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# ANTIFUNGAL THERAPY CONTROL IN NEUTROPENIC CHILD WITH ACUTE LIMPHOBLASTIC LEUKEMIA (ALL)

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## Abstract

In recent years there has been an increasing incidence and awareness of mucosal candidiasis and invasive fungal infections in neutropenic patients. Early diagnosis (before serious morbidity and mortality) is often difficult, emphasizing the continuing need for adequate prophylaxis. Here is proposed a review of studies on the chemoprophylaxis of fungal infections in neutropenic patients. There are a limited number of large, prospective, well-designed studies using proper criteria and end points. No antifungal drug or drug combination has been shown to prevent invasive fungal infection with the exception of fluconazole (mainly *Candida Albicans* infections) in certain high-risk patient groups. Prophylaxis strategies are dependent upon local conditions, patient populations, types of therapies, available resources, etc. Future improvement will be based upon: improved study quality, new strategies for established drugs, development of new and safer drugs, strategies to eliminate or reduce immuno-suppression and cost-benefit studies.

**Key words:** neutropenia, disseminated candidiasis, prophylaxis, invasive aspergillosis.

## Introduction

Beside bacterial pathogens, also fungal infections represent a risk for neutropenic child patients. In fact, fungal infections have emerged as a major problem in heavily pretreated (with antineoplastic agents) children who experience long periods of neutropenia and require extended treatment with broad spectrum antibiotics. Early studies with empirical antifungal therapy, in parallel with antibacterial therapy, have been effectively used to treat patients with persistent or new fever. Pizzo et al. demonstrated the utility of administering empirical antifungal therapy on day 7 of fever whereas the European Organization for Research and Treatment of Cancer showed a similar benefit at day 4.<sup>[1,2]</sup> Although no two studies are in full agreement as to the preferred time of initiating empirical antifungal therapy, it is important to recognize that during this time frame, 4 to 7 days on therapy, strong consideration should be given to initiation of empirical antifungal therapy in the persistently febrile child with prolonged neutropenia.<sup>[3]</sup> Unfortunately, the choice of antibiotics is limited to amphotericin B, which has a relatively high toxicity profile. Nonetheless, the risk of fungal infection is high enough in the persistently febrile patient to warrant its use until return

of neutrophil counts. The efficacy of fluconazole has not been established as a prophylactic measure in children at increased risk, in other words, those with an expected long duration of neutropenia (more than 7 to 10 days). Similarly, fluconazole has not been shown to be equivalent or superior to amphotericin B for the indication of empirical antifungal therapy.

## PREDISPOSING FACTORS

It is well recognized that some neutropenic patients are at much greater risk of developing an invasive fungal infection than others. The likelihood of an infection developing in a leukaemic individual depends on a number of factors, including the nature and status of the underlying illness, its treatment and the use of broad-spectrum antibacterial agents.<sup>[4-7]</sup> Prolonged neutropenia, due to delayed engraftment, is well recognized as a major risk factor for the development of invasive fungal infection among leukaemic patients. Environmental factors are also important in the development of invasive fungal infection. For instance, defective air-conditioning plants or construction work in, or near, units in which neutropenic patients are housed, may be important risk factors for the development of invasive aspergillosis.<sup>[8-10]</sup>

## SPECTRUM OF FUNGAL INFECTION

The fungal infections that occur in neutropenic patients are similar to those encountered in other groups of compromised individuals. The commonest infections are candidosis, aspergillosis and mucormycosis (zygomycosis), which together account for 80% of mycotic infections in these patients. However, a growing number of uncommon organisms, such as species of *Fusarium*, *Scedosporium* and *Trichosporon*, can cause invasive infection that is often unresponsive to current antifungal agents.

## Candidosis

Candidosis is the commonest invasive fungal infection in patients with malignant haematological disorders. In most cases the infection is endogenous in origin,<sup>[11]</sup> but transmission of organisms from person to person can also occur in hospital. Neutropenia is still the most important factor predisposing cancer patients to invasive candidosis. Guiot *et al.*<sup>[6]</sup> noted that patients with

malignant haematological disorders did not recover from this infection unless their underlying illness was in remission. Other major risk factors include the use of broad-spectrum antibacterial agents, and disruption of anatomical barriers following antineoplastic treatment or the insertion of vascular catheters.<sup>[4, 12]</sup> The symptoms and clinical signs of invasive candidosis in the neutropenic patient are non-specific; the most frequent presentation is persistent or recurrent fever, resistant to treatment with broad-spectrum antibacterial agents. Macular or erythematous cutaneous lesions are sometimes evident. Other findings that suggest the diagnosis include muscular pain and tenderness and the development of renal impairment. Endophthalmitis is uncommon in neutropenic patients, but retinal lesions sometimes develop once the neutrophil count has recovered. Chronic disseminated candidosis is a distinct clinical entity that only occurs in leukaemic patients.<sup>[13, 14]</sup> Infection is thought to occur during the neutropenic period, but the disease does not manifest itself until the neutrophil count returns to normal. The presenting signs and symptoms include persistent fever, abdominal pain, elevated levels of alkaline phosphatase and CT scan defects in the liver, spleen, lungs and other organs. Cultures of biopsied lesions and blood are often negative. *Candida albicans* remains the predominant cause of both superficial and deep-seated forms of candidosis in compromised patients, although the proportion of serious infections attributed to other species is increasing. In the late 1970s, *Candida tropicalis* emerged as an important pathogen in neutropenic cancer patients.<sup>[15-18]</sup> Its emergence was associated with the introduction of more intensive cytotoxic treatment regimens, which resulted in increased gastrointestinal mucosal damage and longer periods of neutropenia. Although *C. tropicalis* is less common in the mouth or gastrointestinal tract than *C. albicans*, its isolation from stool specimens is more often predictive of invasive infection in neutropenic patients.<sup>[19, 20]</sup> In recent years, the spectrum of organisms causing invasive candidosis in neutropenic cancer patients has continued to change. One reason for this is the selection pressure resulting from changes in antifungal practice. Prophylactic treatment with fluconazole has reduced the number of *C. albicans* and *C. tropicalis* infections, but its use has led to increased rates of colonization and infection with *Candida krusei* in some hospitals.<sup>[21, 22]</sup> Like *C. krusei*, *Candida glabrata* is much less susceptible to fluconazole than *C. albicans* or *C. tropicalis*<sup>[23]</sup> and there have been reports of higher colonization rates following prophylactic treatment.<sup>[24]</sup> *Candida lusitanae* is less susceptible to amphotericin B than *C. albicans* and previous polyene usage might be a factor in the increased rates of infection with this organism that have been noted in several institutions.<sup>[25, 26]</sup>

#### Aspergillosis

The incidence of invasive aspergillosis tends to vary greatly between institutions. In part this relates to patient selection and differences in conditioning regimens or other supportive measures. However, one critical factor influencing the infection rate is the level of environmental contamination. Elevated spore counts have been detected in

haematological units with ongoing adjacent building work or defective air filtration and these have been associated with an increase in the rate of infection. Factors other than environmental contamination are also important in determining the risk of development of aspergillosis. As in candidosis, prolonged neutropenia is a major predisposing factor for this infection.<sup>[5, 27]</sup> Moulds of the genus *Aspergillus* are among the most widespread of fungi in the human environment, being found in the soil, in the air, on plants and on decomposing organic matter.<sup>[28]</sup> In the home, these moulds are often found in dust and on food. Similar contamination occurs in the hospital environment and can result in outbreaks of aspergillus infection amongst neutropenic cancer patients.<sup>[9, 10]</sup> Air filtration can reduce the incidence of nosocomial aspergillosis,<sup>[29]</sup> but exposure to aspergillus spores cannot be avoided after patients have been discharged from hospital. Moreover, although inhaled spores have been suggested as the major source of invasive infection, there is evidence that reactivation of endogenous organisms can also produce significant infection.<sup>[30]</sup> As in other groups of compromised patients, the commonest clinical presentation of aspergillosis is unremitting fever and the development of lung infiltrates despite treatment with broad-spectrum antibacterial agents. The diagnosis is difficult because the radiological signs are varied and non-specific, ranging from focal (often peripheral) nodules to diffuse consolidation or cavitation.<sup>[31]</sup> CT scanning is sometimes helpful in diagnosing aspergillus infection in a neutropenic patient with antibiotic-resistant fever: a distinctive halo of low attenuation tends to surround the lesions.<sup>[32]</sup> The isolation of aspergillus from sputum is not a particularly sensitive method for confirming the diagnosis: no more than 25% of patients who are later shown to have invasive aspergillosis have positive sputum cultures *ante mortem*.<sup>[33]</sup> On the other hand, the isolation of an *Aspergillus* sp. (particularly *Aspergillus fumigatus* or *Aspergillus flavus*) from sputum of a high-risk patient, on even a single occasion, is often indicative of invasive infection and should never be dismissed. The definitive diagnosis of invasive aspergillosis of the lungs depends on the demonstration of the fungus in histological sections, but patients are often too ill to undergo invasive investigations. In this situation, bronchoalveolar lavage (BAL) is the most helpful diagnostic procedure. Nasal cultures were noted to be predictive of invasive *A. flavus* infection during one outbreak of nosocomial aspergillosis associated with building renovation. However, their usefulness has not been confirmed in other studies of routine microbiological surveillance. The brain is involved in about 10% of cases of invasive aspergillosis, but cerebral infection is seldom diagnosed during life. This infection commonly follows haematogenous dissemination from the lungs and it is unusual for it to result from spread from the nasal sinuses.<sup>[34]</sup> Patients present with focal rather than meningeal signs. The prognosis is poor.

#### Mucormycosis

As in aspergillosis, long-term neutropenia is a major risk factor for mucormycosis. Many different organisms

have been implicated, but the commonest cause of human infection is *Rhizopus arrhizus*. Other less frequent aetiological agents include *Absidia corymbifera* and *Rhizomucor pusillus*. These moulds are widespread, being found in the soil, in the air, in food and on decomposing organic matter. Infection usually follows inhalation. Nosocomial mucormycosis is not as common as hospital-related aspergillosis. The two commonest presentations of mucormycosis in the neutropenic patient are rhinocerebral and lung infections. Rhinocerebral mucormycosis begins as a nasal or paranasal sinus infection and spreads, as a mass of ischaemic necrosis, through bone to the orbit or to the brain. The presenting symptoms and signs include painful unilateral facial swelling, proptosis and ophthalmoplegia, together with a serosanguinous nasal discharge. Characteristic black intra-nasal or palatal eschars are often found.<sup>[35]</sup> Since rhinocerebral mucormycosis is such an aggressive infection, a rapid diagnosis is essential for successful treatment. Sinus radiographs and CT scans are more useful in delineating the extent of infection than in establishing a diagnosis.<sup>[36]</sup> Smears of nasal scrapings or discharge are often helpful, but if these are unrevealing, biopsies or debridement of necrotic lesions should be performed. Mucormycosis of the lungs is less common than aspergillosis, and is seldom diagnosed during life. Patients often present with cough and fever, but there are no characteristic clinical or radiological signs to distinguish mucormycosis from other bacterial and fungal infections. The radiological signs are varied, but infiltrates or nodules are more common than cavitation or an effusion. Since the Mucorales are common culture contaminants, isolation of these organisms from BAL fluid must be interpreted with caution. However, their isolation from a neutropenic patient must never be ignored. Terminal widespread dissemination is common in neutropenic patients with mucormycosis of the lung. The commonest site of spread is the brain, but metastatic lesions have also been found in the spleen, heart and other organs. The condition is seldom diagnosed during life, but in occasional patients necrotic cutaneous lesions may permit an earlier diagnosis. Amphotericin B is the most effective antifungal agent and, when combined with surgical resection of infected tissue, can improve survival. With progressive dissemination of the infection, surgical intervention becomes less beneficial.

#### Other fungal pathogens

Numerous other fungi have been reported as occasional causes of serious infection in neutropenic patients. These include an increasing number of common environmental moulds, such as *Fusarium* spp. and *Scedosporium* spp., and yeasts such as *Trichosporon* spp. Infections with these fungi tend to be disseminated and are often fatal in neutropenic patients. Their treatment has not been standardized. Invasive fusarium infections are becoming more important among neutropenic cancer patients. These infections usually follow inhalation, but some originate from cutaneous lesions associated with infected nails. The characteristic signs include persistent fever and widespread nodular cutaneous lesions. The

diagnosis depends on the isolation of the organism in culture because the septate, branching mycelium of a *Fusarium* sp. cannot be distinguished from that of other aetiological agents of hyalohyphomycosis or aspergillosis. The most frequent cause of human infection is *Fusarium solani*, but *Fusarium oxysporum*, *Fusarium moniliforme* and a number of other species have also been incriminated.<sup>[37]</sup> Many neutropenic patients with invasive fusarium infection die before the condition is suspected. These moulds are often resistant to amphotericin B56 and, even with high-dose treatment, the prognosis is poor unless the neutrophil count recovers. Limited experience suggests that shortening the duration of neutropenia with colony stimulating factors may be beneficial in treating invasive fusarium infection.

As in aspergillosis, the usual presentation is an unremitting fever and there are no specific symptoms or clinical or radiological signs. The diagnosis depends on the isolation of the organisms because microscopical examination will not distinguish them from other aetiological agents of hyalohyphomycosis or aspergillosis.

#### TREATMENT OF FUNGAL INFECTION

##### Empirical treatment with amphotericin B

Neutropenic patients and those receiving cytotoxic treatment for leukemia, are at increased risk of developing an invasive fungal infection. For this reason, and because it has become clear that the earlier treatment is started the better the prognosis, it has become common practice to begin empirical antifungal treatment without waiting for formal proof that a patient with persistent unexplained fever, resistant to antibacterial agents, has a particular fungal infection. As with other groups of compromised individuals, amphotericin B remains the drug of choice for the empirical treatment of suspected fungal infection in neutropenic patients because no other agent has been shown to have as broad a spectrum of action. Two randomized clinical trials have demonstrated that empirical administration of amphotericin B results in a reduction in the number of patients developing invasive fungal infection. In the first trial, febrile patients received either amphotericin B or no antifungal treatment after 1 week of broad-spectrum antibacterial treatment. Although the number of patients studied was small, a benefit was apparent in those who were treated with amphotericin B. In the second trial, earlier and more frequent resolution of fever was found in the patients randomized to receive amphotericin B rather than no antifungal treatment after 4 days of antibacterial treatment. No difference in the overall survival rate was demonstrated, but four fatal fungal infections occurred among patients who had not received amphotericin B compared with none among patients given the drug. These results are encouraging but, as Walsh *et al.*<sup>[38]</sup> have pointed out, empirical treatment with amphotericin B does not always prevent the development of invasive fungal infection. *Aspergillus* spp., *Fusarium* spp. and *T. beigeli* are among the organisms reported to have caused overt infection during such treatment.

Lipid-based formulations of amphotericin B

Amphotericin B remains the drug of choice for a substantial number of invasive fungal infections, including candidosis, aspergillosis and mucormycosis. Its advantages include its broad spectrum of action and its parenteral administration, often essential for the neutropenic patient with a serious infection. The major disadvantage of amphotericin B is that the dosage that can be administered is limited by unpleasant infusion-related reactions and harmful side effects, particularly renal damage. A further problem has been the poor results of treatment in patients with persistent neutropenia, an outcome seen with both aspergillosis and candidosis. These problems have stimulated attempts to develop new formulations of the drug. Three promising lipid-based formulations have been licensed in the UK and they have been found to be less nephrotoxic than the conventional micellar suspension, because of their altered pharmacological distribution. These are AmBisome, a liposome-encapsulated formulation of amphotericin B, Amphocil, a colloidal dispersion (ABCD), and Abelcet, a lipid-complexed formulation (ABLC).

There are also a number of individual case reports of successful treatment of neutropenic patients with different lipid-based amphotericin B preparations. These include several patients with fusarium infection or mucormycosis. Taken as a whole, the results of recent trials with the three new formulations of amphotericin B are encouraging. However, these agents are expensive and, until the results of larger randomized trials are available, their use should be restricted to those patients who fail to respond or who become intolerant to the conventional formulation.

Azoles

Fluconazole has proved an effective agent for mucosal forms of candidosis in neutropenic patients. Two reports have indicated that it is effective in patients with chronic disseminated (hepatosplenic) candidosis who had failed to respond to amphotericin B. Another report concluded that it is as effective as, but better tolerated than, amphotericin B in the treatment of candidaemia in non-neutropenic individuals. However, it is ineffective as treatment for *C. krusei* infection in neutropenic patients and it should not be used to treat infections with *Aspergillus* spp., *Fusarium* spp. or the Mucorales. Itraconazole is the only oral triazole drug available at present that is effective against both aspergillus infection and candidosis.

PREVENTION OF FUNGAL INFECTION

The problems of detecting invasive fungal infections in neutropenic patients and the often disappointing results of attempts to treat established infections have stimulated interest in methods of preventing these lethal conditions. The main approaches have involved protective isolation of patients at risk or the use of prophylactic antifungal treatment. The most extreme attempts have involved creation of a total protected environment including laminar air flow rooms with HEPA filtration and the administration of combinations of topical and oral antifungal agents.

*Aspergillus* spp., *Fusarium* spp. and the Mucorales are among the numerous environmental moulds that can often be recovered from dust, food, plants or building materials. Therefore, the first steps in the prevention of infection in neutropenic patients should consist of measures to eliminate obvious sources of environmental contamination, such as removing plants from rooms where at-risk patients are being treated. Foodstuffs, such as nuts and spices, that are often contaminated with moulds should not be offered to neutropenic patients. These individuals should not be treated in units with ongoing, adjacent building work, but if this cannot be avoided, measures should be instituted to minimize the entry of dust and contaminated air.

Protected environment

Housing neutropenic patients in isolation rooms supplied with HEPA-filtered air has reduced the incidence of aspergillosis.<sup>[29]</sup> The benefits of this approach have, however, to be weighed against the disadvantages of isolation of the patient and the cost. Infection can still develop if patients are colonized before their admission to hospital, or are moved from the protected environment to other parts of the hospital for irradiation, or insertion of Hickman catheters. Moreover, improper operation or poor maintenance of sophisticated ventilation systems can lead to outbreaks of fungal infection in units fitted with laminar air flow isolation rooms.<sup>[10]</sup>

Antifungal prophylaxis

Antifungal prophylaxis has involved the use of oral non-absorbable compounds, such as nystatin, and oral absorbed drugs, such as fluconazole, itraconazole and ketoconazole. Fluconazole reduced the incidence of fungal colonization, superficial and deep forms of candidosis, and the number of deaths associated with fungal infection. In neutropenic cancer patients, a randomized trial showed that fluconazole prevented oral candidosis. The incidence of invasive fungal infection was halved in the group of patients receiving fluconazole, but the difference did not achieve statistical significance. The use of oral itraconazole represents another possible approach to the prevention of invasive fungal infection in neutropenic patients. The development of a new oral solution formulation of itraconazole should help to overcome the problem of variable absorption in neutropenic patients and those undergoing remission-induction treatment. Neutropenic patients who recover from aspergillosis or hepatosplenic candidosis can suffer from reactivation of these infections during subsequent periods of intensive cytotoxic treatment.<sup>[30]</sup>

Conclusions

In recent years there has been increasing incidence and awareness of mucosal candidiasis and invasive fungal infections in neutropenic patients. Early diagnosis (before serious mortality and morbidity) is often difficult, indicating the continuing need for adequate prophylaxis. Empirical antifungal therapy should always be instituted when invasive fungal infection is suspected. A number of factors

must be taken into consideration with regard to the use of prophylactic antifungal agents in neutropenic patients. [39] The prophylactic drug must be safe and have a well-established efficacy based on properly designed clinical studies. It is imperative to include cost-benefit analysis in such studies. Clinicians must also consider the frequency of fungal infections in their own patients prior to using prophylaxis regimens. In addition, widespread use of azoles in immuno-compromised patients for prolonged periods can potentially select for drug-resistant yeast and mold infections. An illustrative example is the emergence of

resistant *Candida* spp. such *C. krusei* as systemic pathogens. There is a limited number of large prospective well designed studies using proper criteria and end points. No antifungal drug or drug combination has been shown to prevent invasive fungal infection with the exception of fluconazole in certain high-risk patient groups. Future improvement is mainly dependent upon a) improved study quality, b) new strategies for established drugs, c) development of new and safer drugs, d) new strategies to eliminate or reduce immuno-suppression and e) cost-benefit studies.

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# POSSIBILITIES TO DIAGNOSE LIFE THREATENING CONGENITAL MALFORMATIONS

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## Abstract

Genetic and malformative diseases are very diverse, appear at different ages and affect any system or organ. Major structural anomalies appear in 2-3% of live-born children and 2-3% are discovered in children up to 5 years old, summarizing 4-6%. Defects at birth are the main cause of infantile mortality, representing approximately 25% out of the total neonatal deaths. The main possibilities of paraclinical investigation to detect cardiovascular, digestive, renal-urinary and central nervous systems malformations during the postnatal period are presented hereinafter.

**Key words:** congenital malformations, diagnostic methods

## Methods of Diagnosing Cardiovascular Malformations

### *Non-invasive methods of paraclinical diagnosis<sup>1</sup>*

1. Radiological examination – by cardio-pulmonary radiography the volume of the heart, the cardiomeastinal silhouette and the features of the pulmonary circulation may be appreciated.

Heart volume, as it appears on the radiological clichés (subjected to some error factors, such as exposure in expiration, association with a thymic hypertrophy etc) is still estimated by the means of cardio-thoracic index, accepted due to its simplicity (not to its fidelity). It is considered cardiomegaly the cardiac shadow that corresponds to a thoracic index of over 0.60 at the age of 1 month; over 0.55 at the age of 1 year and over 0.50 at 2 years of age. Cardiac insufficiency may be always considered associated to cardiomegaly in clinical practice<sup>1</sup>.

A transversal oriented heart, with the top oriented towards left, suggests right ventricular hypertrophy, while the concavity of the middle left arch is a sign of hypoplasia of the pulmonary artery. The described aspect suggests a cardiac silhouette known as “coeur en sabot”, which is deemed classical in the tetralogy of Fallot. The prominence of the middle left arch suggests post-stenotic dilation, characteristic to the pulmonary stenosis. Pulmonary hyper-vascularisation is typical in the left to right shunts. It is also characteristic to malformations with the reduction of the pulmonary blood debit (stenosis, pulmonary hypoplasia, and pulmonary valves atresia). This is radiologically expressed through an increase in pulmonary transparency. The aspect is associated with some cyanogens congenital diseases without any possibility to demonstrate a direct relation between pulmonary hypo-vascularisation and cyanosis (tetralogy of Fallot). The transposition of the large blood vessels and the common arterial trunk are cyanogens

congenital diseases in which pulmonary hyper-debit is present.

2. The electrocardiography is one of the classical methods to assess the congenital heart malformations. Interpretation is strictly dependent on the patient's age, although the significance of the waves on the route is the same, meaning: where P corresponds to the electrical activity of the atriums, QRS wave corresponds to ventricular depolarisation and T wave to ventricular repolarisation (having the same route as R wave). The heart rate of 130-150 beats/min in newborns progressively diminishes towards puberty. The newborn has right ventricular predominance (a consequence of foetal hemodynamics), while the teenager has left ventricular predominance. In this context the notion of ventricular hypertrophy, right or left, becomes pathological according to age. The affirmation of ventricular hypertrophy on ECG suggests an electrical syndrome and not an anatomical aspect. No ECG modification is patognomonical for a certain congenital malformation; therefore this exam is an adjuvant in establishing the diagnosis of congenital heart disease, its value being unaltered in both rhythm and conduction disorders<sup>1</sup>.

### 3. Echocardiography

The ultrasonography with application in cardiology is the real technical revolution of the last decade, bringing to the top the diagnostic value of non-invasive techniques.

One-dimensional echocardiography studies the heart in one dimension. This technique practically measures, in different moments of the cardiac cycle, the dimensions of the heart cavities, the width of the cardiac walls and of the intra-ventricular septum, as well as the kinetics of the valves.

Bidimensional echocardiography (2D) studies the heart from two perspectives; there are standardised planes through different exploration paths: left parasternal, apical, subcostally, suprasternally. The purpose of the many planes that exist is to specify the anatomy of heart and vessels. Moreover, it is possible to qualitatively study the contraction function of the ventricles<sup>2,3</sup>.

Doppler echocardiography is a useful complement of imagistics. It is based on the physics principle described by C.H. Doppler in 1842, which refers to the interaction of a sound wave when meeting a moving object. The ultrasound emitted by the transducer, which meets a blood current, are in part reflected by its most mobile structures (moving hematies). The echo reflected by these is different from the echo of the ultrasound fascicle. This frequency difference is

the Doppler signal. The reflected sound is heard and is, at the same time, graphically recorded, its qualities being analysed by a computer, with the auditive recording being the qualitative component and the visual recording the quantitative one. Doppler echocardiography allows for the detection of intracardiac blood flows, measures their speed and, indirectly, pressure gradients. There are two types of Doppler echocardiographies<sup>2</sup>.

a) Continuous wave Doppler: a piezoelectric crystal emits a continuous ultrasound signal. This signal is reflected by the figurative blood elements, especially red cells, towards a crystal receptor. As the blood flow comes closer to the sound receiver, the reception frequency is higher than the emission frequency. The frequency difference is more important as the flow is more rapid. Continuous Doppler allows the measurement of the blood speed, even if it is very fast. But it has the inconvenient that it does not allow a precise spatial localisation of the flow, as it studies the speed over the entire ultrasound fascicle.

b) Pulsed wave Doppler uses a succession of ultrasound emissions, interrupted by pauses, while the emission crystal acts as a receptor of the reflected echoes. The returning time of reflected echoes allows estimating the distance to the explored area, as the speed of ultrasounds into tissues is known. Pulsed wave Doppler together with a bidimensional echocardiogram allows precise space localization.

Colour coded Doppler is a variant of pulsed wave Doppler. Digital analysis and colour codification allows for a coloured bidimensional representation of the blood flow. Colours vary according to direction, speed and the laminar or turbulent character of the flow. The colours were arbitrarily used by the builder of this equipment: the red colour indicated a blood stream heading towards the transducer, while the blue colour indicated a blood stream moving away from the transducer. Colour Doppler allows identifying rapidly the normal and pathological flows and also detecting anomalies that may be missed during a bidimensional analysis.

Myocardial function may be studied by the means of echographic methods: the contraction function of the left ventricle (systolic function) and the filling function (diastolic function). For the contraction function of the left ventricle the one-dimensional echocardiography is used to measure the four parameters: shortening fraction, systolic contraction index, average speed of fibre shortening and ejection fraction of the left ventricle; in all the severe disorders of the myocardial function, such as myocarditis, these indicators are abnormal<sup>1</sup>.

Three-dimensional echocardiography brings new details to the non-invasive heart investigation.

4. Magnetic resonance imaging (MRI) and computer tomography (CT), a technological burst of the last decade, brought remarkable progress in evaluating the cardiac child. It has the advantage that it does not use the ionising radiation and it can offer images in three plans, but the examination cost is very high (double unto the one of a computer tomography examination)<sup>4,5,6</sup>.

The adverse biological effect of the high intensity magnetic field (in which the patient is placed during the examination) has not been sufficiently documented. The patient's sedation is mandatory for patients under 7 years of age and the investigation cost limits its extensive usage.

MRI brings valuable information in evaluating the anatomical details of the heart and mediastinum, when the data obtained through bidimensional echography are not considered optimal. The diseases of the aorta (coarctation and supraaortic stenosis), anomalies of the pulmonary arteries, including the obstructive pulmonary vascular disease, the abnormal venous return and the complex congenital cardiopathies are cited as indications for this exam.

#### 5. Radioisotopic exploration

The principle of this method consists of the intravenous injection of a very concentrated radioactive embolus (vol. under 0.5 mm<sup>3</sup>) which reaches the cavities of the heart, the pulmonary blood system and the great vessels at the basis of the heart. The radiotracer is then detected following the emitted gamma radiations, using a gamma camera.

Isotopic exploration is a non-invasive diagnosis method, which produces data comparable to the ones obtained through cardiac catheterism. It is indicated for obtaining data referring to the pulmonary and myocardial blood flow, myocardial perfusion, lung perfusion and detection of cardiac shunts.

#### *Invasive methods of paraclinical diagnosis*

Cardiac catheterism and angiography are invasive diagnosis techniques that bring very exact anatomic and hemodynamic information. They are still the most precise and reliable methods for measuring pressure, debit and resistance. The method is superior to the 2D echocardiography as regards the spatial perspective and less dependent on the human factor. These are indicated especially in the situations in which echocardiography fails: appreciating the extracardiac elements, abnormal pulmonary or systemic venous return, anatomy of the aortic arch, pulmonary trunk and pulmonary artery branches, as well as in the evaluation of intracardiac elements (interventricular septum, the ejection way of the right ventricle). Cardiac catheterism may become therapeutic, perforating the interatrial septum in the transposition of great vessels or efficiently dilating the pulmonary and aortic valvular stenosis. It is currently attempted the dilation of the stenosis of the branches of pulmonary arteries.

The stenosis or valvular regurgitation degree can be accurately determined. A right catheterisation (femoral vein) is usually used and more rarely a left one (arterial retrograde manner, Sedinger technique).

Cardiac catheterism remains an exact technique for appreciating the shunts, evaluating the oximetry and intracavitary pressure, appreciating the pressure gradients between the two parts of the stenotic lesion, measuring the systemic or pulmonary flow, as well as the pulmonary vascular resistance.

Cardiac catheterism can be completed by endomyocardial biopsy, using an adequate biotome. Histological evaluation is allowed in dilative or hypertrophic cardiomyopathy, endocardial fibroelastosis, myocarditis or cardiomyopathy after chemotherapy (Adriamicina).

Using modern methods and equipment, doctors may use digital subtractions angiography, which allows the use of small quantities of contrast substance (20-60% out of the conventional dose) and a smaller dose of radiation (10%). It is because of these advantages that this method is widely used in paediatrics<sup>1</sup>.

### Diagnosis methods in digestive tube malformations

The last two decades have unexpectedly diversified the possibilities of invasive and non-invasive exploration of the digestive tube, starting with the new-born period. Accurate diagnosis of anomalies and lesions have been imposed by the extraordinary growth of paediatric surgery, which, by improving its intervention techniques and resuscitation methods, successfully approaches the medical care of very young children, new-borns and even foetuses. Without using paraclinical exploration methods, the digestive tube is less accessible to the direct clinical exam<sup>1,7</sup>.

1. Radiological exam is still used, from the first day of birth, with or without a contrast substance. We have to remind the fact that the new-born needs to be immobilized using special techniques, in order to avoid the irradiation of the medical stuff and the patient. The radiographic exam can be used to bring useful information in congenital duodenal stenosis, meconial ileus etc.

2. Radiological exam with contrast substance completes the information obtained. The baritate solution is more physiological than the iodate contrast substances, which, being hypertonic can cause dehydration in young patients. This solution is easy to administer and ensures a good resolution, if there are no deglutition disorders or aerodigestive fistulas and if it reaches the lungs. It can be administered through a gavage tube or by bottle feeding. Except for the esotracheal fistulas and the deglutition coordination disorders by cricopharyngeal achalasia, the administration of the contrast substance by catheterising the esophagus brings valuable information in all obstructive lesions of the digestive tube in new-borns, such as hypertrophic pyloric stenosis, duodenal stenosis, intestinal stenosis, rotation vices etc.

3. Percutanate hepatic biopsy, performed with a needle, is still considered an adequate evaluation method for some hepatic lesions, which evolve at pediatric age. Investigating the haemostasis before this procedure is compulsory. It is preferable to be performed in the morning, on an empty stomach, and to be followed by an active period of supervising the patient and the potential complications. It is mandatory to sedate the child and even general anesthesia is required in case of an extremely anxious or uncooperative child. The optimal diameter of the needle is 1.2 – 1.4 mm. The major indications of hepatic biopsy are: extrahepatic biliary atresia, congenital hepatic fibrosis.

The contraindications for hepatic biopsy are: uncooperative child (unless we use general anesthesia), coagulation disorders (frequently associated with hepatic diseases), local infections (cholangitis), ascites, severe obstruction of extrahepatic biliary ducts and severe anemia. Complications are associated with the patient's state, lack of adequate instruments and the professionalism of the doctor executing the manoeuvre. Morbidity is 5% in the case of this procedure and the mortality reported in the literature is 0.15-0.17%.

Echographic exploration of the upper abdomen is currently used in our country too, being the first option for many paediatricians as it is completely un-aggressive and largely indicated. Its main advantage resides in the absence of any unpleasant consequences for the child, the possibility to repeat the exam in order to control the evolution of the lesions, no counter-indications and no preparation of the patient, good resolution of the images, especially in the case of parenchymal organs (liver, pancreas, spleen).

4. Computed tomography (CT) is the method that uses X rays for exploration, which allows the transversal sectioning of the body. The obtained images are in tones of grey, according to each tissue's density. Water is considered to have zero density, while air and fat have negative values. All abdominal viscera have different values, greater than zero. There is indeed a juxtaposition of different densities of abdominal parenchymal organs (for example pancreas is sometimes hard to distinguish from the duodena using only the density criteria). The small dimensions of the adipose paniculum in children make it more difficult to clearly delimitate between the different intra-abdominal organs.

The list of CT indications in children's digestive pathology is continuously diversifying, but the palpable abdominal masses, the appearance of which could not be established echographically, become the first diagnostic choice. The method must be recommended restrictively in very young children in whom the resonance of the abdominal images is unclear, because of the lack of the adipose paniculum. The doctor will take into account the high degree of X-ray irradiation and also the movement problems that require good cooperation with the child and, if necessary, his sedation.

6. The sweat test is a reliable, specific test, positive in 99% of the cases for pancreatic cystic fibrosis. The quantitative determination of the electrolyte concentration of the sweat has as a starting point the stimulation of the sweat through different procedures and the quantities of EC and Na<sup>+</sup> are determined in harvested sweat and expressed in mEq/l.

### Diagnostic methods in malformations of the urinary apparatus

1. Excretory urography has as main principle the kidney's excretion of an injected radio-opaque substance and brings information about the urinary apparatus, but also functional data (the time passed between the injection of the substance and the excretory urogram) as the excretion of the substance depends on the serum level, on the kidney's

concentration capacity (it is not a valid exam for a newborn, who has a reduced capacity of urine concentration) and the glomerular filtration. Normally the secretion of the contrast substance begins immediately, attains its highest point at 10-20 minutes and is much slower in renal insufficiency. The renal radio-opacity increases, because the contrast substance is concentrated in the renal tubes. The best nephrogram is obtained in the first minute and allows the evaluation of the dimensions, form and place of the kidney. It is also very dense in urethral obstructions.

2. Mictional cystography or mictional cistouretrography is practiced to evaluate the lower urinary tract functionality. The urethra is catheterised (attention in boys) and, with the catheter placed in the urinary bladder, the contrast substance diluted with physiologic serum is injected. The introduced volume varies according to the age (30 ml for a newborn, 100-200 ml for a child). A static cystogram is obtained, another one during miction and a last image afterwards, for assessing the urinary residues or the reflux at the end of miction.

