CLINICAL

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GUNA®-FLU *VS* PARACETAMOL IN THE FLU SYNDROME TREATMENT

– A PROSPECTIVE, CONTROLLED CLINICAL STUDY

SUMMARY

This clinical trial on 159 patients (85 F, 74 M) aged between 3 and 12 years (average age: 6 years, 7 months) compared the therapeutic efficacy of GUNA®-FLU, a complex low-dose preparation, vs the one of Paracetamol, routinely used in clinical practice to control flu symptoms. Patients were divided into 2 Groups: Group A (GUNA®-FLU: 78) and Group B (Paracetamol: 81). At the first enrollment visit, within 24 hours of flu, body temperature and possible use of influenza vaccination were evaluated. Symptoms have been recorded, divided into general, respiratory, and intestinal disorders. The follow-up was performed evaluating separately the presence of fever, with controls after 24, 48 and 72 hours, and the other symptoms, with visits after 4 and 7 days. Treatment effectiveness was evaluated using a Questionnaire on general, respiratory, and intestinal symptoms, with scores ranging from 0 (no symptoms) to 3 (severe symptoms). Enrollment in one of the two groups was based on the family's free choice (outcome evaluation). The indicators used to assess the effectiveness of the different treatments were: reduced body temperature below 37°C and the different scores recorded in the Questionnaire at the different clinical visits. From the analysis of results, the therapeutic superiority of GUNA®-FLU is evident: percentage of patients with fever resolution always higher (after 24, 48 and 72 hours) in Group A than Group B. Moreover, also the other clinical endpoints highlight statistical difference in favour of Group A. This shows that, apart from preventive therapy, as already demonstrated by previous studies, GUNA®-FLU can be successfully prescribed to treat the acute symptoms of Influenza-Like Illness (ILI), due to rapid effects on symptoms, excellent compliance and absence of adverse side effects.

KEY WORDS

INFLUENZA, INFLUENZA-LIKE ILLNESS, GUNA®-FLU, PARACETAMOL, PEDIATRICS

https://www.texaschildrens.org/blog/2014/09/vaccine-preventable-disease-facing-influenza

INTRODUCTION

Influenza is an acute disease of the airways, which is caused by influenza viruses.
The clinical expression of influenza, both in epidemics and in pandemics, varies greatly: it ranges from common rhinitis, with or without pharyngitis, to viral pneumonia, which can even be fatal.
There are also asymptomatic forms, which in some epidemics are more frequent than the symptomatic forms. Generally speaking, manifestations of influenza viruses A or B are similar, although the serious forms of virus B are less frequent.

– In younger children, the symptoms are often superimposable to those caused by other respiratory viruses and there is a prevalence of signs and symptoms in either one airway or the other: from common cold to laryngotracheitis, bronchitis, bronchiolitis, and pneumonia.
The temperature is high and the general conditions of the child are in part compromised; coughing is very frequent, as is vomit; mild diarrhoea is present in 15% ≈ of cases.

– In older children, adolescents and adults, there is a sudden onset of fever, with chills, reddening of the face, headache, myalgia (especially in the back), anorexia and malaise; rhinitis and cough, often associated with a sense of heartburn or retrosternal pain, are also frequent; in 50% of cases pharyngitis is present.
Photophobia, tearing, burning and sense of pain in eye movements are also possible. Some epidemics also see nausea, diarrhoea, and abdominal pain.
On average, the fever lasts 2-3 days and at times even longer; cough persists for 7-10 days; a general sense of asthenia may persist for 2-3 weeks if suppressant and anti-reactive drugs are taken.

In general, the many diseases with multiple aetiology (influenza viruses, parainfluenza viruses, respiratory syncytial viruses, rhinovirus, adenovirus, etc.), which are clinically similar, are

TAB. 1

PATIENT GROUPS ACCORDING TO THERAPY	
Therapy	**Patients (N.)**
Group A – GUNA®-FLU	78 (43 F, 35 M)
Group B – Paracetamol	81 (45 F, 36 M)

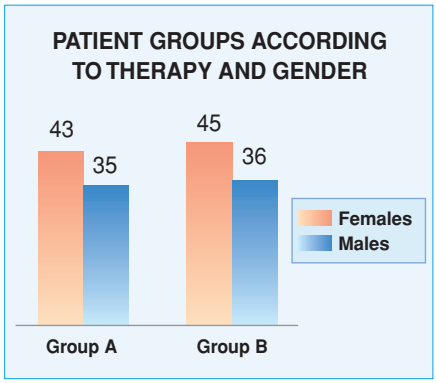


FIG. 1

defined **Influenza-Like Illnesses** (ILI) from a clinical point of view.

AETIOLOGY OF HUMAN INFLUENZA

Human influenza viruses belong to the *Orthomyxoviridae* family, which comprises influenza viruses A, B, and C.
The belonging of the virus to types A, B, and C is based on the characteristics of the nucleoprotein (NP) and of the protein antigens of the matrix (M).

Influenza A viruses are *encapsulated* in a lipid membrane, the surface of which has antigenic structures shaped like rods, namely two viral glycoproteins of extreme pathogenetic importance.
Based on the latter, influenza A viruses are divided into subtypes based on the haemagglutinin **(H)** and neuraminidase **(N)**; at present, 16 subtypes of haemagglutinin (H1 to H16) and 9 neuraminidase (N1 to N9) are known.

