



SNLG16

**Management
of influenza-like syndrome**

GUIDELINES

Publication date: May 2008

Next update: May 2010

Editing
Anna Piseri, Zadig, Milano

Graphic
Giovanna Smiriglia

Translation
Eleonora Lacorte

Responsible of the project

Alfonso Mele, Istituto Superiore di Sanità

Coordinators

Alfonso Mele, Istituto Superiore di Sanità

Cristina Morciano, Istituto Superiore di Sanità

Arianna Vitale, Istituto Superiore di Sanità

Multidisciplinary panel

Antonio Addis, Agenzia Italiana del Farmaco

Elvira Bianco, ASL 1 Avellino, Dipartimento di Prevenzione

Marta Ciofi degli Atti, Istituto Superiore di Sanità

Giulio Cocco, AORN A. Cardarelli, Napoli

Salvatore De Masi, ASL 6 Livorno, Dipartimento di Prevenzione

Vittorio Demicheli, Direzione Programmazione Sanitaria Regione Piemonte

Vania Giacomet, Clinica Pediatrica Ospedale Luigi Sacco, Milano

Alfredo Guarino, Università Federico II, Napoli

Cristina Morciano, Istituto Superiore di Sanità

Paola Marchisio, IRCCS Ospedale Maggiore Policlinico Mangiagalli e Regina Elena, Milano

Caterina Rizzo, Istituto Superiore di Sanità

Luciano Saggiocca, AO G. Rummo, Benevento

Letizia Sampaolo, Istituto Superiore di Sanità

Giuseppe Traversa, Agenzia Italiana del Farmaco

Arianna Vitale, Istituto Superiore di Sanità

Marcello Diego Lograno, Federazione degli ordini dei farmacisti italiani

Mauro Di Bari, Società italiana di gerontologia e geriatria

Pietro Crovari, Società italiana di igiene, medicina preventiva e sanità pubblica

Maurizio de Martino, Società italiana di infettivologia pediatrica

Giampiero Carosi, Società italiana di malattie infettive e tropicali

Alessandro Rossi, Società italiana di medicina generale

Nicola Principi, Società italiana di pediatria

Trainers for the literature assessment

Andrea Cipriani, Dipartimento di medicina e sanità pubblica, Università di Verona

Giovanni Baglio, Asp Lazio

Salvatore De Masi, ASL6, Livorno

Letizia Sampaolo, Istituto Superiore di Sanità

Staff for the literature assessment

Marta Boncinelli, Azienda Ospedaliero
Universitaria Careggi, Università di Firenze
Emanuela Bonfanti, Agenzia Zadig
Patrizia Brigoni, Agenzia Zadig
Daniela Chiarantini, Azienda Ospedaliero
Universitaria Careggi, Università di Firenze
Giuliana Cologni, Università di Brescia
Franca D'Angelo, Istituto Superiore di Sanità
Elisa Dusi, IRCCS Ospedale Maggiore Policlinico,
Mangiagalli e Regina Elena, Università di Milano
Andrea Lo Vecchio, Università Federico II, Napoli
Claudia Pozzi, Azienda Ospedaliero Universitaria
Careggi, Università di Firenze

Documentation Specialists

Scilla Pizzarelli, Settore Documentazione ISS
Luisa Leone, Settore Documentazione ISS
Italo Gentilizi, Settore Documentazione ISS
Maurella Della Seta, Settore Documentazione ISS
GRUPPO DI STESURA DEL DOCUMENTO
Cristina Morciano, Istituto Superiore di Sanità
Salvatore De Masi, ASL6, Livorno
Letizia Sampaolo, Istituto Superiore di Sanità
Luciano Saggiocca, AO G. Rummo, Benevento
Arianna Vitale, Istituto Superiore di Sanità
Alfredo Guarino, Università Federico II, Napoli
Andrea Lo Vecchio, Università Federico II, Napoli

Referees

Pietro Amoroso, Ospedale Cotugno, Napoli
Alessandro Zanetti, Università degli studi di Milano
ORGANIZZAZIONE TECNICA
Linda Agresta, Istituto Superiore di Sanità
Simonetta Crateri, Istituto Superiore di Sanità
Giuseppina Iantosca, Istituto Superiore di Sanità
Fabrizio Marzolini, Istituto Superiore di Sanità

LEVELS OF EVIDENCE

Evidence type

- I** Evidences from randomized controlled clinical trials and/or systematic reviews of randomized trials.
- II** Evidences from one single adequately designed randomized trial.
- III** Evidences from non-randomized cohort studies with concurrent or historical control or their metanalysis.
- IV** Evidences from non-controlled retrospective case-control studies.
- V** Evidences from non-controlled case-series studies
- VI** Evidences from experts' opinions or opinions from panels as indicated in guidelines or consensus conferences, or based on opinions from members of the work group responsible for this guideline.

STRENGTH OF RECOMMENDATIONS

- A** Carrying out the specified procedure or diagnostic test is strongly recommended. The recommendation is supported by good-quality evidences, even if not necessarily type I or II.
- B** It would be inappropriate to always recommend the specified procedure or intervention, considered the still existing doubts, but it should anyway carefully considered.
- C** Significant uncertainties exist against recommending to carry out the specified procedure or intervention.
- D** The specified procedure is not recommended.
- E** The specified procedure is strongly not recommended.

Index

Summary

Guideline objectives and audience
What the guideline does not include
Who drew up the guideline

Methods

Elaboration of the guideline
Creation of the work group and identification of clinical questions and sources
Literature search
Systematic reviews and primary documentation
Other searches
Selection criteria and instruments for methodological evaluation
Data mining, evidence summary and formulation of recommendations
Principles of good clinical practice
External review
Update, implementation, monitoring and evaluation

Management of influenza

Question 1: Should rapid tests be routinely used for the management of influenza in general medicine?

Question 2: Should amantadine and rimantadine be used for the treatment of influenza, considered age and risk conditions?

Question 3: Should neuraminidase inhibitors be used for the treatment of influenza, considered age and risk conditions?

Question 4: Should antibiotics be used for the treatment of influenza, considered age and risk conditions?

Question 5: Should anti-inflammatory and antipyretic drugs be used for the treatment of influenza, considered age and risk conditions?

Question 6: What are the hospitalization criteria/indications to hospitalization in adults, elder people and pregnant women with influenza?

Question 7: What are the hospitalization criteria/indications to hospitalization in children with influenza?

Question 8: Should non-conventional therapies be used in the treatment of influenza, considered age and risk conditions?

Summary

The elaboration of guidelines is part of the National Guidelines System's activities. The SNLG programme is the result of an agreement between the Health Ministry and the Italian National Health Institute (ISS), aimed at promoting a high quality health assistance.

The Clinical Epidemiology and Guidelines Department of the National Centre for Epidemiology, Surveillance and Health Promotion, in the ISS, drew up the document, coordinating the activities of the multidisciplinary panel.

The multidisciplinary panel produced the clinical recommendations related to diagnosis, therapy and hospitalization criteria in children and adults with influenza, on the basis of the evaluation of studies published from 2003 to 2007.

The routine use of the currently available rapid tests used to diagnose influenza is not recommended: their positive predictive ability is low and a negative test is not enough to exclude the diagnosis in suspected cases. Moreover, test results do not affect clinical practice.

The routine use of amantadine and rimantadine is not recommended for the treatment of influenza due to a scarce relevance of outcomes, and to the adverse events and phenomena of resistance connected to their use. The panel of experts therefore confirmed the recommendation included in the previous release of this guideline.

The routine use of oseltamivir and zanamivir is not recommended, but their use is to be evaluated in each case. In fact, in spite of a statistic and clinical significance, the outcomes do not appear too relevant (a one day reduction of fever in adults and half a day in children).

Oseltamivir is instead recommended for the post-exposure prophylaxis in non-vaccinated institutionalized subjects (for example, subjects living in assisted health residences).

The use of antibiotics is not recommended in non-complicated flu, and also in the treatment of flu-related sore throat, unless it is caused by bacterial infections.

Established criteria for the use of antipyretic and anti-inflammatory drugs should be aimed at relieving patients' uneasiness and their difficulty in handling it, and not at the continuous and systematic monitoring of fever. Paracetamol, ibuprofen and diclofenac, considered their average effectiveness and lower potential of inducing gastric lesions, can be used for the treatment of fever and pain in adults. Moreover, the use of paracetamol is recommended for the treatment of flu-related fever and uneasiness in subjects at increased cardiovascular risk. An increased dose of acetylsalicylic acid, the minimum dose needed to obtain an antipyretic and analgesic effect, can be administered to subject already taking low-dose aspirin. Naprossene can be similarly used in subject at increased cardiovascular risk, not taking low-dose aspirin. Ibuprofen and paracetamol are recommended for the treatment of fever and uneasiness in children, but acetylsalicylic acid is not recommended due to its connection with Reye's syndrome. Another significant risk factor that should be taken into account is the administration to small children of paracetamol formulations designed for adolescents or adults.

Scientific literature lacks population studies evaluating clinical factors or conditions that can predict complications requiring hospitalization. Only retrospective researches are available, indicating the categories of patients most frequently hospitalized and those most frequently incurring in complications. Some criteria to identify patients for whom hospitalization is suggested and patients requiring higher medical attention are included, based on available evidences.

Scientific literature published in recent years lacks clinical trials strong enough to recommend the use of non-conventional therapies to prevent flu or to improve its clinical course.

List of recommendations

Question 1: Should rapid diagnostic tests be routinely used for the management of influenza in general medicine?

D/III The routine use of the currently available rapid tests used to diagnose influenza is not recommended: their positive predictive capacity is low and a negative test in suspected cases is not enough to exclude the diagnosis. Moreover, test results do not affect clinical practice.

Question 2: Should amantadine and rimantadine be used for the treatment of influenza, considered age and risk conditions?

D/I The routine use of amantadine and rimantadine is not recommended.

Question 3: Should neuraminidase inhibitors be used for the treatment of influenza, considered age and risk conditions?

D/I The routine use of neuraminidase inhibitors for the symptomatic treatment of influenza is not recommended. Their use is to be evaluated in each case.

C/I Oseltamivir is recommended only for post-exposure prophylaxis in non-vaccinated institutionalized subjects.

Question 4: Should antibiotics be used for the treatment of influenza, considered age and risk conditions?

E/I The use of antibiotics is not recommended in non-complicated flu.

D/I The routine use of antibiotics in the treatment of flu-related sore throat is not recommended, unless symptoms are complicated by bacterial infections.

Question 5: Should anti-inflammatory and antipyretic drugs be used for the treatment of influenza, considered age and risk conditions?

C/VI Considered the widespread practice of auto-prescription, citizens are to be informed that these are only symptomatic therapies and that using drugs is appropriate only in case there is a real need of reducing uneasiness and pain.

B/I Paracetamol and ibuprofen can be used in the treatment of fever and pain in children.

E/III The use of acetylsalicylic acid is not indicated in children younger than 12, due to its connection with Reye syndrome.

E/IV Parents should be warned against using paracetamol formulations for adults that do not allow to adapt the dosage to children's age and weight.