3. The ultrasonography is largely used to acquire statistical data regarding the situation, the morphology and the dimensions of the kidneys, or as a guide for a renal biopsy puncture. In ultrasonographic images the kidneys have an elliptical shape, neither the calyx and pelvis, nor the normal ureters being identified. Suprarenal glands are difficult to be identified echographically, but the pyelocaliceal calculi and the renal cysts can be distinguished<sup>1</sup>.

4. Computed tomography (CT) is essential for appreciating the dimensions of the renal tumours, their reactions with the proximal organs, the situation of the retro-peritoneal space, invasion of the cava vein, hematomas or the renal or peritoneal abscesses. The method used for psoas hematoma is highly valuable.

In assessing the abdominal masses suspected to be of renal origins, all the presented methods will be used for a diagnosis. An exact diagnosis can be obtained, but the sequence in which they are used varies according to the experience of each medical team. Some use the urography as first method to obtain data, the echography and CT being used to obtain complementary information. Other medical teams use the echography as a routine diagnostic method, using the other two afterwards. If surgery is needed, CT must precede it.

5. Nuclear medicine uses radioactive isotopes to establish a diagnosis. Two methods are used for diagnosing renal diseases: isotopic nephrogram and renal scintigram.

### Methods of paraclinical exploration of CNS

There is no other field of pediatrics in which modern investigations have changed so dramatically the diagnosis possibilities as the field of CNS pathology. New methods, that could not even have been imagined two decades ago, are used in daily medical practice, so that we have exact, non-invasive diagnostic methods that require sophisticated and extremely expensive medical equipment, with no

procedure risks, as it is the case when using the classical methods<sup>1,8</sup>.

1. The simple radiography is useful in diagnosing cranium bifidum, spina bifida occulta, cranial dermal sinuses, spinal dermal sinuses, diastematomyelia, syringomyelia, Arnold-Chiari and Dandy-Walker malformations, craniostenosis, and hydrocephaly.

In meningoencephalocele, a simple Rx of the skull reveals the place and the dimension of the bone defect. The defect is well delimited, with clear regular margins, of variable length, but there is no proportional ratio between the dimension of the meningoencephalocele and the bone defect. The bone defect has a round shape; the defects situated basally, profoundly, have an oval shape and are observed through CT. Partial absence of the posterior arch with the enlargement of the vertebral canal on several segments on an Rx leads to a meningoencephalocele /meningomyelocele diagnosis.

The simple radiography and with contrast substance is extremely useful in diastematomyelia. The simple Rx of the thoracolumbar spine distinguishes the centre of the spinal canal, disposed in the area of spina bifida, extended on one or more segments. The spinal canal appears dilated, with the maximum length at the level of the bone spur. This dilation is not associated with changes of the pedicles and vertebral erosions, which differentiates it from the dilations given by intraspinal expansive processes.

In diagnosing the Arnold-Chiari malformation the simple and contrast Rx are extremely useful. A simple exam can show signs of hydrocephaly and a possible anomaly of the cranio-rachial region (basilar impression, occipitalisation of the atlas, cervical rib) or the lumbar-sacral region.

Inconsistent deformations of the skull are seen in Dandy-Walker malformation. These are represented by the growth of the antero-posterior diameter and the prominence of the occipital region in the middle of the posterior fosse, disjunctions of sutures, opening of fontanels.

In congenital hydrocephaly Rx distinguishes a skull with the aspect of a balloon, with round contours, an exaggerated disproportion between the size of the skull and the facial massive, with a big anterior fontanel. The transparency of the skull is increased with a thin skull and no bone structure. The margins disappear and the sutures are invisible, the skull appearing as a big ball with fine limits, in which there is an opalescent uniform aspect. Sometimes there is a "lacuna skull", more visible in the parietal regions. If the sutures appear or become more obvious than at an anterior radiography, that is a proof the hydrocephaly is stabilizing and, after simple radiological exams, an etiological diagnosis of hydrocephaly is set.

The radiological diagnosis of skull lacunas in children is important, as it is associated with other malformations (spina bifida, cleft palate, anomalies of ribs and extremities). The radiological diagnosis of skull lacunas in children is easy in typical forms, congenital skull lacunas being more difficult to diagnose in atypical forms, with all the possible skull lacunas in children (traumatic, tumoral, and generated by systemic maladies). Islands of

demineralization can be observed on radiological images. These transparent islands, having different dimensions, rectangular, contoured, and placed side by side, are separated by narrow septa of dense bone, anastomosed. The images should show especially the parietal bone and are situated bilaterally, but not symmetrically. A bone hierarchy is not respected. The bone lamellae are anarchically disposed and the lacunae portions are poorly vascularised.

The radiological exam is very important in diagnosing the skull stenosis and establishing the exact type.

From a radiological point of view, we can observe:

- anomalies of sutures, one or more being absent;
- disappearance of the toothed aspect of the suture in children;
- persistence of some sutures in the form of linear lights;
- existence of bone bridges on a suture's line;
- marginal densifications at suture level, showing excessive osteogenesis (important presumption sign).

2. Pneumoencephalography is a useful investigation for diagnosing congenital malformations of CNS. In meningoencephalocele it shows the cerebral-ventricular participation to the malformation, important element for surgery.

In the case of agenesis of pellucid septum, diagnosis can be made only based on pneumoencephalography, which brings out the lateral ventricles, forming one cavity. It can also show a concomitant internal hydrocephaly due to the cortical atrophy. Corpus callosum agenesis shows a typical butterfly shaped ventricular aspect. It allows the appreciation of the liquid ways for defining the obstruction level and for guiding the neurosurgeon in executing some interventions.

3. Ventriculography – in Arnold-Chiari malformation shows the status of the cavities (ventricles III and IV, aqueduct of Sylvius), the complete or incomplete blockage and the associated nervous anomalies (volume growth of the inter-hemispheric grey commissure, total or partial absence of septum lucidum).

The dilation of the IV ventricle which occupies the posterior fossa is present in Dandy/Walker malformation. In corpus callosum agenesis may be seen:

- dilation of III ventricle and the dorsal extension between the lateral ventricles;
- increase of the distance between the lateral ventricles;
- dilation of the posterior horns of the lateral ventricles;
- angulation of the dorsal margins of the lateral ventricles;
- concave medial margins of the lateral ventricles.

Ventriculography can show the obstruction of the Mauro hole, the lack of communication between the lateral ventricles and with III ventricle, hydrocephaly and a defect of filling the anterior side of III ventricle. It can be used in the diagnosis of arachnoid cysts and hydrocephaly.

4. Transillumination can reveal, in meningoencephalocele, the transparency of the formation, but it can not show whether cerebral participation is present

or not. It can be useful to reveal the liquid accumulation in meningoencephalocele. It highlights the hyper-transparency in hydrocephaly only when the brain mass is reduced to 1-2 cm, therefore in advanced hydrocephalies.

5. CRL exam, obtained by the means of ventricular or lumbar puncture, is useful in the case of hydrocephaly. A small quantity of liquid, 2-5 ml is taken, not to produce a sudden decompression. Two aspects are envisaged: inflammatory dosage, tumoral and hemorrhagic.

6. Vertebral angiography is used in Arnold-Chiari malformation; by injecting the posterior-inferior cerebral artery, which forms a concave loop round the herniated cerebellar amygdalae, aspect described as “coop sing”.

In Dandy – Walker malformation it highlights the rise of some arteries (posterior cerebral and cerebellar).

Carotid angiography, characteristic in corpus callosum agenesis, shows the absence of the bend of the anterior cerebral artery. It is used in diagnosing arachnoid cysts and basilar impression.

A prognosis can be made in hydrocephaly by the means of angiography. The aspect of the arteries and veins indicates if surgery is possible. A differential diagnosis can be made between severe hydrocephaly and hydrancephaly, tumours, subdural masses, vascular malformations.

7. Myelography with pantopaque and gas contrast is used in the case of meningoencephalocele, and with lipiodol in diastematomyelia.

The opaque iodine substance is separated in two columns that surround the median line spur, accurately visualizing the level and extension of the malformation. In syringomyelia the gas myelography is used, which can show a total or partial blockage or the association of Arnold-Chiari malformation. Myelography can be also used in diagnosing Arnold-Chiari malformation.

8. Cerebral scintigraphy is used in fistulised, endonasal, basal meningoencephalocele. In order to diagnose fistula, the scintigraphy with radioactive iodine-labelled serum albumin (RISA) is recommended.

It is used in the hydrocephaly of the newborn for the study of the ventricular and cisternal spaces and the circulation of CRL. Human iodinated serum albumin, RIHSA or Te, may be used in the case of hydrocephaly. RIHSA albumin is used in studies requiring an observation of 48-72 h and Te albumin is used for detailed exams that last up to 18 h. This investigation is very important to assess the factors responsible for hydrocephaly, providing important data for improving the ways, circulation speed and CRL absorption.

9. Computer tomography is of great importance for the diagnosis of basal encephalocele. It is also used in diagnosing Dandy-Walker malformation and the basilar impression.

10. Electroencephalogram (EEG)

There is no characteristic route in hydrocephaly. In the case of craniostenosis, the frequency of EEG disorders depends on the evolution stage and age. EEG shows bioelectrical anomalies, diffuse in all derivations of the both hemispheres as a result of brain compression. The anomalies recorded on the EEG route are slow Theta waves and even slow Delta waves. The presence of synchronous and

bilateral ample slow wave discharges on the EEG route also indicates an implication of the profound subcortical formations in craniostenosis. The larger the craniostenosis is, the more serious EEG anomalies are.

11. Ecoencephalography may provide indications in hydrocephaly and not only, about the dimensions of the ventricles and the thickness of the cerebral mantle.

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## SYNOVIORTHESIS IN HAEMOPHILIA

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### Abstract

#### *Introduction*

Recurrent haemarthroses will inevitably lead to significant hypertrophic synovitis in patients with haemophilia (PwH), progressive joint cartilage degradation, ultimately resulting in haemophilic arthropathy with significant functional impairment of the affected joints. The degree of haemophilic synovitis is directly related to an increase in bleeding frequency in the affected joint.

Synoviorthesis or non-surgical synovectomy is a therapeutic method which consists in injection into the joint of a substance acting on the synovial membrane by means of a fibrosis that constricts the subsynovial plexus and thus prevents future bleeding. Synoviorthesis can be medical or pharmacological. There are two groups of preparations: chemical and radioactive isotopes.

Chemical synovectomy uses osmic acid, rifampicin. Joint injections with hyaluronic acid, intraarticular corticosteroid therapy and per os D-penicillamine have been proposed as therapy. Radioactive synovectomy uses isotopes like <sup>198</sup>Au (gold), <sup>90</sup>Y (yttrium), <sup>186</sup>Re (rhenium), <sup>169</sup>Er (erbium).

#### *Material and methods*

A review of the international literature on the subject of synoviorthesis and alternative options in case of its failure has been conducted.

#### *Results and discussions*

Synoviorthesis should be the first choice of treatment for persistent synovitis of the joints. It is a simple procedure, which eliminates the risks associated with surgery. Chemical synoviorthesis with osmic acid has been partially abandoned because of occurred complications and semicomplicated pain associated with this procedure. Radioactive synoviorthesis has a higher overall efficiency than chemical synoviorthesis, but is associated with the risk of malignancy, as recently published studies show. Rifampicin has similar results to <sup>90</sup>Y when used in small joints, but needs multiple injections. Besides that it is not suitable for knee synoviorthesis. If three consecutive synoviortheses at 3 to 6 month intervals, as well as 7-8 chemical synoviortheses fail, arthroscopic synovectomy is indicated, which is a surgical method presenting the risk of general anesthesia and associated complications.

#### *Conclusions*

Synoviorthesis is a highly effective procedure that decreases both the frequency and the intensity of recurrent intra-articular bleeds related to joint synovitis. The procedure should be performed as soon as possible to minimize the degree of articular cartilage damage, which, based on many studies, is irreversible. It can also be used in patients with inhibitors with minimal risk of complications.

On average, synoviorthesis has a 75-80% satisfactory outcome in the long term. Global results of treatment with chemical synovectomy seems to be less favourable than with radionuclides. In cases where the synovium is thicker than 5-10 mm, and haemarthroses persist following synoviorthesis, arthroscopic synovectomy is indicated.

**Key words:** hemophilia, chronic synovitis, synoviorthesis

### Introduction

A synoviorthesis consists of the intra-articular injection of a certain material with the aim of 'stabilizing' (orthesis) the synovial membrane of a joint (synoviorthesis). There are two basic types of procedures for synovial control: medical synovectomy (or synoviorthesis) and surgical synovectomy (open or arthroscopic.) It is commonly accepted today that synoviorthesis is the procedure of choice, and that surgical synovectomy should be performed only if a number of consecutive synoviortheses fail to stop or diminish the frequency of recurrent haemarthrosis. Thus, the main indication for a synoviorthesis in a haemophilic joint is hypertrophic synovitis and recurrent bleeding. Synoviorthesis has been utilized for more than 25 years.

In 1959, Margaret Swanton<sup>1</sup>, in a landmark study of haemophilic dogs, showed that the synovium was the initial site of bleeding in the development of an haemarthrosis. Diffuse intrasynovial bleeding was followed by extravasation of blood into the joint space, an inflammatory response with secondary hyperaemia of the synovium, and recurrent bleeding. Untreated haemarthroses resulted in a pattern of joint destruction termed 'Haemophilic Arthropathy'<sup>2</sup>. In 1968 an article appeared in the Lancet entitled, 'Synovectomy for Haemophilic Haemarthrosis'<sup>3</sup>. Professor Storti felt that by eliminating the site of intra-articular bleeding one could eliminate recurrent bleeding and possibly prevent the development of arthropathy. Other authors, Pietrogrande et al.<sup>4</sup>, Mannucci et al.<sup>5</sup>, McCollough et al.<sup>6</sup>, and Kay et al.<sup>7</sup>, reported that most patients studied showed a reduction in bleeding frequency but noted that synovectomy was not without its problems. Kay et al.<sup>7</sup> concluded that 'the post operative complication rate was high'. They reported secondary haemorrhage, infection and a supracondylar fracture of the femur during manipulation under anaesthesia in addition to post operative loss of motion. At the same time that surgical and arthroscopic synovectomies were being investigated there were attempts to limit the sequelae of bleeding and inflammation by nonsurgical means.

Fernandez-Palazzi<sup>8</sup> reviewed his experience in the treatment of recurrent haemarthrosis and chronic synovitis by non-surgical means. Experience with synoviorthesis with

rifampicin and radioactive colloids was analysed, and a multiple chromosomal study to demonstrate safety of radioactive injections was described. The results obtained were adequately satisfactory to recommend synoviorthesis as the treatment of choice to prevent recurrent haemarthrosis.

Rodriguez-Merchan<sup>9</sup> stated that the goal of both synoviorthesis and surgical synovectomy is to remove the inflamed and hypervascular synovium as soon as possible in order to prevent the onset of haemophilic arthropathy. Ideally, these methods should be performed before the articular cartilage has eroded. Radioactive synoviorthesis is an effective, relatively simple, virtually painless and comparatively inexpensive technique for the treatment of chronic haemophilic synovitis, even in patients with inhibitors. Thus, radioactive synoviorthesis is the best choice for patients with persistent synovitis. The current recommendation among orthopaedic surgeons and haematologists is that when three early consecutive synoviortheses (repeated every 6 months) fail to halt synovitis, a surgical synovectomy (open or arthroscopic) should be immediately considered<sup>9</sup>.

The indication for synoviorthesis is chronic hypertrophic synovitis associated with recurrent haemarthrosis that does not respond to haematological

treatment. Synoviorthesis should be performed under clotting factor coverage to avoid the risk of bleeding during the procedure. In patients with inhibitors, synoviorthesis can also be performed with minimal risk. In fact, the procedure is especially indicated in patients with inhibitors because of its ease of performance and low rate of complications compared to surgical synovectomy.

It is important to differentiate between haemarthrosis and synovitis. Acute haemarthrosis is associated with severe pain, and the joint is maintained in a position of comfort (typically in flexion). In contrast, chronic hypertrophic synovitis is not associated with as much pain. The synovium is palpable as a soft-tissue mass whereas a haemarthrosis will have a fluid characteristic. Before making the recommendation of a synoviorthesis, the diagnosis should be confirmed by radiographs, ultrasound and/or magnetic resonance imaging (MRI). Radiographs should also be taken in order to assess the degree of haemophilic arthropathy at the time of diagnosis. In many situations, synovitis and haemarthrosis coexist. (Table 1)<sup>10</sup> The objective of the present paper is to see which are the indications for each type of synoviorthesis, depending on the degree of haemophilic synovitis/arthropathy and the results of these procedures.

Table 1 – Grading system developed by Fernandez-Palazzi and Caviglia to indicate suitability of synoviorthesis<sup>10</sup>

Stage	Indications
I Transitory synovitis	With no post-bleeding sequelae. Synoviorthesis is indicated as preventive if there are more than two episodes of haemarthrosis in 6 months.
II Permanent synovitis	With persistent thickening of the synovial membrane and diminution of range of motion. Synoviorthesis is mandatory
III Chronic arthropathy	As for grade II plus muscular atrophy and axial deformities of the limb. Synoviorthesis is helpful.
IV Fibrous or osseous ankylosis	Synoviorthesis is contraindicated.

## Material and methods

A review of the international literature of the last 50 years on the subject of synoviorthesis and alternative options in this case has been conducted.

## Results and discussions

The results of each type of synoviorthesis will be presented separately:

### 1) Intra-articular injection of corticosteroids

As far back as 1952, before the availability of concentrated factor replacement, MacAusland and Gartland advocated the use of intra-articular Hyaluronidase<sup>11</sup>. Other methods of intra-articular destruction of the synovium were also investigated.

Shupak et al.<sup>12</sup> were among the first to report satisfactory short-term results with the intra-articular injection of corticosteroids in haemophilia.

Rodriguez-Merchan et al.<sup>13</sup> performed a pilot prospective study to investigate the role of the procedure, initially in the short term and later with long-term follow-up. The primary objective of the study was to investigate a less aggressive method for the treatment of haemophilic

synovitis, given that the alternative procedures were synoviorthesis (intra-articular injections of radioactive materials) and surgical synovectomy (open or arthroscopic).

This prospective study evaluated the effectiveness of intra-articular methylprednisolone (80 mg) in 10 knees of 10 haemophilic patients with chronic synovitis. The patients were evaluated by radiographs and ultrasound before initiating treatment, and thereafter periodically for a 5-year follow-up period. One year after injection improvement in pain level was satisfactory, but pain recurred shortly thereafter. Five years after completion of treatment, all results were poor. Thus, it appears that injection of intra-articular methylprednisolone may be beneficial in relieving pain associated with arthropathy for up to 1 year but is not comparable to radiosynoviorthesis in reduction of haemarthrosis.

Fernandez-Palazzi et al.<sup>14</sup> reported that from 1966 to 1988, 34 patients with advanced chronic haemophilic synovitis (25 grade III and nine grade IV of their own scoring system) were treated with intra-articular injections of long-acting dexamethasone (sodium phosphate of dexamethasone plus acetate of dexamethasone) in cycles of three injections with 3-week intervals between each

injection and 6-month rest intervals between cycles for as many as three cycles, depending on the evolution of each case. All patients had chronic severe synovitis, axial deformity, muscular atrophy and diminution of range of movement. The group included 31 knees, two ankles and two shoulders. Subjective and objective evaluations were carried out grouping the results in good, fair and poor categories according to patient satisfaction, presence of synovitis, pain, range of motion and limitation of activities of daily living. Subjective results included 19 good, 12 fair and four poor results. The objective evaluation showed 22 good, nine fair and four poor results at an average follow-up of 1.5 years. The use of intra-articular dexamethasone is an alternative in the short- to medium-term for treatment of advanced chronic haemophilic arthropathy with pain and limitation of function before resorting to surgical reconstruction.

## 2) Chemical synoviorthesis

The most commonly used chemicals have been osmic acid and rifampicin. In fact, they have been utilized as an alternative to radioactive agents because of lack of availability or fear of radiation as a potential source of malignancy.

In 1973, Menkes et al. reported their experience with the use of intra-articular osmic acid<sup>15</sup>. Their results were mixed and this procedure never achieved wide popularity.

Caruso, in the 1980's was one of the first to use rifampicin as a chemical agent for the treatment of synovitis associated with rheumatoid arthritis<sup>4</sup>. Rifampicin was chosen for its proteolytic and fibrinolytic properties. Despite encouraging early results there was, however, a high failure rate.

Salis et al.<sup>16</sup> retrospectively reviewed their experience with non-surgical synovectomy in the treatment of recurrent haemarthrosis with arthropathy in patients with von Willebrand's disease, which is the most common inherited bleeding disorder, with an overall prevalence in the general population of 0.8-1.3%. Haemarthrosis occurs mainly in the most severe forms of the disease (type 3), with a frequency of 3.5-11%, and can cause severe arthropathy similar to that seen in haemophilia. Four of six patients had type 3 disease and the remaining two had type 2 disease. The age range was 13-63 years. The frequency of haemarthrosis prior to synovectomy was 1-4 per month. One (« = 2) or both (n = 1) knees were treated in four cases, one (n = 1) or both (n = 1) ankles in three cases and an elbow in one case. <sup>90</sup>Y was used in a dose of 5 millicuries (mCi) (or 185 mega becquerels (MBq)) for one knee, <sup>186</sup>Re in a dose of 2 mCi (or 74 MBq) for two ankles and the elbow and osmic acid for two knees and one ankle. Clinical and radiological results were evaluated 6 months after synovectomy using the World Federation of Haemophilia score. Radiological lesions remained stable and clinical manifestations improved in every case (P < 0.05). Five patients achieved a complete remission. Safety was satisfactory and there were no complications. The clinical efficacy of synovectomy, using radiocolloids or osmic acid in arthropathy caused by von Willebrand's disease, seems similar to that in haemophilia.

Caviglia et al.<sup>17</sup> reported that, for many years, rifampicin has been used empirically for the treatment of chronic haemophilic synovitis with encouraging results. A clinical study was performed on 48 haemophilic patients (48 joints). Seventeen elbows, eight knees and 23 ankles were treated. The mean age of the patients was 6 years (range 4-23 years) and the mean follow-up was 29 months (range 24-53 months). Overall, 40 excellent and eight good results were obtained. The average number of weekly injections of rifampicin was 3.06 (range 1-10 injections). Eight patients experienced pain on the first injection, which subsided gradually with the subsequent procedures. Synoviorthesis with rifampicin seems to be a good method for the treatment of haemophilic synovitis, especially in small joints (elbows and ankles) and in younger children.

Caviglia et al.<sup>18</sup> reported on the experience of three Latin American centres with rifampicin and compared it to radioactive synoviorthesis results. Results indicated that chemical synoviorthesis with rifampicin is indicated in younger patients (< 15 years) and small joint (ankles and elbows).

Fernandez-Palazzi et al.<sup>19</sup> also assessed the effectiveness of intra-articular rifampicin in haemophilic patients. Two hundred and fifty milligrams of rifampicin was injected into the elbow and ankle joints and 500 mg was injected into knee joints with 3-10 mL of lidocaine, depending on the joint size. The injections were repeated once a week for 7 weeks. Patients were only covered with antihaemophilic factor on the day of the injection at 30% above their coagulation level. The results were evaluated using subjective reports from the patient and objective assessment by the examiner. In the subjective reports the patient graded the results from their own perspective from 1 (poor) to 10 (excellent): 1-3 poor; 4-6 fair; 7-8 good; and 9-10 excellent. In the objective reports the grading was: excellent ('dry joint', full function, no haemarthrosis, no synovitis); good (clinical improvement, synovitis, reduction of haemarthroses, full function); fair synovitis (reduction of haemarthroses, no change in function); poor synovitis (persistent haemarthroses). This paper reports on the results of 38 patients with 39 joints with more than 3 years follow-up (mean 1.8 years). There were 22 knees, nine elbows and eight ankles. Subjectively, there were excellent results in 21 joints (11 knees, six elbows and four ankles), good results in 15 joints (eight knees, three elbows and four ankles), fair results in two knees and a poor result in one knee. Objectively, results obtained were excellent in 20 joints (11 knees, six elbows and three ankles); good in 17 (nine knees, three elbows and five ankles); fair in one knee and poor in one knee.

Radossi et al.<sup>20</sup> have used intra-articular injections of rifamycin. Among a large cohort of nearly 500 patients, they treated 28 patients during a 2-year period. The patients followed an on-demand replacement therapy programme and developed single or multiple joint chronic synovitis. The indications for synoviorthesis were symptoms of chronic synovitis referred by patients reported in a questionnaire.

In Radossi's series there were five patients with inhibitors to factor VIII. Their average age was 34 years.

Rifamycin (250 mg) was diluted in 10 ml of saline solution and 1–5 ml was then injected into the joint. The follow-up ranged from 6 to 24 months. Thirty-five joints were treated with 169 infiltrations in total. Rifamycin was injected once a week for 5 weeks, that is the patient had to come to hospital at weekly intervals. Twenty-four procedures were considered effective in 19 patients according to the evaluation scale, while six treatments were considered fair to poor. Five patients (six joints) with anti-factor VIII inhibitors were treated. In four joints the results were good, while in the two remaining joints the results were poor.

### 3) The use of D-penicillamine

Corrigan et al.<sup>21</sup> have used oral D-penicillamine for the treatment of 16 patients. The drug was given as a single dose in the morning before breakfast. The dose was 5–10 mg/kg body weight, not to exceed 10 mg/kg in children or 750 mg/day in adults. The duration of treatment was 2 months to 1 year (median 3 months). Ten patients had an unequivocal response, three had a reduction in palpable synovium, and three had no response. Minor reversible drug side effects occurred in two patients (proteinuria in one and a rash in the second). The study of Corrigan et al. has two main limitations: the small number of patients, and the lack of use of ultrasound and/or magnetic resonance imaging (MRI) for diagnostic purposes. It is also important to emphasize two potential side effects of D-penicillamine: aplastic anaemia and renal disease. To minimize the possibility of side effects, Corrigan and co-workers have suggested that the drug be used on a short-term basis (3–6 months).

### 4) Radiosynovectomy

Radioactive synoviorthesis is indicated in patients in grade I and II, and exceptionally in some early cases in grade III in the grading system developed by Fernandez-Palazzi and Caviglia. In grade I cases, synoviorthesis is indicated as a preventive treatment if there are more than two episodes of hemarthrosis in 6 months.<sup>22</sup>

Ahlberg<sup>23</sup> reported the use of intra-articular radioactive gold (<sup>198</sup>Au) in the haemophilia population in 1971, and many centres in the world have implemented programmes of intra-articular synovial control using yttrium-90 (<sup>90</sup>Y) and phosphorus-32 (<sup>32</sup>P), <sup>186</sup>Re(rhenium), <sup>169</sup>Er(erbium) or <sup>166</sup>Ho-Ferric Hydroxide.

Fernandez-Palazzi et al.<sup>24</sup> reported that radioactive synoviorthesis with <sup>198</sup>Au, <sup>90</sup>Y, Rhenium-186 (<sup>186</sup>Re) or <sup>32</sup>P would be appropriate treatment for recurrent haemarthroses in haemophilia. The clinical results, obtained by different centres, show a definite diminution of haemarthroses in 88% of cases [3]. The advantages of radioactive synoviorthesis compared with surgical synovectomy are: equivalent or better results; the requirement of substantially reduced antihaemophilic factor; the possibility of performing the procedure on multiple joints concurrently on an ambulatory basis; much less discomfort for the patient; no loss in joint range of motion; and the low cost of the procedure. In cases of failure, the procedure can be repeated after 6 months, and as many as three times on the same joint. Studies performed on the chromosomal changes that could be attributed to the radioactive material show the disappearance of these

alterations a few years after treatment. Despite over 40 years experience, there have been no reports documenting an increased incidence of neoplasia following radiosynoviorthesis.

This is contradicted by the study of Bossard et al.<sup>25</sup>, which shows that few long-term safety issues have been reported to date. Radioactive synovectomy does not seem to induce cartilage or bone toxicity, and the risk of cancer does not seem to be increased. However in a recent review of published studies, five reports of malignancy associated with radioactive synovectomy were identified (four associated with <sup>198</sup>Au and one with <sup>90</sup>Y), all cases occurred in patients treated for rheumatoid arthritis.<sup>26</sup> Two cases of acute lymphocytic leukaemia have been reported in paediatric patients following <sup>32</sup>P intra-articular injection. There are no published reports of malignancy associated with the use of <sup>186</sup>Re.

Selection of the radioisotope should consider the half-life, because the intensity of the inflammatory reaction is directly related to the rate of exposure; and the size of the radiocolloid, the larger the size the less tendency for the material to leak from the joint space. The material should be a pure beta-emitting radioisotope, thereby minimizing the whole body exposure from gamma radiation. Taking into account the high cost and limited supply of these materials, it is best to schedule groups of 6–8 patients to perform radiation synovectomy. This will require some patients to wait upwards of 3–6 months until the whole group is scheduled for the procedure. If possible, patients should be maintained on continuous prophylaxis and therapeutic exercises while waiting for the procedure.

Synoviorthesis can be performed at any age in haemophilia patients. Performing an intra-articular injection in a very young child does pose the problem of patient co-operation which may require conscious sedation or even general anaesthesia. The potential of radiation-induced cellular damage or chromosomal abnormalities remain a concern, particularly in the child.

One possible, although rare, minor complication is a cutaneous burn if the radioactive material leaks out of the joint. These burns are small and superficial, healing in about 2 weeks without residual scar. This problem can be prevented by flushing the needle and needle tract with a mixture of Xylocaine and a depositing steroid solution as the needle through which the radiocolloid was injected and then applying pressure to the injection site. Another potential complication is an inflammatory reaction after injection, which can be managed with rest and non-steroidal anti-inflammatory drugs (NSAIDs). These reactions are less likely with longer half-life agents. Image intensifier or ultrasound-guided articular puncture is commonly used to avoid extra-articular injection of the radioactive material.<sup>26</sup>

It is possible to perform multiple synoviorthesis in a single session. It is probably best to carry out no more than two injections at the same time to reduce the risk should any of the material escape. If two joints are to be injected, consider injecting two joints on the same side (i.e. an elbow and knee, elbow and ankle, knee and an ankle)(Table 2)<sup>27</sup>

Table 2 - Clinical indications of the radioactive isotopes most frequently used for radiosynoviorthesis.<sup>27</sup>

Isotope	Joint
<sup>90</sup> Y	Large-sized joints: knees
<sup>186</sup> Re	Middle-sized joints: shoulder, hip, and tarsus
<sup>169</sup> Er	Small-sized joints: interdigitals, elbow, wrist, ankle

Molho et al.<sup>28</sup> reported on 116 chemical and 90 radioactive synovectomies performed between 1970 and 1994 on 107 patients with severe haemophilia and two with type 3 von Willebrand's disease. The products used were osmic acid in 100 cases, <sup>90</sup>Y in 35 cases, <sup>186</sup>Re in 48, erbium-169 (<sup>169</sup>Er) in two, hexacetonide triamcinolone in 16 and <sup>198</sup>Au in five cases. The use of radioactive colloids is not allowed in France in patients under 15 years of age. Twenty-nine patients had more than one synovectomy in the same joint. All patients were evaluated for 6 months postsynovectomy, using both a clinical and a radiological score. Six months after synovectomy, a good or excellent result was obtained in 81% of the joints treated with isotopes, compared with 44% of those treated with osteoarthritis. This superiority of isotopes over osmic acid was still observed after 6 months for the 89 joints that were re-evaluated, with follow-up ranging from 1 to 9 years. A radiological score was calculated in 84 cases. The best results were from joints with the lowest scores presynovectomy (< 7). No correlation could be established between the clinical and the radiological scores, because of the small size of the sample. Molho et al. concluded that chemical and radioactive synovectomy are simple and safe procedures for haemophilic arthropathy. In their series, the efficacy of isotopic synovectomy was greater than that of chemical synovectomy, and this benefit seems to persist after 6 months, and up to 9 years in the group of patients with longer-term follow-up.

Nuss et al.<sup>29</sup> studied the clinical, plain X-ray and MRI findings in 13 haemophilic joints previously treated with radiosynoviorthesis. <sup>32</sup>P had been injected into the joints in an attempt to halt recurrent haemorrhage. Prior to <sup>32</sup>P injection, the majority of joints demonstrated bone damage evident on plain X-ray, secondary to recurrent haemorrhage. At the follow-up evaluation they found plain X-rays were adequate to identify cysts, erosions and cartilage loss in these very damaged joints. MRI was superior to clinical examination and plain X-ray in identifying synovial hyperplasia and effusions. However, the persistence of synovial thickening did not correlate with the bleeding frequency and clinical result.

Mathew et al.<sup>30</sup> presented their experience beginning in 1993 with 11 paediatric patients who underwent 17 <sup>32</sup>P isotopic synovectomies for chronic haemophilic arthropathy. <sup>32</sup>P was injected into the joint per protocol, approved by the institutional review board. All patients were male. Nine were factor VIII- and two were factor IX-deficient. The following joints were treated: ankle (n = 10 procedures), elbow (n = 5) and knee (n = 2). The first procedure was performed in December 1993. Mean age at the first procedure was 10.8 years (range 5.2-15.2 years). Mean pretreatment joint clinical scores using the World Federation of Haemophilia guidelines for the ankle was 5.5

(SD + 2.3), elbow 4.2 (+ 2.5) and knee 5.5 (± 3.5); the corresponding post-treatment scores were 2.6 (+2.0), 1.4 (+0.5) and 2.5 (+ 3.5), respectively. Presynovectomy mean radiological scores using the Pettersson method were: ankle 1.8, elbow 1.8 and knee 1.5. A scoring system used by the authors for evaluating joints using MRI gave the following mean pretreatment scores: ankle 9.5, elbow 8.4 and knee 5.0. A marked decrease (80-100%) in bleeding was seen in 13 of 17 procedures, and a moderate decrease (51-79%) in two procedures, accounting for 85% reduction in bleeding into the target joints. The procedure was well tolerated and no untoward side-effects were noted as of May 1999, with a median follow-up of 40 months (range 19-65 months). None had any clinical evidence of cancer. Three patients had their joints retreated [elbow (one), ankle (two)]. These procedures were also well tolerated. Matthew et al. concluded that isotopic synovectomy using <sup>32</sup>P appears to be feasible, safe and efficacious in the treatment of haemophilic arthropathy in paediatric patients who have been followed for a median of 40 months. As previously shown, MRI appears to give more detailed information about synovial hyperplasia and joint arthropathy than plain radiographs.