– In humans, **influenza A viruses** are characterised by 3 types of haemagglutinin **(H1, H2, H3)**, and 2 types of neuraminidase **(N1, N2)**.
In addition to humans, influenza A viruses affect other animals as well, such as swine, horses, marine mammals, and birds.
Influenza viruses undergo continuous mutations of its genome.
– The influenza B virus is more stable and undergoes fewer antigenic mutations and has a remarkable immune stability.
– The influenza C virus is seldom present in human pathology, probably because in most cases it is present subclinically; it is not associated with epidemic forms.

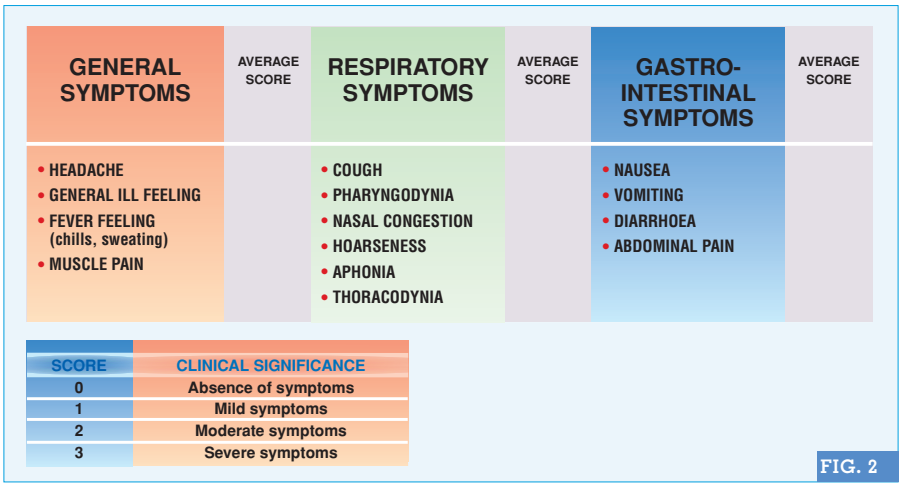


FIG. 2

Since the influenza A virus infects, in addition to humans, other animals as well, such as aquatic birds, chickens, turkeys, ducks, geese, swine, horses and marine mammals (dolphins, whales, seals), this typical characteristic increases exponentially the possibility of viral RNA mutations.

• The reserve of influenza virus is represented by **aquatic birds**.

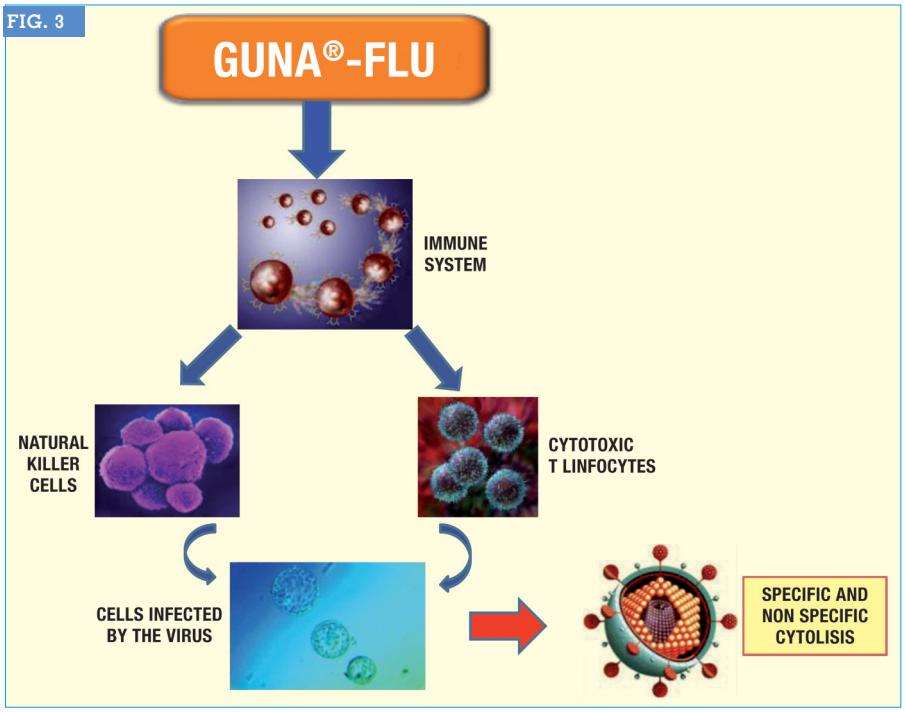
The variations of H and N can be independent from one another; minor modifications **(drifts)** occur almost continuously, as a result of natural selection; more extensive ones **(shifts)** are infrequent and are responsible for pandemics.

• The antigenic **drift** regards point mutations of the amino acid sequence; these are responsible for the antigenic changes, especially of H, in combination sites with antibodies; the new strain is - therefore - favoured.
– Antigenic drift (with variations of less than 5% of the genome) is responsible for the annual epidemics that occur during interpandemic periods.

• Major antigenic modifications, called **shifts**, are responsible for influenza pandemics that occur at irregular intervals, every 10-40 years; only influenza A viruses show this dramatic antigenic variation, for which the population,

without protective antibodies, is the victim of a pandemic, which causes the disease in all age groups.
– The alterations are such that they involve changes of 20 to 50% of the amino acids of the viruses circulating previously; unlike annual epidemics, large-scale pandemics can persist for many years, until immunity reaches high levels throughout the population.
It has been calculated that during an epidemic, generally 10-20% of the population has an influenza attack, but in certain susceptible age groups (preschool and school-aged children), the percentages of these attacks can reach 40-50%. In general, children are the first to be affected; they bring the influenza virus home and even the adults soon begin to fall ill.