B/I Paracetamol, ibuprofen and diclofenac can be used, if needed, for the treatment of fever and pain in adults.

B/VI The use of paracetamol is recommended for the treatment of flu-related fever and uneasiness in subjects at increased cardiovascular risk.

An increased dose of acetylsalicylic acid, the minimum dose needed to obtain an antipyretic and analgesic effect, can be administered to subjects already taking low-dose aspirin.

Naprossene can be similarly used in subject at increased cardiovascular risk not taking low-dose aspirin.

B/VI Doctors prescribing antipyretic and analgesic drugs should carry out a careful anamnesis of the basic gastro-duodenal and cardiovascular damages patients could risk.

B/II Paracetamol can be used for the treatment of fever and pain in pregnant women.

Question 6: What are the hospitalization criteria/indications to hospitalization in adults, elder people and pregnant women with influenza?

B/V In case of complicated flu, taking into account the following risk factors is recommended to determine the appropriateness of hospitalization.

Factors to be taken into account increase the risk of complications and death if overlapped and associated to the patient's clinical and socio-economic status; in any case clinicians' global clinical judgment cannot be disregarded.

- Pregnant women
- Subjects aged 65 or older than 65

Clinical criteria

- concomitant pathologies: chronic respiratory, cardiac and/or liver diseases, cancer, diabetes mellitus, chronic alcohol abuse, malnutrition, cerebrovascular diseases, postsplenectomy, hospitalizations during the last year;
- respiratory frequency ≥ 30 breaths/min, diastolic pressure ≤ 60 mmHg or systolic pressure < 90 mmHg, pulse ≥ 125 /min, body temperature < 35 or $\geq 40^\circ\text{C}$, alterations of the mental status (disorientation, stupor), signs of extra pulmonary sites of infection.

Laboratory data

- white cells $< 4,000$ /ml or $> 30,000$ /ml or absolute neutrophil number $< 1,000$ /ml;
- $\text{PaO}_2 < 60$ mmHg or $\text{PaCO}_2 > 50$ mmHg;
- signs of altered renal function: creatinine > 1.2 mg/dl;
- unfavorable radiographic evolution and/or pneumonia with multiple hotbeds, presence of cavitation or pleuric effusion;

- hematocrit < 30% or hemoglobin < 9g/dl;
- signs of sepsis or of organ damage, such as metabolic acidosis or alterations in blood coagulation;
- arterial PH < 7.35.

GCP/Good Clinical Practice

Hospitalization is recommended in patients with poor economic and social conditions not supported by a social-health assistance network, which could be an adequate alternative to hospitalization, even if presenting clinical conditions less compromised than the one reported in the previous recommendation.

Question 7: What are the hospitalization criteria/indications to hospitalization in children with influenza?

D/IV There are no absolute indications to hospitalization based exclusively on age.

D/V Hospitalization is not necessarily required, but domiciliary or ambulatorial management handled by the pediatrician should be preferred, in presence of the following signs and symptoms:

- dehydration to be treated orally;
- infants younger than 3 months with low birth weight or premature;
- slight respiratory distress

C/V Hospitalization in children with flu should be considered but not necessarily carried out in the following cases:

- family unable to manage the situation
- economic or social conditions not guaranteeing domiciliary assistance
- episodes of non-complicated fever convulsions following the first one (ceased before reaching the hospital)
- respiratory frequency > 60/min or saturation O₂ < 92% (NB: respiratory frequency varies with age)

or in case of children is affected by one of the following chronic pathologies, on the basis of the clinical conditions of the single patient (in particular children younger than 3 months):

- asthma (patients needing a daily therapy with corticosteroids or bronchodilators or cromons or antileucotriens)
- chronic pulmonary diseases (ex. Cystic fibrosis)
- cardiopathies
- immunosuppression (patients with a story of neoplastic pathologies, vasculitis and collagen-related diseases, congenital or acquired immunodeficiency or immunosuppressive therapy > 2 weeks)
- hemoglobin-related diseases
- chronic renal disorders
- diabetes mellitus
- congenital metabolic defects
- long-term therapy with salicylates (ex. ARI, S. Kawasaki)
- neurological and neuromuscular pathologies causing respiratory difficulties

A/III Hospitalization in children with flu is strongly recommended mainly if they show the following symptoms:

- signs of respiratory distress
- cyanosis
- RF > 70/min or O₂ Saturation < 90%
- severe dehydration
- convulsions (first episode) or neurological symptoms
- bronchiolitis < 3 months
- altered state of consciousness

- Signs of septicemia (at least two among: paleness, hypotony, hypotension)
- Cyanogenetic cardiopathies

Question 8: Should non-conventional therapies be used for the treatment of influenza, considered age and risk conditions?

D/I Studies included in the analysis are not strong enough to recommend the use of non-conventional therapies to prevent flu or to improve its clinical course.

Introduction

This guideline is an update of the document published in November 2003 by the National Guideline Plan. This document, following the premise of the previous guideline, evaluates the currently available interventions for the management of influenza, using an evidence-based approach. The evidences themselves are the “core” of this approach. Evidences are to be gathered through a systematic literature search in relation to the topic to be treated and then are to be evaluated using a transparent and reproducible methodology.

During the last four years new studies have been published referring to diagnostics, pharmacological treatment and hospitalization criteria; three critical areas for clinicians managing flu patients. Evidences has been gathered from these new studies, then appropriately analyzed by a multidisciplinary panel made up of experts, and finally used to draw up clinical recommendations. Some of the recommendations included in the previous document have been confirmed, as data from the new studies did not add new elements but reinforced previous recommendations. Some other recommendations have been modified on the basis of new evidences. Modified recommendations refer to treatment, and in particular to:

- Neuraminidase inhibitors (see page ...)
- Non-steroidal anti-inflammatory and antipyretic drugs (see page ...)
- Non conventional therapies (see page ...).

Guideline objectives and audience

Drawing up guidelines is one of the activities carried out by the National Guideline System (SNLG). The SNLG programme is the result of an agreement between the *Health programming, levels of assistance and system ethical principles Department* of the Health Ministry and the *Italian National Health Institute* (ISS), aimed at promoting a high quality and accurate planning of the health services provided by the National Health Service.

The objective of the guideline is to identify the effective and safe interventions in the management of flu patients on the basis of the best available evidences.

Influenza is a relevant public health issue, due to the strong impact it has on population health and on commitment of resources. During the season 2006-2007, 22,111 flu cases have been registered and 60,095 cases of acute febrile respiratory diseases. (Surveillance Influciri – Influnet). This survey is based on a sample of approximately 2% of the Italian population; flu incidence during the season 2006-2007 can be esteemed on this basis to have been 6.5%. Uncertainties in the management of influenza remain in the area of diagnostics and therapy.

Tests allowing real-time identification of flu viruses are available in the most usual health care locations, such as ambulatories and patients’ houses. However, more than two thousands viral strains and species cause the typical symptoms, limiting the interpretation.

Treatment is thus focused on relieving symptoms and preventing complications. This area is characterized by a high variability in prescription and administration of antipyretics, non-steroidal anti-inflammatory drugs (FANS) and antibiotics.

The guideline, in relation to antibiotic and antiviral drugs, focuses on assessing their efficacy in treating symptoms and preventing complications, considering also the issues of resistance phenomena and the high costs associated to their use. In relation to anti-inflammatory-antipyretic drugs, the main objective is instead to assess their safety.

The issue of hospitalization has also been treated, to define the hospitalization criteria and indications to hospitalization in children and adults with flu. The definition of these criteria can be considered as a useful instrument to reduce inappropriate hospitalizations, incidence of nosocomial infections, health expenses and hospital overcrowding during flu epidemics.

The audience of this guideline includes general practitioners, independent pediatricians, hospital doctors, pharmacists, health programmers. A version for citizens of this guideline will be drawn up.

What the guideline does not include

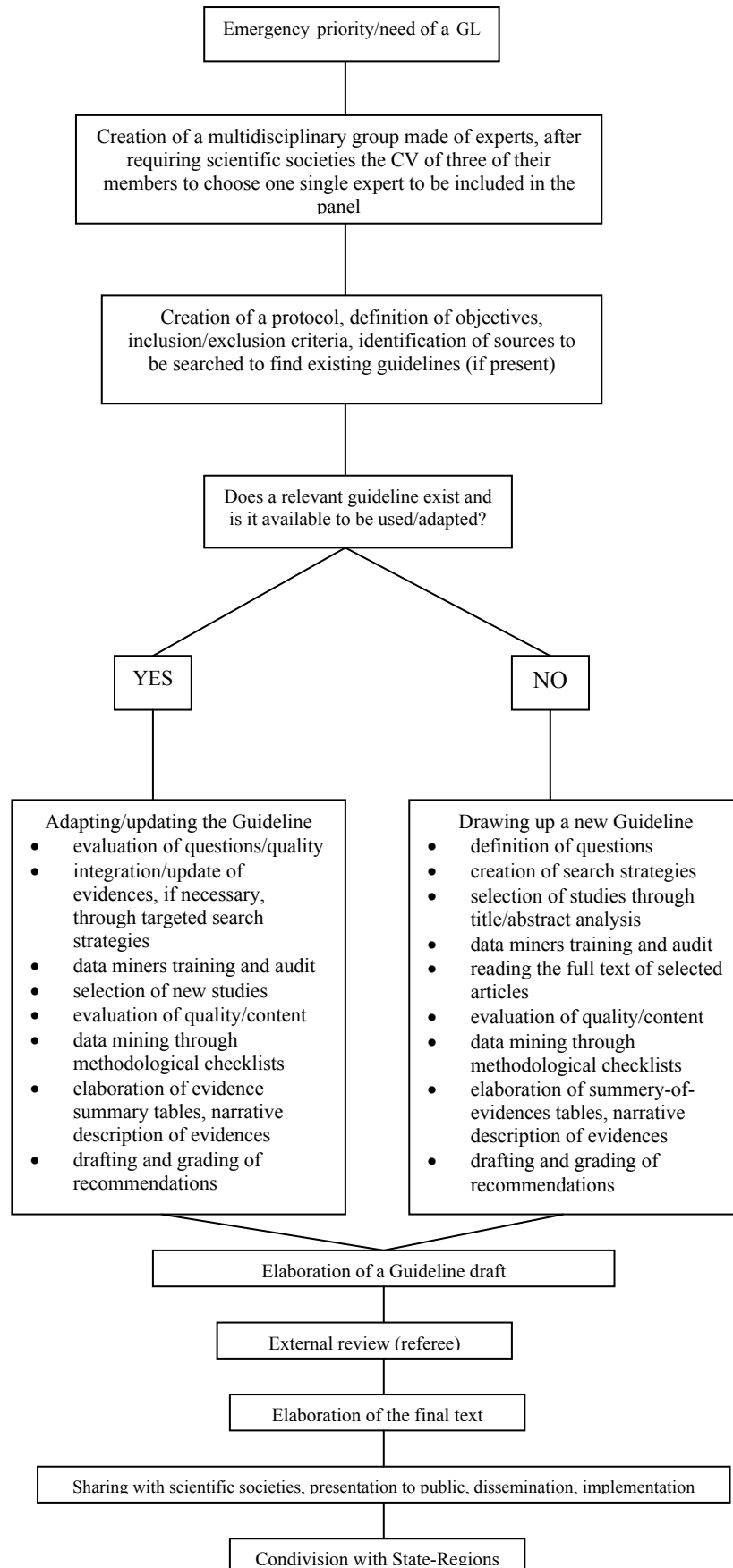
This document does not treat specifically single questions regarding pandemic flu nor primary and secondary prevention. Post-exposure prophylaxis is exceptionally treated only in relation to neuraminidase inhibitors. Indications to flu vaccine are not included in this document. **For further information on this issues please refer to the concerning ministry letter.**

Who drew up the guideline

Drawing up the guideline required the collaboration of several work groups.

