CLINICAL

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CITOMIX™ IN THE PREVENTION OF THE MOST COMMON COMPLICATIONS OF CHICKENPOX IN PEDIATRIC AGE

SUMMARY

Chickenpox is a mainly pediatric, epidemic infectious disease that is usually of limited clinical importance, though it can be associated with complications or leave sequelae. The etiological agent is the varicella Zoster virus (VZV).

- This study was conducted on 106 pediatric patients (M/F; mean age 4 years and 4 months) to evaluate the efficacy of CITOMIX™ in the prevention of the most common complications developing after acquiring this herpes infection. Such post-varicella diseases, which are generally of bacterial etiology, affecting the respiratory apparatus in immunocompetent children, are on the increase.
The patients in the study presented no severe post-varicella complications, nor were they immunodepressed.
- Our results showed a marked reduction in post-varicella respiratory diseases (9.4% in the CITOMIX™ group vs 41.5% in the untreated controls) thanks to a therapeutic protocol that was easy to implement, gave rise to an excellent compliance, and caused no side-effects.

KEY WORDS

CHICKENPOX, COMPLICATIONS, IMMUNOLOGICAL EFFICIENCY, CITOMIX™, PROPHYLAXIS

INTRODUCTION

Varicella, or chickenpox, is a highly contagious disease (1) that mainly affects patients in pediatric age.
The incidence of the disease is much the same, year by year, as a birth cohort (2, 3).
Post-varicella respiratory diseases, and **otitis** and **bronchitis** in particular, are caused by the transient immunodeficiency consequent to infection by the varicella Zoster virus, and they are frequently seen in pediatric practice.
The etiological agent behind chickenpox is the **varicella Zoster virus (VZV)**, which causes a latent infection in the ganglia of the posterior roots of the spinal nerves. Its reactivation takes the form of Herpes zoster (shingles).
- VZV is a human herpes virus classified as alpha herpes virus because of its affinities with the prototype of this group, i.e. the herpes simplex virus.
VZV is an encapsulated DNA virus. The capsid has an icosahedric structure (162 capsomers) and is surrounded by a lipid coating membrane.
It is 200 nm in diameter (FIGS. 1, 2).
The viral genome codifies for over 70 immunity target proteins (4).
- The disease begins with the virus, present in infected respiratory secretions, penetrating through the mucosa, or by direct contact with the cutaneous lesions of chickenpox or Herpes zoster.
This phase is followed by a period of incubation lasting 10-21 days, during which the virus spreads.
The disseminated cutaneous symptoms become apparent when the infection enters the viraemic phase; the mononuclear cells in the peripheral bloodstream carry the virus, generating new

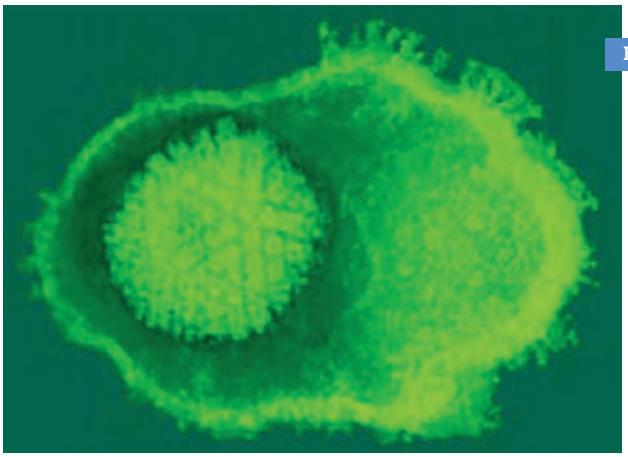
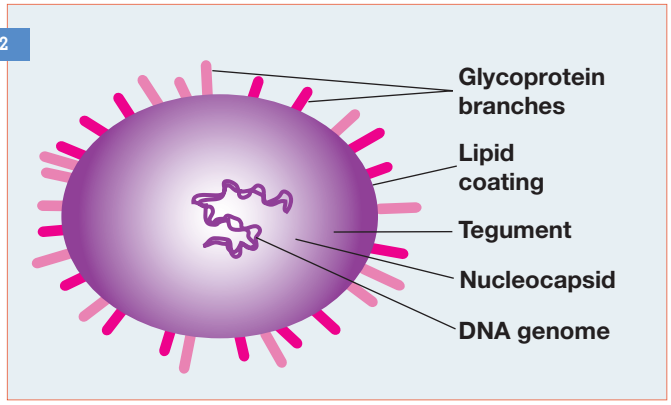


FIG. 1

The virion of a Herpes virus.