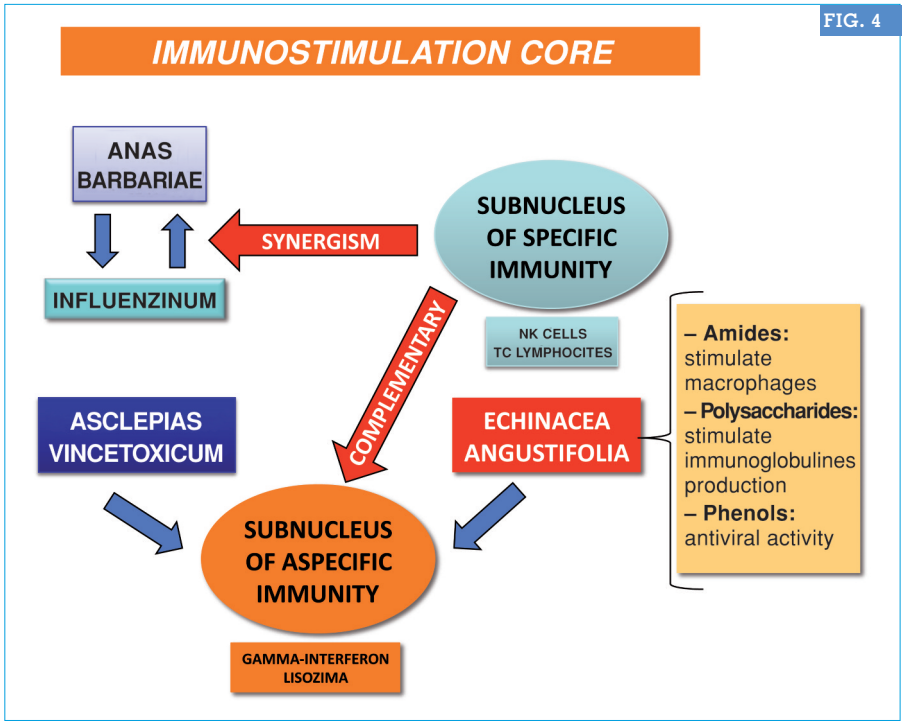
FIG. 3



– Influenza mainly affects individuals aged under 15 years: in kindergartens, the percentage reaches 60%.
Incidence is much lower among individuals aged 65 years and over, although the disease presents with a more uncertain prognosis.

The World Health Organization (WHO) has created an international surveillance network (110 laboratories in 82 countries) for early detection of the prevailing strains or of those strains that have a high degree of antigenic mutation.
– These laboratories are supported by four WHO centres located in Atlanta (USA), London (UK), Melbourne (Australia), and Tokyo (Japan).
Based on the data collected, the WHO notifies manufacturers of the strains to be inserted in the vaccines for the vaccination campaign of the current year. Usually, 2 strains of virus A and 1 of virus B are suggested; the recommended strains are those that are expected to develop the disease in the general population from December to April of the following year.

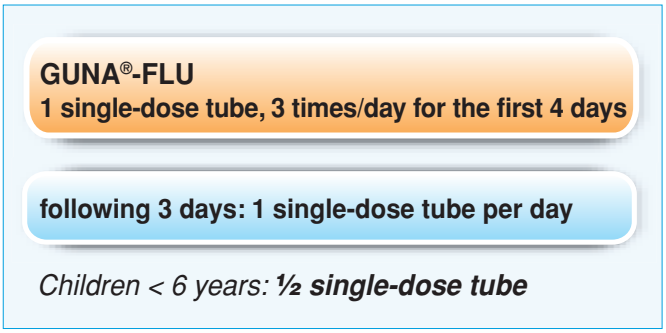
FIG. 4



▶ **First consideration**: the forecast is often wrong.
▶ **Second consideration**: one speaks mainly of Influenza-Like Illness (ILI) and not influenza strictly speaking, linked solely to the influenza virus.
Therefore, prevention with the flu vaccine is incomplete and does not cover a considerable variety of other influenza-like forms, which – from an etiological point of view – are very different from traditional influenza.
▶ **Third consideration**: the antigenic variations of the influenza virus reduce considerably the efficacy of the vaccine.

Based on these considerations, for some time now, alternative prevention to the seasonal influenza and ILI vaccine has been proposed. It is based on the use of the complex low-dose medicinal product **GUNA®-FLU**.

FIG. 5



This medicinal product activates the natural antiviral defences of the body, resulting in increased cell-mediated response with consequent specific and non-specific cytolysis of the cells infected by the virus and concurrent triggering of the humoral response linked to the increased levels of lysozyme and γ-interferon.
The validity of such prevention is corroborated by a series of clinical studies (see References).
– The use of GUNA®-FLU is not limited to **prevention**: the medicinal product can be successfully prescribed also in the **treatment** of the flu syndrome, by modulating the expression of the episode of acute fever and of all other inflammatory symptoms, also avoiding the possible septic evolution of the disease.