- The multidisciplinary panel – made up of experts such as: epidemiologists, pediatricians, geriatrists, general practitioners and experts in the elaboration of guidelines – that reconsidered the clinical questions and the studies inclusion/exclusion criteria, evaluated evidences and defined recommendations.
- The group of documentalists of the ISS documentation unit, that, after a thorough debate with clinicians, created a search strategy for each question and searched the databases.
- The data mining group, made up of specifically trained clinicians, that evaluated each single study and filled the evidence tables.
- The coordinators who handled organization, management of work groups, programming and supervision.
- The drafting group, that wrote the final version of the document.
- The training group, that trained the clinicians who evaluated literature.
- The technical-scientific secretariat.

Methods Guideline elaboration path



Creation of the workgroup and identification of clinical questions and sources

The multidisciplinary Work Group (WG) that drew up this guideline includes representatives of the main disciplines involved in the diagnosis and early treatment of flu, experts in EBM (evidence based medicine) and in guideline development methodology.

The panel met in September 2007 and in January 2008; some of the debates needed to monitor the workflow and to plan the drafting of the guideline have been carried out via e-mail or phone.

The national scientific societies involved have been contacted during the starting phase.

In the first place, the WG verified if the clinical questions included in the previous release of the guideline were still valid and/or needed to be amended. The panel decided to confirm the previous questions but to draw them up focusing the research according to age (children, adults) and to groups of fragile population (pregnant women, elder people). The panel decided also to include a new question regarding the treatment of flu with complementary and alternative medicine and four monographic appendixes focused on issues requiring a more narrative information.

The panel identified also the biomedical databases to be searched, defined the studies inclusion and exclusion criteria and the keywords to be used to build up the search strategy.

Literature search

To update evidences, targeted search strategies have been created for each question, different according to the issue treated. The time span between the release of the last guideline update, November 2003, and the date the research for the new update has been completed, October 2008, has been chosen to be the time span of reference for literature search.

The following databases are the online resources searched:

PubMed/Medline

Cochrane Library

BIOSIS

Cochrane Controlled Trials Register

Embase

SciSearch

The following filter has been used as main search filter:

(influenza or influenzas or grippe or flu)

Systematic reviews and primary documentation

The series of search strategies, specific for each question, defined by the panel have been carried out in September 2007. As in some cases difficulties were found in gathering studies, the inclusion criteria for each question have been modified on the basis of necessities and during the elaboration of the bibliographic search. The complete strategies carried out for each question are available on the website www.snlg-iss.it. Sources has been always searched with the aim of gathering systematic reviews and primary documentation focused exactly on the management and treatment of flu. The results of this search provided an heterogeneous material, that has been subsequently selected and evaluated, both from a methodological point of view and on the basis of relevance.

Other searches

Search groups and individual researchers have been engaged to obtain information on studies or projects in progress and still not published, and to evaluate and amend the list of studies already identified. Panel members themselves suggested bibliographical material of interest not included in the bibliographies obtained after searching databases. The suggested bibliography has been included if considered relevant and if published during the same time span adopted for primary search.

Selection criteria and instruments for methodological evaluation

The online search originated 3788 titles and abstracts, among which 309 titles were selected as considered relevant, and requested in full text. After further evaluation, only 77 studies were used

for data mining. More articles were added following panel members' directions. After the final evaluation only 80 documents have been included on the basis of methodological rigor and relevance to the guideline topic.

Data evaluation and data mining have been carried out on each single study with the support of the methodological checklists drawn up by the *Scottish Intercollegiate Guidelines Network*, SIGN, translated and suitably adapted by the SNLG-ISS. The intermediate work documents, such as the data mining forms and summary tables, are available on the SNLG-ISS website, www.snlg-iss.it.

Data mining, evidence summary and formulation of recommendations

The selection of studies, their methodological evaluation and the data mining process carried out on each selected study have been performed by specifically trained personnel. Evidences gathered from each study have been summarized in tables, each table specific for each single question and type of study. The summary tables adopted are those drawn up by NICE or, if not available, specifically created by the panel. The evidence grading method adopted is the one described in the PNLG Methodological Handbook (only available in Italian at: http://www.pnlg.it/doc/Manuale_PNLG.pdf), defining six levels of evidence (I-VI) and five grades of recommendation (A-E). Levels of evidence have been assigned taking into account the study design and the methodological evaluations, which were discussed inside the panel with the aim of assigning the strength of recommendation.

Principles of good clinical practice

In the currently adopted evidence hierarchy, experts' opinions are considered low level and adopted only in absence of experimental evidences or in relation to specific questions. Drawing up recommendations based on the experience derived from the best clinical practice can be very useful in areas in which experimentation cannot be carried out^{1,2}. These principles have been included in the present guideline and identified with the following acronym: GCP (Good Clinical Practice).

External review

The document defined by the work group has been sent to external experts, explicitly requiring them to evaluate its preciseness and clearness, and the clinical relevance and feasibility of recommendations. The referee group is made of a clinician and a virologist.

Update, implementation, monitoring and evaluation

This guideline is to be updated before the end of 2010.

Multiple techniques of active dissemination and implementation of the document will be carried out, including the following approaches:

- dissemination of the initiative on media and press;
- mail deliveries to Regional health structures, local health agencies, hospitals, specialized health professionals and general practitioners, opinion leaders;
- publication on websites (SNLG-ISS, ASP, scientific societies, health agencies, others);
- scientific publications;
- training courses (ECM);
- promotion of formal implementation of the guideline in Italian hospitals;
- presentation in national and international congresses;
- adaptation of the guideline to local environments, through the promotion of integrated clinical paths at a structural level, focusing on the overcoming of implementation barriers.

All initiatives aimed at spreading knowledge of this document will be registered to monitor nationally the guideline dissemination.

Monitoring markers are indicated for each question, and suggested as audit markers to assess the guideline implementation at structural level, and at district and hospital level.

Bibliography

1. National guideline programme. Italian National Health Institute (ISS). Agency for Regional Health Services. Methodological Handbook. How to produce, disseminate and update clinical practice recommendations. Zadig 2002. Available only in Italian.
2. SIGN. A guideline developers' handbook. Published in 2002 and updated in 2004. www.sign.ac.uk/guidelines/fulltext/50/index.html

The management of influenza

Question 1 Should rapid diagnostic tests be routinely used for the management of influenza in general medicine?

Full amount of gathered studies: 122

Full amount of selected studies: 25

Full amount of extracted studies: 19

Included studies: 19 diagnostic studies

Background

Viral culture is the only reliable means to diagnose influenza. It provides results after 3 days and is considered the gold standard in a large number of diagnostic studies. Several diagnostic tests are available, able to provide results in less than 30 minutes.

Studies

Studies included were focused on assessing the efficacy of the various available instruments, comparing their outcome with the one obtained with viral culture and molecular biology tests.

The most studied factors determining sensitivity and specificity are: the type of biological sample examined, the incubation period and the subjects' age. Predictivity is on the other hand strongly influenced not only by sensitivity and specificity values, but also by disease prevalence.

Simmerman¹ studied the validity of a specific rapid test (*QuickVue Influenza Test*) using viral culture as the standard, on the basis of epidemic peaks. As foreseen, predictive positive values (PPV) shift from 73% to 88% in high incidence periods and sensitivity (77%) and specificity (96%) remain steady, differently from what happens in low incidence periods.

Grijalva² analyzed the sensitivity and specificity of tests carried out on hospitalized subjects younger than 5, using viral culture as reference test. A PPV fluctuation, related to the disease prevalence in non-hospitalized subjects, has been observed, against a 63% sensibility and a 97% specificity.

Harnden and Grondahl^{3, 4} showed a low sensitivity of rapid tests in hospitalized (29%) and non-hospitalized (44%) subjects younger than 16. Tests' positive predictivity resulted very low in non-hospitalized subjects (14.2%), while reached satisfactory results (85.7%) in hospitalized subjects.

Relatively low (44-64%)^{3, 5, 6, 7} or very low (29%)⁴ sensitivities have been registered in several other studies carried out in subjects of all ages and in different environments.

Rapid tests are more sensitive in children younger than 5^{8, 9, 10, 11} showing noteworthy differences even between subjects younger and older than 90 days¹¹. Ruest¹² registered similar results among adults and children older than 5.

Rawlinson's study¹³, focusing on different incubation periods, showed that tests' sensitivity notably varies with the length of the incubation period of samples obtained with pharyngeal aspiration. The specific training of professionals assigned to carry out such tests considerably increases tests' sensitivity.

Characteristics and quality of biological samples used represent a factor strongly determining the validity of rapid tests used to diagnose influenza. Obtaining samples with nasopharyngeal aspiration

increases sensitivity more than obtaining them with pharyngeal and nasal tampons or other types of biological samples^{13, 15, 16}.

A relevantly higher sensitivity has been registered among tests carried out on nasopharyngeal tampons and on nasal washing.

Rawlingson, on the other hand¹³, shows the steady superiority in terms of sensitivity of tests performed with nasopharyngeal aspiration, against those performed using nasal and pharyngeal tampons. The assessment has been carried out on subjects of all ages and confirmed even after stratification for incubation period.

Several studies, in the end, show rapid tests' higher efficacy, in terms of sensitivity, in diagnosing influenza type A, than in diagnosing influenza type B^{4, 16, 17, 18, 19}.

Conclusions

Rapid tests appear generally to perform unsatisfactorily. They result to have scarce sensitivity, slightly improved if they are used in children and with some specific types of samples. A strong correlation between positive predictive values and disease prevalence has been observed. Moreover, the inadequate sensitivity turns into a reduction in negative predictivity. Such lack would not allow in clinical practice to guarantee a correct diagnosis in all subjects actually affected by influenza (a negative result would not allow to confidently exclude influenza). An overall uncertainty on the therapeutic actions to be taken after a specific test result should be added to all of the above. Tests should be therefore used with extreme caution.

A large part of analyzed studies were based on hospitalized patients, thus lacking in directness and raising difficulties in generalizing results to non-hospitalized subjects and patients treated in general practitioners' ambulatories.

All analyzed studies are diagnostic studies and of these almost all are prospective and lack in methodological rigor, allowing results to be distorted. Still, a substantial consistency of results provides a certain reliability to the obtained test validity assessments.