There is always the question about the cost of treatment in haemophilia, so Siegel et al.<sup>31</sup> made a comparative analysis of surgical synovectomy vs. radiosynoviorthesis with <sup>32</sup>P. The cost analysis was done comparing radiation and surgical synovectomy using Medicare billing records. Surgical synovectomy requires large quantities of factor, and cost ranges from \$50,000 to more than \$100,000. In addition, the patient's stay in the hospital, including professional fees, operating room costs, and physical therapy costs, is approximately \$50,000. Radiosynovectomy requires only one or two doses of clotting factor in most patients and does not require physical therapy or a stay in the hospital. Currently, P-32 chromic phosphate is available only in 10-mCi quantities (1 mCi = 37 MBq) from the manufacturer, and the minimum quantity that can be ordered costs more than \$2000. However, when several patients are scheduled for treatment in a day, and the local radiopharmacy divides this quantity into unit doses. This practice markedly reduces the cost of one dose. The radiopharmaceutical costs range from \$250 to \$300, and the cost of a dose of clotting factor ranges

from \$1000 to \$1500. The World Federation of Hemophilia has estimated that there are 350,000 patients with hemophilia in the world and 28,000 in the United States. At the Orthopaedic Hospital of Los Angeles Hemophilia Center, designated as an international training center for the World Federation of Hemophilia, an estimated 25% of patients with hemophilia are potential candidates for a synovectomy. Thus, if each of these potential candidates in the United States had a radiosynovectomy, rather than a

surgical synovectomy (7000 × \$150,000 surgical compared with 7000 × \$4000 radiation), it would result in a savings of more than \$1 billion in national health care.<sup>31</sup>

Heim et al.<sup>32</sup> injected radioactive <sup>90</sup>Y into 163 joints. Of these patients 115 were haemophiliacs with recurrent haemarthroses. The age at the time of the initial procedure was between 11 and 15 years and the median follow-up period was 11 years. Over 80% of the patients with haemophilia reported a decrease in the number of haemarthroses and 15% stopped bleeding altogether in the treated joint.

Between 1994 and 1999, Rodriguez-Merchan et al.<sup>33</sup> performed 66 <sup>90</sup>Y synoviortheses on 44 persons with haemophilia (45 knees, 12 elbows, nine ankles). At the time of injection 23 patients were HIV-positive and two had inhibitors. The average age was 21.1 years (range 9-39 years). FivemCi (185 MBq) of <sup>90</sup>Y were injected into the knees, and 3 mCi (111 MBq) into the elbows and ankles. The average follow-up was 3.5 years (range 1-6 years). Of the 45 knees, there were eight excellent, 10 good, 15 fair and 12 poor results. Of the 12 elbows there were three excellent results, five good, three fair and two poor. Of the nine ankles there were no excellent results, four good, three fair and one poor. The elbows had better results than the knees and ankles. The best results were obtained in the youngest patients, and in those with a moderate degree of synovitis, regardless of their HIV status and the presence of inhibitors. <sup>90</sup>Y synoviorthesis should be performed early, in patients when the amount of synovium is still moderate and there is minimal joint damage. Usually, these patients are in the first decade of life. Once the degree of synovitis has become severe and the joint surface is significantly eroded, the results of radioactive synoviorthesis are worse.

Silva et al. reported the experience of Luck and Siegel<sup>34</sup> who performed 170 radiosynovectomies using <sup>32</sup>P chromic phosphate between 1988 and 2000. Results of 130 procedures (115 primary procedures and 15 repeat procedures), in 97 haemophilic patients (88 of them type A and nine type B), were analysed. Patients in this study group had a bleeding frequency of at least three episodes per month in a target joint and failed conservative treatment, which included a combination of clotting factor concentrate and physical therapy. The 115 primary procedures, including 50 knees, 44 elbows, 14 ankles, five shoulders and two subtalar joints, were followed for an average of 3 years (range 0.5-11.6 years). The 15 repeat procedures, including seven knees, six elbows and two ankles, were followed for an average of 2.7 years (range 0.5-7.2 years). The average postprocedure bleeding frequency reduction, including primary and repeat procedures, was 70%. For primary procedures, excellent and good results (haemarthrosis reduction from 75 to 100%) were obtained in 79.2% of cases at 6 months to 8 years. For repeat procedures a combination of excellent and good results were obtained in 62.4% of cases at 6 months to 3 years. Regression analysis showed no correlation between results in terms of bleeding reduction, and age or degree of arthropathy. Radiation was well contained within the joint and there were no observed or identified complications. The authors concluded that the

procedure is effective, safe and highly cost-effective in comparison to open surgical or arthroscopic synovectomy.

Lofqvist et al.<sup>35</sup> reported on nine patients with haemophilia and clotting factor inhibitors (six with haemophilia A, three with haemophilia B). Nineteen joints were treated with radioactive synoviorthesis using <sup>198</sup>Au. Ages ranged from 3 to 40 years. Synoviorthesis was performed when the antibody titre was low (< 10 Bethesda units), thus making haemostasis possible by factor administration for 2-4 days. On five occasions, radioactive synoviorthesis was performed simultaneously with tolerance induction according to the Malmo protocol. A bleeding-free interval of more than 6 months was obtained in 11 joints, six of which remained haemarthrosis-free for more than 1 year. At long-term follow-up (range 18-182 months) five joints were rated good, one joint was fair and 11 joints were poor. Although the results were inferior to those for patients with haemophilia without inhibitor, radioactive synoviorthesis should be considered because of its ease of performance and the definite decrease in joint bleeding frequency that it brings about. This is of particular interest in patients with haemophilia caused by factor inhibitor who otherwise are difficult to treat.

Falcon de Vargas and Fernandez-Palazzi<sup>36</sup> assessed chromosomal structural changes (CSCs) studied by conventional lymphocyte cultures and banding techniques in 79 haemophilic patients with haemarthrosis treated with radioactive synoviorthesis, 31 haemophilic patients with haemarthrosis not treated by this procedure and 110 non-haemophilic patients matched by age and sex (control group). In 14 patients treated with <sup>198</sup>Au (group A), premalignant CSCs and non-specific CSCs were found in 1.69 and 17.23% of metaphases, respectively. The former disappeared, but 1.7% of the non-specific changes persisted 2 years after injection. In 31 patients treated with <sup>186</sup>Rh (group B), CSCs were not found previous to radioactive synoviorthesis but were present as non-specific changes in 1.25% of metaphases 6 months later; they disappeared 1 year after injection. In 34 patients treated with <sup>90</sup>Y (group C), CSCs were not found previous to radioactive synoviorthesis but were present as non-specific changes in 0.89% of meta-phases 6 months later; they disappeared 1 year after injection. Only non-specific CSCs were found in 0.79% of metaphases in haemophilia patients not treated with radioactive synoviorthesis (group D). CSCs were not present in control subjects. The authors concluded that in some haemophilic patients with haemarthrosis treated with radioactive synoviorthesis using <sup>198</sup>Au, <sup>186</sup>Rh or <sup>90</sup>Y, reversible premalignant or non-specific CSCs could be present; non-specific CSCs may persist in a low proportion of metaphases up to 2 years after injection when <sup>198</sup>Au is used as the radioactive agent. <sup>198</sup>Au is both a beta and gamma emitter. Radioactive synoviorthesis with a pure beta emitter seems to be, from a cytogenetic point of view, a safe alternative for these patients.

There is always a concern about the use of radiosynovectomy and the effects on joint cartilage and the incidence of cancer after this kind of treatment. Jahangier et al.<sup>37</sup> have found that radiation synovectomy with <sup>90</sup>Y for

persisting arthritis has harmful effects in vitro on human cartilage that cannot be prevented by co-administration of glucocorticoids. These results urge for a more detailed in vivo evaluation of cartilage changes after radiosynovectomy. Dunn et al.<sup>38</sup> reported about two patients which developed acute lymphocytic leukemia (ALL), one T-cell ALL and one precursor B-cell ALL, within one year of radioactive synovectomy with <sup>32</sup>P.

There are also new radiocolloids tested. Calegaro et al.<sup>39</sup> reported of the results in the treatment of chronic haemophilic arthropathy with <sup>153</sup>Samarium hydroxyapatite (<sup>153</sup>Sm-HA) in 31 patients with haemophilia.

#### 5) Alternatives to synoviorthesis

Rodriguez-Merchan et al.<sup>40</sup> reported a prospective study carried out from 1974 to 1996 to determine optimal treatment for chronic haemophilic synovitis of the knee and synovitis of the elbow. Sixty-five patients with synovitis affecting 65 knee joints and 40 patients who had synovitis of the elbow (44 elbows), despite a 3-month trial of prophylactic substitution therapy, were treated by synovectomy. Radiation synovectomies (<sup>198</sup>Au synoviorthesis) were performed on 38 knees, open surgical synovectomy on 18 and nine had an arthroscopic procedure. Radioactive gold synoviorthesis was performed on 29 elbows, and 15 had a resection of the radial head and partial open synovectomy. Synovectomy (by any method) significantly reduced bleeding episodes, but did not halt the radiographical deterioration of the joints. It is thought that radiation synovectomy is the best choice for patients with persistent synovitis of the knee and elbow unresponsive to a 3-month trial of prophylactic factor replacement. If two to three consecutive synoviortheses with 3-6 months intervals had been ineffective, or when the radiographical score is more than two points, a surgical synovectomy is indicated.

When chronic synovitis is allowed to persist, the membrane can hypertrophy to the point where it cannot be adequately ablated by a pure beta-emitting radiocolloid, which only penetrates about 5 mm. In these cases as well as those in which repeated radiosynoviorthesis has failed, arthroscopic synovectomy is often effective.<sup>4</sup>

#### Conclusions

Synoviorthesis is a highly effective procedure that decreases both the frequency and the intensity of recurrent intra-articular bleeds related to joint synovitis. The procedure should be performed as soon as possible to minimize the degree of articular cartilage damage, which, based on many studies, is irreversible.

It can also be used in patients with inhibitors with minimal risk of complications. On average, synoviorthesis has a 75-80% satisfactory outcome in the long term. From the clinical standpoint, such efficacy can be measured by the decrease in the number of haemarthroses, with complete cessation for several years in some cases.

Synoviorthesis of any kind is a highly cost-effective method compared to open or arthroscopic synovectomy.

One should bear in mind that in 20-25% of cases, synoviorthesis fails to control haemarthroses. In such cases, it can be repeated.

<sup>90</sup>Y should be used in large joints (knees) and <sup>186</sup>Re in small joints (interdigitals, elbow, wrist, ankle). Global results of treatment with chemical synovectomy (osmic acid and rifampicin) seems to be less favourable than with radionuclides (<sup>90</sup>Y, <sup>32</sup>P, <sup>186</sup>Re), except for small joints, where the results are comparable.

In cases where the synovium is thicker than 5-10 mm, and haemarthroses persist following synoviorthesis, arthroscopic synovectomy is indicated.

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# MYASTHENIA GRAVIS IN PEDIATRICS

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## Abstract

Myasthenia Gravis is a chronic autoimmune neuromuscular disorder characterized by abnormal fatigability of muscle after repeated or sustained activity and improvement after rest. Peak incidence is seen in young adults but it may also occur in infancy and childhood. Three separate entities are characteristic in childhood period (a) transient neonatal myasthenia in an infant of myasthenic mother, (b) congenital or infantile myasthenia in an infant of non-myasthenic mother and (c) juvenile myasthenia similar to adult myasthenia.

The author focuses on the neuroimmunological mechanism, clinical features, laboratory and electrodiagnostic testing.

**Keywords:** Myasthenia Gravis, Child, Congenital, Neuroimmunology.

Myasthenia gravis (MG) is an autoimmune disorder that affects the neuromuscular junction at the postsynaptic level (1).

The neuromuscular transmission efficacy will be readily blocked, due to the morphological changes in the neuromuscular junction which could cause an increased diffusion of acetylcholine from the synaptic cleft, by reducing the ability of acetylcholine to interact with the functional receptors. Most of the acetylcholine molecules delivered in the synaptic terminal by an action potential will be faster hydrolyzed by acetylcholinesterase.

## Physiological abnormality in Myasthenia Gravis

The pathophysiology of MG is nearly well understood today. The main mechanism is generated by sensitized T-helper cells and an immunoglobulin antibody (IgG) – directed attack on the nicotinic acetylcholine receptor of the neuromuscular junction.

Acetylcholine receptor antibodies are present in most patients with Myasthenia Gravis, but they are not the only ones.

Acetylcholine receptors antibodies can be transferred passively to animals producing experimental autoimmune myasthenia gravis. The physiopathological features of myasthenia are described by a diminished numbers of acetylcholine receptors that are disposed on the muscular postsynaptic membrane (2). The postsynaptic folds are flattening or “simplified”. These abnormalities cause a defective efficiency of the neuromuscular transmission. Antibody binds to the  $\alpha$ - subunit of the acetylcholine receptor, because this subunit is also called the main immunogenic region. Removal of acetylcholine receptors (by plasmapheresis) leads to recovery.

Animals immunized with an acetylcholine receptor (purified extract from *Torpedo Californica*) will begin to produce acetylcholine receptor antibodies, which can develop an autoimmune disease experimental induced.

## Clinical manifestations of Myasthenia

Being the most common disorder of the neuromuscular junction, involving also a defective neuromuscular transmission, the degree and the variations of muscle weakness are located in ocular, bulbar, limb and respiratory muscles. In child, the muscular deficit occurs frequently at bulbar and respiratory level. According with the clinical course of the disease myasthenia gravis could be: generalized, ocular and with bulbar involvement. The immunitary attack is directed at proteins in the postsynaptic membrane of the myoneural junction, reason for why, sometimes myasthenia is accompanied by a myopathic episode that could be transitory or prolonged. The changes in the topography of muscular deficit depend by the muscle group affected, and for the clinician is also important to establish the motor deficit trough so called Myasthenic score. Due to the fact that the disorder is limited to the neuromuscular junction, no abnormality of cognition, sensory function or automatic function is incriminated.

## Particularities regarding the neonates and children with myasthenia

About 15% of children are born from mothers with myasthenia and due to the transplacentally passing of IgG antibodies some of them have generalized weakness. This clinical aspect can happen to MuSK- positive myasthenia gravis and with seronegative mothers. Nevertheless no respiratory distress may present at birth, generalized muscle weakness and difficulties bin suckling could be a signal alarm. These symptoms tend to improve spontaneously in 2-3 weeks. Exceptionally, Mestinon and plasma exchange could be used. In neonates with congenital myasthenic syndrome which also is clinically manifest at birth, a differential diagnosis should be performed. A false friend could be the syndrome of floppy infant. Arthrogryposis multiplex congenital occurs in rare cases.

Children have usual antibody-mediated myasthenia, easy to diagnose if antibodies anti acetylcholine receptors or MuSK are present. We must have in our attention that an antibody-negative test could indicate a late onset congenital disease.

### Immunogenetics of myasthenia

In myasthenia, class II molecules of the major histocompatibility complex (MHC) are expressed on the antigen presenting cell, in this way, the T cells become reactive against the acetylcholine receptor. The MHC class II is very important in determining the susceptibility. Patients with myasthenia gravis have the histocompatibility subtypes DR3 and DQ2. The HLA system is involved by HLA –B8 and HLA-DR3 antigens. C3, C4 complement system polymorphisms could be depended by the circulating acetylcholine receptors and immune circulating complexes.

### Immunoserological investigations

Certain studies should be performed to exclude other disorders that could interfere with myasthenic symptoms. Laboratory tests for Myasthenia Gravis are more specific from serologically point of investigation. The following studies should be performed:

Antibody tests: Anti -AChR antibodies, Anti-MuSK antibodies, Antistriated muscle antibodies, Antinuclear antibodies, Anti –ds-DNA antibodies, Anti-Jo 1 antibodies, Anti-Smith antibodies, Immune circulating complexes, Immunogram, C3, C4 complement compounds.

Hematology: Complete blood cells count.  
Biochemistry: Liver and renal profiles, rheumatoid factor, electrolyte panel.

Endocrine serological markers: Thyroid –stimulating hormone (TSH), Triiodothyronine (T3), Thyroxine (T4).

### Electrodiagnostic

In clinical practice, the pathological features of neuromuscular transmission in myasthenia can be performed by electromyography. This electrophysiological technique involves nerve conduction activity, diagnosed by repetitive nerve stimulation (RNS) and single fiber electromyography (SFEMG). In myasthenia gravis a decrement greater than 10% is characteristic. Regarding the single fiber electromyography, when jitter is present on the electromyographic route, could be a certain sign of myasthenia, although for 80% of the patients could not be specific.

In Child, Myasthenia represents about 10% from the total sum of clinical cases of disturbances of the synaptic transmission at the level of neuromuscular junction. 75% of cases appears between 10 and 15 years of age. In pediatrics practice Myasthenia Gravis is described by four clinical types: (a) Transient neonatal myasthenia, (b) Persistent neonatal myasthenia, (c) Juvenile myasthenia, (d). Congenital and familial myasthenic syndromes. Autoimmune myasthenia gravis (MG) encompasses all of the immunologically-mediated disorders affecting the endplate region of the postsynaptic neuromuscular junction. Nearly all of these disorders involve a loss of immunological self-tolerance, though transitory neonatal MG is a self-limited disorder that follows passive transfer of maternal antibodies to the fetus (3, 4).

### *Transient neonatal myasthenia*

Occur at approximately 10-15% of new born from myasthenic mothers. This clinical manifestation is the consequence of the transfer of maternal antibodies through placenta, in the fetal circulation (4). The presence of acetylcholine antibodies at mothers and fetus was proved through serological investigations. It is still unknown why some of the new born of myasthenic mothers develop an transient neonatal myasthenia

Clinical features: The symptoms make them first appearance precocious. In the first 48 hours of life is find out an important hypotonia, poor or weak suck, weak scream, and sometimes respiratory distress. Palpebral ptosis is present only in a reduced percent of the cases. The symptoms can persist from some days of neonatal life, at 4-6 weeks (5). The course of the symptoms is leading to a remission of them once with acetylcholine antibody depletion or disparition.

### *Persistent neonatal myasthenia*

The symptoms are like in transient neonatal myasthenia form. Mother don't have myasthenia, but at least of a relatives can be affected. The disease persist the whole life. The eyelids and the ocular muscles are severe involved.

### *Juvenile Myasthenia*

Is a rare disease in children. Clinically it usually occurs after ten years of age with palpebral ptosis and diplopia. The intercostal and facial muscles are frequently affected. It is characterized by the improvement after rest and exacerbation through repeated movements. The "myasthenic crisis" occur in inter-current infections or certain state of stress being a hasten exacerbation which menace the life.

### *Familial and Congenital myasthenic syndromes*

These genetic features of Myasthenia Gravis are not immunologically mediated, being the expression of different abnormalities of the synaptic neuromuscular transmission. Most of them are autosomal recessive inherited (6). Depending by the site of the abnormality, and by the neuromuscular transmission, the myasthenic congenital syndromes are divided in: presynaptic defects –abnormality in resynthesis and storage of the acetylcholine plus a reduced number of synaptic vesicles and impaired release of acetylcholine – and postsynaptic defects –decreased number in acetylcholine receptors, abnormality in binding affinity, prolonged opening time of acetylcholine channels with clinical features like slow channel syndrome and fast channel syndrome. The clinical evolution is heterogeneous. In near 2% of cases the symptoms the symptoms appears from birth or can be present in the first two years of infancy. Sometimes could exist an anamnesis of diminished fetal movements, in this case the clinical debut of the disease being prenatal (arthrogryposis /arthrogryposis multiplex congenital).

The postsynaptic defects, generally show a moderate symptomatology, in this area being involved Congenital Myasthenia Gravis too. Grace to the histopathological

examination through immunofluorescence it was described a deposition of IgG and complement at the level of neuromuscular junction.

Familial Myasthenia, represent the clinical prototype of a synaptic defect, abnormality in acetylcholine storage and resynthesis being essential. The beginning of the disease can be noted from birth with variable hypotonia, sometimes severe, in contrast with extraocular motricity which is usually normal although a degree of facial muscle affection can also exist.

The course of the disease is characterized by repeated episodes of muscle weakness sometimes apnea or neonatal respiratory distress that are life menacing. These episodes could be present end long to suckling period and in childhood rarely in adult life.

The congenital and familial myasthenic syndromes are immunohistochemically differentiated depending by the proteins that cause the mutations into acetylcholine receptor subunits.

### Thymectomy and ocular myasthenia gravis in child

In the research literature is already specified that the disease will progress in about 50% of patients with initial ocular myasthenia gravis (7). Ocular myasthenia gravis in child is less common, but not the same thing happens with ocular onset of the disease. Thymectomy is generally considered the long term surgical therapy with good results in generalized myasthenia gravis. Regarding the ocular myasthenia gravis in child and benefits of thymectomy, the best improvement makes felt his presence if the children are thymectomized on early after the onset of the disease.

### The usage of intravenous immunoglobulin

Venous access in child is a little bit disputable regarding the infusion with immunoglobulins. Its effectiveness has been disputable too with variable acetylcholine receptor antibody responses. Children should be assessed after treatment, heaving in view that a high dosage of immunoglobulin infused doesn't mean a quick clinical improvement and could influence in a bad way the turnover of acetylcholine receptor. The adequate treatment scheme for children with regards of intravenous immunoglobulin administration is about 2mg/kg body weight infused at variable rates of 2 g/kg for one day, 0,66 g/kg daily for three days, and 0,5 g/kg daily for four days. The therapy should gradually institute. Concluding with this, in one patient the total dose should be about 0,8 g/kg adjusted to body weight. Usually, the children shows a good tolerance when treatment is applied. An important remark is

to mention that in some cases after intravenous immunoglobulin administration, a decrease in anti AChR antibody levels could be observed, despite that a correlation between clinical response to therapy and antibody titers, doesn't exist. The addressability and specificity of intravenous immunoglobulin therapy aimed especially in juvenile myasthenia gravis, myasthenic crisis and the patient preparation for surgery, but unfortunately offers a limited long-term benefit.

### Myasthenic crisis

A serious complication of myasthenia gravis is respiratory failure. According to Drachman (8), this may be secondary to an exacerbation of myasthenia (myasthenia crisis) or to treatment with excess doses of a cholinesterase inhibitor (cholinergic crisis). Managing respiratory failure and differentiating a myasthenia from a cholinergic crisis is reviewed. Due to the unpredictable appearance of respiratory failure, hospitalization is recommended for most children with exacerbations or complications of myasthenia gravis. Anticholinesterase therapy and specific antibiotherapy, should be properly conducted, the separation from mechanical ventilator support being extremely vital in the course of the disease and clinical improvement(9)

### Conclusions and discussions

Myasthenia gravis is diagnosed in children via blood tests, a drug test that challenges the muscle weakness, which is positive if strength improves, and muscle fatigability tests by observing a child doing repetitive movements which bring about weakness. It can be treated with medications to upgrade chemical messages in the neuromuscular junction, and medications to dampen down the immune response, removal of the thymus gland that is important in childhood immunity, and cleaning the blood of antibodies via plasmapheresis. Occasionally the condition can spontaneously resolve, but there is no cure. It can become fatal if the muscles controlling breathing are involved, but the majority of cases are well maintained on medication.

The purpose of this review article was to bring a short and better understanding of pediatricians, neurologists and general practitioner medicine in the front of a clinical cases as regards the clinical manifestations of Myasthenia Gravis in pediatrics. The pediatric neurologist and family physician should play an important role in the diagnosis and management of children with Myasthenia Gravis. Laboratory testing and an autoimmune evaluation of the disease are addressed to general immunologist or neuroimmunologist too.

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# NEONATAL SEPTICEMIA – RETROSPECTIVE STUDY ON PREMATURE NEWBORN

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## Abstract

Septicemia in neonates (newborn children) refers to generalized bacterial infection documented by a positive blood culture in the first four weeks of life. The study was carried out retrospectively on a one year period (2008) in the Newborn and Infant care Clinique from “Louis Turcanu” Children Hospital, on a number of 34 hospitalized premature newborn children, selected based on anamnesistic, clinical, epidemiologic and biological criteria. The prevalence of the disease was 4.03% and the mortality was high 14.71% even in the presence of a specific anti-biotherapy. Any baby who is not well must be considered at risk of sepsis and appropriate antibiotics commenced as soon as possible after taking cultures.

**Key words:** septicemia, premature.

## Introduction

Neonatal septicemia appears especially in premature newborns in neonatal intensive care units. Generally, the incidence is 1- 8 cases per 1000 live newborn children (7). It is a severe affliction with high mortality, even in the presence of specific anti-biotherapy. Depending on onset age of the disease, septicemia is divided in: a) early neonatal septicemia or maternal-fetal infection, with onset in the first 7 days of life; b) late neonatal septicemia or postnatal infection, with onset after the first 7 days of life. The risk factors for early neonatal septicemia can be factors related to the mother (early membrane rupture and the long time between the rupture and the birth, being the most significant) and fetus related factors (prematurity represents the most important risk factor for infections). Nosocomial infections are the most significant risk factor in late neonatal septicemia.

The authors of this study have proposed to analyze the risk factors of this disease based on prematurity grades and onset age, correlated with the clinical and biological aspect on one hand, and with morbidity and mortality, on the other hand.

## Material and method

The study was carried out retrospectively on a year period (2008) in the Newborn and Infant care Clinique from “Louis Turcanu” Children Hospital, on a number of 34 hospitalized premature newborns, selected based on anamnesistic, clinical, epidemiologic and biologic criteria.

The newborns were divided in two groups:

1. First group – lot A – 16 newborns with early onset septicemia, in the first 7 days of life.
2. Second group - lot B – newborns with septicemia with onset after the first 7 days of life

What were put under observation are the risk factors of the condition, on prematurity grades and onset age of the disease. The prevalence was 4.03 %.

## Results and discussions

Prematurity represents one of the most important risk factor for infections. The risk of developing complications increases with decreasing gestational age and birth weight. Preterm infants have a 3- to 10-fold higher incidence of infection than full-term normal birth-weight infants. Possible explanations could be: an immune system much more immature than those of the full-term infants; maternal genital tract infections are considered to be an important cause of preterm labor and an increased risk for vertical transmission to the newborn; the incidence of intraamniotic infections increases with decreasing gestational age; the premature infants need a long period of hospitalization and very often invasive care techniques that can be source for infections (3).

Based on different degrees of prematurity we noticed that in the studied group 32 % were first degree preterm, 24 % were II degree preterm, 38 % preterm III degree and 6% preterm were IV degree (table 1).

Table 1. Septicemia incidence based on prematurity degrees

	Early neonatal septicemia (lot A)	Late onset septicemia (lot B)	
I degree prematurity BW *2500- 2000g	9	2	11 cases (32 %)
II degree prematurity BW 2000- 1500g	3	5	8 cases (24 %)
III degree prematurity BW 1500- 1000 g	3	10	13 cases (38 %)
IV degree prematurity BW under 1000g	1	1	2 cases (6 %)
	16 cases (47.06%)	18 cases (52.94 %)	

\* BW - birth weight

Early onset septicemia occurred to 16 infants (47.06 %). Apart from prematurity, the following risk factors were observed in the studied group:

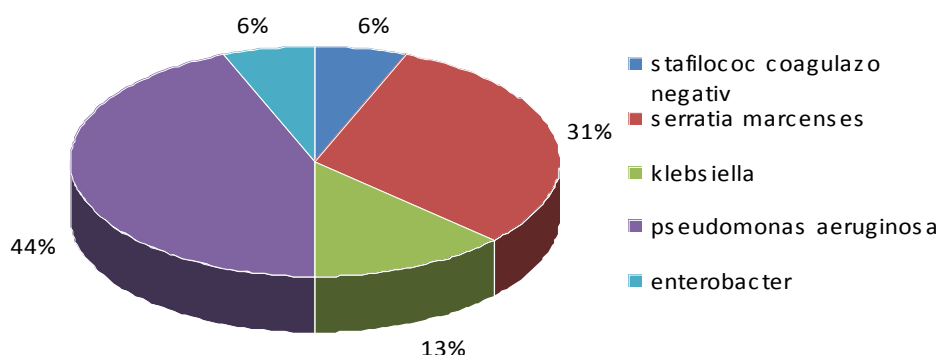
1. In 7 cases (43.75%) ruptured membranes for more than 18 hours occurred. According to Milunsky A., in 50 % of cases, amniotitis occurs and after 3 days since premature rupture of fetal membranes, and when ruptured membranes are present during labor germs ascension from vagina is facilitated, so, after 12 hours since the rupture, the amniotic liquid infects 100% of cases. 6 cases from our group that were infected that way, had rupture of membranes for over 24 hours. That is why right monitoring of labor and specific medications for birth finalizing are required (6).

2. Four newborns (25%) have presented with green amniotic liquid and have necessitated reanimation measures, which can be sometimes invasive (endotracheal tubes, venous catheters) and this increases the risk for infections.

3. Another major risk factor for maternal-fetal infection is represented by the fever over 39°C during labor. In 5 cases (31.25 %) pregnant women have had fever during labor.

In early onset septicemia there is a high risk of mortality, percentages between 10 % and 30 % being mentioned in literature (7). In lot A there was a high mortality, approximately 25%, affecting especially the infants with very low birth weight, under 1500 grams. Thus, from the 4 deceased 3 were premature with birth weight under 1000 grams and one with birth weight under 1500 grams.

The most frequently implicated microbial flora is represented by gram negative bacillus, 15 cases (94%). From this, *Pseudomonas Aeruginosa* represented 44%, followed by *Serratia Marcenses* and *Klebsiella Pneumoniae* (graphic 1). *Pseudomonas Aeruginosa* is an opportunist pathogen which causes severe infections in patients with immune deficiency and newborns. It was encountered in 3 of the deceased infants. Otherwise, in 6% of the cases the blood cultures showed the presence of Coagulase-Negative *Staphylococcus*. According to the specific literature, in early neonatal septicemia the main implicated factor, 30-40 % from cases, is represented by the group B *Streptococcus* (4). But in our lot none of the infants presented positive blood cultures for this germ.



Graphic 1. Incidence of microbial flora in early onset septicemia.

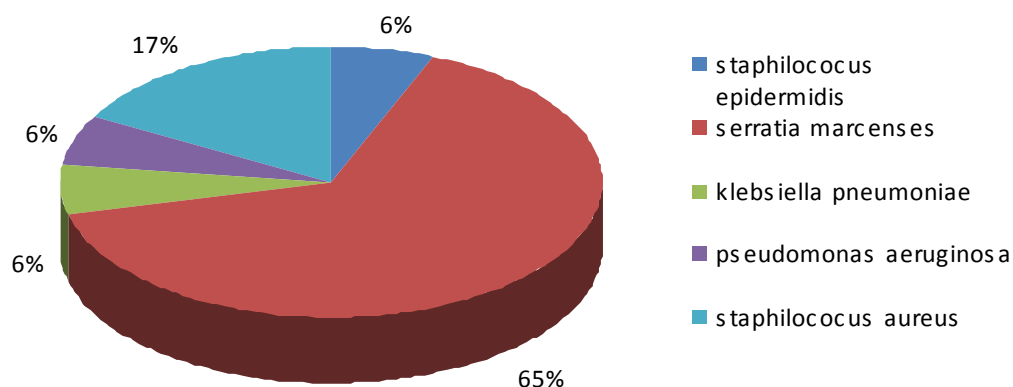
Late onset septicemia occurred in 18 cases (52.94 %) increases in premature infants with gestational age lower than 32 weeks and birth weight under 1500 grams; 11 of the studied cases in lot B (61.1%). The Center for Diseases Control and Prevention defines a nosocomial infection as any infection occurring after admission to the Neonatal Intensive Care Unit (NICU) that was not transplacentally acquired (3).

Long term hospitalization represents an important risk factor for the late onset septicemia because the hospital pathogens are a permanent threat for the premature infants because of their unusual susceptibility to infections. Due to low birth weight all infants from this study necessitated a long period of hospitalization. Frequent contact with

medical stuff and invasive care techniques (gavage tubes, venous catheters) are source for systemic infections, all the newborns from this study needed this type of care and 5 cases (27 %) were intubated and mechanically ventilated.

Mortality in lot B was 5.5%, lower compared with lot A, affecting especially premature newborns with weight lower then 1000g .

The most frequently found germ in lot B was the gram negative bacillus – 14 cases (77%), most common being *Serratia Marcenses*, followed by *Klebsiella Pneumoniae* and *Pseudomonas Aeruginosa*. 23 % of the microbial flora was formed by gram positive cocci (graphic 2).



Graphic 2. The incidence of microbial flora in late onset septicemia.

Clinical findings in all newborns were very severe. On clinical examination we found a profound altered general status, paled, marble skin, prolonged re-coloring time more then 2 seconds, apnea crisis, moaning, tachycardia VB > 170 b/min, gastric residue more then 3 ml before gavage. All the deceased had presented signs of disseminated intravascular coagulation, clinical finding being petechiae and ecchymoses, bleeding, either at puncture site or spontaneous. DIC represents the most important risk factor for unfavorable evolution in neonatal septicemia.

The final diagnosis is based on bacteriologic examination, blood cultures representing the final and major argument for the diagnosis of a systemic infection. Beside blood cultures, some other lab tests have been carried out, which have neither the specificity nor the necessary sensibility to impose the sepsis diagnosis, but help for orientation towards it.

1. Blood count – leukocyte number is useful but unspecific, leukocytosis was between 17240 – 44000 /mm<sup>3</sup>. Thrombocytopenia appears later in severe bacterial infection but despite of this it is registered most of the time as a first

sign of infection. The thrombocytes values were between 15000 – 12000/ mm<sup>3</sup>.

2. C-reactive protein increases towards maximum values in 8-60 hours from the onset of the inflammatory process and decreases promptly under efficient treatment. CRP values were comprised between 8.92 mg/l and 220 mg/l.

3. Acid-base disorders are characteristic for septicemia as well as appearance of metabolic acidosis. All the studied cases presented a disturbance of acid base balance with metabolic acidosis.

### Conclusions:

Neonatal septicemia remains a major clinical issue in neonatology, with increased rate of mortality and morbidity. In the studied group there was a high mortality rate, 14.71 %. However, lot A had a higher mortality rate (25 %) than lot B (5.5 %).

The most afflicted are premature newborns with gestational age under 32 weeks and birth weight lower then 1500g.

Global prevalence of disease in our section was 4.03 % among which, 47.06% presented early onset septicemia and 52.94 % had late onset septicemia.

Beside prematurity, the most frequently encountered risk factors in lot A were premature amniotic membrane

ruptures for more then 18 hours (43.75 %) and prolonged hospital stays in lot B.

Global incidence of the implicated germs is 85.29 % gram negative bacilli and 14.71% gram positive cocci, so in both groups the gram negative bacilli had a greater incidence.

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# INCIDENCE AND MAJOR PERINATAL COMPLICATIONS IN EXTREMELY LOW BIRTH WEIGHT

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## Abstract

**Introduction:** Newborns with extreme prematurity are considered those who have a birth weight under 1000 grams. Morpho-functional plurivisceral immaturity lead to particular diseases, through frequency and gravity.

**Objectives:** The authors aim to study a lot of newborns with extremely low birth weight and to determine the major complications specific for this category.

**Material and method:** the study was carried out in the Premature and Neonatology Department during two years, on a group of 20 premature newborns with birth weight under 1000 grams (800 grams- 1000 grams), with gestational age between 27-32 weeks.

**Results:** In the group studied the distribution by sex showed a number of 11 (55% ) male newborns and 9 (45% ) female newborns.

