, definitive diagnosis is made most frequently
Mucormycosis in Pediatric Population

The mucormycosis treatment with antifungal medicine is an important factor affecting the outcome. According to the literature, the mainstay of therapy for treating mucor remains as amphotericin B, primarily in its liposomal formulation. Furthermore, delayed antifungal therapy would increase mortality of mucormycosis among patients with neutropenia. In our series, the first line treatment was cAmB or LAmB in all patients, at different daily doses up to 10 mg/kg. In our experience, higher doses of LAmB were well tolerated. For combination therapy, Pagano et al. reported the beneficial effect of posaconazole in addition to LAmB in hematological patients failing to respond to LAmB monotherapy. Though posaconazole was not available to give in the first years in our study. In recent years, 7 patients were given parenteral AmB followed by decalation to oral posaconazole. The optimal total duration of antifungal drug administration required for mucormycosis is controversial and varies depending on the extent of the disease. In children successfully treated in our series, we discontinued antifungal therapy only when clinical resolution was evident and adequate immune recovery had occurred.

Because of the risk of rapid progression to dissemination of pediatric mucormycosis cases, when feasible, surgery should be considered as a treatment choice. Surgery and antifungal combination therapy are mostly the mainstays of management of invasive mucormycosis. Children who received combined therapy had a mortality rate of 18.5% compared

on the basis of direct microscopic examination. However, tissue identification is a very important diagnostic tool, since it distinguishes the presence of the fungus as a pathogen in the specimen from a culture contaminant. Direct microscopy of clinical specimens allows a rapid presumptive diagnosis and differentiation of mucormycosis from aspergillosis and other hyalohyphomycoses and phaeohyphomycoses and is strongly recommended for treatment decisions. In recent registries of mucormycosis, histopathology led to the diagnosis in 63% and 66% of cases. The diagnosis of 75 cases from an Indian tertiary-care hospital was based on histopathology. Culture of a clinically relevant isolate enables identification and susceptibility testing of the pathogen. Culture is poorly sensitive because Mucorales hyphae are friable in nature, hence may be damaged easily during sample collection (avoidance of excessive tissue homogenization is recommended before culturing). Additionally, some species fall to sporulate in standard media, precluding a timely and easy morphological identification. Better recovery is seen if slices of minimally manipulated tissue are placed onto the culture medium or baited with bread to promote mycelial growth. As a result, approximately only one-third of all histopathologically proven specimens result in a positive fungal culture. Countless reports of negative culture results are scattered throughout the literature.

Imaging techniques are helpful; although they are non-specific and do not correlate well with surgical and pathological findings. According to the revised version of EORTC/MSG published in 2008, all of our patient’s diagnosis were documented with proven mucormycosis by histopathology and none of them were culture positive. As our opinion, in our center negative culture may be explained by various factors, such as aggressive processing of the specimen and inappropriate storage of samples before plating. Although the limitation in our study was biased by the selection of cases that were only proven by biopsy, the diagnosis of our patients was confirmed by histopathological and radiological examination in addition to clinical findings. Despite the limitations to the study, we retrospectively gave a good estimate for the burden of mucor infections in pediatric cases in Turkey, highlighting the index of clinical suspicion and the important role played by histology especially from suspected cases in the diagnosis that will be able to guide towards early surgery.
with 60% for those who received antifungal therapy alone. The majority of the patients suffered from serious underlying conditions (thrombocytopenia, pulmonary infection) limiting the possibility for surgery. Surgery was just performed on 15/20 patients in this study. Of these cases, there was a 60% response rate.

Despite aggressive surgical intervention and intensive antifungal treatment, mucormycosis is associated with a greater mortality rate (47-56%). It rises to range from 50-100% depending on the disease form, which is in agreement with our findings in the current study. Our survival rate was 55%. Despite the fact that most of the disseminated cases received a combined treatment, the high mortality rate shows that this treatment is not sufficient.

Empirical treatment for mucormycosis is emergent if there are suspicions. The cases in our study were definitively diagnosed cases. In fact it is certain that the rate is higher than it is in this series, because we think most cases have not been appropriately diagnosed. Although surgery was performed in most of the cases, the mortality rate was high due to the severity of the disease. Perhaps an earlier intervention should be made. Unfortunately, we did not have a chance for postmortem examination to prove this claim.

In conclusion, a steady increase in the reports of mucormycosis during the last decades may be due to increased awareness of a fungal infection in risk groups, and early diagnosis and treatment of these invasive fungal infections can improve the outcomes of children. The recommended management for overall survival of invasive mucormycosis has been surgical debridement combined antifungal therapy and restoration of the underlying immune status should be considered a key factor for a better outcome of the disease. As can be seen from these, good management of risk factors, especially neutropenia and hyperglycemia, prevents this disease from occurring.

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