PATIENTS AND METHODS

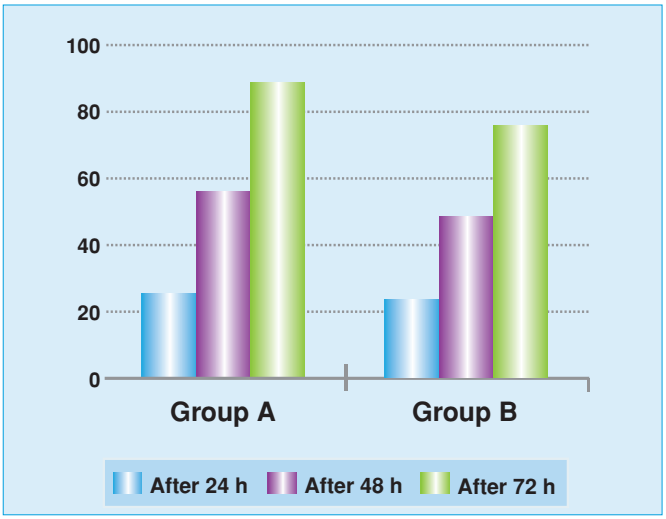
This clinical trial evaluates the efficacy of **GUNA®-FLU *vs* paracetamol** in the symptomatic therapy of the flu syndrome.

TAB. 2

FEVER SYMPTOM
Resolution after 24-48-72 hours

	After 24 h (% patients)	After 48 h (% patients)	After 72 h (% patients)
Group A – GUNA®-FLU	25%	56%	89%
Group B – Paracetamol	23%	49%	76%

FIG. 6



▶ Inclusion criteria

Children referred for personal observation to the Group Paediatrics Clinic (Studio Pediatrico San Giovannese; Dr. Arrighi, Dr. Fiorini) as patients affiliated with Local Health Unit (ASL) No. 8 of the National Health Service of Arezzo (Italy) and private patients [2-month period (January-February)].

The patients, aged between 3 and 12 years (average age 6 years, 7 months), had not received flu vaccine, and did not have a clinical history of positivity to RRI.
At the time of admission to the study, the following symptoms had been identified:

- Abrupt and sudden onset of fever at a temperature > 38.5°C associated with at least one of the following general symptoms:
  - headache
  - generalized malaise
  - chills, sweating
  - asthenia.
- One of the following respiratory symptoms:
  - cough
  - pharyngodynia
  - nasal congestion.

Gastrointestinal symptoms (nausea, vomiting, diarrhoea, abdominal pain), which do not constitute diagnostic criteria for ILI according to the Italian Ministry of Health, could also be present.

▶ Exclusion criteria

Onset of the illness over 24h prior to inclusion in the study.
Children suffering from a chronic pathology (diabetes, heart disease, renal insufficiency), receiving immunosuppressive therapy and cortisone, with allergies and receiving prophylactic antibiotic therapy.

– In total, **159 patients**, divided into two groups, were studied (TAB. 1; FIG. 1).

- **Group A**: 78 patients,treated with **GUNA®-FLU**.
- **Group B**: 81 patients, treated with **Paracetamol**.

VISIT n.1 – ENROLLMENT – GUNA®-FLU (78 patients)			
CLINICAL SCORE	GENERAL SYMPTOMS	RESPIRATORY SYMPTOMS	GASTROINTESTINAL SYMPTOMS
0 **No Symptoms**	0	0	60
1 Symptoms: **Minor**	9	12	6
2 Symptoms: **Moderate**	29	39	8
3 Symptoms: **Severe**	40	27	4

TAB. 3

VISIT n.1 – ENROLLMENT – PARACETAMOL (81 patients)			
CLINICAL SCORE	GENERAL SYMPTOMS	RESPIRATORY SYMPTOMS	GASTROINTESTINAL SYMPTOMS
0 **No Symptoms**	0	0	64
1 Symptoms: **Minor**	6	13	5
2 Symptoms: **Moderate**	35	38	8
3 Symptoms: **Severe**	40	30	4

TAB. 4

During the first visit of admission, the following parameters were assessed:

1. Body temperature
2. Possible flu vaccination and belonging to one or more cases excluding recruitment in the study
3. Symptoms and clinical objectivity.

– For the collection and statistical analysis of the clinical symptomatology, a questionnaire was used in which symptoms were scored from 0 (no symptom) to 3 (severe symptoms) and divided into:

- General
- Respiratory
- Gastrointestinal (FIG. 2).

GUNA®-FLU

GUNA®-FLU is a low-dose medicinal complex composed of *Aconitum napellus* 5CH, *Belladonna* 5CH, *Echinacea* 3CH, *Asclepias vincetoxicum* 5CH, *Anas barbariae hepatis et cordis extractum* 200K, *Cuprum* 3CH, *Influenzinum* 9CH, sucrose.

The product contains two nuclei of action:

1. Nucleus of **immunostimulatory ingredients**.
2. Nucleus of **symptomatic ingredients**.

1 Immunostimulatory nucleus:

Anas barbariae 200K, *Influenzinum* 9CH, *Vincetoxicum officinale* 5CH, *Echinacea angustifolia* 3CH.

- *Anas barbariae* 200K

It is prepared starting from the autolysate of duck liver and heart, a species that is a healthy carrier of influenza viruses; the homeopathic preparation of these tissues that carry specific antigens implements a "indirect nosode therapy".