Respiratory distress syndrome was present in 14 cases (70%), prematurity apnea in 16 cases (80%). It was diagnosed a case of necrotizing enterocolitis. The patent ductus arteriosus was revealed by ultrasound in 8 cases (40%), in 2 cases was associated with septal atrial defect. Intraventricular hemorrhage of several degrees revealed with transfontanelar ultrasound in a ratio of 60%-12 newborns. Within the screening program for prematurity retinopathy the entire group was evaluated, 9 of them (45%) presenting signs of retinopathy in several stages. All the premature presented several degrees of anemia.

**Conclusions:** Extreme prematurity is an important risk factor in increasing neonatal morbidity and mortality, premature with very low birth weight being the most

exposed to all major complications of prematurity both in neonatal period and after this.

**Keywords:** Extreme prematurity, complications.

## Introducion

Plurivisceral morpho-functional immaturity causes some particular diseases through frequency and severity: respiratory distress syndrome, peri- and intraventricular hemorrhage, apnea crisis, patent ductus arteriosus, enterocolitic ulceronecrosis and infections.

Premature newborns have dominant respiratory clinical manifestations but the lesion background is mostly cerebral. By Rusul (1981) the complications of prematurity can be clasified as follows:

- Early pathology : idiopathic respiratory distress syndrome, recurrent apnea, intra and periventricular hemorrhage, lung hemorrhage, jaundice, infections
- Late Sechele : at eyes (retinopathy of prematurity-retrolental fibroplasia, myopia, strabismus), auditive (hypoacusis, deafness), neurological (cerebral paralysis, diplegie, choreoathetosis, epilepsy), intelectual (IQ lower than 70), psychic (behavior disturbances).

## Respiratory distress syndrome

By the old statistics respiratory distress syndrome affects 5% of the 1st degree premature, 20% of the 2nd degree premature, 50% of the 3rd degree premature, 70% of the 4th degree premature, and only 0,5% of the term newborn. Related to the gestational age the incidence of the disease is: 20% when gestational age is 34-32 weeks and 40% when gestational age is 32-30 weeks.

The frequency of respiratory distress syndrome related to gestational age and antenatal steroids therapy :

Gestational age	Antenatal steroid therapy	
	without	Yes
<30 weeks	60%	35%
30-34 weeks	25%	10%
>34 weeks	5%	-

**Radiologic examination:** At more then 90% of the patients the radiological image is characteristic since the age of 5 hours and shows characteristic "ground glass image.

**Lab examination** emphasizes hipoxemia ( $PO_2$  arterial <50mmHg)  $\pm$  hipercapnia ( $PCO_2$  >55-60 mmHg). It was observed that  $PCO_2$  in arterial blood at the beginning of disease can be normal or decreased and, as far as the disease evolves, it increases.

The disesse being characteristic to premature newborn, the treatment will consist of prevention the

premature birth. The antenatal therapy with corticosteroids is indicated for women with risk of premature birth. The treatment will be individualized according to the severity of disease. The therapy aims to maintain, in reasonable limits, the  $PaO_2$  (45-70 mmHg) and the  $PaCO_2$  (34-45 mmHg).

## Peri and intraventricular hemorrhage

Intraventricular hemorrhage is the most frequent form at newborn, more often met at premature than at term newborn. Its' importance comes out not only in the high

incidence of this pathology, while raising the number of small and very small surviving premature, but also in the major impact on the perinatal and postneonatal morbidity and mortality, by secondary neurological sequelae, by lesion associations and complications.

Intraventricular hemorrhage occurs usually at premature with gestational age under 34 weeks. With the support of transfontanelar ultrasound it was established that 50% of the premature under 1500 grams face this type of hemorrhage, and approximately half of them survive. From the survivors 40% develop further normally, 40% remain with minor sequelae and 20% with medium and severe sequelae.

By Perlman and Volpe at premature with birth weight between 500 and 700 grams incidence of intraventricular hemorrhage is 62%, out of which 97% are severe forms (degree III and IV), while at those with birth weight between 700 and 1500 grams the incidence is 25% and only 32% are severe forms. These data are in accordance with data offered by other studies. Gleissner shows, in another study, that incidence of intraventricular hemorrhage is 48,5% at 27 weeks of gestation, 32,4% between 28 and 32 weeks of gestation and goes down at 26% after this gestational age.

The incidence of peri and intraventricular hemorrhage decreased constantly in the last years, from approximately 40% at newborns with birthweight <1500g in initial studies, to approximately 20% in the recent studies.

Although the incidence of the disease went down, its prevalence between the surviving infants is still substantial due to high rate of surviving infants with birth weight under 1000 grams.

#### Patent ductus arteriosus

Definition: abnormal communication between lung and systemic flow at the level of persistent arterial channel, situated between lung and thoracic artery, where it goes up to 5-10mm distal from left subclavicular artery emergence.

The arterial channel is a remaining of the 6th aortic arch identified in the 6th gestational week, having an important role during embriofetal flow, and being the location of pasive shortcut of lung flow. So the blood is lead in a teritory with low vascular resistance (placental flow). This anatomic formation, characteristic to fetal life, is closing, functionally, in the first 12 hours of life and anatomically in the first 3 weeks, through afibrosis process. Remaining fiber belr is known as ligamentum arteriosus. For closing the channel interferences a constrictive effect of increasing the volume of oxygen in blood, immediately postnatal. This effect is directly related with gestational age, being less obvious at large premature bigger than 1000 grams If we want to maintain the arterial channel open immediately postnatal we must interfere with prostanglandine infusion.

PDA at premature under 1000 grams, with severe respiratory distress in the first days of life: surfactant administration leads to lung healing, but as the lung disease is healing the lung vascular resistance decreases, the

volume of blood through PDA increases, identified in 80% of cases. Mechanical ventilation bigger pressures to beat the lung resistance; blood flow through PCA can be so big that the suflul might be not heard. Paralel with lung overloading other organs are less irrigated (during diastolic the diastolic pressure in aorta decreases too much). In these cases it was shown that surgically closing the PDA before the age of 10 days has a positive effect, decreasing the period and pressure for assisted ventilation. In practice, even without major hemodynamic complications, it is tried to close, pharmacologically, the PCA at any premature under 1000 grame, in the 3rd day of life. Only if, after 72 hours of indometacin administration, the left ventricular deficiency is not controlled will be taken in consideration surgical closing of arterial channel.

#### Premature Retinopathy

In the last decade it was described as a new complication which come out at premature, as a multi factor disease. It is characterized by abnormal retinian vascular development, leading to retinal detachment serious visual affection up to blindness. The disease occurs especially at former premature with very low birth weight. The incidence of the disease increases as long as gestation period and birth weight are smaller. International studies show presence of retinopathy at 65% of the premature with birth weight less than 1250 grams and 80% of the newborns with birth weight less than 1000 grams. In SUA, premature retinoathy is the second cause of blindness at the age of 6 years. Those with gestational age <28 weeks present a higher risk of ROP.

Clinical picture:Diagnosis of premature retinopathy is made by ophtalmoscopic examination (an indirect ophthalmoscope). Examination of the retina of a premature infant is performed to determine how far the retinal blood vessels have grown (the zone), and whether or not the vessels are growing flat along the wall of the eye (the stage). Retinal vascularization is judged to be complete when vessels extend to the ora serrata. The stage of ROP refers to the character of the leading edge of growing retinal blood vessels (at the vascular-avascular border). The stages of ROP disease have been defined by the International Classification of Retinopathy of Prematurity (ICROP).

ICROP uses a number of parameters to describe the disease. They are location of the disease into zones (1, 2, and 3), the circumferential extent of the disease based on the clock hours (1-12), the severity of the disease (stage 1-5) and the presence or absence of "Plus Disease". Each aspect of the classification has a technical definition. This classification was used for the major clinical trials. It has been revised in 2005.

The zones are centered on the optic nerve. Zone 1 is the posterior zone of the retina, defined as the circle with a radius extending from the optic nerve to double the distance to the macula. Zone 2 is an annulus with the inner border defined by zone 1 and the outer border defined by the radius defined as the distance from the optic nerve to the nasal ora serrata. Zone 3 is the residual temporal crescent of the retina (fig1).

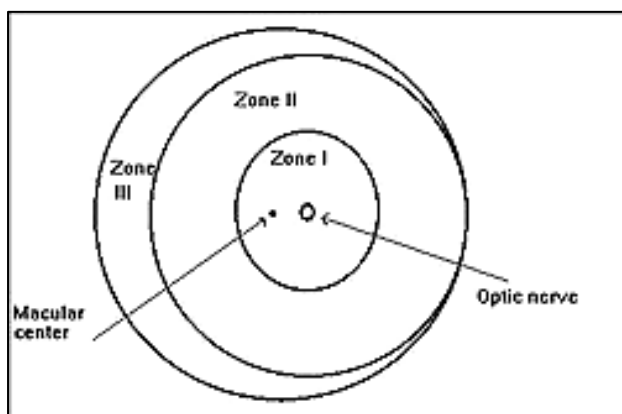


Fig.1 Zones of the retina in ROP.

The circumferential extent of the disease is described in segments as if the top of the eye were 12 on the face of a clock. For example one might report that there is stage 1 disease for 3 clock hours from 4 to 7 o'clock. (The extent is a bit less important since the treatment indications from the Early Treatment for ROP)

The Stages describe the ophthalmoscopic findings at the junction between the vascularized and avascular retina.

- Stage 1 is a faint demarcation line.
- Stage 2 is an elevated ridge.
- Stage 3 is extraretinal fibrovascular tissue.
- Stage 4 is sub-total retinal detachment.
- Stage 5 is total retinal detachment.

Retinal examination with scleral depression is generally recommended for patients born before 30-32 weeks gestation, with birthweight 1500 grams or less, or at the discretion of the treating neonatologist. The initial examination is usually performed at 4-6 weeks of life, and then repeated every 1-3 weeks until vascularization is complete (or until disease progression mandates treatment).

#### Ulceronecrotic enterocolitis

Described in 1960 ulceronecrotic enterocolitis seems to be an affection which belongs to modern intensive care units, where its frequency is 1-15%. The incidence of EUN is variable from one medical center to other and it seem to be 10% amongst the premature with very low birth weight. This variation makes some authors consider EUN as epidemic. Mortality through EUN is 20-30%.

**Etiopathogeny.** Etiopathogeny of EUN is incompletely cleared. Today it is believed that it has a multifactor determinism. The most important risk factors are prematurity, intestinal ischemia, infection and enteral feeding.

**Prematurity.** EUN is, first of all, a disease of prematurity. From the total of ill persons 50% are premature of 3rd și 4th degree, 30% premature of 1st and 2nd degree and only 20% have birth weight over 2500 grams. Morphologic and functional immaturity of intestine and

imunitară imaturity are the base of increased incidence of EUN at premature. Now it is mentioned that EUN incidence is lower at premature with mothers who received glucocorticoids before birth. Glucocorticoids are ahead of lung and gastrointestinal tract development. The immaturity of defense mechanisms of gastrointestinal tract was mentioned as risk factor, bacterial colonisation of premature intestine favorising the aggression of bacteria and toxins.

The extremely low birth weight (ELBW) premature infant is an infant born at 1000 grams or less, generally before 28 weeks gestation.

Survivability correlates with gestational age for infants who are appropriate for gestational age (AGA). Infants with extremely low birth weights (ELBW) are more susceptible to all of the possible complications of premature birth, both in the immediate neonatal period and after discharge from the nursery.

#### **Objectives**

The authors aim to study a lot of newborns with extremely low birth weight and to determine the major complications specific for this category.

#### **Material and method**

The study was carried out in the Prematurity and Neonatology Department during two years, on a group of 20 premature newborns with birth weight under 1000 grams (800 grams- 1000 grams), with gestational age between 27-32 weeks. A number of 750 premature newborn were included in the study, hospitalized on anamnestic, clinical and paraclinical criteria.

#### **Results**

Case distribution by prematurity degree was: 1<sup>st</sup> degree 48,27%, 2<sup>nd</sup> degree 30,93%, 3<sup>rd</sup> degree 18,14%, 4<sup>th</sup> degree 2,66% (fig.2).

In the group studied the distribution by sex showed a number of 11 (55%) male newborns and 9 (45%) female newborns (fig.3).

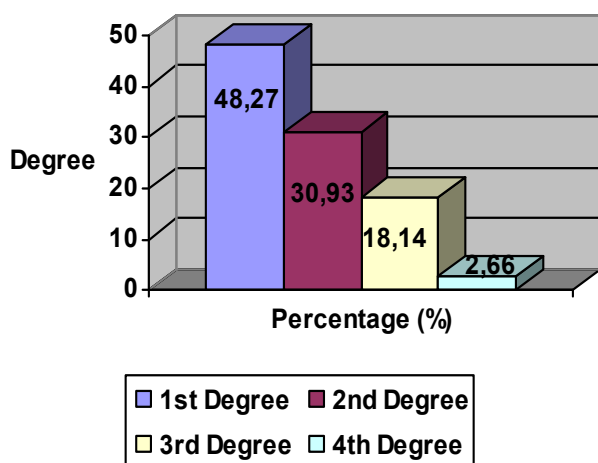


Fig.2 Distribution by prematurity degree.

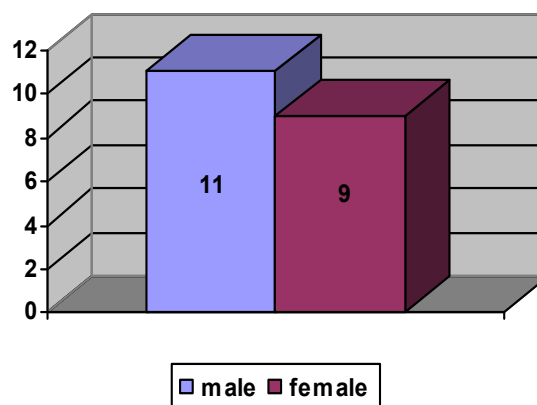


Fig.3 Distribution by sex.

An early complication of extreme prematurity is respiratory distress syndrome (RDS) caused by surfactant deficiency was present in 14 cases (70%). The diagnosis was set clinically and based on the chest x-ray. Apnea of prematurity is common in infants with extremely low birth weights and is defined as cessation of respiratory activity of more than 20 seconds, with or without bradycardia or cyanosis. She was present in 16 cases (80%). It was diagnosed a one case of necrotizing enterocolitis who present the following clinical signs: abdominal distension, hemorrhagic stools, vomiting, edema of the abdominal wall. The patent ductus arteriosus was revealed by cardiac ultrasound in 8 cases (40%), in 2 cases was associated with septal atrial defect (Fig.4)

Babies with extremely low birth weights are at particular risk for IVH because of vulnerability of the germinal matrix and because the protective cerebral

autoregulation present in older babies has not yet developed. Any event that results in disruption of vascular autoregulation can cause IVH, including hypoxia, ischemia, rapid fluid changes, and pneumothorax. Presentation can be asymptomatic or catastrophic, depending on the degree of the hemorrhage. Symptoms include apnea, hypertension or hypotension, sudden anemia, acidosis, changes in muscular tone, and seizures. Intraventricular hemorrhage of several degrees revealed with transfontanelar ultrasound in a ratio of 60%-12 newborns. The neurological exam showed: hypotonia, diminished or abolished primitive reflexes, seizures, myoclonus.

Within the screening program for prematurity retinopathy the entire group was evaluated, 9 of them (45%) presenting signs of retinopathy in several stages. Two of them needed laser treatment. All the premature presented several degrees of anemia.

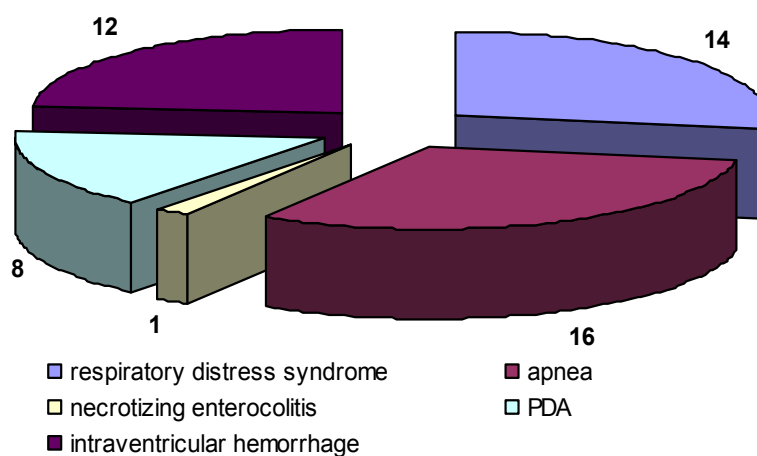


Fig.4 Distribution of complications.

**Conclusions**

Extreme prematurity is an important risk factor in increasing neonatal morbidity and mortality, premature with very low birth weight being the most exposed to all major complications of prematurity both in neonatal period and

after this. Pre term babies with under 32 weeks of gestation period must be investigated in the ROP screening program beginning with the 3<sup>rd</sup> week of life and then every 2 weeks until de age of 44 weeks after birth.

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# NUMERIC CHROMOSOMAL CHANGES OF THE SMALL ACROCENTRICS IN ACUTE LEUKEMIA

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## Abstract

Acute leukemia is a clonal disturbance due to malign transformation of a myeloid or lymphoid progenitor cell, which allows the classification of leukemia in acute lymphoblastic leukemia and acute myeloblastic leukemia.

50 cytogenetic analyses of patients with leukemia with ages between 2 -73 years have been performed in the Cytogenetic laboratory of the University of Medicine and Pharmacy Victor Babes Timisoara during 2004-2009.

The diagnostic cytogenetic analysis has been shown to be an important prognostic factor, capable of predicting remission duration and the therapeutic management. For the confirmation of previous data, CGH may provide useful information regarding the nature of genomic aberrations that take place in cases with complex karyotypes.

**Keywords:** Small Acrocentrics( 21 and 22), chromosomal abnormalities, acute leukemia

## Introduction

Acute myelocytic leukemia (AML) and Acute lymphoblastic leukemia (ALL) is characterized by a variety of numerical and structural chromosome aberrations. Gains and losses of whole chromosomes occur frequently in AML and ALL, both as solitary changes, usually found at diagnosis, and as additional aberrations in later disease stages.

Chromosomal abnormalities in neoplastic marrow cells often correlate closely with specific clinical and biologic characteristics of the disease and serve as a tool to predict the clinical outcome and develop effective therapeutic approaches.

## Material and method

During the period between 2004 and 2009, in Cytogenetics Laboratory of University of Medicine and Pharmacy “Victor Babes” Timisoara, there were performed 50 cytogenetics tests of the patients with the suspicion of acute lymphoblastic leukemia and acute myeloblastic leukemia. Most of the tests were undertaken before the beginning of the treatment. The patients are represented by children with the age between 2 and 14 years, as well as

adults with the age between 20 years and 73 years. The samples were obtained from the bone marrow using the direct method (without cellular cultures) and the indirect method, this method implying cellular cultures with the length of 24, 48, 72 hours. For specimen collection, 1-2 ml of marrow are aspirated aseptically into a syringe coated with preservative-free sodium heparin and transferred to a sterile 15 ml centrifuge tube containing 5 ml culture medium (RPMI 1640, 100 units sodium heparin). For blood specimens, 5 ml are drawn aseptically by venipuncture into a syringe coated with preservative-free heparin. Specimen should be maintained at room temperature and transported in culture medium. To prepare metaphase cells, the sample is exposed sequentially to mitotic inhibitors to accumulate cells in mitosis, hypotonic KCl (0.075M) to swell the cells, and fixative (absolute methanol: glacial acetic acid, 3:1). Slides are prepared by dropping the cell suspension onto precleaned glass microscope slides, and the slides are air dried. The most popular chromosomal banding techniques is trypsin-Giemsa banding. Using this technique, a consistent chromosome banding pattern is induced by exposing cells to a dilute trypsin solution (0,1-0,25 percent), followed by staining in phosphate-buffered Giemsa stain

The assessed metaphases, 20 for each patient, had a proper quality due to the adherence to the protocol. It also was noticed a better dispersion of the chromosomes from the cells with normal karyotype.

## Results

The numeric chromosomal changes of the group G chromosomes are the following: totally 21 trisomy as a single anomaly (fig.1); totally 21 trisomy as a collateral anomaly occurred in a case with totally 6,8,19 trisomy and long arm q17 isochromosome (fig.2); 17 trisomy observed in other case (fig.3); totally tetrasomy of chromosome 21 along with 6 trisomy, 19 trisomy, long arm q17 isochromosome (fig.4); totally 22 trisomy as a collateral anomaly along with 15 monosomy and 11q23 deletion (fig.5). 21 trisomy was encountered at the patients with acute lymphoblastic leukemia and 22 trisomy at a patient with acute myeloblastic leukemia.

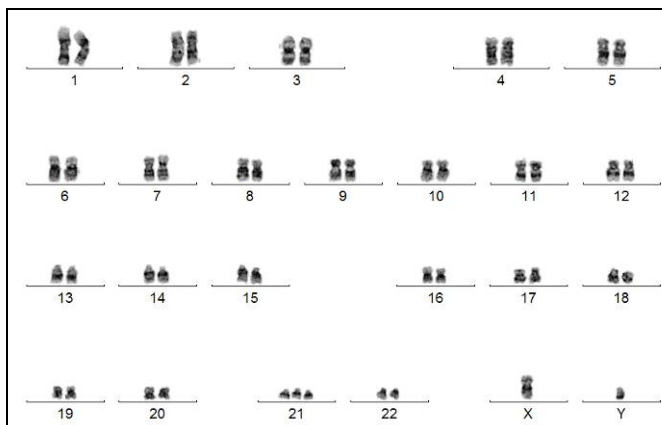


Fig 1- 47,XY,+21

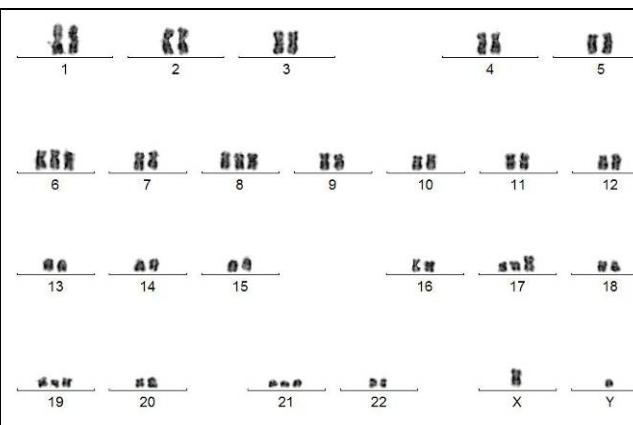


Fig 2 - 51,XY,+6,+8,+i(17q),+19,+21

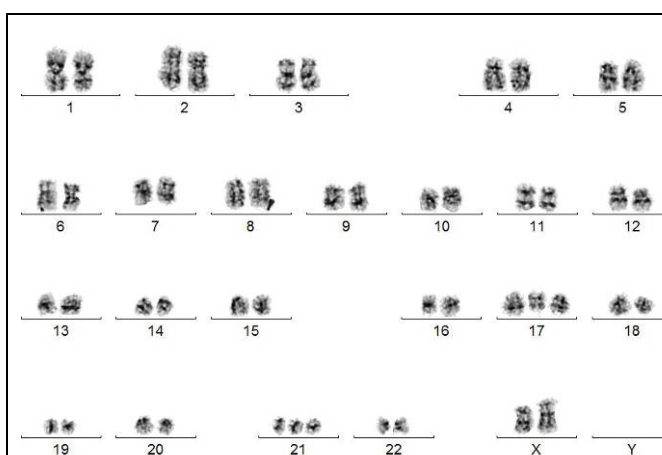


Fig 3 - 48,XX,+17,+21

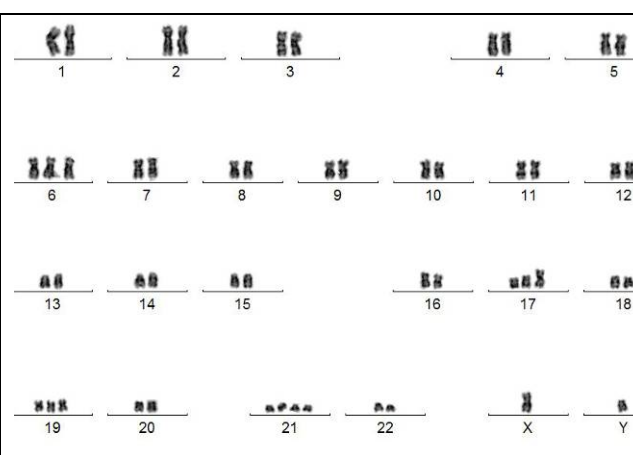


Fig 4 - 51,XY,+6,+i(17q),+19,+21,+21

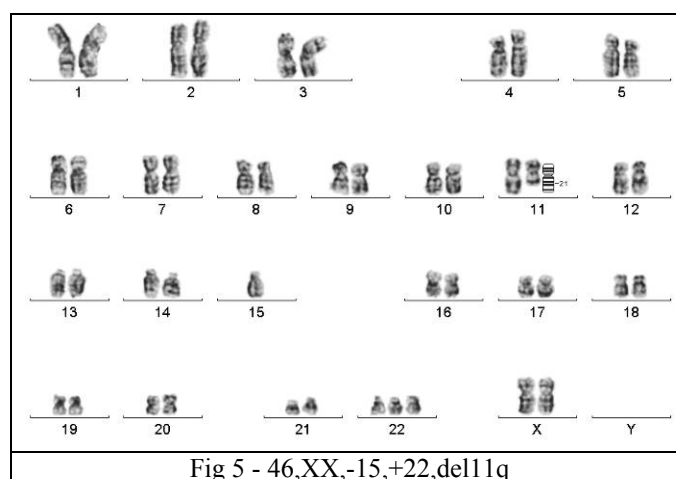


Fig 5 - 46,XX,-15,+22,del11q

### Discussions

21 trisomy is more frequently encountered in acute lymphoblastic leukemia, but is also seen in acute myeloblastic leukemia as a single anomaly or as a collateral anomaly without specificity for any FAB subtype. As unique anomaly it occurred in acute lymphoblastic leukemia

in our study, while in medical literature it is characteristic for acute myeloblastic leukemia type M7 (megakaryoblastic).

21 tetrasomy was also described in megakaryoblastic leukemia as a clonal anomaly.

22 trisomy was found in our study at a case with acute myeloblastic leukemia, in medical literature this anomaly is found more often at the patients with acute myeloblastic leukemia type M4. It seems that this chromosomal disorder is the cause of the erythropoiesis's decreasing. In 90 percent of the cases it was encountered as a collateral anomaly.

Besides the numeric changes of the 21 and 22 chromosomes, these patients present totally 6, 8, 19, 17 trisomies, as well as 17q isochromosome and 11q deletion.

Totally trisomies frequently encountered in acute lymphoblastic leukemia are: 4, 6, 10, 14, 17, 18, 20, 21. 8 trisomy occurs in acute lymphoblastic leukemia but is more frequent in acute myeloblastic leukemia. 11q23 deletion without rearrangement of the MLL gene is associated with a favorable evolution. 4, 6, 10 and 21 trisomies are markers for a good prognostic along with a good survivorship.

## Conclusions

The cytogenetics diagnosis is a prognostic factor with the capacity to predict the remission rate, the length of the remission and the survivorship period, regardless of the haematological, immunological and clinics parameters.

Hyperdiploidia is a disorder frequently encountered in acute lymphoblastic leukemia, the one characterized by more than 50 chromosomes leading to a favorable evolution, while hyperdiploidia with less than 50 chromosomes denotes a poor prognosis. Nevertheless 6 and 21 trisomy indicate a favorable prognosis, 11q23 deletion does not imply the rearrangement of the MLL gene. Even if 8 trisomy is a characteristic of the myeloid disorders, in our study it was encountered in acute lymphoblastic leukemia.

Even if 21 and 22 trisomies are not particularities of any type of acute leukemia, they are frequently encountered.

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## VALUATION OF MODERN DIAGNOSTIC METHODS IN DETECTING INITIAL CARIOUS LESIONS

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### Abstract

**Introduction:** Modern investigation methods used in the diagnosis of dental caries may bring substantial improvements to the classic ones. However, their implementation requires specific knowledge, appropriate endowment and prior assessment. It is the aim of this research to replace the classic concepts of early dental caries diagnosis by modern methods. **Material and methods:** Studies are focused on the testing of various diagnosis methods in order to compare them, as well as to validate them histologically by the means of stereomicroscopy to develop applications for teaching and basic research purposes. Quantitative light-induced fluorescence (QLF) and Diagnodent will be assessed so as to optimise these methods. As the present diagnosis systems are very diverse, the choice of one or another in practice needs to be estimated beforehand. In vitro analysis is therefore mandatory. Computer-assisted diagnosis is employed to get additional data by using the related softwares that will enable the clinician to store information, as well as to subsequently assess and monitor. **Results:** Following this research, we expect the new computerised work methods to may be optimised, customised, multiplied and implemented in practice as regards both the design, and the execution technology. **Conclusions:** Computer-assisted work methods in the early diagnosis of caries lesions are laborious; they involve a series of work phases and specific knowledge.

**Key words:** dental caries, diagnosis methods.

### Introduction

Modern management of dental caries comprises three major components: prevention, control and treatment. It is based on the adequate diagnosis of the disease and on the detection of pathological changes of the lesion in the initial stages. A great drawback for the clinician regarding the caries management strategies based on the risk assessment is the lack of methods to certainly determine the degree of profound dental tissues decay. It is possible to detect the lesions in an early phase, before the emergence of cavity lesion by using the modern methods. This is of particular importance in order to take adequate preventive measures in due time [1, 2]. If the modern diagnosis methods are not used, the risk of caries lesions is increased, as the classic methods do not allow for the detection of early carious lesions that are still in the reversible stage of remineralisation. Besides the visual examination, the most widespread exam to improve the initial carious lesion

diagnosis and also the only one used in most dental offices is the radiographic examination [3, 4]. Although the bite-wing radiographic examination is thought to be important in the detection of proximal caries, this type of exam shows poor results in the detection of enamel occlusal caries [5, 6]. Several new methods were introduced in the early 1990's, some of them as research tools, while others were used in the dental offices. These were intended to increase the reliability of occlusal caries detection besides the visual examination and the radiographic methods. FOTI, DIFOTI, ECM, QLF, DIAGNOdent and D-Carie are some of them. [7, 8, 9,10]. In the case of **optical based methods for detecting carious lesions**, the light interacts with hard dental tissues in different ways: it can be reflected, scattered, transmitted or absorbed. Fluorescence, in which the electrons having a lower energy level move to a higher level, is a possible consequence of absorption. When they reach back the initial level, the energy is emitted as light, which is known as fluorescence. In other words, fluorescence is the result of interaction between the electromagnetic radiation and molecules in the tissue. It is still not clear what causes the enamel fluorescence. The most part of fluorescence is induced by organic components, protein chromophores, but a portion is probably due apatite. Dentine fluorescence has been suggested to be caused by inorganic complexes, as well as by organic components. In healthy enamel wave lengths are large, with a high probability that photons will hit a chromophore. Thus, fluorescence is relatively intense. Demineralisation of dental hard tissue, enamel or dentine leads to the loss of auto-fluorescence, the natural fluorescence. Several factors may contribute to the decreased fluorescence of early carious lesions. Four possible mechanisms have been proposed: the light scattering in the lesion causes the light path to be much shorter than in the healthy enamel: light absorption per volume is much lower in the lesion, so the fluorescence is weaker; light scattering within the lesion acts as a barrier for excitation light to reach the underlying fluorescent dentine and for fluorescent light in the dentine to reach the surface; fluorescence is ended by a switch in molecular environment of chromophores; protein chromophores are removed by dental caries evolution. **The QLF method – light-induced quantitative fluorescence** (fig.1) measures the fluorescence induced after use of green-blue laser light at approximately 488 nm wavelength, quantifying demineralisation and severity of lesion. It is used for *in vitro*, *in vivo* and *in situ* studies in the diagnosis of early lesions, both for deciduous

and permanent teeth [11]. Effects are higher *in vitro* than *in vivo*, were a humid environment exists [12]. The QLF method has been tested in several *in vitro*, *in situ* and *in vivo* studies for caries lesions of tooth surfaces [13, 14, 15, 16]. This method has high *in vivo* repeatability and reproducibility, which means it can monitor the effects of preventive programmes [16]. Examples of factors that may influence in different ways the measurements results include: presence of bacterial plaque, dental calculus and/or stains on tooth surface, ambient light, daylight or artificial light and dehydration de degree of dental tissue [17, 18].



Fig.1 QLF sistem - Inspektor™ Pro.

**The DIAGNOdent device** (fig.2). Sundstrom and co-workers performed in 1985 a comparative study on the fluorescence of healthy tooth surface for different excitation wavelengths and reported the absence of fluorescence in the visible area for red light illumination (633 nm). Studies by Hibst and Gall showed the red light induced fluorescence (638–655 nm) could differentiate between healthy and carious tooth tissue [19, 20]. The DIAGNOdent device has been assessed in several *in vitro* and *in vivo* studies [21, 22, 23, 24].



Fig. 2. DIAGNOdent device and DIAGNOdent – pen device.

In a study by Lussi and co-workers that compares traditional examination and treatment to concurrent use of DIAGNOdent device, good to excellent sensitivity and excellent reproducibility were reported [21]. Reproducibility is high, the device is therefore used for the longitudinal monitoring of caries, for the differentiation between active and inactive lesions and for establishing the treatment plan [25]. Stained dental materials might affect DIAGNOdent readings and consequently result in false-positive diagnoses of secondary caries. Dental fillings should be polished prior to DIAGNOdent measurement [26]. As the DIAGNOdent accuracy concerns, it is influenced by the presence of bacterial plaque and dental calculus; thus the professional hygiene prior to measurements is required. A prolonged drying will also modify the reading [27]. DIAGNOdent accuracy is superior to that of radiography, while its specificity is higher than that of ECM [28, 29]. The factors that can influence in different ways measurement results are: presence of plaque, dental calculus and/or stains on tooth surface, dehydration degree of dental tissue, the presence of sealing materials or professional hygiene [27,30,31]. For measurements performed on occlusal surfaces it is important the tip to be tilted, so all the surfaces to be scanned.

#### Aim

The main purpose of this study is to investigate if correlations between data from the **modern methods of early carious lesion detection** (QLF, Diagnodent) and

**histological validation** exist. This study aims to test fidelity, reproducibility and validity of the methods designed to detect and quantify the caries in terms of statistical analysis; this study investigate if data from the diagnostic methods may improve the performance of investigator in the diagnosis caries as compared with the visual inspection, and to examine the way in which they may influence treatment decisions.

#### Materials and methods

The study material was formed by 192 human extracted teeth: premolars extracted for orthodontic purposes and impacted molars with macroscopically intact occlusal surface- without any loss of tooth substance, extemporaneous stains, hypoplasias, or other enamel abnormalities or restorations. In order to perform the extractions, the written and verbal consent of the patient was previously obtained. Clinical diagnosis, clinical inspection was performed by three calibrated investigators which individually assessed each dental piece, establishing the treatment indication: monitoring - absence of treatment, non-invasive treatment (topical applications with de fluoride, sealing) or invasive treatment (tooth restorations). Indications will be recorded in an individual file of each tooth piece; these will be lately compared to the results obtained after measurements by modern methods of detecting early carious lesion, as well as to the anatomic-pathological exam of the lesion. One week after the visual

examination QLF examinations were conducted by the same three examiners. Four weeks following the initial visual examination/treatment decision, all examiners were requested to re-evaluate the designated examination sites, this time having available to them the results from the other detection methods, to make another decision regarding their recommended treatment.