Recommendation

D/III The routine use of the currently available rapid tests used to diagnose influenza is not recommended: their positive predictive capacity is low and a negative test in suspected cases is not enough to exclude the diagnosis. Moreover, test results do not affect clinical practice.

Expected benefits

Reducing the use of rapid kits.

Monitoring and audit markers

Number of purchased rapid diagnosis kits.

Bibliography

1. Simmerman JM, Chittaganpitch M, Erdman D, Sawatwong P, Uyeki TM, Dowell SF. Field performance and new uses of rapid influenza testing in Thailand. *Int J Infect Dis* 2007 Mar; 11(2): 166-71.
2. Grijalva CG, Poehling KA, Edwards KM, Weinberg GA, Staat MA, Iwane MK, Schaffner W, Griffin MR. Accuracy and Interpretation of Rapid Influenza Tests in Children. *Pediatrics* 2007; 119; 1: e6-e11.
3. Harnden A, Brueggemann A, Sheppard S, White J, Hayward AC, Zambon M, Crook D, Mant D. Near patient testing for influenza in children in primary care: comparison with laboratory test. *BMJ* 2003 Mar 1; 326(7387): 480.
4. Gröndhal B, Puppe W, Weigl J, Schmitt HJ. Comparison of the BD Directigen Flu A+B Kit and the Abbott TestPack RSV with a multiplex RT-PCR ELISA for rapid detection of

- influenza viruses and respiratory syncytial virus. *Clin Microbiol Infect* 2005 Oct; 11(10): 848-50.
5. Drinka PJ. Experience with the rapid Directgen test for influenza. *J Am Med Dir Assoc* 2006 Jan; 7(1): 37-9. Epub 2005 Jul 22.
 6. Pregliasco F, Puzelli S, Mensi C, Anselmi G, Marinello R, Tanzi ML, Affinito C, Zambon MC. Influenza Virological Surveillance in Children: The Use of the QuickVue Rapid Diagnostic Test. *Journal of Medical Virology* 2004; 73: 269-73.
 7. Weitzel T, Schnabel E, Dieckmann S, Börner U, Schweiger B. Evaluation of a new point-of-care test for influenza A and B virus in travellers with influenza-like symptoms. *Clin Microbiol Infect* 2007 Jul; 13(7): 665-9. Epub 2007 Apr 17.
 8. Alexander R, Hurt AC, Lamb D, Wong FY, Hampson AW, Barr IG. A comparison of a rapid test for influenza with laboratory-based diagnosis in a paediatric population. *Commun Dis Intell* 2005; 29(3): 272-6.
 9. Landry ML, Cohen S, Ferguson D, Comparison of Binax NOW and Directigen for rapid detection of influenza A and B. *J Clin Virol* 2004 Oct; 31(2): 113-5.
 10. Fader RC. Comparison of the Binax NOW Flu A enzyme immunoassay and R-Mix shell vial culture for the 2003 to 2004 influenza season. *J Clin Microbiol* 2005 Dec; 43(12): 6133-5.
 11. Cruz AT, Cazacu AC, McBride LJ, Greer JM, Demmler GJ. Performance characteristics of a rapid immunochromatographic assay for detection of influenza virus in children during the 2003 to 2004 influenza season. *Ann Emerg Med* 2004; 43(3): 250-4.
 12. Ruest A, Micheud S (Reprint), Deslandes S, Frost EH. Comparison of the Directigen flu A+B test, the QuickVue influenza test, and clinical case definition to viral culture and reverse transcription-PCR for rapid diagnosis of influenza virus infection. *J Clin Microbiol* 2003 Aug; 41(8): 3487-93.
 13. Rawlinson WD, Waliuzzaman ZM, Fennell M, Appleman JR, Shimasaki CD, Carter IW. New point of care test in highly specific but less sensitive for influenza virus A and B in children and adults. *J Med Virol* 2004 Sep; 74(1): 127-31.
 14. Cazacu AC, Demmler GJ, Neuman MA, Forbes BA, Chung S, Greer J, Alvarez AE, Williams R, Bartholoma NY. Comparison of a new lateral-flow chromatographic membrane immunoassay to viral culture for rapid detection and differentiation of influenza A and B viruses in respiratory specimens. *J Clin Microbiol*. 2004 Aug; 42(8): 3661-4.
 15. Agoritsas K, Mack K, Bonsu BK, Goodman D, Salamon D, Marcon MJ. Evaluation of the Quidel QuickVue test for detection of influenza A and B viruses in the pediatric emergency medicine setting by use of three specimen collection methods. *J Clin Microbiol* 2006 Jul; 44(7): 2638-41.
 16. Smit M, Beynon KA, Murdoch DR, Jennings LC. Comparison of the NOW Influenza A & B, NOW Flu A, NOW Flu B, and Directigen Flu A+B assays, and immunofluorescence with viral culture for the detection of influenza A and B viruses. *Diagn Microbiol Infect Dis* 2007 Jan; 57(1): 67-70.
 17. Weinberg A, Walker ML. Evaluation of three immunoassay kits for rapid detection of influenza virus A and B. *Clin Diagn Lab Immunol* 2005 Mar; 12(3): 367-70.
 18. Booth S, Baleriola C, Rawlinson WD. Comparison of two rapid influenza A/B test kits with reference methods showing high specificity and sensitivity for influenza A infection. *J Med Virol* 2006 May; 78(5): 619-22.
 19. Hurt AC, Alexander R, Hibbert J, Deed N, Barr IG. Performance of six influenza rapid tests in detecting human influenza in clinical specimens. *J Clin Virol* 2007 Jun; 39(2): 132-5. Epub 2007 Apr 23.

Question 2: Should amantadine and rimantadine be used for the treatment of influenza, considered age and risk conditions?

	Full amount of gathered studies:	237
	Full amount of selected studies:	58
	Full amount of extracted studies:	9
Included studies:	3 Systematic reviews	
	4 Cost-effectiveness analysis studies	
	1 RCT	
	1 Prospective Cohort study	

Background

In recent years, the concrete risk of a flu pandemic has raised a special attention towards antiviral drugs, whose use should be aimed at restraining viral circulation.

Amantadine and rimantadine are among these drugs. Their mechanics of action is interfering with the replication cycle of the type A virus only, blocking the M2 ionic channels, essential for the virus to enter the host cell.

Studies

Jefferson's works^{1, 2} include several RCTs aimed at verifying amantadine and rimantadine therapeutic and prophylactic efficacy in subjects aged 16 to 65.

Amantadine resulted somewhat effective in prophylaxis, being able to reduce 61% (35%-76%) of type A flu cases and 25% (13%-36%) of flu-like syndrome cases: the effect on the disease is mainly a one day reduction of fever in type A infections. The administration of the drug did not affect viral charge nor virus persistence in the breathing apparatus, while side effects were much more significant than in subjects treated with placebo (OR for nausea 2.56 IC 95% 1.37-4.79; OR for insomnia and hallucinations 2.54 IC 95% 1.50-4.31).

Authors point out the eventuality of resistance phenomena, reported also in Gravenstein's study³. Gravenstein reports rimantadine-resistant viruses in 38% of the isolated group of American long-term patients who underwent evaluation of zanamivir and rimantadine effectiveness in protecting against flu.

A Japanese observational study⁴ compared amantadine efficacy *versus* oseltamivir in the treatment of fever symptoms among patients from pediatric ambulatories and from general practitioners. An early administration more than the type of drug used reduced the days of fever. Administering the drug within the 12 hours produced the maximum effect, while a higher efficacy has been registered in flu type A cases. Turner's review⁵ confirmed that amantadine is somewhat effective, as it reduces the days of fever in children with a laboratory flu diagnosis.

In Rothberg's studies^{6, 7, 8} different strategies for using antiviral drugs have been evaluated to the purpose of comparing costs and effectiveness. These studies are often simulations carried out on "virtual" patients. Oseltamivir results quite effective among patients older than 65, *versus* amantadine, rimantadine and zanamivir. The various strategies result more convenient than no treatment in subjects aged from 20 to 50 and in children. A cohort study⁹ compared two post-exposure prophylaxis strategies administered to subjects hospitalized in long-term structures. The prophylaxis carried out with oseltamivir resulted more effective than the one carried out with amantadine and than no prophylaxis, both in terms of costs and benefits, the last measured as disease cases, hospitalization and deaths.

Conclusions

Updating the evidences related to the efficacy of flu symptomatic treatment with amantadine did not produce relevant news. The panel thus confirmed the recommendation included in the previous release of this guideline, that is, to not recommend the routine use of these drugs for the treatment of influenza, due to the irrelevance of outcomes, the adverse events and the resistance phenomena associated to their use.

Recommendation

D/I The routine use of amantadine and rimantadine is not recommended.

Expected benefits

Reducing the expenses for antiviral drugs; preventing viral resistance; reducing adverse reactions connected with the use of antiviral drugs.

Monitoring and audit markers

Number of defined daily doses of antiviral drugs.

Bibliography

1. Jefferson T, Demicheli V, Rivetti D, Jones M, Di Pierantonj C, Rivetti A. Antivirals for influenza in healthy adults: Systematic review. *Lancet* 2006; 367(9507): 303-13.
2. Jefferson T. Amantadina and Rimantadina for preventing and treating Influenza A in Adults. *Cochrane Database Syst Rev* 2004.
3. Gravenstein S. Inhaled Zanamivir Versus Rimantadine for the Control of Influenza in a Highly Vaccinated Long-term Care Population. *J Am Med Dir Assoc* 2005; 6: 359-66.
4. Kawai N. Factors Influencing the Effectiveness of Oseltamivir and Amantadine for the Treatment of Influenza: A Multicenter Study from Japan of the 2002-2003 Influenza Season. *Clinical Infectious Diseases* 2005; 40: 1309-16.
5. Turner D. Systematic review and economic decision modelling for the prevention and treatment of influenza A and B. *Health Technology Assessment* 2003.
6. Rothberg MB. Management of Influenza in adults Older than 65 Years of age: Cost-Effectiveness of rapid testing and Antiviral Therapy. *Ann Intern Med* 2003; 139: 321-29.
7. Rothberg MB. Management of Influenza Symptoms in Healthy Children. *Arch Pediatr Adolesc Med* 2005; 159: 1055-62.
8. Rothberg MB. Management of Influenza Symptoms in Healthy Adults. *J Gen Intern Med* 2003; 18: 808-15.
9. Risebroough NA. Economic Evaluation of Oseltamivir Phosphate for Postexposure Prophylaxis of Influenza in Long-term care facilities. *J Am Geriatr Soc* 2005; 53: 444-51.

Question 3: What are the indications to the use of neuraminidase inhibitors (Should neuraminidase inhibitors be used) for the treatment of influenza, considered age and risk conditions?

Full amount of gathered studies:	178
Full amount of selected studies:	93
Full amount of extracted studies:	4

Included studies: 4 Systematic reviews

Background

Neuraminidases are enzymes that can be found inside the flu virus envelope. They take part into the viral replication cycle, in particular in the phase of viral progeny release from the infected cell, cutting the bond between neo-formed viral particles and host cells. The role of neuraminidase inhibitors, zanamivir and oseltamivir, is to interfere with the cutting activity of these enzymes, preventing the detachment of new virus particles from the host cell, the invasion of new cells and the consequent propagation of the infection.