- *Influenzinum* 9CH

Nosode of influenza that acts in synergy with *Anas barbariae* 200K. It activates the "specific" antiviral defenses constituted by cytotoxic T cells and lymphocytes NK; these cells are "alerted" against influenza viruses and other viral forms typical of the winter season (prevention) (FIG. 3).

- *Asclepias vincetoxicum* 5CH

Stimulation of non-specific immunity through the increase of the macrophages, T cells, and polymorphonuclear cells; in addition, it stimulates the network of cytokines and in particular γ-interferon and lysozyme.

- *Echinacea angustifolia* 3CH

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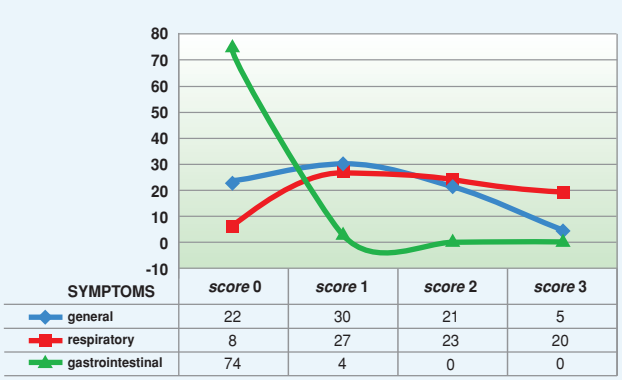
FIG. 7

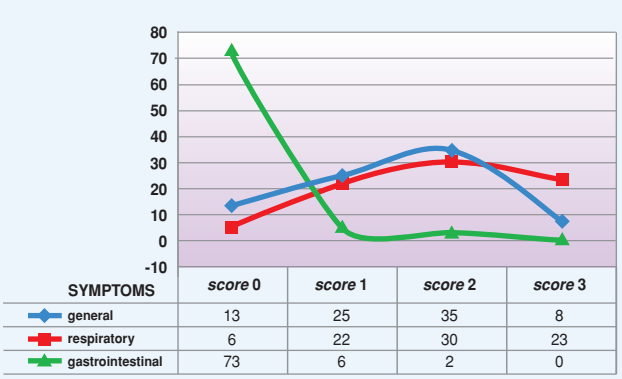
VISIT n.2: GROUP A – CLINICAL SCORE AFTER 4 DAYS



SYMPTOMS	score 0	score 1	score 2	score 3
general	22	30	21	5
respiratory	8	27	23	20
gastrointestinal	74	4	0	0

FIG. 8

VISIT n.2: GROUP B – CLINICAL SCORE AFTER 4 DAYS



SYMPTOMS	score 0	score 1	score 2	score 3
general	13	25	35	8
respiratory	6	22	30	23
gastrointestinal	73	6	2	0

FIG. 9

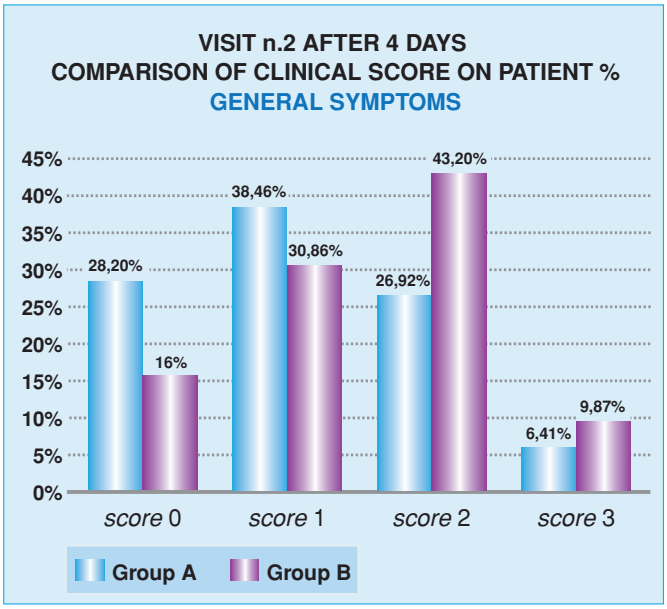


FIG. 10

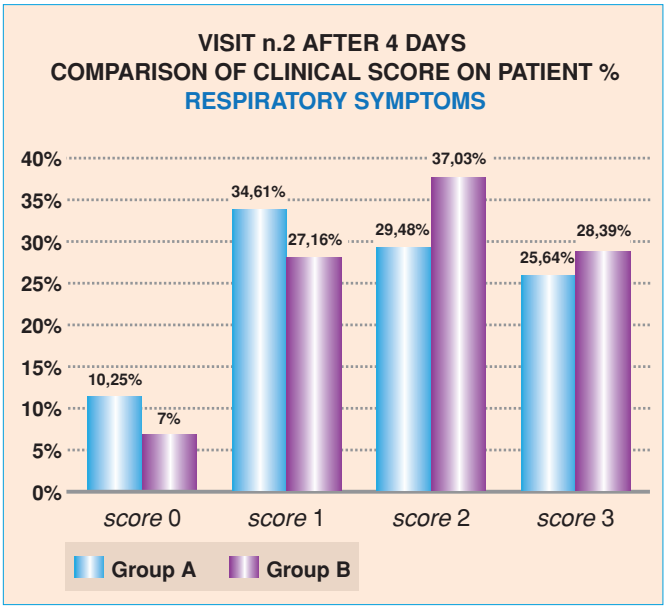
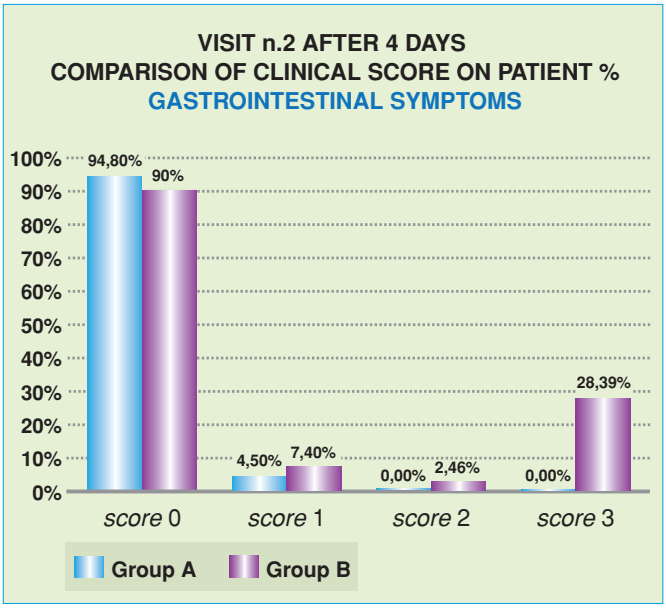