FIG. 2

Schematic structure of the varicella virus.



groups of vesicles, for 3-7 days.
VZV is also carried back at respiratory mucosa level during the late incubation period.
The viral infection's route of transmission in the droplets exhaled on breathing distinguishes VZV from other human herpes viruses (5) (FIG. 3).
The dissemination of the virus is a result of the host's inability to block the viraemia, which may lead to lung, liver and brain infections.
VZV becomes latent in the ganglia cells at the posterior roots of the spinal nerves in all individuals who have been infected.
The histopathological picture is identical for chickenpox and Herpes zoster.
The infecting VZV is found in the lesions in cases of Herpes zoster just as it is in cases of chickenpox, but it is not seen in the bronchial secretions.
VZV induces a cell-mediated and humoral immunity that affords a strong protection against symptomatic reinfection.
Suppression of the cell-mediated immunity against VZV is associated with an increased risk of VZV reactivation in the form of Herpes zoster (6).

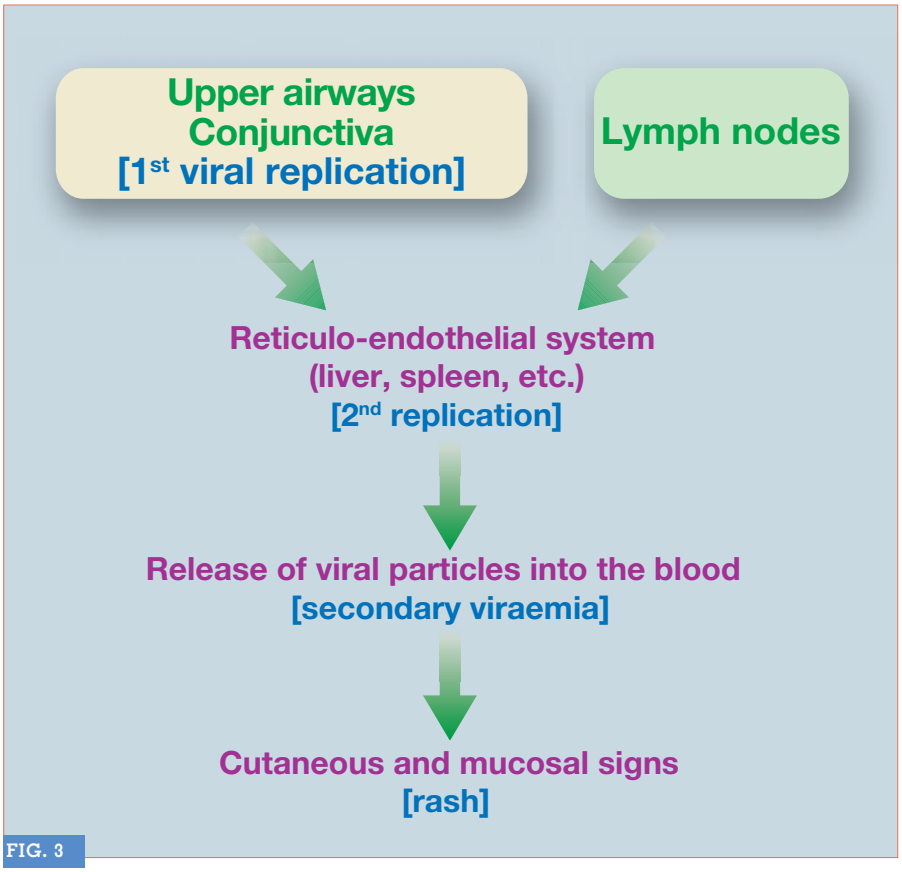


FIG. 3

The pathogenic process of varicella.

In countries with a temperate climate, 90-95% of individuals become infected during their childhood. Annual epidemics of chickenpox occur in winter and spring (7).
The wild strains of VZV that cause these annual epidemics of chickenpox reveal no variations in terms of their virulence, judging from estimates of the clinical severity of VZV primary infections over the years.
The family transmission rates are around 80-90%, while contagion at school is associated with a rate of transmission of around 40%.
Chickenpox is contagious from 24-48 hours **before** the rash becomes apparent and for as long as there are vesicles without scabs, i.e. generally for 3-7 days.
Herpes zoster shows no seasonal variations because it is triggered by a reactivation of the latent endogenous virus. Herpes zoster is rare in children under 10 years old, unless they have been given immunosuppressant therapies, or contracted HIV infection and been infected *in utero* or in their first year of life.
The risk of severe VZV (primary or recurrent) infection correlates with intrinsic host factors rather than with any variations in the pathogenicity of the VZV strains.

CLINICAL SIGNS

Although the incubation period for chickenpox varies (10-21 days), the disease generally begins 14-16 days after exposure. All susceptible children exposed to the virus develop a rash, with a variable number of lesions (FIG 4).
The presenting symptoms are generally malaise, fever, anorexia, cough, headache and, occasionally, mild abdominal pain; they become apparent 24-48 hours before the onset of the rash.
The increase in body temperature can vary from moderate to severe. The fever and other systemic symptoms persist for the first 2-4 days after the onset of the rash.