Considering the peculiar potentialities of this new generation of drugs, the evaluation of their efficacy and safety in relation to the treatment of flu and to the post-exposure prophylaxis has been considered very important. Information is taken from the analysis of systematic reviews of clinical trials and refer to children and adults.

Studies in children

Oseltamivir, if administered within 48 hours from the disease onset, causes a 36 hours shortening of the average disease course in children younger than 12 with a laboratory-confirmed diagnosis^{1,2}. As documented by one single study, the treatment in the same population seems to be also associated to a 40% decrease of incidence of complications requiring the use of antibiotics. Among these the incidence of otitis media, which shows a 44% decrease¹. The treatment results less effective in children with clinically-diagnosed flu (23 hours reduction of average disease course).

Zanamivir causes a 1.25 days reduction of average disease course in children aged 5 to 12 with laboratory-diagnosed flu and of 0.5 days in those with clinically-diagnosed flu.

The total amount of adverse events is similar between patients treated with oseltamivir and patients treated with placebo, even though a significant increase in vomit incidence (OR 1.68 IC 95% 1.15-2.47) is pointed out. On the other hand, the frequency of adverse events after administration of zanamivir is similar to the one observed after administration of placebo.

Studies in adults

Jefferson³ evaluated the effectiveness of neuraminidase inhibitors in subjects aged 14 to 60. Both oseltamivir and zanamivir, if administered within 48 hours from the symptoms' onset, reduced of the time needed to relieve symptoms and to return to normal activity, both in flu-like syndrome and in confirmed flu. These data are equal to those reported by other recent systematic reviews^{2,4}. Jefferson's review reports a reduction consequent to oseltamivir administration in relation to the ability to prevent all complications (OR 0.39 IC 95% 0.28-0.55). This reduction mainly regards cases of confirmed flu, not of flu-like syndrome, and is documented by one single study. The treatment with neuraminidase inhibitors in adults does not appear to be associated to the onset of adverse events.

Use of neuraminidase inhibitors in post-exposure prophylaxis

Two studies included in Jefferson's review show oseltamivir efficacy in post-exposure prophylaxis among cohabitants (58%) and among contacts of flu cases (68%-89%). Family contacts seem to benefit also from administration of zanamivir. Adverse events caused by the prophylactic administration of oseltamivir result significantly higher than those caused by placebo in relation to nausea (OR 1.79 IC 95% 1.10-2.93).

Conclusions

Updating evidences related to the symptomatic treatment of flu with antiviral drugs did not in general produce relevant news. The panel does not recommend their routine use because, in spite of a certain statistic and clinical relevance of evidences, the outcome is scarcely relevant (one-day reduction of fever in adults and half-day reduction of fever in children).

The applicability of results to the actual environment – the general practitioner's ambulatory and the patient's house – is also discussed, considering that the efficacy of antiviral drugs is basically connected to two variables: laboratory-confirmed diagnosis, and early administration of neuraminidase inhibitors (within 48 hours from symptoms onset and ideally during the first 12 hours).

General practitioners could prescribe specific antiviral drugs through a diagnosis with rapid tests, but these test are not recommended due to their scarce reliability (see question 1, page ...).

New data relate to oseltamivir efficacy in post-exposure prophylaxis. In this case the panel drew up a new recommendation taking into consideration post-exposure prophylaxis in non-vaccinated institutionalized subjects (for example subjects living in **assisted care centres**).

Recommendation

D/I The routine use of neuraminidase inhibitors for the symptomatic treatment of influenza is not recommended. Their use is to be evaluated in each case.

Expected benefits

Reducing expenses for antiviral drugs; preventing viral resistance; reducing adverse reactions connected to the use of antiviral drugs.

Recommendation

C/I Oseltamivir is recommended only in the post-exposure prophylaxis in non-vaccinated institutionalized subject.

Expected benefits

Reducing the transmission of the infection.

Monitoring and audit markers

Number of defined daily doses of antiviral drugs.

Bibliography

1. Matheson NJ. Neuraminidase inhibitors for preventing and treating influenza in children (Review). Cochrane Database of Systematic Reviews 2007; Issue 1.
2. Turner D. Systematic review and economic decision modeling for the prevention and treatment of influenza A and B. Health Technology Assessment 2003; Vol. 7, No. 35.
3. Jefferson TO. Neuraminidase inhibitors for preventing and treating influenza in healthy adults (Review). Cochrane Database of Systematic Reviews 2006; Issue 3.
4. Bettis R. Impact of influenza treatment with Oseltamivir on health, sleep and daily activities of otherwise healthy adults and adolescents. Clin Drug Invest 2006, 26(6): 329-40

Question 4: Should antibiotics be used for the treatment of influenza, considered age and risk conditions?

Full amount of gathered studies:	525
Full amount of selected studies:	63
Full amount of extracted studies:	8

Included studies: 5 Systematic reviews
1 Observational study
2 Guidelines

Background

Flu is one of the most frequent pathological conditions in all ages and is associated to a high number of medical interventions answering patients' needs. The etiology of influenza is in most of cases viral. Flu viruses, para-influenza virus, adenoviruses, metapneumoviruses and syncytial respiratory viruses are responsible for fever and respiratory symptoms. Bacteria, in few cases, can be involved as agents directly responsible for infections or as agents responsible for infectious complications leading occasionally to a severe course (in particular bacterial pneumonia). Two issues to be underlined are that etiology is not a routine research and that medical interventions are largely based on the evaluation of patients' clinical conditions. The clinical situation is generally not severe and can resolve spontaneously. The use of antibiotics in the treatment of influenza is a common practice, even if their efficacy is questionable. Several studies showed a too high disposition to prescribe antibiotics, in particular to children.

Studies

The analysis of literature on this topic was aimed at assessing the usefulness of the treatment with antibiotics in patients of all ages showing flu symptoms. It included studies focused on the efficacy of antibiotics in relieving symptoms and in preventing flu-related complications. 5 systematic

reviews and one observational study, carried out on subject of all ages and in different environments, have been evaluated.

Effects on symptoms

Arroll's review¹, including 13 RCTs, report no efficacy of antibiotics in reducing nasopharyngeal symptoms in children and in adults; it demonstrates, on the other hand, a positive effect in the treatment of purulent rhinitis (sinusitis) and in non-purulent rhinitis among patients of all ages (respectively RR 0.62 and RR 0.52).

Del Mar² analyses 27 studies, up to a total amount of 12,835 cases, and assesses the benefits of antibiotics *versus* placebo in subjects with sore throat.

Flu symptoms, such as acute sore throat (OR 0.44), fever (OR 0.62) and headache (OR 0.33), benefit from the treatment with antibiotics, showing a significant reduction and a more evident efficacy in subjects with positive bacterial cultures.²

Fahey's systematic review, including 13 RCTs, focuses on patients with a clinically-diagnosed acute bronchitis, and reports a reduction of cough (RR=0.64 IC 95% 0.49-0.85), night coughing (RR=0.67 IC 95% 0.54-0.83), abnormal results on thoracic examination (RR=0.54 IC 95% 0.45-0.70).

Benefits in terms of reduction in days of cough and productive cough are also reported.

All described benefits seem to be reduced in patients showing other symptoms of upper respiratory tract infections and in those whose symptoms last since less than one week.

Revez's review⁴ is based on only two RCTs and has several methodological limitations. Studying a population of 206 adults with laryngitis, it shows an absence of improvements in voice **quality** after administration of antibiotics.

Effects on complications

The use of antibiotics has proved to be effective in reducing the risk of some bacterial complications. This efficacy results statistically significant in relation to otitis media (OR 0.23 IC 95% 0.12-0.44) and tonsillitis (OR 0.16 IC 95% 0.07-0.35), but not to glomerulo-nephritis (OR 0.07 IC 95% 0.00-0.32), sinusitis (OR 0.46 IC 95% 0.10-2.05) and rheumatic fever (OR 0.07 IC 95% 0.20-0.45) of which no cases are registered after 1975². The lack of a clear distinction between subjects with a positive culture and subjects with a negative culture in Del Mar's evaluation of antibiotics effects on complications, should be nonetheless underlined.

A well designed retrospective cohort study⁵ including more than 3 millions respiratory events in patients of all ages reports after administration of antibiotics a reduction of the risk of complications among patients with upper respiratory tract infections (pneumonia after upper respiratory tract infection, $p < 0.001$; mastoiditis after otitis, $p=0.008$; peri-tonsillar abscess after sore throat, $p=0.02$; pneumonia after thoracic infection $p < 0.001$).

It is worth noting that, against a net benefit gained in using antibiotics, the Number Needed to Treat, which means the number of subjects to be treated with antibiotics to avoid 1 complication, reported by the authors, results $> 4,000$ (except cases of pneumonia after thoracic infection) due to a low prevalence of bacterial complications among flu patients.

Side effects

The inappropriate use of antibiotics is responsible for significant expenses charged to the national health system and for the risk of bacterial resistance phenomena. Moreover, it expose single patients to the risks connected to all drugs' side effects. The risk of adverse events has been evaluated by two systematic reviews^{1, 3} highlighting an incidence rate higher in flu patients taking antibiotics, than in those taking placebo (RR 1.22 IC 95% 0.94-1.58). The same analysis has been carried out also in children, even if the results reported in the systematic review are not statistically relevant¹.

Reliable data show the efficacy of the delayed antibiotic therapy included in the strategies aimed at promoting an appropriate use of antibiotics. Spurling's study⁶ includes 9 RCTs and reports modest

results after comparing two strategies of antibiotics administration (immediate vs delayed > 48 hours) in relation to the disappearance of symptoms (fever, cold, vomit, pain, cough) and to the prevention of some complications (diarrhea OR = 0.27). Several RCTs included in the same review assess patients' satisfaction, that results higher in those receiving treatment during the first day, and the efficacy of the reduced use of antibiotics in case of delayed strategy.

Two guidelines^{7, 8} recommend the use of antibiotics only in flu pandemics and/or in patients at high risk of complications, in patients with severe symptoms and in case a reasonable certainty of bacterial infection exists.

Conclusions

Evidences confirm the indications to the use of antibiotics in the treatment of influenza included in the previous release of this guideline. Recommendations remain the same in relation to non-complicated flu and sore throat.

Recommendations

E/I The use of antibiotics is not recommended in non-complicated flu.

D/I The routine use of antibiotics in the treatment of flu-related sore throat is not recommended, unless the symptoms are complicated by bacterial infections.

Expected benefits

Preventing bacterial resistance; reducing adverse reactions connected to the use of antibiotics; reducing expenses for antibiotics.

Monitoring and audit markers

Number of defined daily doses of antibiotics; rate of antibiotics-resistant infections; reports of adverse reactions connected to the use of antibiotics.