**Visual examination** was carried out using only a dental operating light and air-drying up to 5 s. No explorer was used during the examination. Each predetermined site on the occlusal surfaces was scored using the criteria described by Ekstrand et al. [32], as presented in Table 1. The tooth selection included scores 0–3, but not score 4 (Table1).

Table 1. Criteria for visual examination.

Score	Criteria
0	No or only a slight change in enamel translucency after prolonged air drying (>5s)
1	Opacity or discoloration hardly visible on the wet surface, but distinctly visible after air drying
2	Opacity or discoloration distinctly visible without air drying
3	Localized enamel breakdown in opaque or discoloured enamel and/or grayish discoloured from underlying dentine
4	Cavitation in opaque or discoloured enamel exposing the dentine beneath

**Laser fluorescence measurements** were made using the DIAGNOdent device (Kavo, Biberach, Germany). The device was calibrated before use with a porcelain standard provided by the manufacturer. The probe tip A was adjusted to each tooth separately by holding the tip against a sound smooth surface and pressing the ring button until calibration was complete. The tooth surface was dried, then the conical probe tip was positioned perpendicularly over each selected site, as indicated in the photographs, and rotated around its long axis. A score of 5 or higher was considered to indicate the presence of caries. Each site was measured three times using the above-mentioned procedures and the average of these readings (0–99 range) was considered as the definitive score.

**Quantitative light-induced fluorescence.** Images of occlusal surfaces of tooth specimens were captured using a portable intra-oral camera device connected to a computer (QLF; Inspektor Research Systems, Amsterdam, the Netherlands). Each occlusal surface was illuminated with 13 mW cm<sup>2</sup> of violet–blue light (wavelength: 290–450 nm, average 380 nm) from the camera handpiece and the images were captured using a camera fitted with a yellow 520-nm high-pass filter. The images were not analyzed, but were scored subjectively from the stored images displayed on a cathode ray tube (CRT) monitor. The scoring criteria were as follows: 0, no change in enamel fluorescence; 1, slight change in enamel fluorescence; 2, loss of fluorescence distinctly visible without broken enamel; 3, loss of fluorescence distinctly visible with enamel broken; and 4, loss of fluorescence distinctly visible with cavitation.

**Histological validation.** Studies conducted to the date are the result of cooperation with the Department of Technology of Materials within “Politehnica” University Timisoara and with the Department of Histology within UMF Timisoara. They focused on processed extracted dental fragments (polished dried tooth, initially sectioned at 50µm, and later at 15µm thickness; it is fixed between blade and lamella with the luting of edges to prevent the air to permeate) for stereomicroscopic analysis. The

stereomicroscopy allows the study of higher quality tridimensional and of laterality images. These interpretative qualities of stereomicroscopy are given by the large examination fields and large work distances ranging between 92 mm and 286 mm, with an increase from 1.95 to 225 x. Basic principles of stereomicroscopy include coaxial, oblique and annular lighting techniques. Optical adjustment of optical and mechanical alignment is required for optimal lighting and micrometry. It allows for the morphological and colour absorption study, as well as for the assessment of the depth of lack of substance, which is very useful in the evaluation of carious lesion progression. Isotropy versus anisotropy and birefringence by Michel Levy phenomenon are determined by using polarised light. Colour interference and quantitative position of particle extinction are also determined. Olympus SZ x 7 and Olympus camera 2.5 x digital zoom and 3 x optical zoom were used to study the specimens in stereomicroscopy and polarised light.

In order to clarify the diagnostic methods, it was by statistical analysis of the results, establishing the sensitivity, specificity and accuracy degree. GraphPad PRISM, prism 5 for Windows, data processing in Excel, EPI and SPSS ver.17

## Results

Validity of clinical diagnosis was correlated with the measurements obtained by laser fluorescence device, KaVo DIAGNOdent, QLF device as well as with *the investigation in polarised light and stereomicroscopy – gold standard*, allowing for the histological study of lesion morphology. *Evaluation of the relationship between presence and depth of histologically confirmed carious lesion and diagnosis based on clinical inspection only or clinical inspection combined with QLF, Diagnodent*, as well as *evaluation of relationship between presence and depth of histologically confirmed carious lesion and treatment decision based on clinical inspection only or clinical inspection and examination by QLF, and Diagnodent* has been aimed. Computer-assisted diagnosis has been used for QLF. (fig.3).

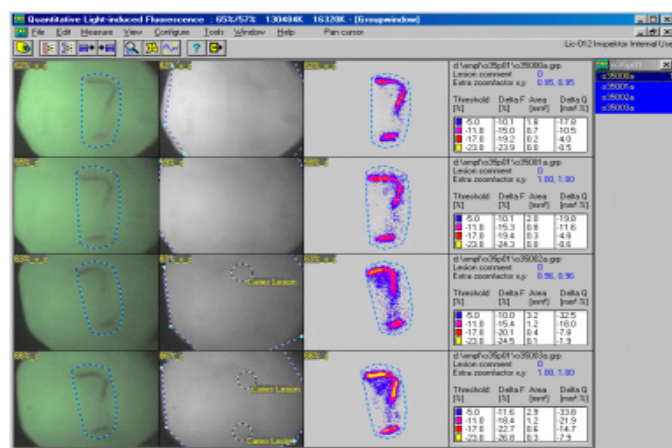


Fig.3. Images interpreted with QLF system software.

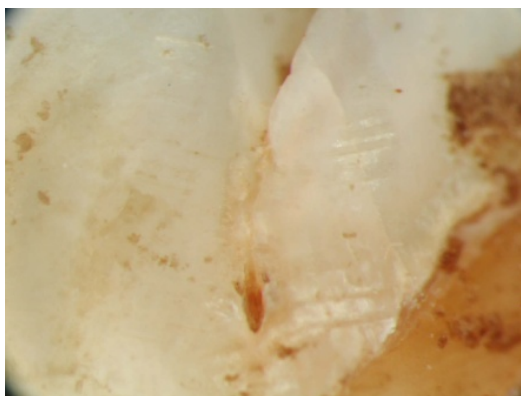


Fig.4. Occlusal surface with deep grooves and plaque deposits, stereomicroscopy aspect of polytopic lysis of enamel and dentine proximal to the carious lesion body,



Fig.5. Stereomicroscopic study of a carious lesion bacterial diffused along the amelo-dentinal line presenting an in polarised light, x 32.

Histological examination of the teeth (fig.4,5) revealed that 82 teeth (42.7%) were sound, 62 (32.3%) had demineralization in the enamel, and 48 (25.0%) had demineralization extending into the dentin.

Table 2 presents the sensitivity, specificity, for the visual examination by all three examiners and for the results obtained by combining all diagnostic methods at the D1

diagnostic threshold. The mean sensitivity of visual examination combined with the other methods was significantly higher than that of visual examination alone. Concurrent reduction in specificity was also statistically significant.

Table 2. The examiner's sensitivity and specificity in detecting occlusal caries using visual examination and combination of visual examination and Diagnodent and QLF.

Type of the examination	examiner	sensitivity	specificity
Visual examination	1	0,73	0,80
	2	0,67	0,83
	3	0,91	0,59
Combination of visual+ other methods	1	0,84	0,73
	2	0,80	0,73
	3	0,91	0,56

Table 3 shows the number and type of treatments indicated by each examiner for occlusal surfaces, based on the visual examination alone, as opposed to visual examination combined with other detection methods.

The weighted kappa agreement between the initial and revised decisions is also shown. An increase was observed in the number of invasive treatments indicated for

the occlusal surfaces when the examiners had assessed data from all methods combined, in comparison with treatments indicated after visual examination alone. This increase ranged from 11 to 20% of the teeth. A considerable difference in the number of calls for invasive treatment among the examiners was observe.

Table 3. Number and type of treatments indicated by each examiner for occlusal surfaces, based on visual examination alone and on visual examination combined with Diaagnodent and QLF.

Examiner	Visual			Visual + other methods			
	Nothing	Non-invasive treatment	Invasive treatment	Nothing	Non-invasive treatment	Invasive treatment	Weighted Kappa
1	102	68	22	74	58	60	0,50
2	106	82	04	42	82	68	0,59
3	48	96	48	34	86	72	0,61

### Discussions

It is obvious that the decision to restore an occlusal tooth surface should not be made solely on the basis of detecting disease by visual examination or with the help of other diagnostic methods, as observed in the present study. In making a decision to place a restoration, the dentist should assess the caries risk and activity of the individual patient, the tooth age and morphology, and rationally interpret the reading of any mechanical device. Various authors have suggested that if visual examination was followed by the use of an additional method, the accuracy of occlusal caries diagnosis would be improved [31,33]. This theory is corroborated by data from studies that indicated that detection technologies, as such ECM and DIAGNOdent, performed better in detecting early carious lesions in occlusal surfaces than traditional visual examination. By using visual criteria developed more recently this advantage of the detection technologies has greatly diminished; the detection methods mainly improve sensitivity, but by compromising on the specificity side of the equation. According to Lussi [31], when high values of both sensitivity and specificity cannot be achieved, the test providing high-specificity values is to be preferred. This study failed to find any improvement in the overall accuracy of the detection, although shifts in sensitivity and specificity

reached statistical significance. Those shifts would lead to an increase in the number of false positive diagnoses and may have affected the decision of the examiners towards invasive treatment.

From the data presented in Table 4, it was observed that examiners showed a tendency towards more invasive treatment when more data were available. This occurred even though the examiners were well aware of the danger involved in the situation. Future studies should focus on defining and improving the diagnostic process resulting from data from diagnostic methods, under in vivo clinical conditions, and need to take into consideration variables of patient and dentist factors, with the aim of finding the best combination to assist dentists in their treatment decision-making.

### Conclusion

Having data available from multiple methods did not improve the accuracy of examiners in detecting early occlusal caries lesions, but it had a great influence on the number of surfaces indicated for operative treatment. The potential decrease in overall specificity while using multiple methods may be of concern in populations with a low prevalence of occlusal caries lesions.

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## SECONDARY BACTERIAL PERITONITIS IN CHILDREN - A BACTERIOLOGICAL APPROACH

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### Abstract

**Introduction:** Despite advances made by medical science, secondary bacterial peritonitis (SBP) still remains a threat for children.

**The objectives** of this study were to identify aerobic bacteria responsible for SBP in children and to find the proper antibiotic treatment to cure it.

**Materials and method:** We analyzed medical charts and microbiological data of children suffering from SBP (0-18 years old), admitted to the Pediatric Surgery Department of "Louis Turcanu" Children Emergency Hospital.

**Results:** Out of 93 children diagnosed with SBP between January 2008-March 2009, 49 had positive peritoneal cultures with aerobic bacteria. *E. coli* was the dominant bacteria encountered, while *Enterococcus* isolates were the only Gram-positive bacteria found. Imipenem, Ertapenem, Ticarcillin/Clavulanic acid and Ciprofloxacin seems to be the best choice in the treatment of SBP. Perforated appendix was the common cause of SBP (87.75%), followed by the intestinal perforation (6.13%), necrosis (4.08%), or trauma (2.04%).

**Conclusions:** An adequate management of SBP assures decreased hospitalization, prevents emergence of antibiotic resistance and it is cost effective too.

**Key words:** secondary bacterial peritonitis, antibiotic, children

### Introduction

Despite advances in diagnosis, surgery, antimicrobial therapy and intensive-care support, severe secondary bacterial peritonitis (SBP) remains a potentially fatal distress. It represents a major cause of morbidity, with a mortality rate of 30%<sup>1</sup>. SBP generally occurs due to the entry of enteric bacteria into the peritoneal cavity. This pathway is due to necrotic defect in the intestinal wall or abdominal organs, caused by infarction, obstruction, or direct trauma<sup>1</sup>. In children, SBP is mainly associated with perforated appendicitis (PA), but may associate with intussusception, incarcerated hernia, volvulus, or rupture of a Meckel's diverticulum. Although less common in children than in adults, SBP can occur as a complication of intestinal mucosal disease, including peptic ulcers, ulcerative colitis, and pseudomembranous enterocolitis<sup>1</sup>. Intra-abdominal infection in the neonatal period is often a complication of necrotizing enterocolitis but may also be associated with meconium ileus or spontaneous rupture of the stomach or intestines or Hirschsprung's disease<sup>1</sup>.

The specific bacteria involved in SBP are generally those from the normal gastrointestinal tract flora, at the site of entry to the peritoneal cavity. Some retrospective studies evaluated the microbiology of the peritoneal cavity and post-operative wounds following perforated appendix in children<sup>1,2</sup>. The predominant aerobic bacteria were *Escherichia coli*, *Pseudomonas aeruginosa*, while *Bacteroides fragilis* and *Peptostreptococcus* spp. were dominant in the anaerobic group. In addition, bacteria responsible for SBP differed in newborns than in older children. *Klebsiella*, *Enterobacter*, *Streptococcus* spp, and *Clostridium difficile* were the main isolated from peritoneal fluid in newborns that had peritonitis associated with necrotizing enterocolitis<sup>1</sup>.

The dynamics and changes in the microbial flora from the gastrointestinal tract influence the nature and severity of infections that follow perforation. The alkaline environment of the lower intestines, the biliary effect and the decrease in oxygen tension in the lower intestine explains the increase in the number of bacteria found at the distal portions of the gastrointestinal tract.

The necessity of obtaining cultures from the peritoneal cavity of pediatric patients with SBP is believed to be an absolute necessity by many surgeons. It is axiomatic to identify the bacteria present and their antibiotic sensitivities, as they are vital to the care of the child after the surgery. Examining the results of intra-operative cultures, evaluating the bacterial sensitivity and resistance, as well as making appropriate adjustments of antibiotic coverage are necessary for good childcare.

### Objectives

The aim of our study was to identify aerobic bacteria responsible for acute SBP in children. In addition, their antibiotic susceptibility was tested.

### Method and materials

Our study took place at the Pediatric Surgery Department of "Louis Țurcanu" Children Emergency Hospital, between January 2008 and March 2009. All children (aged 0-18 years) admitted in hospital for SBP were included in the study group. Exclusion criteria consisted in the presence of intra-abdominal or visceral abscess, invasive abdominal procedures in the last month, or no previous positive peritoneal-culture. SBP is to be defined as a positive result when obtained from peritoneal fluid culture, which is performed within 72 hours after admission, in a child with abdominal pain, fever, vomiting, or anorexia.

The following data were obtained after reviewing medical charts: age, gender, infection sites, initial presentation defined according to the criteria of ASA (American Society of Anesthesiologists) score, severity of the underlying disease, total hospital stay and mortality rate. Microbiological data and antibiotic susceptibility were noted.

One or more peritoneal fluid specimen(s) were collected during surgery. Inoculation of these samples was on aerobic medium and then incubated at 37°C for 5-7 days. Antibiotic susceptibilities of bacterial isolates were determined using the disk-diffusion method, according to the actual recommendations. The susceptibilities of aerobic bacteria were determined for antibiotics (Ciprofloxacin, Levofloxacin, Ampicilin, Trimethoprim/Sulfamethoxazole,

Gentamicin, Amikacin, Ticarcillin/Clavulanic acid, Cefotaxime, Ceftazidime, Ceftriaxone, Meropenem, Imipenem, Ertapenem, Colistin, Rifampicin, Clindamicyn, Vancomycin and Linezolid).

### Results

During the study period, 93 children were admitted to the hospital having SBP. Out of these, 49 children (74.46% boys and 25.53% girls) had SBP with aerobic bacteria. Their age ranged between 10 days and 18 years, with a mean of 10.29 years. Among these, perforated appendix was the common cause of SBP (87.75%), followed by the intestinal perforation (6.13%), necrosis (4.08%), or trauma (2.04%) (Figure 1). Severe underlying disease included sepsis with multiple organ failure, tetraparesis, and neurofibromatosis.

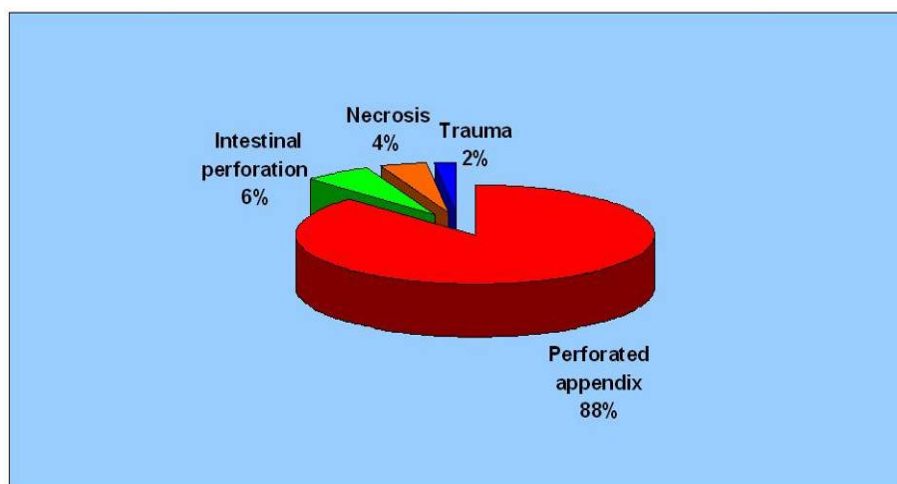


Figure 1 Common causes of SBP encountered.

Upon admission to the Pediatric Surgery Department, four children presented severe conditions having an ASA score of 4, 7 children had an ASA score of 3 and the rest were with ASA 2. The median length of stay at the hospital was 10 days (range 3-40 days). In all patients, surgical treatment consisted of evacuation of pus and peritoneal lavage. The types of surgeries carried out were as follows: appendectomy (n = 43), small bowel suture (n = 1), small bowel resection with anastomosis (n = 4), and colonic resection (n = 1). Mortality rate was 4.08%, in two newborns. One of them was small for gestational age, with neonatal peritonitis due to a cecal volvulus complicated with intestinal ischemia. The other was a preterm baby with Gram-negative sepsis having multiple organ failure associated with necrotizing enterocolitis accompanied by severe acid-base and electrolyte disorders.

Fifty-four specimens were collected from 49 children, including 51 Gram-negative isolates. *Escherichia coli* (72.22%) were by far the most frequently encountered bacteria in our study, followed by *Pseudomonas aeruginosa* (12.96%), *Enterobacter* (3.70%), *Chromobacterium violaceum* (3.70%) and *Klebsiella ascorbata* (1.85%). Three

isolates of *Enterococcus faecium* were the only Gram-positive strains found in our lot. Five children had polymicrobial infections (*E. coli* + *Pseudomonas aeruginosa* or *E. coli* + *Enterococcus faecium*).

Gram-negative bacteria were highly sensible to Carbapenems, Ticarcillin/Clavulanic acid and Ciprofloxacin as presented in figure 2. *E. coli*, the dominant bacteria encountered, was 100% susceptible to Ticarcillin/Clavulanic acid. High rate of sensibility was found to Carbapenems, Quinolones, 3<sup>rd</sup> and 4<sup>th</sup> generation Cephalosporin and Aminoglycosides. *Pseudomonas aeruginosa* was susceptible to the same antibiotics as *E. coli*, but was 100% susceptible to Colistin. Both *Klebsiella ascorbata* and *Enterobacter* isolates were sensible to penicillin plus a beta lactamase inhibitor, Carbapenems and Cephalosporins. In addition, *Enterobacter* isolates were susceptible to Colistin and Quinolones. All *Enterococcus faecium* isolates were 100% susceptible to Vancomycin, Linezolid, Teicoplanin and Rifampicin (Figure 2). Only three isolates of extended beta lactamases (ESBL) producing strains were present as multiple drug resistant bacteria. We recovered no Vancomycin resistant *Enterococcus*.

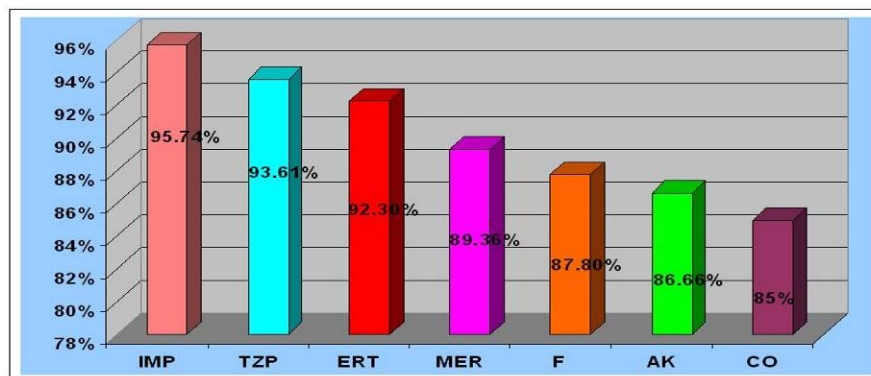


Figure 2 Antibiotics susceptibility of Gram-negative isolates in SBP.  
(IMP-Imipenem, TZP-Ticarcillin/Clavulanic acid, ERT-Ertapenem, MER-Meropenem, F-Ceftazidime, AK-Amikacin, CO-Colistin)

## Conclusions

In our study, *E. coli* was the most frequently encountered bacteria, similar with previous reports of children with gangrenous and perforated appendicitis<sup>4,1</sup>. *Enterococcus* spp. recovered in peritoneal cultures significantly increased morbidity but not the mortality rate<sup>1</sup>. The treatment of other bacteria, such as *E. coli* or anaerobic bacteria stops the development of *Enterococcus*, a fact that suggests its pro inflammatory role<sup>1</sup>.

Perforated appendicitis was responsible for the majority of SBP found in our study. Alexander noticed that between one third and three quarters of children present with PA at the time of diagnosis depending on age<sup>1</sup>. The high rates of perforation mainly encountered are due to delays in seeking care at a hospital rather than errors in diagnosis or hospital delays<sup>1</sup>.

"Triple" antibiotic therapy (Ampicillin, an Aminoglycoside and Metronidazole or Clindamycin)<sup>1</sup> has been the gold standard in treating SBP and PA in pediatric patients. According to our study, implementation of this triple regimen is not possible because of the antibiotic resistance encountered; Ampicillin had high resistance (72.5%). Aminoglycosides were significantly more nephrotoxic than 3<sup>rd</sup> generation Cephalosporins, and are inefficient in the low pH level of the infected peritoneal environment<sup>1</sup>. In addition, these antibiotic regimens require multiple doses of various antibiotics, a fact that makes it inappropriate for child administration.

According to the Surgical Infection Society, monotherapy with broad-spectrum agents in SBP and PA is equally effective, possibly even more cost-effective; children are treated in the same manner as adults<sup>1</sup>. In addition, a retrospective study demonstrated that single broad-spectrum antibiotic in the treatment of PA used with increasing frequency might offer improvements in terms of length of stay, pharmacy charges and hospital charges<sup>12</sup>.

Medical studies illustrated that single-agent therapy with Carbapenems (Imipenem, Ertapenem) or penicillin plus a beta lactamase inhibitor (Ticarcillin-Clavulanic acid) were at least as effective as combination therapies<sup>1,2,3</sup>. These drugs have single or double daily dose administration schedule and are generally better tolerated by children.

Cephalosporins are efficient as single-agent therapy in the management of peritonitis following trauma<sup>1</sup>. The advantages of single-agent therapy consist in elimination of Aminoglycosides side effects, as well as reduction of associated costs.

Sganga<sup>1</sup> recommended the use of antibiotics in the treatment of SBP according to the severity of infections. Mild and moderate infections need a short-term therapy with a single active drug against anaerobic bacteria. Severe infections require a more aggressive therapy specifically, an association between antibiotics that cover anaerobic, Gram-positive and Gram-negative bacteria.

According to our results, the treatment of mild-to-moderate SBP (ASA score 2) consists in the use of antibiotics with narrower spectrum of activity e.g. Ticarcillin/Clavulanic acid or Ertapenem, similar with medical literature<sup>1</sup>. Pediatric patients with more severe infections, as defined by ASA score 3 or 4, might benefit from regimens with a broad spectrum of activity against facultative and aerobic Gram-negative organisms. Our recommendations consist in monotherapy with Imipenem or Meropenem<sup>1</sup>.

Despite common beliefs that Ciprofloxacin association with Metronidazole is very efficient against Gram-negative bacteria responsible for SBP, its activity against anaerobic bacteria is only moderate<sup>1</sup>. For the same reason, 3<sup>rd</sup> or 4<sup>th</sup> generation Cephalosporins are suitable for the treatment of SBP just in association with Metronidazole<sup>1</sup>.

Switch therapy from injection to oral antibiotic in SBP is associated with good evolution. The proper time of the switch is when the body temperature has dropped to 37.5 °C and blood, as well as clinical findings has demonstrated the tendency to improve by the 4<sup>th</sup> day<sup>1</sup>.

SBP still represents the "bread and butter" for pediatric surgeons. SBP controlled effectively and with low associated morbidity by removal or repair of the infected focus, antibiotic treatment according to antibiograms sensibility, infection severity and restoration of anatomy if resection is performed for definitive source control. Proper management of SBP in children is cost effective, decreases

hospitalization, and can prevent the emergence of antibiotic resistance.

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## WERDNIG-HOFFMANN DISEASE WITH DEXTROCARDIA AT CHILDREN - CASE PRESENTATION

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### Abstract

Werdnig-Hoffmann disease or type I spinal amyotrophy is a rare, severe neuromuscular affection, with recessive autosomal remittance, characterized by degeneration of the motor neurons from the anterior medullar horns. Clinic signs start from the first months of life and are characterized by marked hypotonia, with severe evolution towards severe respiratory insufficiency and death. The authors describe the case of the female patient S.R. (F.O. 21718), aged 1, who had repeated admissions between December 2008 – April 2009 at the Pediatric Clinics of the Emergency Clinical Hospital Craiova, for respiratory failure. Despite the complex treatment: volemic rebalancing, nourishment through gavage, antibiotherapy, bronhodilators, and finally mechanic ventilation, evolution was towards exitus.

### Introduction

Progressive spinal amyotrophies represent a heterogenous group of genetic disorders which in the first stage of childhood, characterized by progressive degeneration of the motor neurons from the anterior medullar horn and sometimes, of the motor neurons from the cerebral trunk and is manifested by marked hypotonia.

Today, this group of affections represent the second cause as frequency, of lethal genetic disorder, which begins in childhood, after the cystic fibrosis.

### Case presentation

We present the case of the female patient S.R. aged 1, who had repeated admissions in 2009 at the Pediatric Clinics of the Emergency Clinical Hospital Craiova.

From heredocolateral antecedents we learned that a first grade female cousin of her father had a similar disease, dying at 13 years old, and the first child of the couple, also a girl, deceased at 7 months old with the diagnostic Werdnig-Hoffmann disease.

The patient is the second child of a couple of young genitors, coming from a physiologic pregnancy and an eutocic birth, having birth weight 3800g.

The patient S.R. was diagnosed at the age of 2 months with Werdnig-Hoffmann disease – type I spinal amyotrophy. The reasons for her last two admissions in 1<sup>st</sup> Pediatric Clinic were similar: fever, coughing, tachypnea, moans, epigastric and intercoastal tirage, deglutition turbulences.

At the objective examination we noticed: deficitary nutrition status, weight 6000g (grade II dystrophy), severe

neuromotor retardness, feeble screams, generalized muscular hypotonia, characteristic position of the members in abduction, “bell-like” aspect of the chest, toracoabdominal balance (paradoxal breathing), breathe rate 56/min, pulmonary stet acoustic crepitant waves, tachycardia (heart rate 116-130b/min), apexian shock in the right part of the breastbone, liver with the inferior edge 1 cm under ribs boundary, normal limits spleen, tongue fasciculations with severe difficulties in nourishment, absence of ROT.

Neurologic examination: infant with extreme hypotonia and proximal motor deficiency, segmented active movements possible only distal with reduced amplitude, tongue fasciculations, paradoxal breathing. She didn't sit, didn't emit syllables, absence ROT, late response at tactile stimulus, soft nape, absent meningeal syndrome.

Paraclinic investigations: hemoglobin 10,4g/dl, hematocrit 31%, platelets 363000/mm<sup>3</sup>, leucocytes 5100/mm<sup>3</sup>, neutrophils 46%, lymphocyte 45%, monocyte 9%, ALT 14,8U/l, AST 4U/l, urea 30mg/dl, amylase 31U/l, creatinine 0,1mg/dl, total bilirubin 0,3 mg/dl, glycemia 116mg/dl, alkaline reserve 20mEq/l.

Thorax radiography: thoracic asymmetry, peribronchovascular interstitial opacities; trachea movement, mediastinum, cardiac shadow towards right.

At the first admission she received treatment consisting of antibiotics, bronhodilators, oxygenotherapy using mask, nourishment through gavage, then oral. She was discharged with improved general status, diminished breathing failure syndrome, present appetite.

After 2 days from discharging, she was readmissioned with the symptomatology of an aspiration bronchopneumonia, extremely grave general state, grade I/II coma.

She was supervised in the Intensive Therapy Clinic where she was intubated oro-tracheal and mechanical ventilated, hydroelectrolitical and acidobasic rebalanced, treated with antibiotics, simptoms, but the general state gradually got worse, presented signs of decerebration, and in the 9<sup>th</sup> day since admission, irreversible cardiac arrest.

At the necroptic examination, the aspiration bronchopneumonia and dextrocardia were confirmed.

### Discussions

Depending on the age it began and the grade of severity of the disease, there are described four types of spinal amyotrophy: type I, Werdnig-Hoffmann disease or the severe infantile acute form, type II or the infantile cronic

form, type III or Kugelberg-Welander disease or the juvenile form and type IV with the beginning at adult stage. All types are determined by recessive mutation on the SMN1 gene (survival motor neuron).

Werdnig-Hoffmann disease or type I is the most severe form of spinal amyotrophy, present only at the infant and little child; it is a rare, progressive neuromuscular disease, characterized by the degenerescence of the motor neurons.

The frequency of the disease is 1/25 000 births. The pathogenic layer seems to be, after the latest studies, a process of apoptosis or programmed cellular death. In over 95% of the cases the affection is determined by deletions or anomalies of the SMN1 gene from the cromozome 5, training a major deficit of the SMN protein. Genetic studies linked this affection to the the cromozome 5q11.2-q13.3, the same region being affected by spinal amyotrophy types II and III. The disease has ereditary transmission of recessive autosomal type. The deletion of the NAIP gene (Neuronal Apoptosis Inhibitory Protein) is also associated with the spinal amyotrophy (4,9).

The cause of the disease is a defective gene. All humans are born with many extra neurons which are genetically programmed to die successively. Healthy children have a gene capable to communicate to the body the moment when sufficient nerve cells have died. Children with the Werdnig-Hoffmann disease don't have this gene and the nerve cells continue to die until the organism and especially the muscles are severely injured.

Other authors reached the conclusion that the axonogenesis defects represent the major cause of spinal amyotrophy, which could leads to new therapeutic options in neuromuscular diseases (5).

Some studies proved the existence of a link between the starting age and the decease age; so, the patients with the disease starting age of under 2 months had a severe prognosis, with a sooner decease, compared to the ones who had a somehow later starting age but who met the diagnostic criteria for the type I disease (8).

At the presented case, the clinic signs which suggested the early diagnostic were: hypotonous newborn, with nourishment and respiratory problems. After 2 months the neurologic examination confirmed the diagnostic of Werdnig-Hoffmann disease. It was noticed that she can't hold or turn her head. The limbs' aspect was revealing: infant with "batrachian" characteristic position, with thighs in abduction and external rotation, arms in abduction and internal rotation, and forearms in pronation. Also she had generalized hypotonia, muscle atrophy, hypokinesis, paralysis at the members' roots, slow movements in joints; irregular breathing, "bell-like" aspect of the chest, slow movements of the fingers, tongue fasciculations, balanced head.

In evolution, appears the paralysis of the intercoastal muscles and of the abdominal muscles. As a consequence the child presents feeble screams, rough and inefficient coughing, anomalies of the active breathing kinetics. When inspiring, the thoracic wall depresses because of the

paralysis of the intercoastal muscles and the abdominal wall curves under the pressure of the diaphragm (the only spare muscle) because of the paralysis of the abdominal muscles. Also phonetic and deglutition turbulences appear.

The diagnostic was evoked by the presence of a motor deficit with proximal and symmetric predominance, associated with an amyotrophy, ROT absence and muscular fasciculations presence.

The electromyogram (EMG) and the study of nerve flow speed shows a table of denervation, which allows seeing the difference between a spinal amyotrophy and a sense-motor periferic neuropathy.

The muscular biopsy shows fascicular neurogenous atrophy, at the optic microscope. At the electronic microscope one can notice the predominant touch of the miofibrils with the loss of filaments and the diminishing number of mitochondria. Biopsy is not needed if the genetic diagnostic is made.

The association of the dextrocardia at the presented case is a rare association which I couldn't find in the literature.

From the literature, some studies concluded that the heart congenital malformations are caused by major deficits of the SMN protein. The authors met most frequently atrial and ventricular septal defects, but also other minor cardiac anomalies, like the oval foramen persistency or the arterial channel persistency. It was also noticed that on the patients with associated cardiac malformations, the evolution of the neuromuscular affections was more severe (7).

A curative treatment of the disease doesn't exist, only the intercurrent infections are treated. The physiotherapy can't increase the life of these children over 18 months. The devices that help in alimentation, the gastrostome or nazogastric sonds, the mechanical ventilation, which is used in terminal cases, can reduce the decease risk, increasing the survival time (6).

Other studies specify that the treatment with salbutamol determines the increase in level of the SMN protein, in researches done on fibroblasts from patients with spinal amyotrophy type I, II and III (1). Other authors reported the generation of pluripotent stem cells inducted from samples of fibroblastic cells from skin from a child with spinal amyotrophy type I (3).

The genetic advice is necessary in all cases and especially at the mentioned couple. Each parent is heterozygote for the pathologic recessive gene. The prenatal diagnostic is possible and is done directly, analyzing the 7<sup>th</sup> exon of the SMN gene (the search for a homozygote deletion), analysis of the polymorphic markers which flank the genetic anomaly (C212 and C272); the indirect method permits the exclusion of an eventual maternal contamination and the detection of an eventual new mutation.

The particularity of this couple of heterozygotes is that they had, one after another, two daughters with the Werdnig-Hoffmann disease without recognizing that they are cosanguineous. At the analized patient the dextrocardia was associated with the Werdnig-Hoffmann disease.

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# ANALGESIA AND SEDATION DURING MECHANICAL VENTILATION IN CHILDREN

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## Abstract

**Introduction:** Sedation and analgesia are important parts of patient management in the intensive care unit. It is necessary to minimize the perception and response to anxiety and pain. Children who are not adequately sedated or are experiencing pain may become tachycardic and hypertensive, and are at risk of losing their airway and central lines.