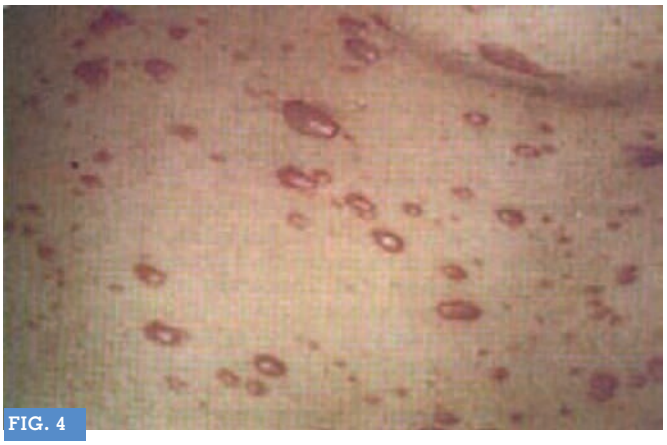


FIG. 4

Varicella - vesicular lesions of various shape and size.

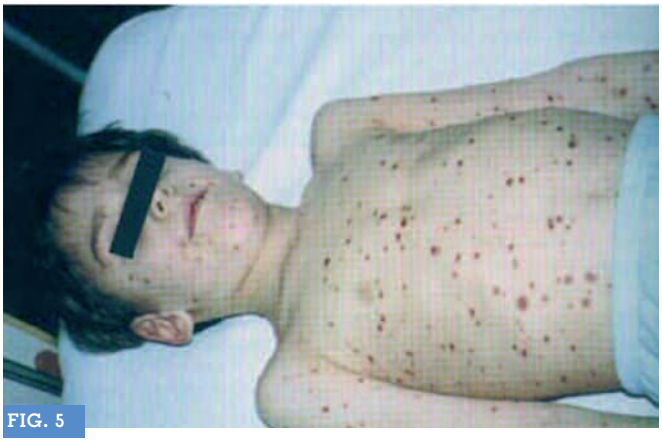


FIG. 5

Varicella - rash on chest and face. Note the lesions in various stages of evolution, with the characteristic "starry sky" appearance.

- The rash initially consists of very itchy erythematous macules that evolve into clear blisters, rich in fluid. The paresthesia and the umbilication of the lesions begins over the next 24-48 hours. While the initial lesions form scabs, new groups of vesicles appear.
The number of lesions can vary from less than ten to several hundred (the mean number is around 200).
The simultaneous presence of lesions in various phases of evolution is characteristic and pathognomonic of varicella, the so-called "starry sky" skin rash (FIG 5).
Ulcerative lesions in the oropharynx and vagina are also common.
Many children develop vesicular lesions on the eyelids and conjunctiva too, but severe ocular involvement is rare. In cases of familial reinfection, or in older children, it is common for the new lesions to occur in larger numbers and to last for more days. In children who already suffer from skin diseases (atopic dermatitis, eczema), the rash is more extensive and poses a greater risk of superinfections.
Hypopigmentation at the sites of the lesions persists for days and, in some cases, for weeks, but permanent scarring is not very common (8).

COMPLICATIONS

In the majority of immunocompetent children, chickenpox is a benign and self-limiting disease. In adolescence and adulthood, the symptoms are more severe and more prolonged. In the immunosuppressed host, the incidence of severe or complicated clinical pictures is quite high and the mortality rate becomes far from negligible (around 7%).
The risk of clinically relevant complications of the disease has been demonstrated even in immunocompetent children, the most common of which are: (1) bacterial superinfections of the skin rash (impetiginization, FIG 6), which can sometimes cause permanent scarring; (2) anomalous skin conditions (varicella bullosa [FIG 7], hemorrhagic varicella), generally more frequent in immunodepressed patients (9).
During and immediately after having chickenpox, the upper and lower respiratory tract may also be affected by bacterial superinfections (bronchitis, otitis, pneumonia) or by interstitial lung diseases caused by the VZV (more likely in neonatal age).
Complications involving the CNS are relatively common and can develop in the first few days of the course of the disease, or after 1-2 weeks (cases of post-infective encephalitis of immunomediated pathogenesis).
- The most frequent clinical signs of CNS involvement take the form of a cerebellitis (ataxia, tremors, nystagmus, motor coordination problems), which takes a benign course in the majority of cases. There are reports in the literature of rare episodes of cranial nerve palsy, myelitis and Guillain-Barré syndrome.
Hemorrhagic signs (varicella gangrenosa, purpura fulminans) can develop, while other organs and systems are rarely involved (myocarditis, glomerular nephritis, pancreatitis, arthritis) (9).
- Around in 10% of cases Reye syndrome (a potentially lethal liver disease associated with encephalopathy) occur in correlation with chickenpox and the concomi-

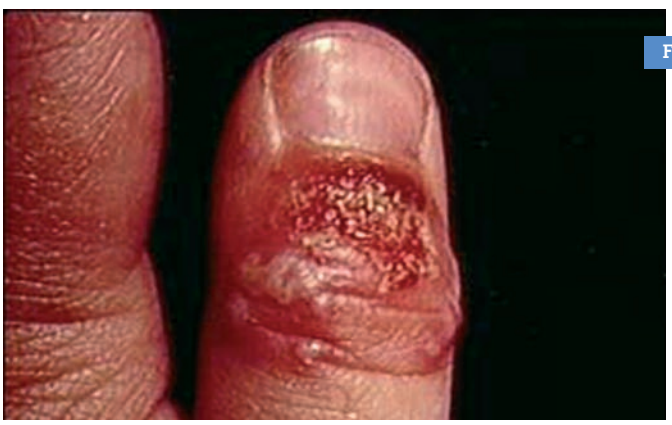


FIG. 6

Varicella - impetiginized skin lesions.