Bibliography

1. Arrol B. Antibiotics for the common cold and acute purulent rhinitis. Cochrane Database of Systematic Reviews 2005.
2. Del Mar CB. Antibiotic for sore throat. Cochrane Database of Systematic Reviews 2006.
3. Fahey T. Antibiotics for acute bronchitis (Review). Cochrane Database of Systematic Reviews 2007.
4. Reveiz L. Antibiotic for acute laryngitis in adults. Cochrane Database of Systematic Reviews 2007-
5. Peterson I. Protective effect of antibiotics against serious complications of common respiratory tract infections: retrospective cohort study with the UK General Practice Research Database. *BMJ* 2007.
6. Spurling GK. Delayed antibiotics for respiratory infections. Cochrane Database of Systematic Reviews 2007.
7. Lim WS. Pandemic Flu: clinical management of patients with an influenza-like illness during an influenza pandemic. *Thorax* 2007.
8. Agenzia Sanitaria Regionale, Regione Emilia Romagna. Faringotonsillite in età pediatrica. Linea guida regionale 2007.

Question 5: Should anti-inflammatory and antipyretic drugs be used for the treatment of influenza, considered age and risk conditions?

	Full amount of gathered studies:	1846
	Full amount of selected studies:	22
	Full amount of extracted studies:	17
Included studies:	8 RCTs	

- 1 Meta-analysis
- 1 Systematic review
- 3 Narrative Reviews
- 3 Case-control studies
- 1 Guideline

Background

Antipyretic and anti-inflammatory drugs are largely used in the treatment of influenza and more generally in acute febrile syndromes. They are commonly recommended in case of fever higher than 38.5 °C, though it is known they are not able to affect the disease course, while it is less known the clinical benefit of the systematic control of fever.

Studies in children and adults

Available evidences in relation to the risk-benefit profile of these drugs generally present limits in **feasibility/transferability** due to a lack of homogeneity in populations and in type of febrile syndrome. Moreover, the strongest evidences in relation to safety come from studies on chronic inflammatory pathologies generally treated with higher dosages and for longer time lapses, due to the rarity of adverse events registered during administration of these drugs in acute inter-current conditions (few days of treatment and low-medium dosage).

The use of antipyretic and anti-inflammatory drugs should not be aimed at a constant and systematic control of fever, but at relieving the uneasiness of patients and their difficulty in handling it.

Recommendation

C/VI Considered the widespread practice of auto-prescription, citizens are to be informed that these therapies are only symptomatic and that using drugs is appropriate only in case there is a real need of reducing uneasiness and pain.

Expected benefits

Reducing the use of anti-inflammatory drugs.

Monitoring and audit markers

Number of defined daily doses of anti-inflammatory and antipyretic drugs; reports of adverse reactions connected to the use of anti-inflammatory and antipyretic drugs.

Children

Acetylsalicylic acid is not recommended in children due to its proved connection with Reye syndrome^{16, 17, 18}.

Ibuprofen and paracetamol are the more widely used drugs studied in pediatric clinical experimentations and chosen as a standard for their lower potential of inducing gastric lesions. A systematic review of 17 RCTs, a narrative review and more recent RCTs^{1, 2, 3, 4, 5, 6, 7} show a substantial equivalence of these two drugs in the treatment of pain and fever.

The strategies adopted for the use of these two drugs, combined or alternated, did not show clinically relevant benefits and the RCTs^{3, 5, 9}, being small in range, did not allow a correct evaluation of the effects connected to the different dosages considered in each strategy.

The regular administrations of antipyretics to control fever do not reduce the incidence of fever convulsions.

Moreover, the administration of high doses of paracetamol (generally higher than 90mg/kg/day) increases the risk of liver diseases. The administration to **infants (small children)** of formulations designed for adolescents or adults is an important risk factor¹⁴.

Recommendations

B/I Paracetamol and ibuprofen can be used in the treatment of fever and pain in children.

E/III The use of acetylsalicylic acid is not indicated in children younger than 12, due to its connection with Reye syndrome.

E/IV Parents should be warned against using paracetamol formulations for adults which do not allow to adapt the dosage to children's age and weight.

Expected benefits

Using drugs with a lower potential of inducing gastric lesions and reducing the risk of liver diseases consequent to paracetamol overdose.

Monitoring and audit markers

Number of defined daily doses of anti-inflammatory and antipyretic drugs; reports of adverse reactions connected to the use of anti-inflammatory and antipyretic drugs.

Adults

Data related to the efficacy of anti-inflammatory and antipyretic drugs in adults come from two RCTs showing that ibuprofen and diclofenac, exactly as acetylsalicylic acid and paracetamol, once compared have equal effects^{10, 11}.

Safety however deserves in adults an *ad hoc* discussion. The risk of gastric lesions is associated in different ways to: type of drug, dosage, associated use of other drugs and previous ulcers. The most frequently prescribed drugs causing the higher risk of gastric lesions, even if a lower dose is administered, are: ketorolac, piroxicam, indomethacin, ketoprofen, naproxen and acetylsalicylic acid¹⁹.

Some RCTs did not show differences in terms of adverse events after comparing acetylsalicylic acid and paracetamol in adult flu patients, nor did they identify an increase of adverse events after comparing the combination ibuprofen/paracetamol with paracetamol alone^{10, 12}. All studies had limitations in power in the evaluation of results, due to the rarity of expected adverse events in this clinical context.

A recent meta-analysis on the efficacy and safety of coxibs compared to traditional NSAIDs (ibuprofen, diclofenac and naproxen), nonetheless, showed that diclofenac and ibuprofen increase the risk of cardiovascular adverse events and so do Coxibs if taken in a high dosage and for a long period of time (more than a month). Naproxen, on the other hand, is not associated to this type of risk²⁰. The *American Heart Association* has recently drawn out the recommendation of avoiding the use of these anti-inflammatory drugs in patients at increased absolute cardiovascular risk (recent bypass surgery, infarction, unstable angina, presence of factors indicating high risk of ischemia), on the basis of these results²¹. The basic cardiovascular risk must be taken into consideration in choosing therapy, even though the results of these trials are not immediately applicable to the treatment of acute pathological conditions.

Recommendations

B/I Paracetamol, ibuprofen and diclofenac can be used, if needed, for the treatment of fever and pain in adults.

B/VI The use of paracetamol is recommended for the treatment of flu-related fever and uneasiness in subjects at increased cardiovascular risk.

An increased dose of acetylsalicylic acid, the minimum dose needed to obtain an antipyretic and analgesic effect, can be administered to subject already taking low-dose aspirin.

Naprossene can be similarly used in subject at increased cardiovascular risk not taking low-dose aspirin.

B/VI Doctors prescribing antipyretic and analgesic drugs should carry out a careful anamnesis of the basic gastro-duodenal and cardiovascular damages patients could risk.

Expected benefits

Using drugs with a lower potential of inducing gastric lesions in subjects not specifically at risk; identifying the drug minimizing risks in subjects with previous ulcers or at high absolute cardiovascular risk.

Monitoring and audit markers

Number of defined daily doses of anti-inflammatory and antipyretic drugs; reports of adverse reactions connected to the use of anti-inflammatory and antipyretic drugs.

Populations at risk

A narrative review suggests to prefer the use paracetamol in treating pregnant women. Moreover, a connection between neural tube defects and use of antipyretics in preconceptional period has been reported¹⁵.

Recommendation

B/II Paracetamol can be used for the treatment of fever and pain in pregnant women.

Expected benefits

Reducing adverse reactions connected to the use of anti-inflammatory drugs during pregnancy.

Monitoring and audit markers

Number of defined daily doses of anti-inflammatory and antipyretic drugs; reports of adverse reactions connected to the use of anti-inflammatory and antipyretic drugs.

Bibliography

1. Perrott David A. Efficacy and safety of acetaminophen vs ibuprofen for treating children's pain or fever. *Arch Pediatr Adolesc Med* 2004; 158: 521-6.
2. Leroy S. Ibuprofen in childhood: evidence-based review of efficacy and safety. *Archives de pediatrie* 2007; 477-84.
3. Sarrel E.M. Antipyretic treatment in young children with fever. *Arch Pediatr Adolesc Med* 2006; 160: 197-202.
4. Autret-Leca. Ibuprofen versus paracetamol in pediatric fever. *Current Medical Research and opinion* 2007; 23 (9): 2205-11.
5. Erlewyn-Lajeunesse S. Randomised controlled trial of combined paracetamol and ibuprofen for fever. *Arch Dis Child* 2006; 91: 414-6.
6. Prado J. Antipyretic efficacy and tolerability of oral ibuprofen, oral dipyron and intramuscular dipyron in children: a randomized controlled trial. *Sao Paulo Med J* 2006; 124(3): 135-40.
7. Ylmaz H. Intramuscular Dipyron versus Oral Ibuprofen or Nimesulide for Reduction of fever in the Outpatient setting. *Clin Drug Invest* 2003; 23(8): 519-26.
8. National Collaborating Centre for Women's and Children's Health, Feverish illness in children. 2007 May.
9. Nabulsi MM. Alternating ibuprofen and acetaminophen in the treatment of febrile children: a pilot study. *BMC Medicine* 2006 Mar; 4: 4.
10. Grebe W. A multicenter, randomized, double-blind, double-dummy, placebo-and active-controlled, parallel-group comparison of diclofenac-K and ibuprofen for the treatment of adults with influenza-like symptoms. *Clinical Therapeutics* 2003; 25: 444-58.
11. Bachert C. Aspirin Compared with Acetaminophen in the Treatment of Fever and Other Symptoms of Upper Respiratory Tract Infection in Adults: A Multicenter, Randomized,

- Double-Blind, Double-Dummy, Placebo-Controlled, Parallel-Group, Single-Dose, 6-Hour Dose-Ranging Study. *Clinical Therapeutics* 2005; 27(7): 993-1003.
12. Eccles R. Efficacy and safety of over the counter analgesic treatment of common cold and flu. *Journal of Clinical Pharmacy and Therapeutics* 2006.
 13. Kauffmann R. Ibuprofen and increased morbidity in children with asthma. *Pediatr Drugs* 2004; 6(5): 267-72.
 14. Ranganathan S. Fulminant hepatic failure and paracetamol overuse with therapeutic intent in febrile children. *Indian J of Pediatrics* 2006; 73: 871-5.
 15. Li Z. Maternal flu or fever, medication use and neural tube defects: a population-based case-control study in northern China. *Birth Defects Research* 2007; 79: 295-300.
 16. Hurwitz ES, Barrett MJ, Bregman D, et al. Public Health Service study on Reye's syndrome and medications: report of the pilot phase. *N Engl J Med* 1985; 313: 849-57.
 17. Hurwitz ES, Barrett MJ, Bregman D, et al. Public Health Service study of Reye's syndrome and medications: report of the main study. *JAMA* 1987; 257: 3366.
 18. Belay ED, Bresee JS, Holman RC, Khan AS, Shahriari A, Shonberger LB. Reye's Syndrome in the United States from 1981 through 1997. *N Engl J Med* 1999; 1377-82.
 19. Laporte JR, Ibáñez L, Vidal X et al. Upper gastrointestinal bleeding associated with the use of NSAIDs. Newer versus older agents. *Drug Safety* 2004; 27(6): 411-20.
 20. Kearney PM, Baigent C, Godwin J, Halls H, Emberson JR, Patrono C. Do selective cyclooxygenase-2 inhibitors and traditional non-steroidal anti-inflammatory increase the risk of atherothrombosis? Meta-analysis of randomised trials drugs. *BMJ* 2006; 332: 1302-8.
 21. Antman EM et al. Use of Nonsteroidal Antiinflammatory Drugs: An Update for Clinicians: Scientific Statement From the American Heart Association. *Circulation* 2007; 115: 1634-42.