FIG. 11



stimulate macrophages. The polysaccharides determine an increased production of immunoglobulins.

– The phenols have an antiviral action.
A summary of these actions is shown in FIG. 4.

2 Nucleus of symptomatic ingredients:

Aconitum 5CH, *Belladonna* 5CH, *Echinacea angustifolia* 3CH, *Cuprum* 3CH.

• *Aconitum* 5CH, and *Belladonna* 5CH are indicated in the initial stages of an inflammatory process (neurogenic and vascular stage), modulating their clinical expression and duration; in particular, they are indicated in the case of episodes of acute fever.

• In addition to the immunostimulating function, *Echinacea angustifolia* 3CH has an anti-inflammatory action and prevents the bacterial complications that occur during the flu syndrome.

• *Cuprum* 3CH has an anti-inflammatory and antiseptic action; it is effective in myalgia.

Paracetamol

Paracetamol is a drug with outstanding analgesic and antipyretic properties.
Known and used for over a century, its efficacy and tolerability profiles are such that it is one of the most used synthetic molecules in the world among those available in this pharmacological category.

The commercial availability of several pharmaceutical forms makes it possible to choose the most suitable one for the situation, as well as the one that best meets a patient's needs.
The analgesic and antipyretic properties are due to the direct effect on pain and thermoregulation nerve centres, probably through the local inhibition of the synthesis of prostaglandins.
The effect of Paracetamol lasts 4/6 h, with the start of the analgesic and an-

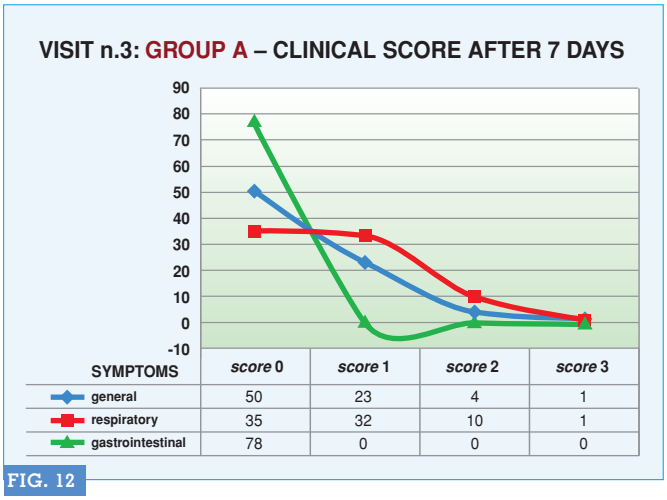


FIG. 12

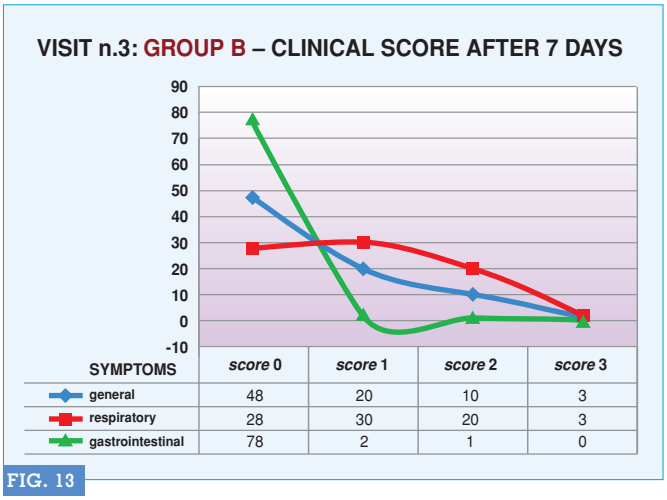


FIG. 13

tipyretic action within 30 minutes ≈ after administration.
At the recommended therapeutic doses, Paracetamol has no side effects; in the case of severe overdose, the most serious side effect is hepatic necrosis.
It should be borne in mind that N-acetylcysteine, if taken within 12h of intoxication, is an antidote to Paracetamol.