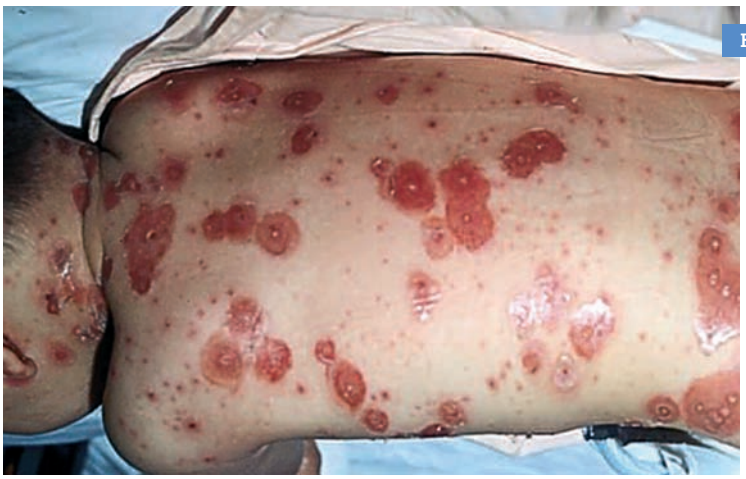


FIG. 7
Varicella bullosa.

tant administration of salicylates (10).
The disease can take a more severe course in immunodepressed patients, with a greater frequency of forms of hemorrhagic or gangrenous rash and a higher incidence of complications, and even the clinical picture of the so-called "progressive varicella", which is an extremely severe clinical form characterized by the involvement of numerous internal organs (leading to pneumonia, hepatitis, encephalitis, protracted skin infections, etc.) and which is lethal in up to 7% of cases.
VZV can be transmitted from mother to fetus by primary infection during pregnancy. Congenital disease (the risk of which is around 5% in the first trimester of pregnancy) can give rise to a broad spectrum of variously-associated conditions, including low birth weight, microphthalmia, cataract, chorioretinitis, deafness, cicatricial limb lesions, microcephaly and psychomotor developmental delay.
Neonatal varicella (which affects newborns who contract the disease from their mother who has become ill between 5 days before and 2 days after delivery) is exacerbated by a high rate of complications (affecting the respiratory system, the CNS, disseminated infection).
- The onset of Herpes zoster is characterized by hyperesthesia and pain in the region of the affected dermatome, associated with malaise and mild fever, and followed after 2-3 days by the appearance of macular papules, which subsequently evolve into vesicles with erythematous contours and scabby pustules (11).
The cutaneous lesions are generally distributed unilaterally along the infected dermatome (in children, this mainly concerns the dorsal and lumbar regions, while the cervical and sacral regions are more rarely involved) and they spread centrifugally in subsequent bouts over the course of 2-4 days.
The accompanying symptoms (fever, pain, paresthesias and pruritus) persist throughout the course of the disease (1-2 weeks in children), associated with enlargement of the satellite lymph nodes.
Distribution to one or more branches of the trigeminal nerve is rare in pediatric age, while involvement of the ophthalmic branch is a concern in children as well as adults because of the risk of severe ocular complications (keratitis, uveitis).
The most frequent complication in pediatric age is represented by bacterial superinfections of the zoster-induced skin lesions.
Post-herpes neuralgia is rare in children. The herpes zoster that emerges in severely immunodepressed cases can often involve multiple dermatomes and become complicated by the onset of a generalized form (disseminated zoster) that often leads to the involvement of the viscera (lung, liver, brain) and carries a mortality rate of 1-3%.

LABORATORY FINDINGS

Where necessary, VZV infection can be confirmed in the laboratory by identifying the characteristic multinucleated giant cells containing inclusion bodies on the microscopic examination of smears obtained by scraping the cutaneous or mucosal lesions (Tzanck test).
VZV can be isolated using cultures, or identified directly on pathological material using immunofluorescent methods.
The histopathological picture and the procedures for identifying the virus are naturally identical in the case of chickenpox and herpes zoster.
- Serological investigations can be performed using complement fixing reactions, immunofluorescence against the membrane antigens, hemagglutination, and immunoenzymatic techniques (ELISA), but they are of little use in this setting.
Altered laboratory values are common in patients with varicella. Leukopenia is a typical finding during the first 72 hours, followed by a relative or absolute lymphocytosis.
Liver function tests are often moderately altered. Patients with neurological complications of chickenpox or with uncomplicated Herpes zoster reveal a mild lymphocytic pleocytosis and a mild to moderate increase in proteins; glycorrachia is generally within normal limits.