**Material and method:** This study was a retrospective review of pediatric patients undergoing endotracheal intubation and mechanical ventilation in PICU (Pediatric Intensive Care Unit) of Emergency Hospital for Children “Louis Turcanu” Timisoara between January 2005 and December 2009. The aim of this study was to evaluate the sedation and/or analgesia regimens in PICU patients undergoing endotracheal intubation in our clinic.

**Results:** A total of 134 PICU patients receiving mechanical ventilation were included in the study. 88 (65.67%) patients were male. We use for sedation during mechanical ventilation continuous infusion of midazolam and fentanyl in 54 (40.30%) patients, continuous midazolam infusion in 38 (28.36%) patients, and bolus intermittent sedation with midazolam in 20 (14.93%) patients. All newborns (n=45) received continuous infusion only with midazolam. The median duration of mechanical ventilation was 7.7 days, range 48 hours to 83 days. The medium length of stay in hospital was 14.22 days, range 48 hours to 97 days. There were 63 (47.01%) deaths in the PICU, consisting of 60 who died without weaning from mechanical ventilation. Highest mortality rate can be observed in newborns and highest survival rate in infants.

**Conclusions:** Our experience in the management of mechanically ventilated patients showed that the combination of midazolam and fentanyl in continuous infusion is the best option for children, and adequate analgesia and sedation are achieved relatively in a short period of time. In ventilated newborns, continuous midazolam infusion is enough for obtaining a proper sedation.

**Key words:** PICU, mechanical ventilation, analgesia, sedation, midazolam, fentanyl

## Introduction

In the emergency room and critical care environment, management of the airway to ensure optimal ventilation and oxygenation is of prime importance. Although initial efforts should be directed toward improving oxygenation and

ventilation without intubating the patient (1), these interventions may fail and the placement of an endotracheal tube may be required.

Sedation and analgesia are important parts of patient management in the intensive care unit (ICU). It is necessary to minimize the perception and response to anxiety and pain. Children who are not adequately sedated or are experiencing pain may become tachycardic and hypertensive, and are at risk of losing their airway and central lines. Conversely, oversedation can cause cardiovascular and respiratory depression and may interfere with a comprehensive neurologic examination. In patients who undergo prolonged sedation, tolerance and tachyphylaxis develop, and these lead to increasing sedative requirements (2).

A wide variety of pharmacological agents are now available for sedation and analgesia, and while recommendations have been made regarding “the best” sedative and analgesic regimens for ICU patients (3) practice varies widely between and within ICUs. An ideal sedative agent would have rapid onset of action, be effective at providing adequate sedation, allow rapid recovery after discontinuation, be easy to administer, lack drug accumulation, have few adverse effects, interact minimally with other drugs, and be inexpensive (4). Unfortunately, sedatives have adverse effects, have the potential to prolong mechanical ventilation, and may increase health care costs.

However, despite their widespread use, analgo-sedative drugs still lack data supporting appropriate dosing, safety, and efficacy of combination therapies, and optimal drug regimens for sedation during mechanical ventilation (5). Many clinical tools available for assessing and monitoring sedation have limited utility in children (3,4).

In many intensive care units, sedatives are infused continuously (6,7). As compared with intermittent bolus infusion, this approach provides a more constant level of sedation and may increase patients’ comfort (8,9). However, administration of sedatives by continuous infusion has been identified as an independent predictor of a longer duration of mechanical ventilation as well as a longer stay in the intensive care unit and in the hospital (10).

## Material and method

This study was a retrospective review of pediatric patients undergoing endotracheal intubation and mechanical ventilation in PICU (Pediatric Intensive Care Unit) of Emergency Hospital for Children “Louis Turcanu” Timisoara between January 2005 and December 2009.

All patients mechanically ventilated over 24 hours were eligible for inclusion. Data elements included the following: demographic variables (age, weight, sex), underlying diseases, intubation indication, medications used, and administration of an additional sedative.

Criteria for intubation were: apnea, impaired alveolar ventilation ( $\text{PaCO}_2 > 55$  mmHg), inadequate oxygenation despite  $\text{FiO}_2 > 60\%$  ( $\text{PaO}_2 < 55$  mmHg) and the inability of patients to maintain their airways open.

All patients were mechanically ventilated A/C (assist control) or SIMV (Synchronized Intermittent Mandatory Ventilation). Vital parameters including respiratory rate, heart rate, and non-invasive blood pressure (NIBP) were documented. The oxygen saturation of each child was

monitored continuously by pulse oximetry. Sedation was achieved on central line.

Sedation on our intubated patients was achieved with benzodiazepine (midazolam)  $\pm$  fentanyl as a continuous sedation or as intermittent bolus sedation. We excluded paralyzed patients who are a separate group and should not be included in the continuous sedation group, because those patients particularly need continuous sedation while being paralyzed.

The protocols for the infusion of sedatives are shown in Table 1. Nurses adjusted the dosage and rate of infusion according to standard procedures at our institution (to achieve a score of 3 or 4 on the Ramsay sedation scale, which measures sedation on a scale of 1 [agitated or restless] to 6 [asleep and unresponsive to stimuli]<sup>15</sup>).

Table 1: Protocols for analgesia and sedation in the study patients.

Sedative and analgesic drug	Protocol
Midazolam	Intravenous bolus of 0.1–0.2 mg/kg every 15 min as needed
	Continuous infusion at 0.1–0.2 mg/kg/hr; dosage to be increased at 0.3 mg/kg/hr until adequate sedation is achieved
Fentanyl	Intravenous bolus of 1–2 mcg/kg every 15 min as needed
	Continuous infusion at 2–4 mcg/kg/hr; dosage to be increased at 5–10 mcg/kg/hr
Propofol	Intravenous bolus of 2–4 mg/kg every 1 hour as needed

The aim of this study was to evaluate the sedation and/or analgesia regimens in PICU patients undergoing endotracheal intubation in our clinic. Additional sedation and analgesia were achieved in order to maintain endotracheal tube placement, to facilitate continued oxygenation and ventilation in an intubated patient.

## Results

A total of 134 PICU patients receiving mechanical ventilation were included in the study. Distribution of cases by the year of admission (Figure 1) was as follows: 28 children (20.89%) in 2005; 27 (20.14%) in 2006; 30 (22.38%) in 2007; 28 (20.98%) in 2008 and 21 (15.67%) in 2009.

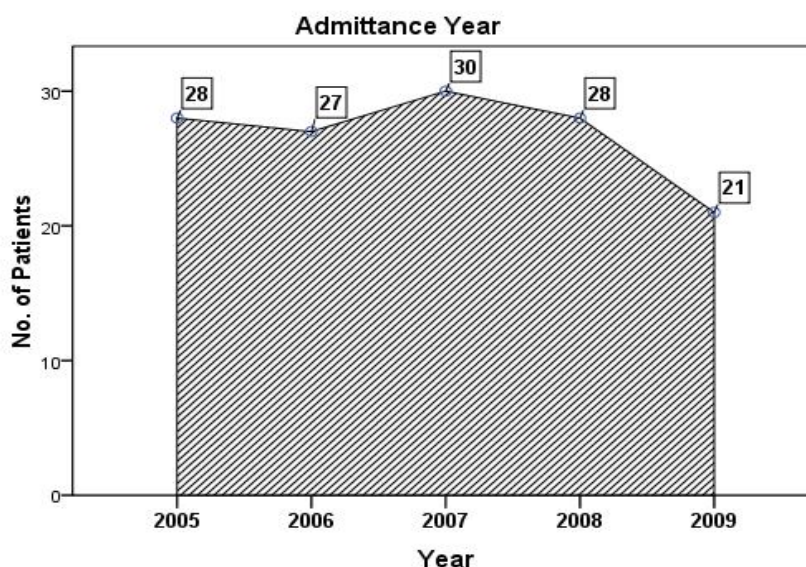


Figure 1: Admittance year repartition.

Of the 134 mechanically ventilated children, 88 (65.67%) patients were male (Figure 2). Forty-five (33.58%) patients were newborn, 40 (29.85%) infants, 23 (17.16%) patients aged 1 to 3 years, 10 (7.46%) patients aged 3 to 6 years, and 16 (11.90%) patients over the age of six years (Figure 3). Of them, age distribution on year of admission was: in 2005 – 10 newborn, 8 infants, 5 patients aged 1 to 3 years, 2 patients aged 3 to 6 years, 3 patients over the age of six years; in 2006 – 10 newborn, 7 infants, 5 patients aged 1 to 3 years, 2 patients aged 3 to 6 years, 3 patients over the age of six years; in 2007 – 10 newborn, 8 infants, 7 patients aged 1 to 3 years, 2 patients aged 3 to 6 years, 3 patients over the age of six years; in 2008 – 11 newborn, 8 infants, 4 patients aged 1 to 3 years, 2 patients aged 3 to 6 years, 3 patients over the age of six years; and in 2009 – 4 newborn, 9 infants, 2 patients aged 1 to 3 years, 3 patients aged 3 to 6 years, 3 patients over the age of six years (Figure 4).

to 3 years, 1 patient aged 3 to 6 year, 4 patients over the age of six years; in 2007 – 10 newborn, 8 infants, 7 patients aged 1 to 3 years, 2 patients aged 3 to 6 years, 3 patients over the age of six years; in 2008 – 11 newborn, 8 infants, 4 patients aged 1 to 3 years, 2 patients aged 3 to 6 years, 3 patients over the age of six years; and in 2009 – 4 newborn, 9 infants, 2 patients aged 1 to 3 years, 3 patients aged 3 to 6 years, 3 patients over the age of six years (Figure 4).

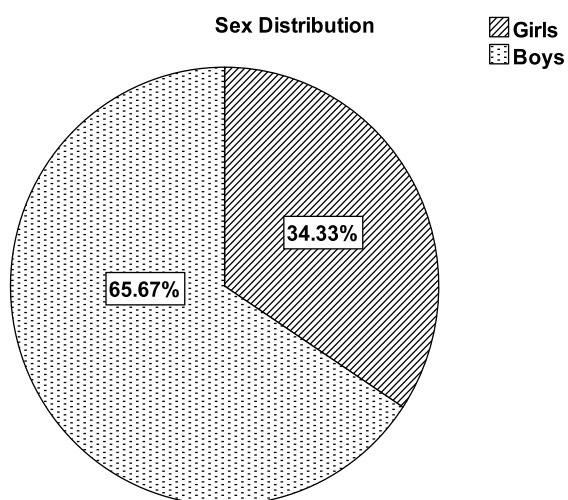


Figure 2: Sex distribution.

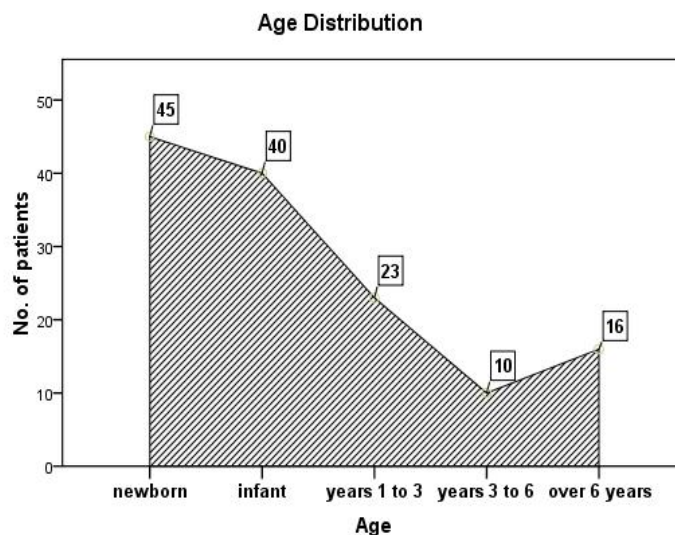


Figure 3: Age distribution.

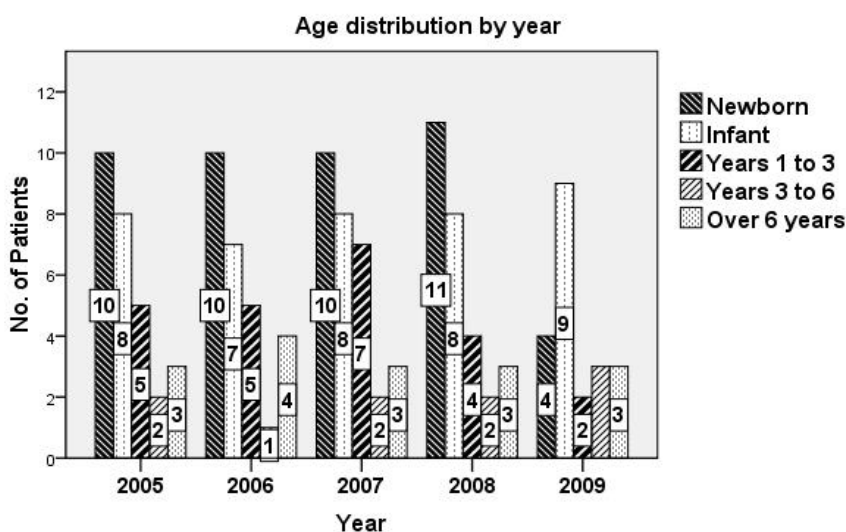


Figure 4: Age distribution by year.

Main diagnosis in patients that required mechanical ventilation was: bronchopneumonia (n=36), neonatal respiratory distress syndrome (n=16), pneumocystis carinii pneumonia (n=12), bacterial pneumonia (n=11), meningoencephalitis (n=10), status epilepticus (n=10), neonatal sepsis (n=9), pleuropneumonia (n=8), severe sepsis (n=6), meningitis (n=5), severe heart malformations (n=4), brain hemorrhage (n=4), lung tumor (n=2), electrocution (n=1), and chilothonax (n=1) (Figure 5). The associate

conditions in mechanically ventilated patients were: brain hemorrhage (n=16), cerebral palsy (n=11), acute renal failure (n=11), heart malformations (n=9), Duchene muscular dystrophy (n=6), hydrocephaly (n=5), chronic renal failure (n=3), nephrotic syndrome (n=2), laryngomalacia (n=2), Down syndrome (n=1), systemic lupus erythematosus (n=1), epidermolysis bullosa (n=1), and hypertrophic cardiomyopathy (n=1) (Figure 6).

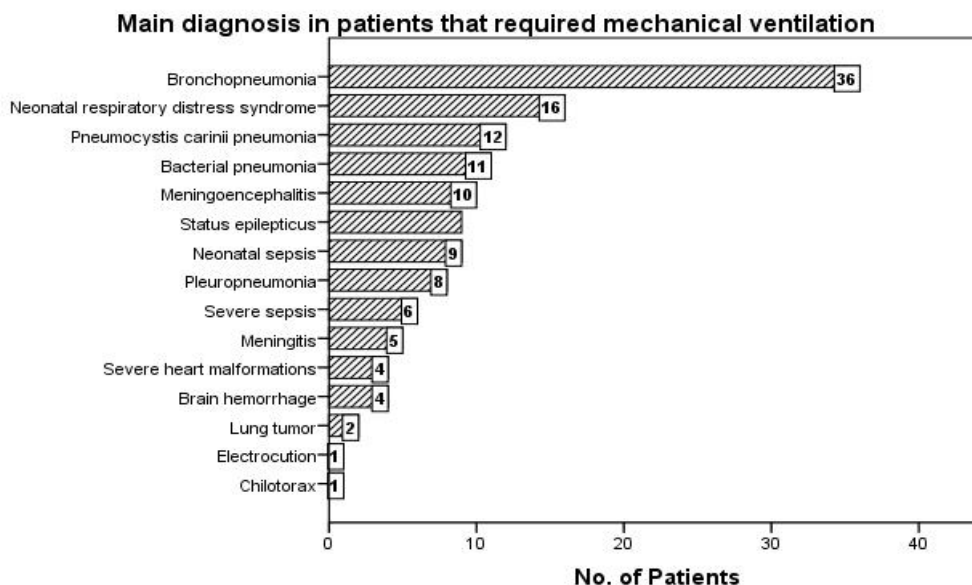


Figure 5: Main diagnosis in patients that required mechanical ventilation.

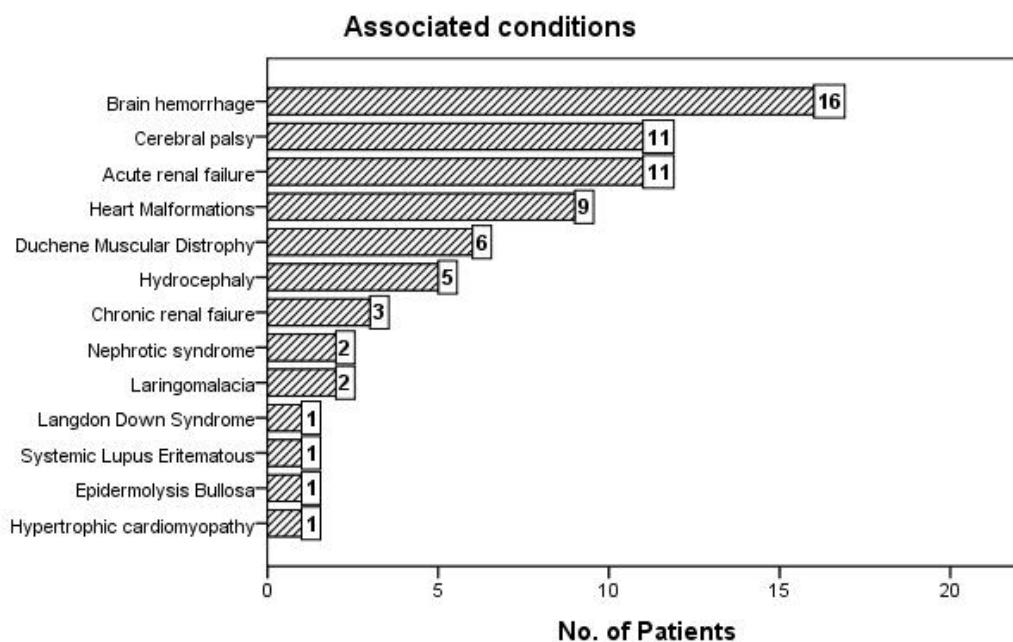


Figure 6: Associated conditions on intubated patients.

We use for sedation during mechanical ventilation continuous infusion of midazolam and fentanyl in 54 (40.30%) patients, continuous midazolam infusion in 38 (28.36%) patients, and bolus intermittent sedation with midazolam in 20 (14.93%) patients. Twenty-two (16.42%)

children did not require continuous or intermittent sedation (Figure 7) because they were with severe brain damage (hemorrhage or palsy). All newborns (n=45) received continuous infusion only with midazolam.

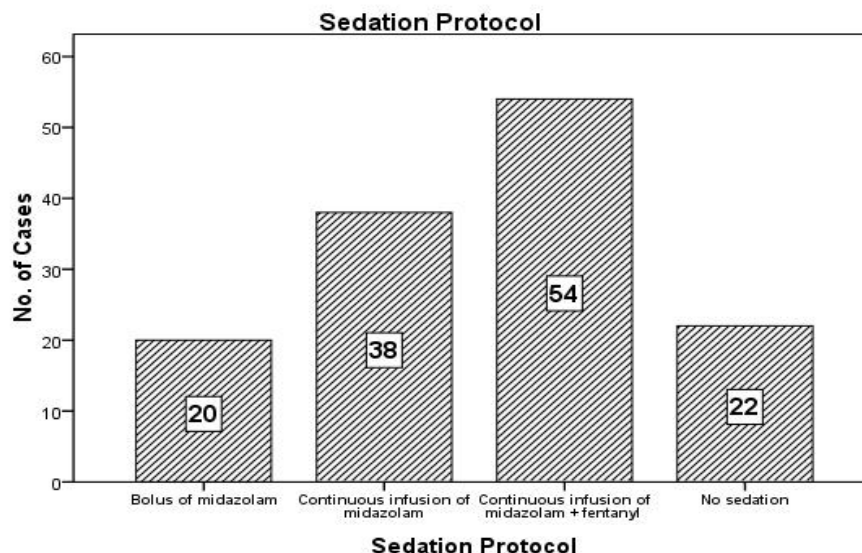


Figure 7: Sedation protocol.

We started continuous infusion with midazolam at 0.1 mg/kg/hr and with fentanyl at 2 mcg/kg/hr. After 24 hours, because of the patient agitation, we had to increase dosage at 0.2-0.3 mg/kg/hr for midazolam and 4-10 mcg/kg/hr for fentanyl. Patients with continuous infusion sedation protocol (n=92) required additional sedation boluses for patient-ventilator asynchrony episodes, which were made with midazolam (0.1–0.2 mg/kg/bolus); midazolam (0.1–0.2 mg/kg/bolus) and fentanyl (1–2

mcg/kg/bolus); or propofol (2–4 mg/kg/bolus) (Table 1). The withdrawal was made subtracting half the rate of infusion at 24 hours. As side effects for continuous infusion with midazolam ± fentanyl, 8 patients presented bradycardia without hemodynamic consequences.

The median duration of mechanical ventilation was 7.7 days, range 48 hours to 83 days (Figure 8). The medium length of stay in hospital was 14.22 days, range 48 hours to 97 days (Figure 9).

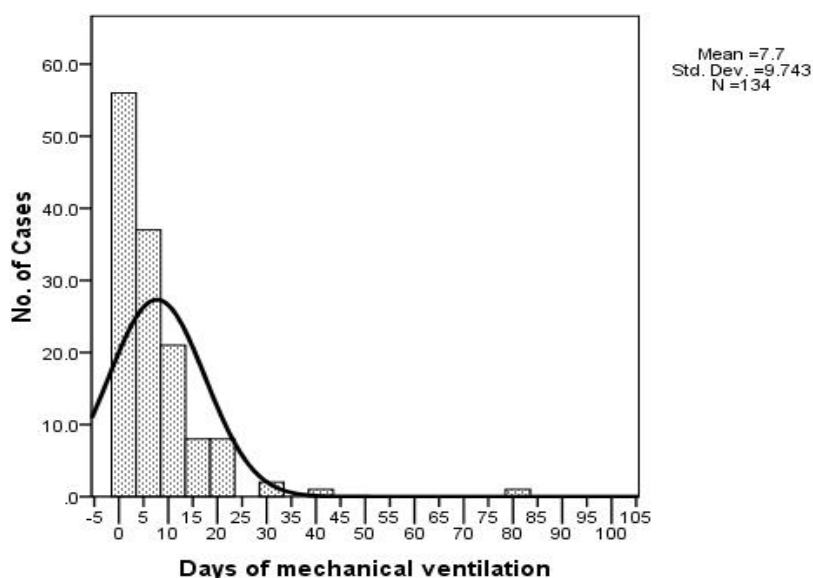


Figure 8: Days of mechanical ventilation.

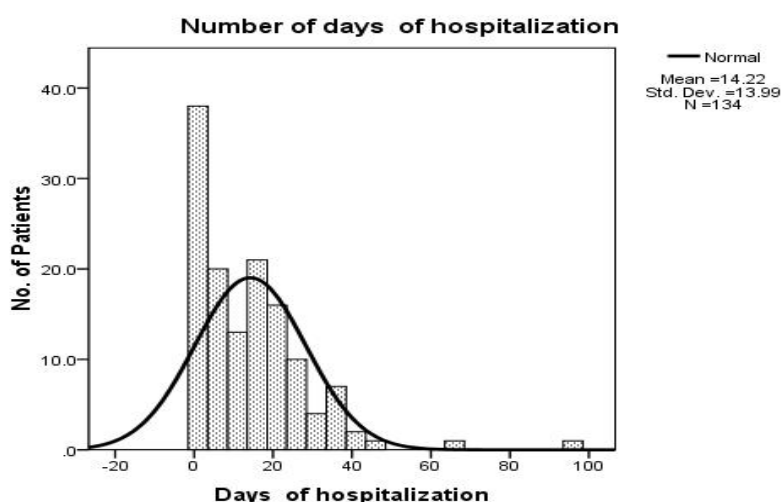


Figure 9: Days of hospitalization.

There were 63 (47.01%) deaths in the PICU (Figure 10), consisting of 60 who died without weaning from mechanical ventilation. Survival rate by age was as follow: newborn – 30 (22.38%) deceased and 15 (11.19%) discharged; infants - 10 (7.46%) deceased and 30 (22.38%) discharged; aged 1 to 3 years - 11 (8.20%) deceased and 12

(8.95%) discharged; aged 3 to 6 years - 6 (4.47%) deceased and 4 (2.98%) discharged; over the age of six years - 6 (4.47%) deceased and 10 (7.46%) discharged (Figure 11). Highest mortality rate can be observed in newborns and highest survival rate in infants.

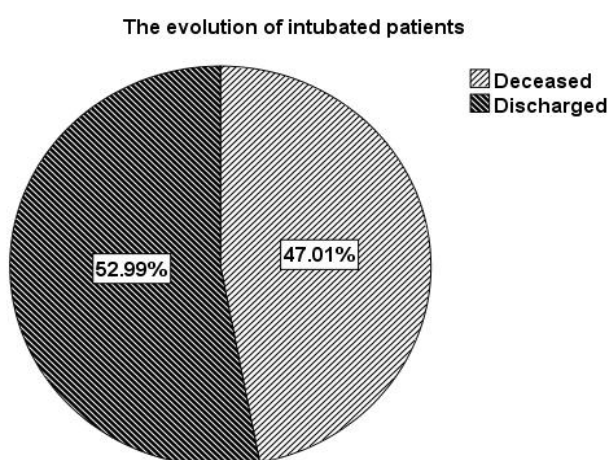


Figure 10: The evolution of intubated patients.

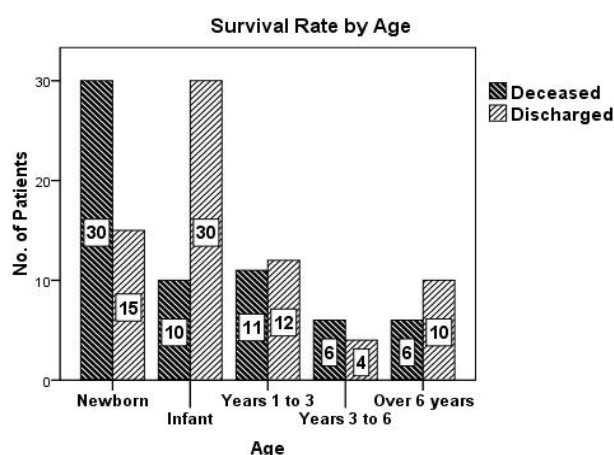


Figure 11: Survival rate by age.

All of the patients received low tidal volume ventilation, antibiotics, continuous correction of homeostasis, management of enteral feeding and pulmonary physiotherapy. After extubation we applied noninvasive respiratory therapy.

### Discussions

We had an average of 26.8 mechanically ventilated patients per year (Figure 1). Of these, most (65.67%) were male (Figure 2).

In terms of allocation by age group may find that most patients (63.43%) were aged less than 1 year, while the age group 3-6 years had the lowest number of cases (7.46%) (Figure 3).

Analyzing annual distribution by age group may find a significant reduction in the number of newborn patients since 2008, explained by the establishment of a Neonatal Intensive Care Department in our Hospital (Figure 4).

Principal diagnosis which required mechanical ventilation was bronchopneumonia (28.86%), severe respiratory pathology being involved in 50% of cases

followed by neonatal pathology (24.62%) and CNS disorders (18.65%) (Figure 5). 51.49% of cases had an associated chronic pathology, the most common being brain hemorrhage in newborns and cerebral palsy in children (Figure 6).

The highest survival rate was in 1 month-1 year (75%) and over 6 years (62.5%) age groups and the highest death rate was in newborns (66.6%) (Figure 11).

The largest number of days of ventilation was met at the age group 1 month-1 year (mean = 10.15) and the lowest number of days of hospitalization in children aged between 3 and 6 years (mean = 3.20) (Figure 12).

**Days of Ventilation**

Age group	Mean	N	Std. Deviation
0-1 luna	5.76	45	12.410
1 luna - 1 an	10.15	40	8.634
1-3 ani	7.74	23	7.454
3-6 ani	3.20	10	1.874
> 6 ani	9.81	16	8.175
Total	7.70	134	9.743

Figure 12. Number of days of ventilation related do age group.

The most important goal during mechanical ventilation in the ICU is to achieve patient comfort and patient-ventilator synchrony. Once proper analgesia has been established, a sedative should be added. Currently, multiple agents are used, usually according to personal preference. Few agents have been evaluated rigorously by more than one or two randomized controlled trials. The Society of Critical Care Medicine and the American College of Critical Care Medicine formed a panel of experts to establish practice guidelines for intravenous analgesia and sedation of adult patients in ICUs. A national survey of the use of sedating agents (11) showed that most ICUs do not use protocols nor do they adhere to practice guidelines. A recent randomized trial in Australia provided no evidence of a substantial reduction in the duration of mechanical ventilation or length of stay, in either the intensive care unit or the hospital, with the use of protocol-directed sedation compared with usual local management (12).

The choice of agent and the way in which they are used varies widely between and within ICUs. Recent surveys of PICU practice in the United States and Great Britain (U.K.) indicate that there is wide variation in practice both within the U.S. and between countries (13,14,15). In the United States, 11 different sedatives are commonly used for the same or similar indications, and at least 20% of PICU's recently surveyed responded that they either "routinely" or "frequently" used eight different sedatives to reduce anxiety and facilitate mechanical ventilation (14,15). In the United Kingdom, the most common sedative agents in use in PICU's continue to be midazolam and morphine (16). A prospective multicenter patient-based study in France shown that midazolam is the agent most commonly used for sedation, and for analgesia sufentanil and fentanyl are the most frequently used opioids (17). Recent Italian guidelines for sedation cite that benzodiazepines are the most commonly used drugs to sedate mechanically ventilated patients (18). Propofol is the preferred IV infusion sedation agent in most U.S. ICU's and

is gaining in popularity compared with other sedatives (19). Like others European country, we prefer a continuous combination infusion of midazolam and fentanyl for infants and children, and continuous midazolam infusion in newborn.

Recent interest has centered on dexmedetomidine, a selective alpha-2 agonist with sedative and anxiolytic properties, with comparison primarily to benzodiazepines on the assumption that benzodiazepines represent the standard of care for patients requiring mechanical ventilation for more than short periods of time (20,21).

Several recent papers have directly compared benzodiazepine use to propofol. The study by Carson et al (22) concluded that propofol resulted in fewer ventilator days when compared with intermittent lorazepam for patients ventilated > 48 hrs.

Richmann PS et al, in a recent study, observed that in mechanically ventilated patients, co-sedation with midazolam and fentanyl by constant infusion provides more reliable sedation and is easier to titrate than midazolam alone, without significant difference in the rate of adverse events (6).

## Conclusions

In our study, we had better results using continuous infusion sedation protocol. Our experience in the management of mechanically ventilated patients showed that the combination of midazolam and fentanyl in continuous infusion is the best option for children, and adequate analgesia and sedation are achieve relatively in a short period of time. In ventilated newborns, continuous midazolam infusion is enough for obtaining a proper sedation.

Directing treatment to specific and individualized goals will assure that patient needs are met. All currently available sedatives for use in the ICU have limitations. Kress JP et al (23) reported no important differences in any important patient outcomes when comparing different

classes of drugs as long as a strategy directed at limiting complications of drug accumulation was adhered to. Rather than seeking an ideal drug, strategies of drug administration

that focus attention on principles of sedative pharmacology in critical illness should be utilized.

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## GLYCOGENOSIS TYPE II – CASE REPORT

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### Abstract

Cytolysis is commonly found in pediatric daily practice. Paper aim is to present the case of 9 years old boy admitted in Clinic II Pediatrics for cytolysis syndrome with unknown etiology.

**Key words:** glycogenosis type II, Pompe disease, child.

### Background

Glycogen storage disease or glycogenosis type II (GSD II) is in fact a lysosomal storage disease (Pompe disease –juvenile form) is an autosomal recessive disorder with an incidence of 1/40 000 live births. The disorder is a progressive, multisystemic, debilitating, and often fatal disorder. It was first defined in 1932 by Dutch pathologist Joannes C. Pompe in a seven-month-old girl who died of idiopathic cardiac hypertrophy and was found to have massive glycogen accumulation in many tissues, but predominantly skeletal and cardiac muscles. Infantile –onset Pompe disease is thought to be uniformly lethal without specific therapy. Affected infants present in the first few months of life with hypotonia, a generalized muscle weakness, feeding difficulties, macroglossia, hepatomegaly and a hypertrophic cardiomyopathy followed by death from cardiorespiratory failure or respiratory infection usually by 1 year of age. Juvenile and adult –onset disease (late onset forms) is characterized by a lack or absence of severe cardiac involvement and a less severe short-term prognosis. Symptoms can start at any age and are related to progressive dysfunction of skeletal muscles. The initial symptoms in some patients may be respiratory insufficiency manifested by somnolence, morning headache, orthopnoea and exertional dyspnoea.

### Case report

We present a 9 years old boy admitted in our clinic for the evaluation of a cytolysis syndrome associated with somnolence and muscle pain. He is the unique child of a non-consanguineous healthy couple. The child was born at term, normally delivered after an uncomplicated pregnancy. He received natural alimentation for 4 months and after that with a milk formula. Diagnosed at 6 six years old (during a routine check) with cytolysis syndrome with unknown etiology is admitted in our clinic for the evaluation of this syndrome.

Clinical examination revealed a boy with 35 kg weight, 136 cm height, without any abnormal clinical findings, except muscle weakness.

Laboratory findings revealed elevated levels of serum creatine kinase 1263 u/l, aspartate aminotransferase 251 u/l, alanil aminotransferase 266 u/l, lactate dehydrogenase 635 u/l and aldolase 16.9 u/l. A chest X-ray, electrocardiography, echocardiography, electromyography and nervous conduction velocity were in normal parameters. Abdominal ultrasound findings include large gallbladder, and hypoechoic inhomogeneous liver structure. Muscle biopsy excludes an inflammatory myopathy.

After these laboratory findings we thought at Pompe disease. The next step was enzyme assay 39,3 nmol/h/mg (n= 51- 215), performed in Department of Cell Biology and Genetics, Erasmus University, Rotterdam. The confirmatory step for a diagnosis of Pompe disease is enzyme assay demonstrating deficient acid alpha- glucosidase.

For differential diagnosis many conditions were considered as follows:

1. Polymyositis: excluded by the biological investigations and muscle biopsy.
2. Duchenne and Becker muscular dystrophies: elevated levels of serum creatine kinase, aspartate aminotransferase, alanil aminotransferase, lactate dehydrogenase and aldolase were excluded by the positive enzyme assay for glycogenosis.
3. Danon disease: elevated levels of serum creatine kinase, aspartate aminotransferase, alanil aminotransferase, lactate dehydrogenase and aldolase but with normal enzyme activity.
4. Mitochondrial myopathy: excluded by the enzyme assay.

Also other muscular glycogenosis were considered but no positive enzyme dosing. Treatment options were limited to supportive or palliative care. For patients with the late-onset form of disease a high protein diet may be beneficial.