Question 6: What are the hospitalization criteria/indications to hospitalization in adults, elder people and pregnant women with influenza?

Full amount of gathered studies:	476
Full amount of selected studies:	20
Full amount of extracted studies:	5

Included studies: 5 non-controlled case-series studies

Background

Defining hospitalization criteria and indications to hospitalization in adults with flu is a useful means to reduce inappropriate hospitalizations, incidence of hospitalization-related nosocomial infections, health expenses and the overcrowding of hospitals, typical in epidemics.

As a rule, to define a characteristic as “hospitalization criterion”, people with that characteristic should be prospectively proven – possibly in randomized controlled trials – to have a more favorable outcome if hospitalized (in terms of morbidity and mortality), when compared to others in the same conditions but treated at home.

Studies designed as such are not present in literature, while several researches have been published that only “take a photo” of the *status quo*, reporting the exceeding number of hospitalizations – due to all causes or to specific pathologies – and the exceeding number of deaths during epidemic peaks, and identifying retrospectively all factors associated to the decision of hospitalizing patients.

Studies

Five case-series, non-controlled studies have been included. One of these studies¹ examines patients from the Emergency and Triage (DEA – Dipartimento di Emergenza e Accettazione) during flu epidemic. Patients actually needing hospitalization, among those with a laboratory-confirmed diagnosis (72.8%), showed the following characteristics: age ≥ 65 , high co-morbidity (one or more chronic pathologies), flu-related complications.

Two of the included studies validate the use of prognostic grades, defined on the basis of scoring systems that consider different parameters pertaining to personal and physiological data, aimed at rapidly assessing the need of hospitalizing specific patients with flu symptoms^{2,3}.

Challen's study³ describes the *Pandemic Medical Early Warning Score* (PMEWS) considering physiological and non-physiological parameters that can be potentially identified in a general medical context. Parameters to be evaluated to define the PMEWS score are: age, physiological parameters (respiratory and cardiac frequency, oxygen saturation, arterial pressure, temperature, neurological conditions), symptoms (fever > 38° C, sore throat, dyspnoea, myalgia, diarrhoea), socio-economic conditions (patients living alone, homeless), co-morbidity, global assessment of patient's psycho-physical conditions (*performance status*).

The PMEWS results to be an instrument easier to apply if compared to other scores, such as the British Thoracic Society's CURB-65, the American Thoracic Society's indicator and the Pneumonia Severity Index. These last systems are in fact used limitedly to the hospital context, because the adopted parameters are assessed through imaging and/or laboratory diagnostics and patients need to have access at least to the hospital emergency room to carry out such examinations³. Prognosis worsens and risk of complications increases with the increasing of the PMEWS score. Nonetheless, a PPV = 100% is observed for scores higher than 7, but with a PNV = 44%: which means that, on the basis of a too rigid application of the score, a significant risk of not hospitalizing patients needing to be hospitalized do exist (see page ...).

Hak's study⁷ describes instead a prognostic score aimed at quantifying the flu-associated risk of severe results – such as pneumonia-related hospitalization and death for all causes – in non-institutionalized elder subjects (age ≥ 65).

Variables considered in the score are: age, sex, number of ambulatory visits in the year before infection, previous pneumonia or flu-related hospitalizations, pathologies more frequently associated to flu-related hospitalization (subjects with pulmonary, cardiac, renal pathologies; transplanted subjects; subjects with dementia or stroke; subjects with haematological and non-haematological cancers). This study indirectly suggests that the subjects at highest risk of complications are those for whom hospitalization in case of flu should be seriously considered.

Cancers are another risk condition associated to an increase of flu-related hospitalizations and/or to flu-related complications. Hospitalization rates in cancer patients are twice those in common people⁴.

Pregnant women, in all pregnancy phases, have been considered to be at increased risk of respiratory complications during flu season, even with no co-morbidity (diabetes, asthma, respiratory, cardiac, renal pathologies, anaemia).

Conclusions

The panel decided to include in this document one new issue not treated in the previous release. The new issue included is pregnancy seen as risk factor inducing to consider hospitalization in case of complicated flu.

Recommendations

B/V in case of complicated flu, taking into account the following risk factors in considering hospitalization is recommended.

Factors to be taken into account increase the risk of complications and death if overlapped and associated to the patient's clinical and socio-economic status; in any case clinicians global clinical judgment cannot be disregarded.

- Pregnant women
- Subjects aged 65 or older than 65

Clinical criteria

- concomitant pathologies: chronic respiratory, cardiac and/or liver diseases, cancer, diabetes mellitus, chronic alcohol abuse, malnutrition, cerebrovascular diseases, postsplenectomy, hospitalization during the last year;
- respiratory frequency ≥ 30 breaths/min, diastolic pressure ≤ 60 mmHg or systolic pressure < 90 mmHg, pulse ≥ 125 /min, body temperature < 35 or $\geq 40^\circ\text{C}$, alterations of the mental status (disorientation, stupor), signs of extra pulmonary sites of infection.

Laboratory data

- white cells $< 4,000/\text{ml}$ or $> 30,000/\text{ml}$ or absolute neutrophil number $< 1,000/\text{ml}$;
- $\text{PaO}_2 < 60\text{mmHg}$ or $\text{PaCO}_2 > 50\text{mmHg}$;
- signs of altered renal function: creatinine $> 1.2\text{mg/dl}$;
- unfavorable radiographic evolution and/or pneumonia with multiple hotbeds, presence of cavitation or pleuric effusion;
- hematocrit $< 30\%$ or hemoglobin $< 9\text{g/dl}$;
- signs of sepsis or of organ damage, such as metabolic acidosis or alterations in blood coagulation;
- arterial PH < 7.35 .

GCP/Good Clinical Practice

Hospitalization is recommended in patients with poor economic and social conditions not supported by a social-health assistance network, which could be an adequate alternative to hospitalization, even if presenting a clinical condition less compromised than the one reported in the previous recommendation.

Expected benefits

Reducing inappropriate hospitalizations.

Monitoring and audit markers

Number of hospitalizations due to flu/flu-like syndrome and related complications; discharge data for DRG 90.

Bibliography

1. Monmany J, Rabella N, Margall N, Domingo P, Gich I, Vasquez G. Unmasking influenza virus infection in patients attended to in the Emergency Department. *Infection* 2004 Apr; 32(2): 89-97.
2. Hak E, Wei F, Nordin J, Mullooly J, Poblete S, Nichol KL. Development and validation of a clinical prediction rule for hospitalisation due to pneumonia or influenza or death during influenza epidemics among community-dwelling elderly persons. *Journal of Infectious Diseases* 2004 Feb 1; 189(3): 450-9.
3. Challen K, Bright J, Bentley A, Walter D. Physiological-social score (PMEWS) vs CURB-65 to triage pandemic influenza: a comparative validation study using community-acquired pneumonia as a proxy. *BMC Health Services Research* 2007; 7: 33.
4. Cooksley CD, Avritscher EBC, Bekele BN, Rolston KV, Geraci JM, Elting LS. Epidemiology and outcomes of serious influenza-related infections in the cancer population. *American Cancer Society* 2005; 104(3): 618-28.
5. Dodds L, McNeil SA, Fell DB, Allen VM, Coombs A, Scott J, MacDonald N. Impact of influenza exposure on rates of hospital admissions and physician visits because of respiratory illness among pregnant women. *Canadian Medical Association Journal* 2007; 176(4): 463-8.

Question 7: What are the hospitalization criteria/indication to hospitalization in children with influenza?

	Full amount of gathered studies:	370
	Full amount of selected studies:	22
	Full amount of extracted studies:	11
Included studies:	2 cohort studies	
	7 non-controlled case-series studies	
	2 guidelines	

Background

Defining hospitalization criteria and indications to hospitalization in children with flu means providing a useful instrument supporting independent pediatricians, general practitioners and hospital-based pediatricians.

The accurate selection of subjects to be hospitalized or to be treated at home could allow an appropriate use of beds in hospitals, specially during epidemics, thus reducing patients' uneasiness, health expenses, and also the risk of flu-related nosocomial infections.

Unfortunately, literature lacks adequately-designed studies – such as prognosis studies aimed at identifying predictive factors of severity – and studies on the efficacy of hospitalization in reducing outcomes such as infection-related complications and death.

Studies

This guideline includes non-controlled observational and/or descriptive studies reporting data sets and examining the characteristics of patients hospitalized due to influenza. These studies identify the categories of patients at risk and indicate some clinical conditions predisposing to a more severe disease course, to a prolonged hospitalization or to a need of respiratory supports and/or intensive care.

The incidence rate of flu-related hospitalizations decreases from 3-4/1,000^{1, 2} in children younger than 6 months, to 0.9/1,000 in children aged from 2 and 5 years². The average hospitalization length varies from 5 to 7 days³, but this variation has no relation with the age. However, no relation has been demonstrated between severity of symptoms and children's age¹⁰.

Younger children, mainly if premature, are at higher risk of a prolonged hospitalization (4% for patients > 5 months and 22% for premature patients), while children with pre-existing chronic pathologies are more frequently hospitalized and suffer a more severe and prolonged flu course^{4, 5}.

The *Advisory Committee of Immunization Practice (ACIP)* defines the following risk classes in the document for prevention and control of influenza¹²: asthma, chronic lung diseases (ex. Cystic fibrosis), cardiopathies, hemoglobin diseases, chronic renal disorders, diabetes mellitus, congenital metabolic disorders, long term therapy with salicylates, neurological and neuromuscular pathologies, immunosuppression (see recommendation n.3).

A cohort-study carried out on 745 patients younger than 21 (77% < 5 years) hospitalized due to influenza⁶ is based on these risk classes. In this study 43% of hospitalized subject was affected by one or more of the pre-existing chronic pathologies identified by the ACIP, such as chronic lung pathologies, cardiopathies, neurological and neuromuscular diseases; another study also relates higher death rates to these classes⁷.

Pre-existing pathologies cannot be connected, on the basis of the identified studies, to final indications in relation to the criteria to be followed for the admission to intensive care. The presence of at least one of the conditions identified by ACIP, in fact, is not connected to a higher risk of being admitted in intensive care in one of the studies², while in another study 53% of patients treated in intensive care were affected by chronic diseases⁸.

The onset of complications, such as pneumonia and respiratory insufficiency, is another risk factor, and on its basis indications to flu-related hospitalization can be provided. This risk factor is increased by patients' younger age and basic conditions.