PATIENTS AND METHODS

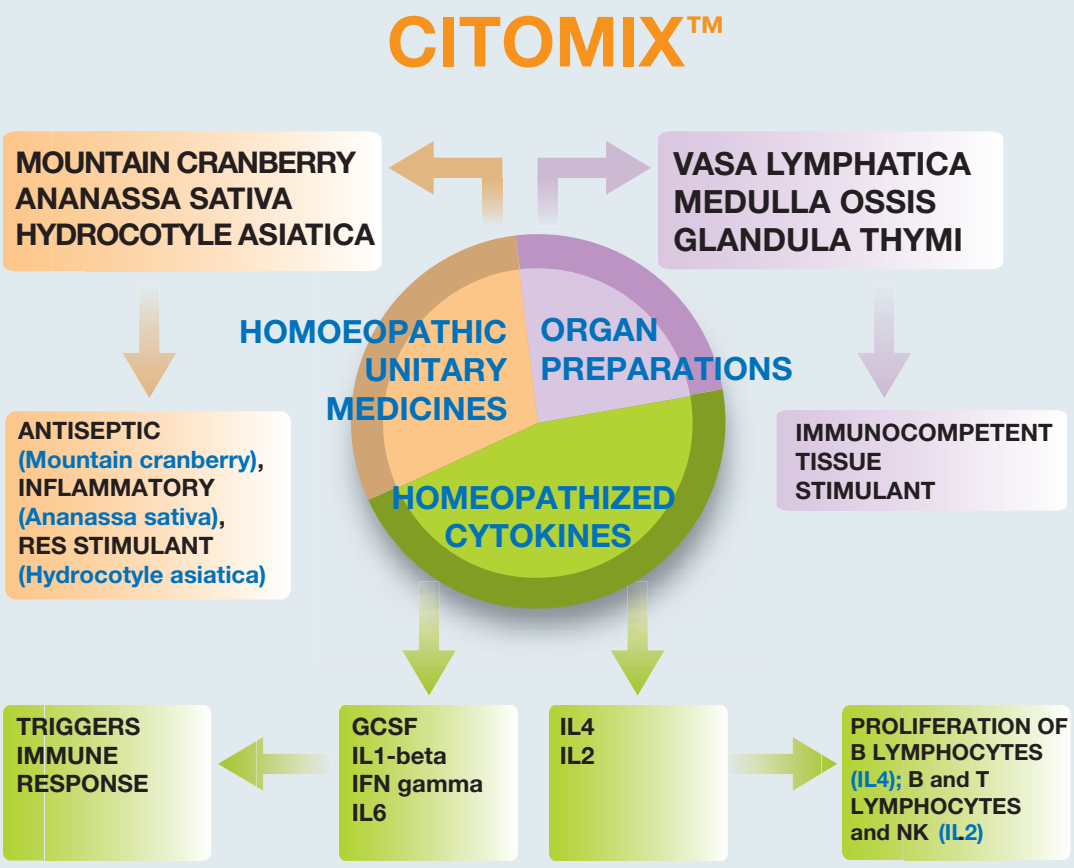
Between 15 October 2008 and 15 January 2009, **106 pediatric patients** were monitored to assess any respiratory complications developing during a period of **30 days after** the scab formation phase of chickenpox.
- The study was designed to assess the efficacy of **CITOMIX™** (Guna Laboratories, Milan) in the prevention of the most common complications of chickenpox in pediatric age, which are known to include respiratory diseases (mainly otitis and bronchitis) of primarily bacterial etiology.
CITOMIX™ is an innovative homoeopathic medicine formulated to protect the body against **viral**, **bacterial and parasitic infections**.

The therapeutic positioning of the drug is self-evident from its composition, i.e. it is for **immune system stimulation and regulation** (TABLE 1).

TAB.I
- Composition;
- Mechanism of action and principal indications of the single ingredients *of Citomix™*.

Composition:

GCSF 4C-9C-15C-30C, Interleukin 4 4C, Interleukin 1-beta 5C, Interleukin 2 5C-7C, Interleukin 6 7C-9C-15C, INF-gamma 4C, Vasa lymphatica 4C, Mountain cranberry 3X, Ananassa 3X, Hydrocotyle asiatica 3X, Medulla ossis 4C, Glandula thymi 4C.