### Discussion

Pompe disease affects patients of all ages and is always characterized by progressive degeneration of skeletal muscles (proximal and respiratory) and, in infants, cardiac muscle. The rate of progression varies, ranging from a rapidly progressive course that is usually fatal by one year of age, to a more variable but still relentless, progressive course resulting in significant morbidity and often premature mortality. Typically, when the disease is manifested early in infancy, the rate of progression is very rapid, and without treatment the prognosis is poor. Children and adults usually display more gradual and variable rates of disease progression; however, the prognosis often remains

unpredictable and poor. Recommended assessments are musculoskeletal tests (radiography, motor function test) cardiac tests (chest x-ray / MRI, electrocardiography, echocardiography), pulmonary/respiratory tests (spirometry, pulse oxymetry), laboratory cytotoxic tests (serum creatine

kinase, alanine aminotransferase, aspartate aminotransferase, lactate dehydrogenase). Muscle weakness is a very common finding in pediatric practice, usually not considered to be a serious symptom.

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## SEPSIS WITH PURPURA FULMINANS - REPORT OF TWO CASES

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### Abstract

Purpura fulminans is a supracute hemorrhagic cutaneous syndrome, characterized by massive and rapid extensive ecchymoses, caused by the disseminated intravascular coagulation (DIC) and dermal vascular thrombosis.

The authors present two clinical cases: a girl (M.A.) aged 3 and a boy (P.A.) aged 1 year and 9 months, who were hospitalized and treated in the Intensive Care Clinic Pediatrics of County Hospital Emergency Craiova, then in the Infectious Diseases Clinic, subsequently in Pediatric Surgery Clinic. In both cases, after a brutal start with high fever, petechial and echimotic elements have been expanding rapidly, within few hours, on the abdomen, buttocks, legs, since the first day of admission. Clinical manifestations had included arterial hypotension, convulsions, coma and cutaneous ecchymoses turned into extensive necrosis. Treatment in both cases included hypovolemia correcting and electrolytical rebalancing, blood and plasma transfusions, broad-spectrum antibiotherapy, corticotherapy, catecholamins, immunoglobulins, local treatment of skin lesions.

Evolution of the sepsis was onto healing in about 21 days, but skin lesions required treatment for another 3-6 weeks. The particularity of these cases, compared with other similar cases of medical literature, consists of the evolution towards healing with restitutio ad integrum without requiring surgical interventions.

**Keywords:** sepsis, purpura fulminans, petechial elements, necrosis.

### Introduction

Purpura fulminans is a grave disease, having as pathognomonic sign the purpuric cutaneous syndrome, manifested by massive and rapid extensive ecchymosis

(especially at members) which appears at the infant in the context of some infections or having as background hyperimmune reactions.

At an infant with meningococcal sepsis it has the name of Waterhouse-Friderichsen syndrome (meningococcal purpura fulminans).

The sepsis is defined as a systemic inflammatory response syndrome provoked by an infection. Severe sepsis continues to be a major cause of morbidity and mortality.

### Presentation of clinical cases

#### Case 1

Presenting the case of the female patient M.A. (F.O. 18468/06.04.2007), aged 3 years and 3 months, weighting 14 kg, brought as an emergency in the Pediatrics of the Emergency Clinical County Hospital Craiova.

Heredo-collateral antecedents: she was the fourth child of parents aged over 35, respectively 45, has 2 deceased brothers (one at 6 weeks having aspiration pneumonia, and the other at 1 year and 3 months having bronchopneumonia). Personal Antecedents: born on the natural way with 2650 g.

The beginning of the affection was at admission, with fever (41°C), convulsions, then lethargy, coma. She was admission in a critical general state, abolishment of the conscience state with lack of reactivity at pain stimulus, febrile (41°C), lethargic, generalized tonic-clonic seizures. Stethacoustic pulmonary harsh vesicular murmur, heart rate (HR) 130 beats per minute, cold extremities, with filiform pulse and arterial hypotension; capilar refill time (CRT) >3 sec, neck rigidity. After a few hours, the rash with petechial elements disseminated on the teguments appeared, having purple hue and with the tendency to confluence in the placards (Fig. 1).



Fig. 1 Purple with the tendency to confluence in the placards.

Paraclinic examination: Hemoleucogram: Hb = 7,3 g%, WBC = 32200 /mm<sup>3</sup>, leucocitary formula PMN = 69%, Lf = 17%, Blood Platelets (BP) = 93000 /mm<sup>3</sup>. AST = 150 u/l, initial creatinine 1,45 mg%, after a few days, repeated, was 0,31mg%. Urea = 40 mg%, glycemia = 104,7 mg%, BT = 0,56 mg%, pH = 7,51, PCO<sub>2</sub> = 37mmHg, SvO<sub>2</sub> = 100%, K = 3,1 mEq/l, negative uroculture. Thorax X-ray: prominent basal bilateral pulmonary interstitial. FO: papillae with optical nerve with dull nasal edge, normal retinian vessels. Lombary puncture: clear LCS, slightly hypertensive, after lyses 26 elements/mm<sup>3</sup>, rare cocci G+ in diplo on the smear, negative cultures, albumin 0,33 g%, Pandy (-), glucose 0,55 g%; normal aspect CT. The lombary puncture was repeated at the Infectious Diseases Hospital – with normal results, hemoleucograma also indicated anemia and leukocytosis.

Because of the wide-spread necrotic lesions, with necrosis and infection tendencies, it was decided to transfer her in the Pediatric Surgery Clinic where she was hospitalized for 6 weeks. Paraclinic investigations from the Pediatric Surgery Clinic pointed out: Hb 8,30 g%, Ht = 28%, BP = 579000 /mm<sup>3</sup>, WBC = 32300/mm<sup>3</sup>, leucocitary formula: PMN = 77%, Lf = 19%, Mo = 4%. After the blood transfusion: Hb = 13,9 g%, WBC = 14000 then 10800 /mm<sup>3</sup>, BP=254000 /mm<sup>3</sup>, total proteins = 5,4 g%, culture from the wound's secretion: 1. Hemolytic Staphylococcus aureus, sensitive at Linezolid, 2. Klebsiella sensitive at Imipenem. Repeated hemocultures were negative (because of the precocious established antibiotherapy)

Sepsis diagnosis was established based on fever, tachycardia, leukocytosis, the evident disseminated intravascular coagulation (petechial rash, thrombocytopenia) and on the infection proved indirectly.

In evolution she became afebrile, after 13 days from admission, her general state improved, she began to receive oral alimentation, but the purple elements evolved into wide-spread cutaneous necrosis.

She received treatment using Penicillin G 2,4 mil units/day and Amikacin 300 mg/day for 3 days, Dexametazone, Diazepam, Fenobarbital, vitamins, continuing the parenteral nutrition and plasma perfusions. Subsequently the before-mentioned antibiotics were replaced with Ceftriaxon and Gentamicine, human immunoglobulines iv being added to the treatment of cutaneous lesions.

The evolution was slowly favourable, towards fully healing, without the need of surgery.

## Case 2

Male patient P.A., aged 1 year and 10 months, was hospitalized in Pediatrics Clinic and Infectious Diseases Hospital, for fever, coughing, alteration of the general state.

From the heredo-collateral antecedents we remember that the mother of the child had TBC, and the parents have a sociocultural and economic level under the medium.

The infant was the first born, coming from a physiological pregnancy and an normal birth with BW = 3400 g, was naturally fed 12 months, diversified at 1 year and had no previous admissions.

The beginning of the affection was 5 days before the admission with fever (39° - 39,7°C), coughing, inappetence and didn't follow any home treatment.

At admission is noted the critical general state, W = 12 kg, fever (39°C), lips cyanosis, cold cyanotic extremities, petechial purple lesions with a diameter >1 cm at the legs, buttocks, belly and chest, with coughing, pulmonary staccastic: harshened breathing, BR = 38 /min, HR = 124 b/min, capillary recoloring time >3 seconds, vomiting, meteorized belly, liver with the lower end at 2 cm below the costal rebord, slightly pointy, palpable spleen at 1 cm below the rebord, granulous and congested oropharynx, oral candidose, meningeal syndrome, problems when walking because of the lesions from the legs, somnolence alternating with impatience (Fig. 2).



Fig. 2 Purple lesions on the legs.

Paraclinic investigations: Ht = 23%; Hb = 6 g%; BP = 220.000 /mm<sup>3</sup>; WBC = 13.600 /mm<sup>3</sup>; PMN = 88%; Lf = 8%; M = 4%; on the smear: anisocytosis, poikilocytosis, hypochromia. After the blood transfusion : Hb = 8 g%; WBC = 30.000 /mm<sup>3</sup>; FL: myelocytes = 3%, metamyelocytes = 4%; PMN segm = 56%; pres PMN with toxic granulations; Eo = 3%; Lf = 20%; Mo = 8%; TQ = 100%; TH = 100 sec; AST = 30 U/l; ALT = 68 U/l; BP = 170.000 /mm<sup>3</sup>; glycemia = 53 mg%; fibrinogen = 220 mg%; ESR (Erythrocytes Sedimentation Rate) = 20/46 mm; urea 46 mg/dl; creatinine = 0,69 mg%. At the Infectious Diseases Hospital, paraclinic examinations: Hb = 11 g/dl; BP = 168.000 /mm<sup>3</sup>; WBC=20.900/mm<sup>3</sup>; PMN = 81%, Lf = 14%; E = 3%; M = 2%; Er = 4,62 · 10<sup>6</sup> /mm<sup>3</sup>; TQ = 13”; ESR= 38/56 mm. Lumbar puncture: LCS with nucleated elements = 95 /mm<sup>3</sup>, Pandy (+), Cytologic examination : Lf = 95%, PMN = 5%. Coproculture: negative. Pulmonary radiography: “Both hiles enlarged, bilateral accentuated interstitial drawing”. Dermatologic examination: “Necrotic crusts on right buttock”. Surgery examination: “Crust on right buttock and multiple small disseminated crusts in the lumbar region and legs”.

In evolution, the fever diminished after three days from admission and the petechial elements (with an aspect of “geographical map”: some small, others with placards with a diameter greater than 1 cm) evolved into necrosis with elimination of the sfacelated tissues, with the persistency of atonous scars similar to the deep crusts. Treatment Pediatrics Clinic and Infectious Diseases Hospital: O<sub>2</sub> therapy, transfusion of erythrocytary mass, fresh plasma, Penicillin G 1 mil/6 hours, then Sulperazone, Aciclovir, Hydrocortisone, symptomatics.

In the Pediatric Surgery Clinic he needed surveillance for another 3 weeks and treatment with Penicillin G, then Ceftriaxon and Cotrimoxazol.

The infant was cured without the need of a tegument graft, in the absence of a wide-spread necrosis which would need amputations.

## Discussions

Purpura fulminans (PF) is a life-threatening affection characterized by cutaneous bleedings and necrosis produced by Disseminated Intravascular Coagulation (DIC) and dermal vascular thrombosis.

There were identified three distinct categories: PF produced by congenital or contracted anomalies of the protein C or of other proteins involved in coagulation (without infectious context); Acute infectious PF – the cases described fit into this category; Idiopathic PF.

The most common affection associated with PF is the meningococcal sepsis. Varicella is also a common context for the installment of PF (but without the shock state). Rarely, it was signaled in association with pneumococcal sepsis and with measles (15). In the neonatal period, PF can be triggered by infections with streptococcus group B in most of the cases, but also with stafilococcus, Escherichia coli, Enterobacter and so on. Infectious purpura fulminans provokes a lose in the equilibrium of the procoagulant and anticoagulant balance activities of the endothelial cells (9).

The endotoxines of the germs causing PF are a trigger factor for the production of cytokine-proinflammation: IL-12, IL-1, TNF $\alpha$  interferon which lead to the consumption of protein C (PC) and protein S (PS). Protein C is a glicoprotein vitamin-K-dependent with anticoagulant and anti-inflammation properties, contributing to survival. In meningococemy there exists a direct correlation between the severity of the contracted deficiency of protein C and mortality (18). That’s why the perfusion with fresh plasma, administered in both cases described, was salutary.

In the USA there has been a study (which results were published in 2006) about the effects of the treatment with activated Drotrecogin ALFA (Drot A A) in pediatric sepsis. Drot A A is even a recombined form of human activated protein C (4). Protein C and protein S are vitamin-K-dependent factors, which are synthesized in the liver. Protein C is controlled by chromosome 2, and protein S by chromosome 3. Deficiency in these proteins is recessive autosomal transmitted, having frequently associated deficits of other factors of coagulation. The state of heterozygote of the anomalies of protein C and S causes hypercoagulability. In rare situations, homozygotes with deficiency of protein C or protein S can present a purpura fulminans which endangers life even from the age of newborn (18).

*Positive diagnosis* must be established very close to the beginning bearing in mind that the evolution of PF is very fast, between a few hours and 12-24 hours. It will be established on: a) toxic infectious syndrome (fever, altered geeral state), b) purple syndrome (petechial echimotic elements which become in evolution necrotic and quickly extensive) and c) shock state: tahicardia, cold, cyanotic extremities, capilar refill time > 3 seconds, polypnea, agitation or somnolence, hypotension. All these diagnostic criterias were present at the two studied patients. As a proof of Disseminated Intravascular Coagulation (DIC), at the female patient could be observed the swerving from thrombocytopenia to thrombocytosis.

The antibiotic treatment with cefalosporines and/or Penicillin G in large doses must be early instituted, after the apparition of purple fever (some echimotic elements are enough) even if it reduces the proportion of pozitive hemocultures from 50% to 5%. The detection of soluble antigenes and especially of meningococcal DNA using Polymerase Chain Reaction (PCR) allowed the proof of the meningococcal disease in 50-85% of the cases, but these investigations were not accessible in our clinics.

Besides shock-state treatment with corticotherapy, vasoactive drugs, O<sub>2</sub>-therapy, it is always recommended the perfusion with fresh plasma for the correction of the deficit of protein S and C.

## Conclusions

The evolution of the sepsis at the two cases was onto healing in about 21 days, but the cutaneous lesions needed treatment for another 3-6 weeks, the girl M.A. presenting complicated sepsis and suprainfection of the postnecrotic lesions.

The presented patients, even if they were in a very grave state at admission, healed without deep scars, without the necessity of graft of teguments and without going to

phalanx amputations like in some cases described in the medical literature (9,18).

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# FUNGAL INFECTIONS IN HIV INFECTED CHILDREN

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## Abstract

HIV as we all know remains to be a global pandemic. HIV infection causes gradual loss of immune system particularly the cell-mediated immunity and hence, predisposing a person to several opportunistic infections including fungal infections. Fungal infections vary in their course depending on geographical regions. Lack of information on patterns of fungal infections initiated us, to conduct this study. Fifty-five HIV sero-positive patients admitted in Civil Hospital, Ratlam, India, during January 2008 to January 2009 were included in this study. The study group comprised of 32 (58.18%) males and 23 (41.81%) female patients. Relevant clinical samples were processed for detection of fungal pathogens using standard mycological technique. Fungal infections were suspected in 43 (78.18%) of the patients. *Candida* species topped the list being present in 27 (62.79%) of the patients, mostly in the form of oropharyngeal Candidiasis. Two patients presented with systemic Candidiasis. Cryptococcal meningitis and Dermatophytosis was documented in equal proportions being in 6 (13.95%) each. *Geotrichosis candidum* in 4 (9.30%) patients were other fungal infection encountered. *Pneumocystis carinii* (*Pneumocystis jiroveci*) in spite of being suspected clinically in 11 (20%) patients could not be confirmed microbiologically.

**Keywords-** HIV, Fungal infections, Candidiasis, children

## Introduction

Infection with HIV results in progressive loss of host immune mechanism. Compromised immune status predisposes to a wide variety of opportunistic infections, being the major cause of morbidity and mortality in these patients [1,2]. However, these patients are subjected to a wide spectrum of pathogens, fungal infections play an important role. As these infections differ in different geographical boundaries, knowledge about the spectrum of them is crucial for clinicians [1, 3]. The number of HIV and AIDS cases is gradually increasing with a lack of knowledge about the disease in general population in this region of India. This study was planned to know the pattern of fungal infections in HIV sero-positive patients with various clinical presentations.

## Material and Methods

A total of 55 HIV seropositive patients admitted in Civil Hospital, Ratlam, India, during January 2008 to

January 2009, were included in the study. HIV infection in these patients was confirmed by at least two different ELISA kits as per WHO strategy II. Whenever needed Western blot (Qualicode Transasia India) was used for confirmation. Detailed clinical history and physical examination was done.

Depending upon clinical presentation, various clinical samples were collected i.e. sputum, urine, blood, CSF, pleural fluid, ascitic fluid, oral scraping, broncho-alveolar lavage, induced sputum, skin scraping, etc. in sterile container and sent to the microbiology laboratory. Samples were processed as per standard mycological technique 4. Each specimen was examined for the presence of fungus by microscopy using wet mounts (KOH mount, Nigrosin) or stained preparations (Gram stain Giemsa stain, or Gomoris methenamine silver stain). Isolation of the fungus was done using Sabouraud dextrose agar (SDA) with antibiotics and with or without cycloheximide and sunflower seed agar [5]. The plates were incubated in two sets, one at room temperature and another at 35° Celsius for a minimum of four weeks. Growth rate, colony characteristics, and microscopic morphology were used to identify the isolate. *Candida* was identified to species level by germ tube test, growth morphology on cornmeal agar and pattern of sugar assimilation.

Serum and CSF samples from suspected cryptococcal infection were subjected to enzyme immunoassay by premier cryptococcal antigen detection kit. Forty HIV positive serum samples were also subjected to fungal immune-diffusion system for detection of precipitating antibody to *Histoplasma capsulatum*. Forty HIV sero-negative samples were randomly selected and run simultaneously as negative control.

## Results

Out of 55 patients examined, 32 were males 23 females (age group 5-22 years). Though in majority of the patients mode of transmission could not be elicited (24/55), vertical transmission still remains the major mode of transmission (13/55) followed by blood transfusions and drug abuse (11/83), and only (7/55) had acquired HIV through sexual transmission (Table-1). Most of these patients came either from low socioeconomic status; farmers or from low wage earners. All the patients were positive for HIV-1; one patient was co-infected with HIV-2. Five patients were co-infected with hepatitis B virus.

All patients presented with more than one symptom, persistent cough (46/55) and fever (41/55) being the most common followed by weight loss more than 10% of body weight in last three months (29/55), chronic diarrhea (15/55), generalized lymphadenopathy (10/55) and altered sensorium (6/83) (Table-2).

Fungal infections were suspected in 49/55 patients but confirmed microbiologically in 43 (78.18%) cases as shown in (Table 3). Candidiasis either in the form of oropharyngeal, esophageal, urinary or systemic topped the list 27 (62.79%) followed by Cryptococcal meningitis 6 (13.95%) and Dermatophytosis 6 (13.95%). Among these 27 samples of Candida infection, *C. albicans* was the main species found in 19 (70.37%) followed by *C. nonalbicans* in 8 (29.62%). This included two *C. kefyr* and *C. parapsilosis*

each and one *C. krusei*. *Geotrichum candidum* was found in 4 (09.30%) cases, as co-infection with *C. albicans*. Urinary tract infection (UTI) due to fungus was found in six cases. *Candida albicans* was the main organism causing UTI found in three cases followed by two *Geotrichum candidum* one *C. kefyr*. *Candida* species isolated from sputum samples was regarded as oral contamination as most of the patients had oral Candidiasis. Cryptococcal antigen in CSF, was detected in 6 (13.95%) out of eleven clinically suspected cases of cryptococcal meningitis. [Table-4]

Six patients had widespread Dermatophytosis caused by *Trichophyton rubrum* in four cases and *Microsporum gypseum* in two. *Histoplasma capsulatum* antibodies could not be detected in any of the test or control serum samples.

**Table -1 Routes of HIV transmission (n=55)**

Routes of transmission	No (%)
Vertical transmission	13 (23.63%)
Blood transfusion + drug addicts	11 (20.00%)
Sexual route	07 (12.72%)
Unknown	24 (43.63%)

**Table – 2 Clinical spectrum of patients with HIV infection (n=55)**

Symptoms	Numbers (%)
Chronic cough	46 (83.63%)
Persistent fever	41 (74.54%)
Weight loss	29 (52.72%)
Chronic diarrhea	15 (27.27%)
Generalized lymphadenopathy	10 (18.18%)
Altered sensorium	06 (10.90%)

**Table -3 Sample wise distribution of fungal isolates (n=43)**

Type of specimen (no)	Fungal isolates found to be positive (no)	Type of isolates (no)
Oral scrapings (42)	23	<i>C. albicans</i> (14) <i>C. nonalbicans</i> (7) <i>G. candidum</i> (2)
Urine (28)	06	<i>C. albicans</i> (3) <i>C. nonalbicans</i> (1) <i>G. candidum</i> (2)
Blood (22)	02	<i>C. albicans</i> (2)
CSF (11)	06	<i>C. neoformans</i> (6)
Skin scrapings (9)	06	<i>T. rubrum</i> (4), <i>M. gypseum</i> (2)
Sputum (23)	00	-
<b>Total (135)</b>	<b>43</b>	

Table -4 Spectrum of fungal infections in HIV/AIDS patients (n=55)

Type of fungus	Clinically suspected in	Confirmed microbiologically
Candida species	30	27
G. candidum	5	4*
P. carinii	11	-
Cryptococcus species	11	6
Dermatophytosis	6	6
Histoplasma species	-	-
Aspergillus	-	-
<b>Total</b>	<b>49 (89.09%)</b>	<b>48 (78.18%)</b>

\*Co-infection

### Discussions

HIV is a deadly disease having its impact on different age groups but specially affecting the productive age people. Implementation of methods to prevent HIV through vertical transmission remains to be a major challenge in the study zone. The age and sex distribution in this area of Madhya Pradesh has not changed over the last ten years [7]. Male to female ratio in this study was found to be 1:3 similar to a study done in Pondicherry, India, where male to female ratio was 1:6 showing a male predominance [6]. In majority of patients no history of sexual contact or BT was elicited probably showing an awareness about the sexual mode of transmission and possibly a non revealing fact on the part of patients. Parents HIV status was unknown in many cases.

Candidiasis in the form of oral/ esophageal/ pharyngeal involvement is the most common fungal infection affecting HIV seropositive patients, contributing significantly to their mortality and morbidity [2, 8]. Ninety percent of patients develop some form of Candida infection at some time of the disease [2, 8]. *C. albicans* is the most common species but other species like *C. tropicalis*, *C. krusei*, *C. glabrata* are also involved [9]. We found 23 (53.488%) patients suffering from oral Candidiasis. Out of which, 10 gave a history of dysphagia suggesting possible esophageal involvement. This has shown the increasing significance of *C. nonalbicans* in HIV infected patients. Species identification of Candida becomes more important keeping in mind the inherent resistance of some Candida spp. to some antifungal agents. Other studies have found the incidence of Candidiasis ranging from 30-70% [1,3]. Candida infections in AIDS cases are usually limited to superficial mucosal involvement. Candidemia occurs rarely [8]. We had only two cases with systemic involvement.

The second common fungal pathogen that was suspected (on the basis of specific presentation like interstitial pneumonia, excessive dyspnea with PO<sub>2</sub> imbalance etc) in these patients was *Pneumocystis carinii* now called as *Pneumocystis jiroveci* as a cause of *Pneumocystis pneumonia* (PCP). PCP is more commonly reported from Western World [10]. In the USA 60-70% of AIDS cases had PCP as their presenting illness with a mortality of 10-20% [10,11]. The reported incidence of PCP

in Indian patients is 4% [3]. We had 11 patients with strong clinical suspicion of PCP but could not be confirmed microbiologically either due to lack of expertise in technique or inappropriate sample collection or possibly due to common

practice to start PCP prophylaxis. Information on the incidence of PCP in Indian patients is very limited [3, 10, 11].

Cryptococcal meningitis is a common life threatening infection in AIDS patients [3, 12-15]. The incidence in HIV infected patients is highly variable ranging from 6-10% in the USA, West Europe, Australia, and France to 15-30% in sub-Saharan countries [12, 13]. Cryptococcal infection was reported for the first time in India in 1952, and since then there are many reports of Cryptococcal infection particularly meningitis in HIV infected individuals [12, 15]. Indian studies have shown variable incidence ranging from 5.6% in Lucknow, India to 34.8% in Tamilnadu, India [15]. We found six patients means 13.95% incidence of Cryptococcal meningitis with 50% mortality. Other fungal pathogens which have been found in HIV infected individuals included histoplasmosis, coccidioidomycosis, penicilliosis and aspergillosis. None of these infections could be detected in our study. Aspergillosis is not as common in AIDS cases as is found in patients with neutropenia and steroid therapy [3]. There are sporadic reports of histoplasmosis in Indian patients [16, 17] particularly with oral involvement but we found histoplasmosis in none of our patients.

Dermatophytes have not been mentioned as important pathogens in HIV infected individuals but it is known that these patients have atypical presentation with more extensive involvement [2]. This was evident in our study as we had six patients out of which four had extensive involvement due to *Trichophyton rubrum* and two had *Microsporum gypseum*. In conclusion it appears that Candida and Cryptococcus are the main fungal pathogens in this part of the country as well as in other parts of India. The incidence and species are variable depending upon geographical area. More efforts are needed to give laboratory evidence of *Pneumocystis pneumonia*. Knowledge about the pattern of pathogens is a must in order to serve the HIV infected patients better.

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## TYPE 2 DIABETES AND METABOLIC SYNDROME IN OBESE CHILDREN – A REALITY

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### Abstract

By the end of the 20th century the incidence of type 2 diabetes mellitus (T2DM) in children had increased dramatically. Once considered a disease of the overweight, middle age person, the incidence of type 2 diabetes is rising rapidly in children and adolescents worldwide, with the highest prevalence in those of American-Indian, Hispanic, African-American, and Asian descent (1,2). The alarming incidence and prevalence of diabetes has been attributed to increasing obesity among younger people (3). The hallmark of type 2 diabetes in the young, as in most adults, is insulin resistance (4, 5). On a global basis, the rise in T2DM rates mirrors the growth in urbanization and economic development – obesity appears to be the key link (6, 7).

**Key words:** childhood, diabetes, obesity, insulin-resistance.

### Introduction

T2DM occurs when insulin secretion is inadequate to meet the increased demand posed by insulin resistance (8). T2DM is commonly associated with other features of the insulin resistance syndrome (hyperlipidemia, hypertension, acanthosis nigricans, ovarian hyperandrogenism, non-alcoholic fatty liver disease -NAFLD) (9).

Diagnosis of type 2 diabetes (10):

Diagnostic criteria for diabetes are based on blood glucose measurements and the presence or absence of symptoms (11, 12). Diabetes is diagnosed when:

- A fasting plasma glucose (FPG) is  $\geq 7.0$  mmol/l (126 mg/dl) **or**
- The post challenge plasma glucose is  $>11.1$  mmol/l (200 mg/dl) **or**
- Symptoms of diabetes and a casual plasma glucose  $\geq 200$  mg/dl (11.1 mmol/L).

Previously, the majority of cases of diabetes in the pediatric population have been type 1. However, the increasing incidence of type 2 diabetes in this population presents a challenge to the clinician, who must be able to distinguish between type 1 and type 2 diabetes in children, to optimize therapy (Table 1).

- with increasing obesity in childhood, as many as 15–25% of newly diagnosed T1DM (or monogenic diabetes) patients may be obese.
- the significant number of pediatric patients with T2DM demonstrating ketonuria or ketoacidosis at diagnosis
- There is considerable overlap in insulin or C-peptide measurements between T1DM, T2DM and MODY at onset of diabetes and over the first year or so. The role of C peptide may be more helpful in established diabetes as persistent elevation of C-peptide above the level of normal would be unusual in T1DM after 12–24 months.

**Table 1.** Major characteristics of T1DM/T2DM/MODY

	<b>T1DM</b>	<b>T2DM</b>	<b>MODY</b>
<b>Genetics</b>	poligenic	poligenic	monogenic
<b>Age at onset</b>	6 months to young adulthood	Mean age 12-14 years	Often post pubertal
<b>Course</b>	Most often acute, rapid	Variable; from slow, mild (often insidious) to severe	Variable
<b>Autoimmunity</b>	Yes	No	No
<b>Obesity</b>	Population frequency	Increased frequency	Population frequency
<b>Acanthosis nigricans</b>	No	Yes	No
<b>Parent with diabetes</b>	2-4 %	80 %	90 %

The American Diabetes Association recommends screening for diabetes among children with a BMI of  $> 85$ th

percentile for age and gender, with 2 additional risk factors for T2DM (Table 2).

**Table 2.** Testing Guidelines for T2DM

Overweight or at risk for overweight
➤ BMI >85th percentile for age and gender; or
➤ Body weight for height >85th percentile; or
➤ Body weight >120% of ideal for height
+ Plus any 2 of the following
➤ Family history of T2DM in first- or second-degree relatives
➤ Race/ethnicity (American Indian, black, Hispanic, Asian/Pacific Islander)
➤ Signs of insulin resistance or conditions associated with insulin resistance (acanthosis nigricans, hypertension, dyslipidemia, polycystic ovary syndrome)
➤ Age of screening initiation: 10 y or at onset of puberty if puberty occurs at a younger age
➤ Frequency of testing: Every 2 years
➤ Test: Fasting plasma glucose (OGTT can also be used to confirm diabetes)

**T2DM and the insulin resistance syndrome**

Insulin resistance is an impaired response to the physiologic effects of insulin, including effects on glucose, lipid, and protein metabolism, and on vascular endothelial function.

Glucose homeostasis is maintained by insulin secretion, insulin action, hepatic glucose production, and cellular glucose uptake (13).

The onset of puberty also contributes to insulin resistance, with insulin sensitivity decreasing by approximately 30% and compensatory increases in insulin secretion (14, 15). All children become more insulin resistant at the time of puberty. Insulin resistance increases immediately at the beginning of puberty, peaks at mid-puberty, and then declines to nearly prepubertal levels by early adulthood. Girls are more insulin resistant than boys during puberty which is related in part to differences in adiposity between the sexes. Growth hormone has been considered a contributing factor in the development of insulin resistance during puberty, with an inverse correlation between growth hormone levels and insulin action.

Diabetes is only one manifestation of the insulin resistance syndrome or the MS (metabolic syndrome). Other associations include:

- Obesity
- Hypertension
- Nephropathy (albuminuria)
- Dyslipidemia (Hypertriglyceridemia and decreased high-density lipoprotein cholesterol)
- Ovarian hyperandrogenism and premature adrenarche (16)
- NAFLD (non-alcoholic fatty liver disease): Hepatic steatosis is present in 25–45% of adolescents with T2DM
- Systemic inflammation: elevated C-reactive protein, inflammatory cytokines in obese

adolescents have been associated with increased risk for cardiovascular disease in adults (17).

**Management goals in obese - diabetics childs :**

- Weight loss
- Increase in exercise capacity
- Normalization of glycemia
- Control of comorbidities: including hypertension, dyslipidemia, nephropathy, and hepatic steatosis

Treatment which includes physical activity and a well balanced diet, with the appropriate amount of carbohydrates and protein to maintain a healthy weight, is vital. Further studies evaluating the long-term benefit of diet and exercise should be conducted in children and adolescents (19).

Pharmacologic therapy should be implemented if glycemic goals are not achieved through proper diet and increased physical activity (maintaining euglycemia with metformin, sulfonylureas, thiazolidinediones, and insulin is recommended). – Table 4.

- The first medication used should be metformin (20). Metformin acts on insulin receptors in liver, muscle, and fat tissue, with a predominant action on the liver. An initial anorexic effect may promote weight loss. Long-term use is associated with a 1–2% reduction in HbA1c. Intestinal side effects (transient abdominal pain, diarrhea, nausea) may occur. It has the advantage over sulfonylureas of similar reduction in HbA1c without the risk of hypoglycemia. Despite hyperinsulinemia and insulin resistance, relatively small doses of supplemental insulin are often effective. If glycemic control on oral agents is inadequate, a long-acting insulin analogue may provide satisfactory therapy without meal related therapy. Metformin should be continued to improve insulin sensitivity (21).

**Table 3:** A range of the published metabolic syndrome definitions in pediatrics (18).

**Three or more of the following**

	Cook et al. <i>Arch Pediatr Adolesc Med</i> , 2003; 157, 821-74	de Ferranti et al. <i>Circulation</i> , 2004; 110, 2494-721	Cruz et al. <i>J Clin Endocrinol Metab</i> , 2004; 89, 108-1322	Weiss et al. <i>N Engl J Med</i> , 2004; 350, 2362-743	Ford et al. <i>Diabetes Care</i> , 2005; 28, 878-8144
<b>1.</b>	Fasting glucose $\geq 110$ mg/dL	Fasting glucose $\geq 6.1$ mmol/L ( $\geq 110$ mg/dL)	Impaired glucose tolerance (ADA criterion)	Impaired glucose tolerance (ADA criterion)	Fasting glucose $\geq 110$ mg/dL (additional analysis with $\geq 100$ mg/dL)
<b>2.</b>	WC $\geq 90$ th percentile (age- and sex-specific, NHANES III)	WC $> 75$ th percentile	WC $\geq 90$ th percentile (age-, sex- and race-specific, NHANES III)	BMI $-Z$ score $\geq 2.0$ (age- and sex-specific)	WC $\geq 90$ th percentile (sex-specific, NHANES III)
<b>3.</b>	Triglycerides $\geq 110$ mg/dL (age-specific, NCEP)	Triglycerides $\geq 1.1$ mmol/L ( $\geq 100$ mg/dL)	Triglycerides $\geq 90$ th percentile (age- and sex-specific, NHANES III)	Triglycerides $> 95$ th percentile (age-, sex- and race-specific, NGHS)	Triglycerides $\geq 110$ mg/dL (age-specific, NCEP)
<b>4.</b>	HDL-C $\leq 40$ mg/dL (all ages/ sexes, NCEP)	HDL-C $< 1.3$ mmol/L ( $< 50$ mg/dL)	HDL-C $\leq 10$ th percentile (age- and sex-specific, NHANES III)	HDL-C $< 5$ th percentile (age-, sex- and race-specific, NGHS)	HDL-C $\leq 40$ mg/dL (all ages/ sexes, NCEP)
<b>5.</b>	Blood pressure $\geq 90$ th percentile (age-, sex- and height-specific, NHBPEP)	Blood pressure $> 90$ th percentile	Blood pressure $> 90$ th percentile (age-, sex- and height-specific, NHBPEP)	Blood pressure $> 90$ th percentile (age-, sex- and height-specific, NHBPEP)	Blood pressure $> 90$ th percentile (age-, sex- and height-specific, NHBPEP)

**Table 4.** Oral antidiabetics.

<b>Oral antidiabetics</b>	<b>Mechanism of Action</b>	<b>Side Effects</b>
<b>INSULINSENSITIZERS</b>		
Biguanides Metformin (the drug of first choice)	Decrease hepatic glucose production Increase muscle glucose uptake and utilization	Nausea Diarrhea Anorexia Lactic acidosis
Thiazolidinediones Rosiglitazone Pioglitazone	Increase insulin sensitivity via activation of PPAR-g receptors	Fluid retention and weight gain
<b>INSULIN SECRETAGOGUES</b>		
Sulfonylureas Glimiperide (Amaryl) Glipizide Tolbutamide Chlorpropamide Tolazamide	Stimulate first-phase insulin secretion by blocking K <sup>+</sup> channel in $\beta$ -cells	Late hyperinsulinemia and hypoglycemia Weight gain
<b>OTHERS</b>		
Meglitinides Repaglinide Nateglinide	Stimulate first-phase insulin secretion by blocking K <sup>+</sup> channel in $\beta$ -cells	Hypoglycemia Weight gain
$\alpha$ -Glucoside Inhibitors Acarbose Miglitol	Decrease hepatic glucose production Delays glucose absorption	Flatulence Abdominal bloating

**Conclusion**

Environmental factors, such as increased caloric intake combined with a sedentary lifestyle, have contributed to obesity and insulin resistance; the key players in the pathogenesis of type 2 diabetes in the young

Because type 2 diabetes is increasing at alarming rates in children and adolescents, all health care providers must play an active role in providing education regarding proper nutrition, physical activity, and pharmacologic therapy to patients.