Follow-up

The study patients were monitored as follows:

1. Fever: the temperature had to be communicated by phone by parents, previously instructed, after measuring it at 5:00 pm and at 24, 48 and 72 h.
2. Clinical symptomatology: outpatient visits or, when not possible, home visits at day 4 and day 7 from the onset of the clinical symptoms.

During the first visit, parents were proposed two alternative therapies (GUNA®-FLU or Paracetamol).
Based on their personal belief, they chose the one they deemed most appropriate.
This type of prospective study, called *outcome evaluation*, has an advantage: the placebo effect is balanced by the choices of the family, without any imposition that may alter reliability of results.

Treatment schemes

Group A was treated with **GUNA®-FLU** at the following dosage:
• 1 dose tube (1/2 in patients under 6 years), 3 times a day for the first 4 days; then once a day for the next 3 days (FIG. 5).
Group B was treated with **Paracetamol** syrup for oral administration according to the following therapeutic scheme:
• 15mg/kg/dose every 8 h for the first 4 days and as needed over the next 3 days, if the temperature was >38.5°C.
Patients of both groups could use amoxicillin, if:
– Fever >38.5°C after 5 days from onset.
– Objective clinical evidence of positivity at the day-4 control in at least one of the two conditions:
  • Chest findings involving the lower respiratory tract
  • Positive pharyngeal finding for suspected bacterial superinfection (RAD test for SBEGA).

Assessment indicators of therapeutic efficacy:

The following indicators were considered:

1. body temperature < 37°C
2. statistical differences between the two groups in the scores of the administered clinical questionnaire.

Analysis of the results

• Body temperature < 37°C.

The analysis of data at 24, 48, 72h showed that the % of patients with lasting, non-occasional resolution of fever was higher in Group A than in Group B. The difference became increasingly more significant as the days went by: 2% at 24 h, 7% at 48 h, and 13% at 72 h. These data demonstrate the efficacy of GUNA®-FLU in controlling the symptom that is certainly the most concerning for patients and families (TAB. 2; FIG. 6).

• Score differences between the two groups in the clinical questionnaire.

During the **first visit of enrollment**, the physician annotated the clinical scores for the various categories of symptoms; the two Groups were homogeneous with regard to the distribution in the different classes (TABs. 3; 4).

At the **second visit, the first check-up at 4 days**, some important differences were found:
FIG. 7 – Group A clinical score at 4 days – shows that the curve of the general and respiratory symptoms reached its peak in score 1, while the curve analysing the gastrointestinal symptoms reached its peak in score 0.
FIG. 8 – Group B clinical score at 4 days – shows that the peak of the general and respiratory symptoms curve moved to

FIG. 14

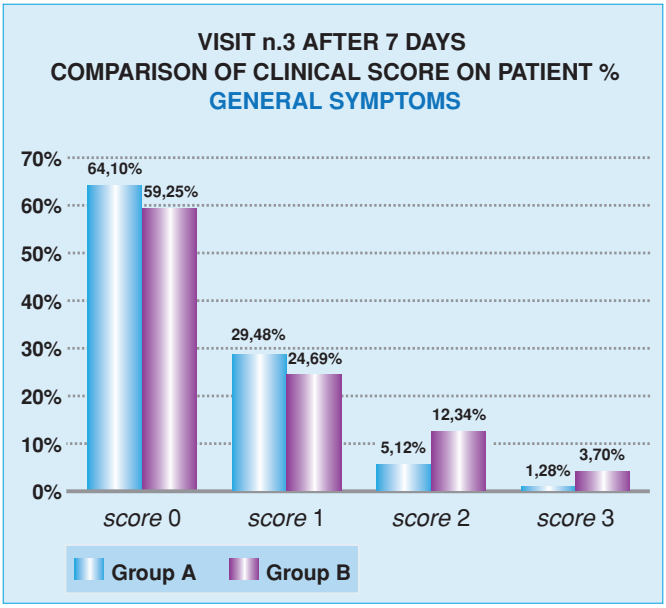


FIG. 15

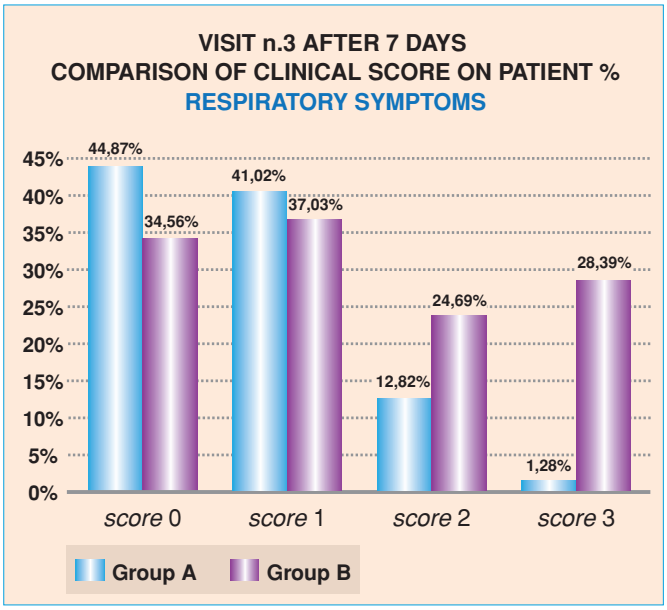
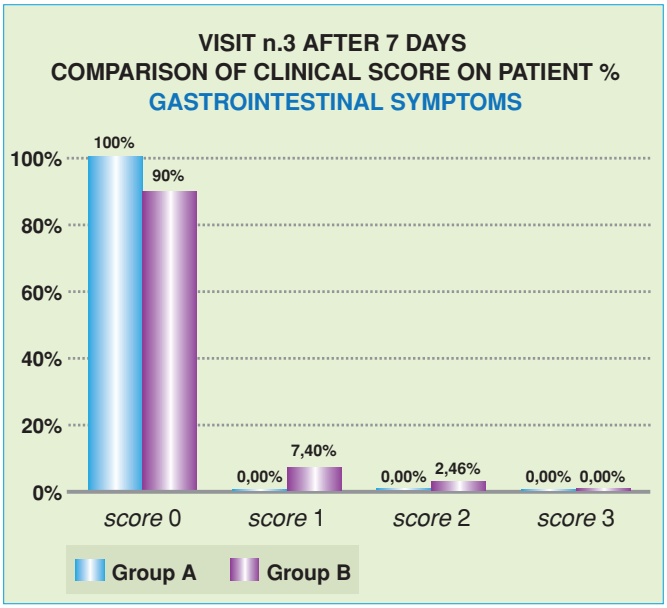