Principal indications of the single ingredients of CITOMIX™

- **IL-2 5/7 C**: to stimulate the immunocompetent cells
- **GCSF 4/9/15/30 C**: to stimulate the granulocytes
- **IL-1-β 5C**: to trigger the "defensive inflammatory" response
- **IL-6 7/9/15 C**: to trigger the "defensive inflammatory" response
- **IFN-γ 4C**: antiviral action
- **IL-4 4C**: to control the immunological mechanisms of inflammation and trigger antibody response
- **Vasa lymphatica 4C**: to stimulate the peripheral organs of the immune system
- **Medulla ossis 4C**: to stimulate the central organs of the immune system to produce white blood cells
- **Glandula thymi 4C**: to stimulate the central organs of the immune system to produce T-lymphocytes
- **Mountain cranberry 3X**: antiseptic action
- **Ananassa sativa 3X**: to modulate inflammatory symptoms
- **Hydrocotyle asiatica 3X**: to stimulate the RES (reticulo-endothelial system)

CITOMIX™- ACTION OF THE CYTOKINE POOL	
CYTOKINE	**Biological action**
GCSF	Stimulates and differentiates the granuloblasts Factor produced by the macrophages in response to a bacterial infection
IL1-β	*Trigger* the "defence" inflammatory response
IFN-γ	Synergic action with IL1. Stimulates maturation of the T lymphocytes CD8. Antiviral activity. Synergic action with GCSF (for activating the macrophages)
IL6	Supports IL 1 activity. Increases the IgA
IL2	Stimulates the cytotoxic functions of the T-cytotoxic and *NK-cells*, and B lymphocytes
IL4	Increases the IgA. Included in CITOMIX™ also to balance the drug's Th1 polarity and to avoid any pro-inflammatory hyperstimulation

TAB.2
The cytokines in CITOMIX™.

Thanks to its cytokine content, CITOMIX™ has a **prevalent Th1 polarity**, suitable for triggering a rapid and effective (mainly cell-mediated) immune response through the physiological mechanisms of inflammation. This consideration is hardly surprising, given that children suffering from chickenpox, as a terrain (in psycho-neuro-endocrino-immunological terms) and environment, have a deficient "inflammatory potential", where inflammation is the first and most important *key* for gaining access to the body's defensive immune response.
Given the presence of **IFN-gamma 4C** and **IL2 4C**, CITOMIX™ is characterized distinctly as an antiviral agent, in particular; thanks to the presence of **IL-4** to activate the B lymphocytes, it is also effective against bacterial infections, and consequently in the typical cases of bacterial superinfection that represent the most common complications of chickenpox (TABLE 2).
The addition of organ preparations helps to stimulate the immune system; **Vasa lymphatica 4C**, **Medulla ossis 4C**, **Glandula thymi 4C** are all capable of gently stimulating the immunocompetent tissues.
CITOMIX™ guarantees that there will be none of the negative side-effects that might develop due to an excessive Th1 polarization (which is temporarily *desirable* in these patients to support their limited capacity to "turn on the inflammation" and thus defend themselves) thanks to the presence of such a powerful (anti-inflammatory) Th2 cytokine as IL**4 4C**, which serves to *balance* the effects of the drug.
- Equally important in balancing the drug and completing its action is the inclusion of three plant remedies with an anti-inflammatory and antiseptic action: Mountain cranberry 3X, Hydrocotyle asiatica 3X and Ananassa sativa 3X.

▸ To support the hypotheses on the mechanism of action of CITOMIX™ and the rationale for its inclusion in treatment plans to prevent the onset of complications in chickenpox, it is worth mentioning the data presented at the *13th Meeting of the Homotoxicology Club*, held in Sorrento (Italy) in 2008, which demonstrated the effect of CITOMIX™ in increasing the number of white blood cells in general, and of the neutrophils in particular (11).
- It is also important to note the findings relating to the **increase in IgA**, a fundamental parameter in pediatrics for combating the pathogens that attack the respiratory mucosa.
The CD3, CD4+ and the CD8+ seem to increase after treatment with CITOMIX™.

STUDY POPULATION

Patients with allergies, cardiopathies, oncological diseases or severe immunodepression were excluded from the study.

The **106 patients** included (59 M; 47 F) were divided into two groups:
- **Group A** was treated with CITOMIX™ for the prevention of post-varicella complications;
- **Group B** served as controls and received no treatment.

• **Group A** (53 pts) comprised (TABLE 3):
- **32 males** aged from 8 months to 7 years and 10 months; mean age 4 years and 1 month;
- **21 females** aged from 2 years and 6 months to 9 years and 1 month; mean age 4 years and 5 months.

CITOMIX™ dosage:
- in patients under 3 years old: **2** pellets twice a day for one month (starting when the chickenpox vesicles began to form scabs);
- in patients over 3 years old: **3** pellets twice a day for one month (starting from when the chickenpox vesicles began to form scabs).

• **Group B** (53 pts) comprised (TABLE 4):
- **27 male**s aged from 1 year and 2 months to 10 years and 2 months old; mean age 4 years and 5 months;
- **26 females** aged from 1 to 9 years old; mean age 4 years and 3 months.