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## PAINFUL ACCESSORY NAVICULAR IN CHILDREN - CASE PRESENTATION

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### Abstract

Accessory bones, called sesamoid bones, may be occasionally located in the foot. Such a situation is seen in the case of accessory navicular. Its presence is mostly asymptomatic, in some cases in teenagers and adults and more rarely before this age, leading to pains in the leg. This paper presents the case of a 10 year girl experiencing such a pathology that was managed surgically.

**Key words:** accessory navicular, leg pain, child, surgical treatment

### Introduction

There are situations in which, either in hand or leg, by a congenital anomaly, the number of bones is greater than normal, as sesamoid bones are present. This may sometimes cause problems. The accessory navicular bone (*os navicularum* or *os tibiale externum*) is an additional bone or a piece of cartilage located on the inner side of the foot, near the head of the navicular bone, frequently incorporated in the posterior tibial tendon or, more rarely, connected through fibrous or cartilaginous tissue to the navicular. Girls are more often affected by this anomaly<sup>1,2</sup>.

Not all the individuals with this accessory bone have symptoms<sup>3</sup>. The symptoms appear when the accessory navicular bone is too large or when a traumatism causes an injury in the fibrous tissue between the navicular and accessory navicular bones, leading to a phenomenon similar to a fracture considered to be the cause of the pain<sup>4</sup>. As the posterior tibial tendon attaches to the accessory navicular, it is constantly stretching the bone, causing with every step a greater displacement between fragments.

Trauma that triggers the pain may be an ankle sprain or irritation from shoes by rubbing. Many patients with accessory navicular syndrome also have flat feet that will put more pressure on the posterior tibial tendon, which can produce inflammation or irritation of the accessory navicular. Signs and symptoms of accessory navicular may appear during adolescence, when the bones are maturing and the growth cartilage is developing into bone. However, sometimes symptoms do not occur until adulthood.

Signs and symptoms of accessory navicular syndrome include: a visible bony prominence on the inner side of the foot, local hyperaemia, swelling, and vague bone pain, usually occurring during or after activity periods.

Diagnosis is commonly suggested by medical history and painful sensitivity within the area of the head of the navicular bone. Radiological examination is needed to allow the surgeon to visualise the accessory navicular. No other

tests are generally required, but MRI or CT can be useful in order to establish the relationship between accessory navicular and posterior tibial tendon<sup>5,6,7</sup>.

The treatment may be non-surgical in order to improve the symptoms. The following may be used: immobilisation by plaster splint, use of boots when walking, which allow the affected area to rest and reduce inflammation, use of an ice bag covered with a thin towel applied on the affected area in order to reduce swelling, oral non-steroidal anti-inflammatory drugs (NSAID), such as ibuprofen, may be prescribed. Orthotically, devices that fit into the shoe and provide support for the plantar arch may be used, and these may play an important role in the prevention of symptoms in the future. Even after a successful treatment, the symptoms of accessory navicular syndrome sometimes reappear. When this happens, non-surgical approaches are usually repeated, often followed by surgical intervention when it seems that all non-surgical approaches failed to control the issue and the pain becomes unbearable.

Surgical treatment of this condition involves removing the accessory bone (this additional bone is not necessary for normal foot function), remodelling the area, and repairing the posterior tibial tendon to improve its function.

The most commonly used procedure to treat the symptomatic accessory navicular is Kidner procedure: a small incision is made on the area in which the accessory navicular is palpated; the bone is then detached from the posterior tibial tendon and excised<sup>8</sup>. Posterior tibial tendon is re-inserted on the remaining normal navicular. Skin incision is closed with threads; bandage and immobilisation by plaster splint are applied. Use of crutches for several days is recommended after surgery and the suture threads are removed within 10 to 14 days.

In some cases, as the one presented hereinafter, the accessory navicular is placed in the thickness of posterior tibial tendon. Thus, undoubling the proximal tendon from the insertion on the navicular bone is sufficient for its excision.

### Case presentation

M.H., 10 years of age, female, addresses the pediatric orthopedics department for pain within the projection area of the right navicular head, debuting approximately two months before, and the pain is accentuated by excessive walking. Local swelling, painful sensitivity at palpation, and discrete skin hyperaemia are observed at the objective exam.

The radiological exam reveals the presence of a bony formation of approximately 5 mm diameter (sesamoid bone) located posterior to the head of right navicular bone –

accessory navicular, confirmed by CT scan (fig 1). Laboratory investigations indicated normal values.

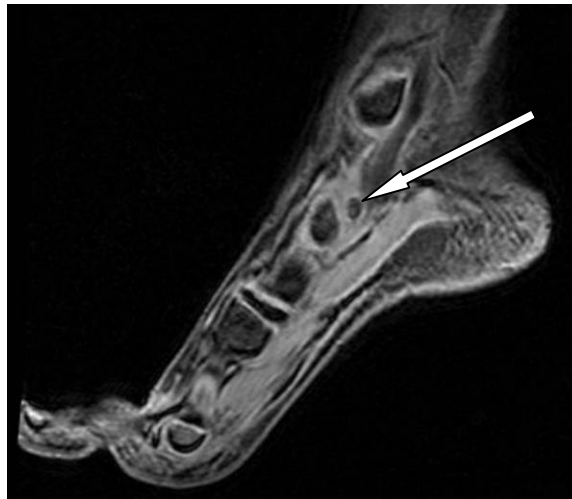


Fig 1. Radiological and CT aspect of accessory navicular.

Surgery is performed under general anaesthesia. An incision centred on the insertion of posterior tibial tendon on the head of navicular bone is made. After the tendon is isolated, cranially to the insertion on the navicular bone may be seen a thickening of the navicular bone by incorporating

the sesamoid bone. The tendon is undoubled, the accessory navicular is excised (fig 2) and the tendon is rebuilt with individual suture threads, haemostasis, and skin suture with individual threads.



Fig. 2 Intraoperative aspects.

After surgery, a radiological exam is performed in order to confirm complete excision of accessory navicular (fig 3) and the foot is immobilised by plaster splint for three weeks, with bandage at two-three days and removal of

suture threads after 10 days. Three weeks after, the patient starts walking with crutches for two weeks. Subsequent periodic check-ups show good healing with relieve of symptoms.



Fig. 3 Postoperative radiological exam.

### Conclusions

1. Existence of accessory navicular, frequently asymptomatic, may sometimes cause pain of the foot.
2. Although clinical signs commonly appear mainly in females during adolescence or adulthood, it is possible to clinically start earlier, at 10 years in this case.

3. Accessory navicular may be located within the thickness of posterior tibial tendon, without affecting its insertion on the navicular bone, for the excision of the sesamoid bone being sufficient to longitudinally undouble the tendon.
4. Post-operative recovery is full and rapid, with relieve of painful symptomatology.

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# SINGLE SYSTEM UNILATERAL ECTOPIC URETER ASSOCIATED WITH CONTRA LATERAL RENAL AGENESIA. CASE REPORT

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## Abstract

Unilateral single ectopic ureters associated with contra lateral renal agenesis and hypoplastic bladder are rare and difficult to treat. Urinary diversion is usually performed because of small bladder capacity. We report a case treated by staged operation without urinary diversion or bladder augmentation.

**Keywords:** ectopic ureter, incontinence, bladder hypoplasia.

## Introduction

Single ectopic ureters are a rare malformation in children. Single-system ureteral ectopia differs from the more common double-system ectopia by a high incidence of associated malformations. Renal dysplasia is common, but does not bear a consistent relationship to the degree of ureteral ectopia. However, in case of bilateral single ectopic ureters or in unilateral ectopic ureter associated with contra lateral renal agenesis, subsequent malformation of the bladder trigone and bladder neck may result in additional voiding dysfunction. (1, 2)

The treatment of unilateral single system ectopia with a healthy contralateral kidney is simple; and it consists in unilateral uretero vesical reimplantation. Cases with bilateral single-system ectopia or unilateral single-system ectopia with contralateral renal agenesis present difficult management.

## Methods

The authors report their experience with a girl, in whom unilateral single ectopic ureter with contra lateral renal agenesis was treated by ureteral reimplantation in early childhood and who did not gain adequate bladder control during following years.

## Case report

We present the case of a female newborn how was presented in our department with ecographic diagnose of postnatal grade V left hydronefrosis, left lumbar palpable mass and no visualization of the right kidney. She also had biological signs of renal failure but with no urinary tract infection. The cistography showed a small bladder with no vesicoureteral reflux. Due to progressive deterioration of the renal function she underwent a CT scan that shows the absence of the right kidney, a hypoplastic bladder and a grade V left hydronephrosis. We decided to make an upper tract urinary diversion, but unfortunately because of the malfunction of the percutan pielostomy, we were forced to place a new pielostomy catheter via an open lobotomy, which was this time functional. At one month of age the descendent pielography shows a dilated left ureter and raise the suspicion of a left primary obstructive megaureter (fig 1). The child was dismissed at home with a left pielostomy and antibioprophilaxy.

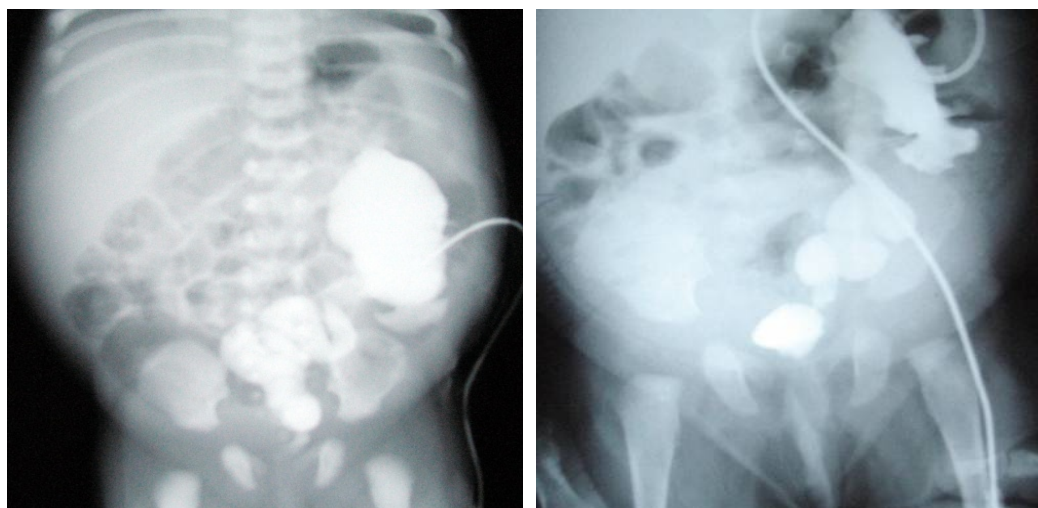


Figure 1 - Postnatal descendent pielography.

She came back 2 month later with normal renal parameters, and an acute urinary tract infection, which required intravenous antibiotherapy. The cystoscopy revealed a hypoplastic bladder, with no right ureteral orifice and an ectopic left ureteral meatus, which was opened in the bladder neck. A repeated pielography showed no passage of the contrast through the ureteral meatus, so at the age of 4 months the ectopic ureter was reimplanted into the bladder by Politano-Leadbetter technique.

Postoperative follow-up revealed a bad functionality of the uretero-vesical junction with an increase of the hydronephrosis and progressive deterioration of the renal function. A new urinary diversion by pielostomy was necessary one month after reimplantation. The very small bladder show no improvement in volume, with a poor function on repeated attempts of pielostomy removal with short dry period at approximately 3 years follow-up. (fig 2)

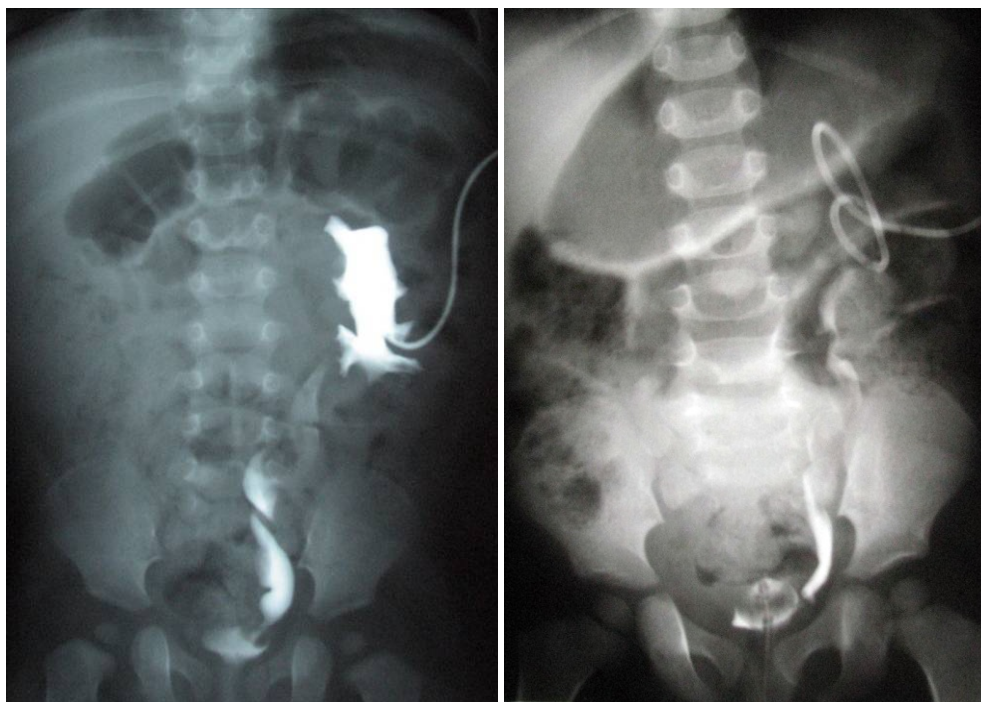


Figure 2. Postoperative pielography.

## Discussions

Ureteral development begins in the 4<sup>th</sup> week of gestation, in close relationship with the renal embryology. At 4 weeks of gestation, a ureteric bud arises as an outpouching from the mesonephric duct and interacts with the metanephric blastema. The segment of the mesonephric duct distal to the ureteric bud becomes a common excretory duct and is eventually absorbed into the developing bladder to become part of the trigone. The point of origin of the ureteric bud is the future ureteric orifice. If the ureteric bud arises more proximally on the mesonephric duct than normal, the future ureteric orifice will be more medial and caudal because it has less time for its normal migration into the bladder, the ureteral orifice can ultimately be incorporated into one of the Müllerian structures instead of into the bladder.(3)

In females, it is possible that the orifice may be distal to the urethral sphincter allowing continuous urinary incontinence, with the ureter inserted into the lower bladder, urethra, vestibule, or vagina. More rarely, it can empty into the uterus or a wolffian duct remnant such as Gartner duct or cyst.

In males, it empties into the lower bladder, posterior urethra, seminal vesicle, vas deferens, or ejaculatory duct. In very rare instances, it can empty into the rectum. The fundamental difference between ureteral ectopia in females and in males is that in females, ectopic ureters can terminate at a level distal to the continence mechanisms of the bladder neck and external sphincter and thus may be associated with incontinence. Approximately one-half of female patients with ectopic ureters present with a classic history of continuous dribbling incontinence despite what appears to be a normal voiding pattern.

An ectopic ureter can drain a single kidney, but about 70% are associated with complete ureteral duplication. In complete ureteral duplication with each segment having its own ureteral orifice in the bladder, the Weigert-Meyer rule applies. This rule states that the ureteral orifice of the upper pole moiety inserts into the bladder medial and inferior to both its normal location and the orifice of the ureter draining the lower renal segment. In these cases, the ureter draining the upper pole moiety frequently ends in an ureterocele, whereas reflux into the lower moiety typically occurs. The renal parenchyma abnormalities associated with duplex

systems are thought to be the result of abnormal origin of the ureteric bud. It is believed that the farther away the ureteral bud arises from its normal location, the more abnormal the resulting renal segment. The embryological defect in the group of children with single-system ectopia is clearly more than an anomalous ureteric bud (4, 5, and 6)

In female single ectopic ureters on unique renal unit cases, the development of trigone and bladder neck musculature does not occur because of the ectopic openings being outside the bladder, which therefore does not have the opportunity to distend with urine. Additionally, a poorly developed bladder neck and an improperly functioning urethral control mechanism prevent bladder growth. The surgical treatment of an ectopic ureter in a female depends on the associated renal function. Single-system ureteral ectopia to the genital system usually has poor function, and a nephroureterectomy is appropriate when the other kidney has a good functionality. With single-system ectopia to the bladder neck or urethra, the function may justify a reimplantation of the ureter into the bladder.

Treatment of unilateral ectopic ureter with contra lateral renal agenesis is challenging, similarly to incontinent epispadias. First of all, preservation of renal function should be the main consideration in these patients. Second,

sufficient bladder capacity is necessary to rampant the dilated ureters. The most popular procedure to increase the size of the bladder is enterocystoplasty; however, there is a concern about future malignancy. A last resort is to abandon the native bladder to select urinary diversions such as ureterocutaneostomy, ileal conduit and continent urinary diversion. Incontinence, and bladder functionality remains the most troublesome problem in patients with unilateral single-system ectopic ureters. (7, 8)

In our case de reason to perform at an early age the neoureterovesicostomy was to improve bladder capacity and function. Unfortunately the damages on bladder neck and capacity were not ameliorated, so the patient had to maintain the pielostomy. On the future it will be necessary to perform a bladder augmentation in an attempt to ameliorate the bladder capacity and the continence. Long-term follow up with regard to bladder function is needed.

The diagnose and treatment of unilateral single system ureteral ectopia associated with contra lateral renal agenesis remains a challenge for the pediatric urologist. Despite of a well placed neoureterostomy these children will develop a bad bladder function, with short dry period and incontinence, which will require further surgical interventions.

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# COMPARATIVE ANALYSIS OF MODIFIED RAVITCH AND MINIMAL INVASIVE NUSS PROCEDURES FOR THE CORRECTION OF PECTUS EXCAVATUM IN CHILDREN

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## Abstract

Pectus excavatum (PE) is the most frequent anterior chest deformity. Despite that since now more than 50 surgical procedures were performed for the correction of PE, only two were widely accepted by the medical community and each one of them was considered, in its own period of time, the gold standard in the surgical treatment of PE. This study is a retrospective comparison of the outcomes of the two main surgical procedures for the correction of PE, modified Ravitch procedure (MRP) and minimal invasive Nuss procedure (MIRPE) in The Department of Pediatric Surgery and Orthopedics, Emergency Children’s Hospital „Louis Turcanu”, Timisoara, Romania and in The Pediatric Surgery Unit, Pediatrics Clinic, University Hospital Szeged Hungary in the last 10 years. A total of 39 cases of children underwent surgical correction of pectus excavatum, 29 by MRP, mean age 9 years and 10 by MIRPE, mean age 13 years. There were no deaths in any group. Mean hospital stay was 13 days for the MRP group and 9 days for the MIRPE group. Mean intraoperative blood loss was 180 ml for MRP and 55 ml for MIRPE. Complications occurred in 19 patients operated by MRP and 3 by MIRPE. The therapeutic and the esthetic results were considered favorable in both MRP and MIRPE groups. In conclusion there are several advantages of MIRPE: hospital stay is shorter, less intraoperative blood loss, fewer and less severe complications, less recurrences and the reintervention. All of this with better cosmetic results.

**Key words:** pectus excavatum, Ravitch, Nuss, comparison

## Introduction

Pectus excavatum (PE) is the most frequent anterior chest deformity occurring in approximately 1 in 1000 live births (1). The first surgical interventions for the correction of PE were performed by Meyer and Sauerbruch in 1911 and 1913 (2, 3). Despite that since now more than 50 surgical procedures were performed for the correction of PE, only two were widely accepted by the medical community

and each one of them was considered, in its own period of time, the gold standard in the surgical treatment of PE (4).

The surgical procedure proposed by M. Ravitch in 1949 remained for almost 5 decades the most important therapeutic method for PE. The surgical technique consists in the excision of the deformed costal cartilages, transverse osteotomy of the sternum and stabilizing the chest wall in normal position (5). The technique was later improved by introducing a substernal metal bar (6). Despite that many modification of the technique were made during time, the main principles of the operation remained the same: to remove the deformed costal cartilages and stabilize the sternum in normal position. An improved version of this technique was performed in over 50 cases, with excellent results, by Prof. Univ. V. Fufezan in Department of Pediatric Surgery and Orthopedics, Emergency Children’s Hospital „Louis Turcanu”, Timisoara, Romania. (7)

In 1998 Donald Nuss reported his 10 year experience with a minimal invasive surgical repair of PE (MIRPE). The principle of the technique consists in applying a force over the sternum from behind forcing it to advance in normal position. This is achieved by inserting a convex steel bar under the sternum through small bilateral thoracic incisions. The steel bar is inserted with the convexity facing posterior, and when it is in position, the bar is turned over in order to correct the deformity (8). No cartilage resection and no sternotomy are necessary (8). In the late decade a whole sort of improvements were added including the routine use of thoracoscopy and the development of a lateral stabilizer (9). Long term favorable outcomes (95%) led to its wide adoption replacing gradually the Ravitch technique (9).

This paper is a comparative analysis of the outcomes of the two main surgical procedures for the correction of PE, modified Ravitch procedure (MRP) and MIRPE. The study was carry out in The Department of Pediatric Surgery and Orthopedics, Emergency Children’s Hospital „Louis Turcanu”, Timisoara, Romania and in The Pediatric Surgery

Unit, Pediatrics Clinic, University Hospital Szeged, Hungary.

### Material and Methods

This study is a retrospective comparison of all patients undergoing PE repairs using MRP and MIRPE, during the period of time between January 2000 and January 2010, in both clinics mentioned above. We reviewed patient's charts, surgical procedures registry, X-rays, photographic images, CT's and other imagistic evaluation recordings. We analyzed data regarding age, sex, demographics, new case/ recidives, evaluation protocol, surgical procedure and outcomes of the therapy.

### Results

A total of 39 cases of children underwent surgical procedures for pectus excavatum repair. Male to female ratio was 4: 1. Age of the patients at the time of the surgical procedures ranged between 13 months and 18 years, mean 11 years. Most of the patients were in the age group 10- 16 years, 10 in the group 5- 10 years, 6 were over 16 years and 3 were between 1 and 5 years old (Fig. 1). The youngest patient operated was a 13 months old boy with sever cardiac impairment due to sternal compression.

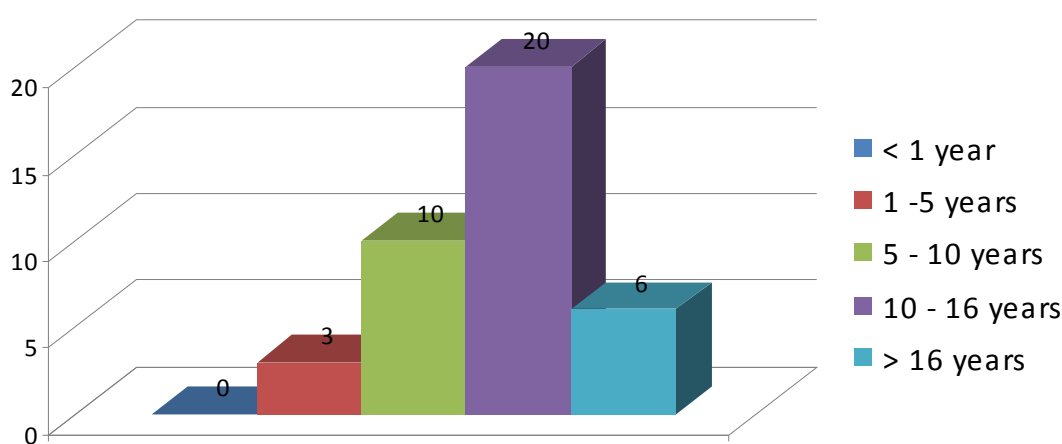


Fig. 1. The age of the patients.

The surgical correction of the deformity was performed in 29 cases, mean age 9 years, by MRP and in 10 cases, mean age 13 years, by MIRPE. Only two of the MIRPE group patients were younger than 10 years old. Both MRP and MIRPE together with our modifications of both surgical techniques were previously presented and is not the subject of this paper (10, 11).

In 3 there was a complex morphology of the deformity, including both protrusion and depression of the sternum. In three cases the deformity was recurrent after a previous repair. In all of these cases, a girl 15 years old and

2 boys 15 and 17 years old, the primary correction was made by MRP and was performed at the age of 5, 8 and 13.

Mean hospital stay was 13 days for the MRP group and 9 days for the MIRPE group. Mean blood loss was 360 ml in the MRP group and 55 ml in the MIRPE group. In 4 patients postoperative blood transfusion was necessary. The bar was removed after a mean period of 13 months for the MRP group and 36 months for the MIRPE group. For 8 patients, 4 MRP and 4 MIRPE the bar was not removed yet. The main parameters compared are presented in Table 1.

Table 1. Main parameters compared.

	MRP	MIRPE
Number of cases	29	10
Age	9 (13 months – 17 years)	13 (8 – 15 years)
Mean hospital stay	13 days (7 – 26 days)	8 days (6 – 11 days)
Blood loss	180 ml	55ml
Early complications	21	0
Late complications	7	3
Nonelective bar removal	1	0
Recurrences	3	0
Reoperation	4	1

No major intraoperative accidents and no deaths occurred in none groups. Early complications occurred in 16

patients operated by MRP and none operated by MIRPE technique (Table 2).

Table 2. Early complications.

	MRP	MIRPE
Number of patients	16	0
Pneumothorax	10	0
Wound dehiscence	4	0
Pleural effusion	3	0
Hemothorax	2	0
Pleuresy	1	0
Pulmonary contusion	1	0
Total	21	0

Late complications occurred in 6 patients, 3 from each group. There were a total of 7 complications for the MRP: 3 bar mobilizations, 1 cheloid, 1 pleuresy, 1 pericarditis and a cheloid. The most severe complication occurred in a 9 years old boy. One year after the operation the bar mobilized and migrated by erosion in the pericardial cavity producing pericarditis and massive pericardial

effusion. Emergency surgical intervention and removal of the bar was necessary. For MIRPE patients there was a late pleural effusion, a pleuresy and a wound dehiscence. Reintervention was necessary for 5 patients, 3 for reattaching the bar, all in the MRP group and 2 for closing the wound dehiscence, one for each group.

Table 3. Late complications.

	MRP	MIRPE
Number of patients	3	3
Bar mobilization	3	0
Pericarditis	1	0
Pleuresy	1	1
Pleural effusion	0	1
Wound dehiscence	1	1
Cheloid	1	0
Total	7	3

In total complications occurred in 19 patients operated by MRP and 3 by MIRPE. The therapeutic and the

esthetic results were considered favorable in both MRP and MIRPE groups (Fig. 2, Fig. 3)

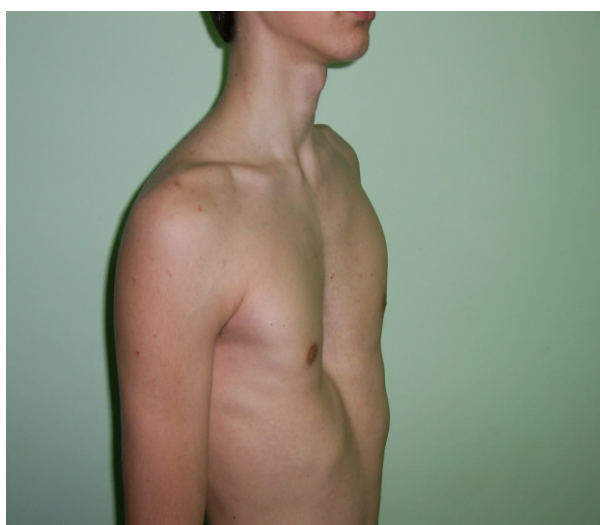


Fig. 2. Pre- and postoperative aspect, MRP, 17 years old patient.



Fig. 3. Pre- and postoperative aspect, MIRPE, 16 years old patient.

### Discussions

Since the introduction of the minimal invasive Nuss technique for the correction of PE in the late 90's there is an intense debate over the advantages and disadvantages of this technique over the classical Ravitch procedure. Both procedures are widely spread over the world with multiple variations regarding the surgical technique, age of the operations, length of hospital stay and other parameters. This could be a potentially source of errors when carry out a multicentre comparative study. This is not the case of our study because, despite the fact that this study was made in two different pediatric surgery departments in two different countries, both types of operations were performed in both clinics and the majority of them were performed by the same teams of surgeons.

It is now widely recognized that age of the patient is one of the main factors influencing the outcomes of surgery. The latest recommendations in the medical literature indicates that for optimal results, regardless of the surgical procedure, the patient should be at the time of the operations just before puberty when the rib cage is still malleable enough and the bar remains inside the thorax during the pubertal growth spurt (9, 12). In our series the MRP group had a median age of 9 years with limits between 13 months and 17 years. This fact is mainly due to the fact that in the early years comprised in this study, when most of the MRP were performed, according with the literature of the time there was the believe among surgeons that the optimal age for operation is between 6 and 10 years. The youngest patient operated was 13 years old for which the indication of

the operation was made upon the presence of severe cardiac impairment. In fact only 3 of the patients were beyond the age of 5 at the time of surgery, all of them in the MRP group. In the MIRPE group the mean age of the patients was 13 years. Only two of them were beyond the age of 10, an 8 years old girl and 9 years old boy, but the risk of recidives can be overcome by leaving the bar inside the thorax for a longer period.

In 3 patients the disease was recurrent after previous MRP. The initial operation was performed at the age of 5, 8 and 13. While in the first two cases the small age of the patients at the initial operation is the most obvious cause, in the third case this is no longer valid. This last case was first operated in another services and we don't have sufficient data about it, but the fact that the period between the initial operation and the recurrence is relatively small (4 years), is an indication that the most probably cause is a precocious surgical technique during the initial operation. Anyway the main cause for recurrence remains the two early correction of the chest deformity.

Previous reports indicated a longer hospital stay for the patients operated by MIRPE (13). In our series the mean hospital stay was longer for the MRP group 13 vs. 8 days. The reason for this is that in patient operate by MRP we considered necessary at least 7 days of parenteral antibiotics, the patients needs special attention because of the amount of tissue damage during the operation and because the wound has serious proportion. The maximal hospital stay was in 7 years boy from the MRP group in which wound infection and dehiscence occurred. Perhaps in more rich countries

with better transport infrastructure and better medical education in the general population, there is the possibility of managing this patients ambulatory, but in our country the reality is that in only a minor number of cases the patients can be released from the hospital previous than to the removal of the wound stitches (10-14th day). In the MIRPE group the main factor influencing the hospital stay is the postoperative pain and the need for epidural catheter analgesia. In our cases this was rarely needed more than 3 days so the mean hospital stay of 9 days is caused mostly by a more precocious approach characteristic of the early phases of the learning curve. Blood loss was higher for the MRP group, for of the patient from this group necessitating a postoperative blood transfusion. This seems logical for us thinking that the MRP involve a longer skin incision, section of the pectoral muscles, excisions of the costal cartilages and sometime osteotomy of the sternum (7), despite that other reports had different results (13).

Despite that the therapeutic and the esthetic results were considered favorable by the majority of the patients from both groups, by placing the incisions in less visible location, the cosmetic advantages of the MIRPE are obvious. In contradiction with the previous reports which indicated fewer complications for the MRP than for MIRPE, in our series the most frequent and the most severe complications occurred in patients operated by MRP, 65% vs. 30% (13). Pneumothorax occurred in almost 30% of the patients in the MRP group and in none of the patients in the MIRPE group. This is in contradiction with the medical literature that indicates a rate of 2% for the MRP and 3.6% for the MIRPE. There are two main reasons for this: First is that despite that during MRP it is preferred not to enter the pleural cavity, in many cases this is impossible due to the intimate contact between the pleura and the posterior aspect of the chest wall; the second reasons is that in the variation of the MIRPE performed by us instead of insufflating CO<sub>2</sub> in the pleural cavity we induced the pneumothorax at the start of operation in order to create the spaces necessary for the operation (11). After the operation we routinely drained the pleural cavity for a few days avoiding in this manner the accumulation of air inside the pleural cavity. One of the most common complications for the MRP is wound infection (14). In our series wound infection and dehiscence occurred in 4 (13%) of the MRP patients altering the

esthetic results and prolonging the hospital stay. This complication did not occur in the MIRPE patients. The reason for this is that compared to the MIRPE in MRP the incision of the skin is significantly higher and stabilizing the sternum in normal position induces great tension in the skin and in the underlying tissue. Other complications like hemothorax, early pleural effusion, pleurisy occurred only in the MRP patients and are the expression of higher trauma over the chest wall during the operation. Skin erosion and exteriorization of the bar without previous infection occurred in two case, one for each group. This is a common complication for metallic implants and is due to the fact that the end of the implant is too close to the surface and friction forces damage the skin.

One of the most severe complications of the surgical intervention for PE is the mobilization and the migration of the bar. In the past this complication occurred in as high as 15% of the cases for MIRPE (15). Nowadays the rate of this dropped to 1% after lateral stabilizers were introduced (9). For MRP this complication is very rare, mainly in the latest two decades (16). Contrary to the expectations in our series migration of the bar occurred only in the MRP group. In two of the cases the migration was minimal and reintervention with the suture of the bar resolved the problem. In the third case the bar eroded the pericardium putting in real danger the life of the patients. This was the most severe complication in our series and is an indication of how important is to firmly secure the bar to the chest wall. After that we learned our lessons and always secured tightly the bar and for the MIRPE patients we always used bar stabilizers.

### Conclusions

1. The age of the patient is an important factor for the outcome of the surgical correction, 2 of the 3 recurrences in our series being operated before the age of 10.
2. Hospital stay is shorter for the MIRPE patients
3. Intraoperative blood loss was greater for the MRP than MIRPE patients.
4. MIRPE has fewer and less severe complications
5. The recurrences and the need for reintervention is lower for MIRPE than MRP
6. All of this with better cosmetic results

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### **MANUSCRIPT REQUIREMENTS**

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The article should be organized in the following format: Title, Names of all authors (first name initial, surname), Names of institutions in which work was done (use the Arabic numerals, superscript), Abstract, Keywords, Text (Introduction, Purpose, Materials and Methods, Results, Discussions and/or Conclusions), References, and first author's correspondence address.