FIG. 16



the right in score 2, indicating less therapeutic efficacy, while the curve of the gastrointestinal symptoms was less inclined, though having its peak too in score 0.

FIGs. 9, 10, and 11 show the separate comparison of the three different types of symptoms in the two groups.

These findings are confirmed if the percentage out of the total number of patients is considered instead of the absolute numerical values.

At the **third visit, i.e., the second control at 7 days**, the differences between the two groups continued to be in favour of Group A – though less significant – and showed a therapeutic efficacy of GUNA®-FLU that exceeded expectations.

– In fact, the curves relating to Group A have a greater inclination (gastrointestinal symptoms); as regards the general and respiratory symptoms, a very sharp peak was observed in score 1 of Group A compared to Group B (FIGs. 12 and 13). This is confirmed by an analysis of the symptoms in FIGs. 14, 15, and 16.

Major differences between Groups **were also found in the use of antibiotics**.

In Group A only **3%** used them, *versus* **24%** of the patients in the Paracetamol Group. This also means a net saving in pharmaceutical expenditure (FIG. 17).

DISCUSSION

Influenza and Influenza-Like Illnesses (ILI) are infectious diseases with a significant social impact in terms of direct and indirect costs: medicines, working hours loss, cost for care of children or elderly patients. These illnesses generally have a benign course and heal even without any major therapeutic intervention. Usually, it is sufficient to control the patient's symptoms with rest.

However, it is necessary to carefully monitor patients belonging to at-risk groups in order to detect the early signs of possible complications.

There is no need to stress the impor-

tance of proper prevention of flu syndromes to be pursued conventionally but even better with low-dose medicinal products, like GUNA®-FLU, which in some studies has demonstrated a remarkable efficacy in prevention and absence of side effects.
It is also important to address the flu syndrome in its clinical expression in the acute phase, using in this case also low-dose medicines that control the symptoms, stimulate the body's ability to react and allow rapid recovery, without side effects.

CONCLUSIONS

This prospective, controlled study shows the superiority of the low-dose therapy compared to the conventional therapy from various viewpoints:

a. Superiority in lasting and stable control of body temperature that decreases more quickly < 37°C.

b. Superiority in the remission of the clinical symptoms, as regards the general, respiratory and gastrointestinal symptoms at day 4 and 7.
– It should be noted that the difference between the two Groups is clear at day 4 and then narrows, while remaining evident at day 7. This indicates a more rapid therapeutic action of GUNA®-FLU compared to paracetamol, which inhibits the inflammatory reaction, without modulating it.
GUNA®-FLU favours a natural healing and has a more linear and homogeneous clinical response.

c. Minor use of antibiotic therapy and, consequently, minor bacterial complications in the GUNA®-FLU Group compared to the Paracetamol Group.

The absence of side effects, good compliance and the results obtained fully justify the use of GUNA®-FLU in the treatment of the flu syndrome. ■

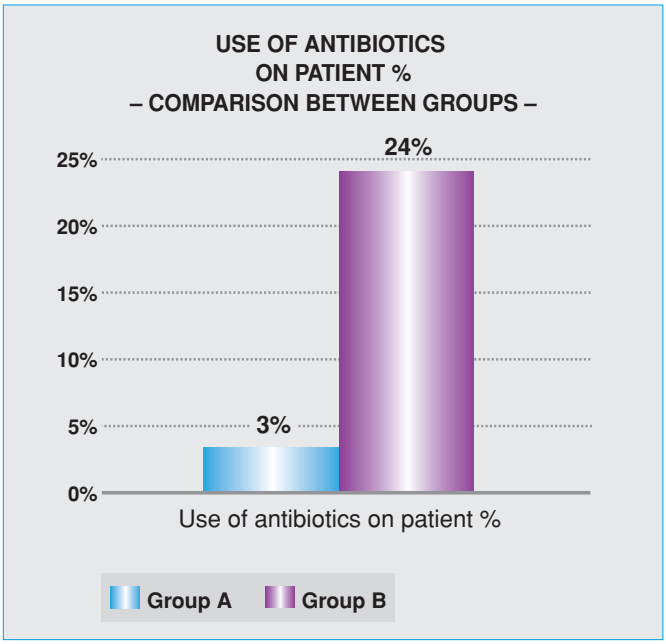


FIG. 17

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