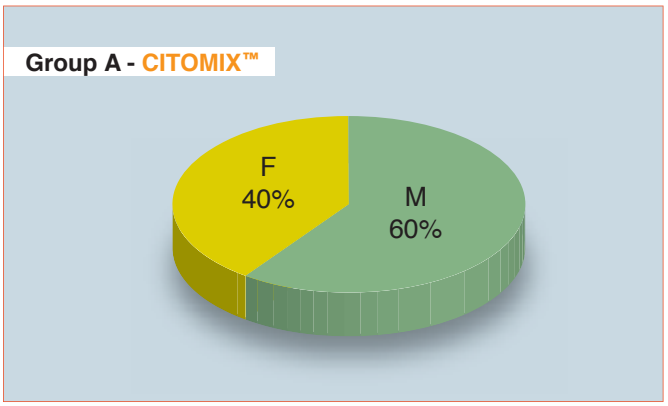
- The two Groups (A and B) were comparable in terms of disease, male/female ratio, and mean age by gender.

RESULTS

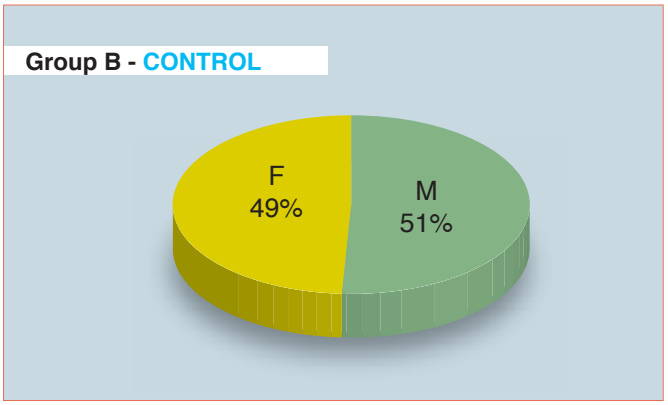
After the observation period of **30 days** established by the study:

• in **Group A** (CITOMIX™) there were **5 complications** (9.4%) (TABLE 5):
- 1 M: acute otitis media
- 4 F: 1A beta-hemolytic *Streptococcus* infection, 2 cases of bronchitis, 1 of acute otitis media (TABLE 6);

• in **Group B** (controls) there were **22 complications** (41.5%) (TABLE 7):
- 11 M: 2 had acute otitis media, 6 bronchitis, 1 tracheitis, 1 laryngitis, 1 tonsillitis,
- 11 F: 3 had otitis media + bronchitis, 3 acute otitis media; 1 bronchitis; 1 A beta-hemolytic *Streptococcus* infection, 1 adenoiditis, 1 asthmatic bronchitis, 1 tracheitis (TABLE 8).



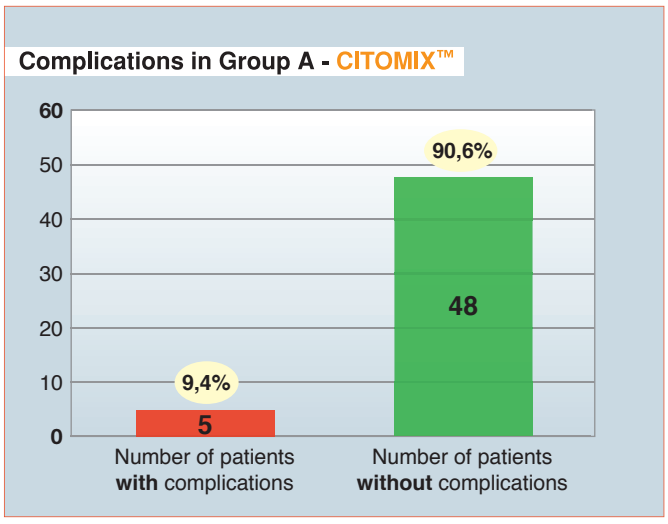
TAB.3
CITOMIX™ : Percentages of patients in Group A by gender.



TAB.4
CONTROL: Percentages of patients in Group B by gender.

DISCUSSION

Pediatricians who have to deal with the annual outbreak of chickenpox among their patients are well aware that severe complications after exposure to VZV are rare, as reported in the scientific literature.
It is also common knowledge, however, that - after a period of acute disease - it is not unusual to find the patient previously infected with VZV more susceptible to bacterial infections, particularly those affecting the respiratory tract, which demand adequate antibiotic therapy.
- The increase in bacterial infections during the course of viral epidemics is an empirically well-known and epidemiologically demonstrated fact. It is worth taking the time here to analyze the biological grounds for this process because it enables us to understand the **utility of CITOMIX™ for the purposes of prevention**.
Viruses interfere with the Immune System in various ways: we can see imbalances in cell-mediated immunity with phenomena of hyper-reactivity, for instance, among subpopulations such as those of the T suppressor lymphocytes, with a consequent disruption of the normal relationships between these lymphocytic subpopulations. Moreover, the viruses cause the release of cytokines with an immunosuppressant activity from the infected immunocompetent cells - as we see, for instance, in influenza infections (12).
- Some viruses can evade the immune defenses thanks to a non-exposure of the surface antigens of the infected cell, or by means of antibodies removing these antigens.
- Basically, the viral infection interferes with the activity of many cellular and humoral effectors at immune level, both by means of a functional depression of these effectors and as a result of direct lytic activities.
The macrophages are hindered in their normal functioning, either in terms of the removal of potentially pathogenic microorganisms, or due to the depressed T lymphocyte subpopulations, to activities that also stimulate the B lymphocytic compartment.
The "director" of the host's immune efficiency during the course of a viral infection is the macrophage.
- The macrophages perform various immune functions, including phagocytosis, uptake, localization, antigen degradation and their presentation to the various lymphocyte subtypes, the secretion of cytokines and pro-inflammatory proteins, and a suppressor activity.
The interaction between macrophage and virus is complex and can give rise to different outcomes: the infection may be

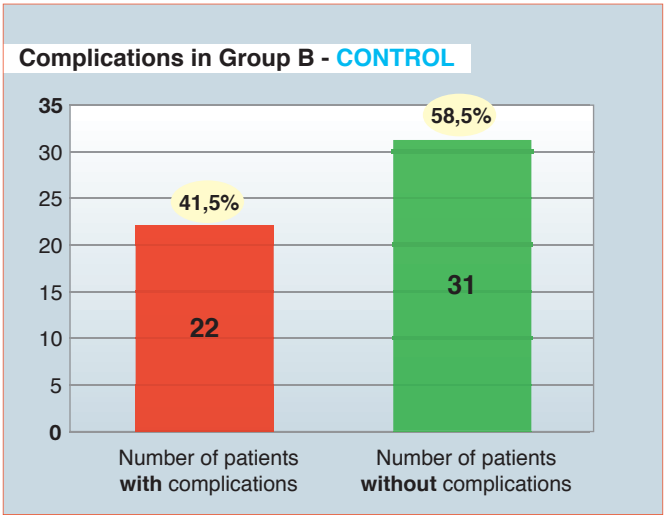


TAB.5

inapparent, persistent or lytic.
The macrophages' capacity to resist a viral infection depends on its genetic characteristics and age.
Unlike those of adult individuals, the neonatal macrophages are not activated in response to herpes infections, and this explains the severity of these infections in the newborn. The stage of maturity of the macrophage is also important for the immune response because mature macrophages, unlike their precursors, have a strong resistance to the majority of viruses. Viruses can directly damage the macrophage or interfere with different aspects of its functionality, such as chemotaxis, phagocytosis, the capacity to develop antigens, and the capacity to suppress T lymphocyte activity.
The above considerations explain why diseases with a bacterial etiology develop in the case of immune deficiency.
-The data emerging from our study clearly show the role of the immune stimulation exerted by CITOMIX™ (reducing the post-varicella respiratory infections from **41.5%** in the untreated control group to **9.4%** in the group treated with CITOMIX™).
These results can be explained in the light of the pharmacological rationale behind CITOMIX™.
The association between the pool of cytokines and the homoeopathic unitary medicines makes this drug a genuine **immune system stimulant**.
It is also worth noting the excellent compliance achieved in the pediatric patients treated with CITOMIX™ and the absence of any side-effects.

Details of complications in Group A - CITOMIX™	
Acute otitis media	2
Group A beta-hemolytic *Streptococcus* infection	1
Bronchitis	2
Total	**5**

TAB.6



TAB.7

CONCLUSIONS

This study enables us to recommend the use of CITOMIX™ in children suffering from chickenpox to limit the onset of bacterial infections. The therapeutic protocol adopted achieved an excellent compliance, the product was easy to ingest (in sugar-coated granules readily appreciated by children) and the treatment caused no side-effects, consequently representing an effective prophylactic treatment for pediatricians. ■

Details of complications in Group B - CONTROL	
Acute otitis media	5
Group A beta-hemolytic *Streptococcus* infection	1
Bronchitis	7
Tracheitis	2
Laryngitis	1
Tonsillitis	1
Adenoiditis	1
Asthmatic bronchitis	1
Acute otitis media - Bronchitis	3
Total	**22**

TAB.8

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FIG. 1 was drawn from (Photo taken under E.M.) www.kimicontro.com/microorg/Herpes%20zoster%20(varicella).jpg

FIG. 2 (modified) was drawn from www.expertreviews.org/fig001jbl.gif

FIG. 3 was drawn from www.unisa.it

FIGS. 4, 5 were drawn from Rocchi G. - Le infezioni da virus Varicella-Zoster. Aspetti di rilievo in età pediatrica. Il Pensiero Scientifico Editore. Prima edizione; 1996.

FIGS. 6, 7 were drawn from http://z.about.com/f/p/440/graphics/images/en/1373.jpg http://www.vaccineinformation.org/photos/varipmh004.jpg

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