For example, the risk of pneumonia is significantly increased in children younger than one year (OR 6.2) or in children with cardiopulmonary diseases (OR 16.5)⁹; the risk of respiratory insufficiency is significantly associated to the presence of chronic lung diseases (excluded asthma), cardiac disorders, and neurological and neuromuscular disorders⁶.

Conclusions

As a new issue, not treated in the previous release of the guideline, the panel decided to consider as risk factors some pathologies and treatments (see recommendation n. 3) to be taken into account in assessing the need of hospitalizing a child with flu, as such conditions can expose patients to a more severe disease course.

Moreover, the panel decided to include in the indications to hospitalization also the presence of some symptoms, such as altered state of consciousness, signs of septicemia (paleness, hypotony, hypotension), as suggested in the guideline drawn out by the British Infection Society and the British Thoracic Society.

Recommendations

D/IV There are no absolute indications to hospitalization based exclusively on age.

D/V Hospitalization is not necessarily required, but domiciliary or ambulatory management handled by the pediatrician should be preferred, in presence of the following signs and symptoms:

- dehydration to be treated orally;
- infants younger than 3 month with low birth weight or premature;
- slight respiratory distress

C/V Hospitalization in children with flu is to be considered, but is not necessarily required, in the following cases:

- family unable to manage the situation
- economic or social conditions not guaranteeing domiciliary assistance
- episodes of non-complicated fever convulsions following the first one (ceased before reaching the hospital)
- respiratory frequency > 60/min or saturation O₂ < 92% (NB: respiratory frequency varies with age)

or in case of children affected by one of the following chronic pathologies, on the basis of the clinical conditions of the single patient (in particular children younger than 3 months):

- asthma (patients needing a daily therapy with corticosteroids or bronchodilators or cromons or antileucotriens)
- chronic pulmonary diseases (ex. Cystic fibrosis)
- cardiopathies
- immunosuppression (patients with a story of neoplastic pathologies, vasculitis and collagen-related diseases, congenital or acquired immunodeficiency or immunosuppressive therapy > 2 weeks)
- hemoglobin-related diseases
- chronic renal disorders
- diabetes mellitus
- congenital metabolic defects
- long-term therapy with salicylates (ex. ARI, S. Kawasaki)
- neurological and neuromuscular pathologies causing respiratory difficulties

A/III Hospitalization in children with flu is strongly recommended mainly if they show the following symptoms:

- signs of respiratory distress
- cyanosis

- RF > 70/min or O2 Saturation < 90%
- severe dehydration
- convulsions (first episode) or neurological symptoms
- bronchiolitis < 3 months
- altered state of consciousness
- signs of septicemia (at least two among paleness, hypotony, hypotension)*
- cyanogenetic cardiopathy

* these recommendations are based on grade V evidences.

Expected benefits

Reducing inappropriate hospitalizations.

Monitoring and audit markers

Number of hospitalizations due to flu/flu-like syndrome and related complications; discharge data for DRG 91-98.

Bibliography

1. Montes M, Vincente D, Perez-Yarza EG, Cilla G, Perez-Trallero E. Influenza-related hospitalisations among children aged less than 5 years old in the Basque Country, Spain: a 3-year study (July 2001-June 2004). *Vaccine* 2005; 23: 4302-6.
2. Schrag S, Shay DK, Gershman K, Thomas A, Craig AS, Schaffner W, Harrison LH, Vugia D, Clogher P, Lynfield R, Farley M, Zansky S, Uyeky T. Multistrata surveillance for laboratory-confirmed influenza-associated hospitalization in children 2003-2004. *Pediatric Infectious Diseases Journal* 2006 May; 25(5): 395-400.
3. Coffin SE, Zaoutis TE, Wheeler Rosenquist AB, Heydon K, Herrera G, Bridges CB, Watson B, Localio R, Hodinka RL, Keren R. Incidence, Complications, And Risk Factors for Prolonged Stay in Children Hospitalized With Community-Acquired Influenza. *Pediatrics* 2007; 119: 740-8.
4. Moore DL, Vaudry W, Sheifele DW, Halperin SA, Déry P, Ford-Jones E, Arishi HM, Law BJ, Lebel M, Le Saux N, Grimsrud K Tam T. Surveillance for Influenza Admissions Among Children Hospitalized in Canadian Immunization Monitoring Program Active Centers, 2003-2004. *Pediatrics* 2006; 118:e610-9.
5. Neuzil KM, Wright PF, Mitchel EF et al. The burden of influenza illness in children with asthma and other medical conditions. *J pediatr* 2000; 137: 856-64.
6. Keren et al. Neurological and neuromuscular disease as a risk factor for respiratory failure in children hospitalised with influenza infection. *JAMA* 2005; 294: 2188-94.
7. Bhat N, Wright JG, Broder KR, Murray EL, Greenberg ME, Glover MJ, Likos AM, Posey DL, Klimov A, Lindstrom SE, Balish A, Medina M, Wallis TR, Guarner J, Paddock CD, Shieh WJ, Zaki SR, Sejvar JJ, Shay DK, Harper SA, Cox NJ, Fukuda, Uyeki TM. Influenza-Associated Deaths among Children in the United States, 2003-2004. *N Engl J Med* 2005; 353: 2559-67.
8. Louie JK, Schechter R, Honarmand S, Guevara HF, Madrigal NY, Woodfill CJI, Backer HD, Carol A. Severe Pediatric Influenza in California, 2003-2005: Implications for Immunization Recommendations. *Pediatrics* 2006; 117: e610-8.
9. Katz MA, Tharmaphornpilas P, Chantra S, Dowell SF, Uyeki T, Lindstrom S, Balish A, Peret TCT, Chittaganpitch M, Simmerman JM, Olsen SJ. Who gets hospitalized for influenza pneumonia in Thailand? Implications for vaccine policy. *Vaccine* 2007; 25: 3827-33.

10. Edelbauer M, Wurznner R, Jahn B, Zimmerhackl L. C-reactive protein and leukocytes do not reliably indicate severity of influenza A infections in childhood. *Clinical Pediatrics* 2006 Jul; 45(6): 531-6.
11. Lim. Pandemic flu: clinical management of patients with an influenza-like illness during an influenza pandemic. *Thorax 2007 Guidelines British Infection Society, British Thoracic Society* .
12. MMWR-CDC- recommendation and report prevention and control for influenza july 13, 2007/55; 1-54).
http://www.cdc.gov/mmwr/preview/mmwrhtml/rr5606a1.htm?s_cid=rr5606a1_e

Question 8: Should non-conventional therapies be used in the treatment of influenza, considered age and risk conditions?

Full amount of gathered studies: 34
 Full amount of selected studies: 6
 Full amount of extracted studies: 2

Included studies: 2 systematic reviews of clinical randomized controlled trials

Background

The panel chose to include this question *ex novo*, because more and more frequently general practitioners and clinicians observe flu patients using non-conventional therapies.

Non-conventional therapies include the use of Chinese medicinal herbs for the prophylaxis and therapy of non-complicated flu. These products are available in several different combinations of active principles taken from herbs such as: *Herba Schizonepetae*, *Radix Ledebouriellae*, *Radox Bupleuri*, *Radix Platycodi* and *Rhizoma Zingiberis Recens*. Other substances taken from vegetable principles are used to prevent and treat flu-related symptoms. Some of these are: *Echinacea spp.*, *Sambucus nigra*, *Larch arabinogalactan*, *Astragalus membranaceous*, *Baptisia tinctoria*, *Allium sativa*, *Panax quinquefolium*, *Eleutherococcus senticosus*, *Andrographis paniculata*, olive leaf extract and *Isatis tinctoria*. The administration of dietary supplements, such as vitamin A and vitamin D, zinc, lactoferrin and N-acetylcysteine, is considered in literature as an alternative or non-conventional therapy.

Oscillocoquinum is included among non-conventional therapies. Oscillocoquinum is a widely used formulation made of wild duck heart and liver (natural reservoir of flu viruses) and is one of the most requested over-the-counter drugs.

Studies

The panel, to answer the question, decided to include systematic reviews in English indexed on databases in the period 2006-2007.

A systematic review¹ included the analysis of 7 randomized controlled clinical trials. Three trials examined the efficacy of oscillocoquinum-like formulations and homeopathic mixtures of inactivated viruses and bacteria in terms of flu prevention. Gathered evidences are not strong enough to suggest the routine use of these formulations. One of the trial reports adverse events associated to the use of homeopathic mixtures of inactivated viruses and bacteria.

Four trials were aimed at assessing oscillocoquinum efficacy (osillocoquinum vs placebo) in the treatment of flu.

The overall results provide weak evidences in relation to the efficacy of this homeopathic formulation in shortening the disease course. No statistically relevant differences appear between patients treated with oscillocoquinum and patients treated with placebo regarding the efficacy of the first one in relieving symptoms such as cough, fever and sore throat.

Chen's systematic review² concerning the use of Chinese medicinal herbs as a treatment for flu (2 randomized controlled trials) showed a certain efficacy of Ganmao capsules *versus* amantadine and

no differences between E Shu You and ribavirin. However, it should be noted that both trials included in the review have significant methodological limitations.

All identified studies refer generally to adults, so the effects of these therapies in specific populations at risk, such as children, pregnant women and elder people cannot be predicted.

Conclusions

All scientific evidences gathered and included to answer this question are not enough to prove non-conventional therapies efficacy in the treatment of flu.

Recommendation

D/I Studies included in the analysis are not strong enough to recommend the use of non-conventional therapies to prevent flu or to improve its clinical course.

Expected benefits

Limiting adverse events.

Monitoring and audit markers

Number of defined daily doses of non-conventional formulations; reports of adverse reactions connected to the use of non-conventional therapies.

Bibliography

1. Vickers AJ, Smith C. Homeopathic Oscillococcinum for preventing and treating influenza and influenza-like syndrome (Review). The Cochrane Library 2007; Issue 4.
2. Chen WY. Chinese medicinal herbs for influenza (Review). The Cochrane Library 2007.

Influenza vaccine

Nicola Principi

Vaccination is the most simple and effective intervention to prevent flu. Health authorities of all Countries recommend the vaccine to elder people (age >64 or, in some nations, age > 50) and to subjects of all ages affected by severe chronic pathologies.

No widely shared recommendations exist for healthy adults and children. Vaccination in adults is generally not recommended, while an agreement on what to recommend in children has not been reached yet. American and Finnish health authorities suggest the systematic use of vaccines in subject from 6 months to 5 years, while health authorities from other western Countries believe that vaccination should not be definitely recommended. Such disagreements are the consequence of a widely differing definition of the impact of flu in subject with no chronic pathologies and of the actual immunogenicity and efficacy of vaccines in protecting infants. Those in favour of vaccination believe that data clearly show that the medical, social and economic impact of flu in children accounts for universal vaccination, while those against it believe that available data are not enough to justify universal vaccination because are all gathered in subject with flu-like syndrome without a virological demonstration of the disease aetiology. Moreover, infants immune response is not always optimal and the induced protection could consequently result sometimes unsatisfactory. Starting every initiative aimed at improving vaccination of subjects at risk seems nowadays the most important issue to be faced, suspending the question of children vaccination until further scientific information is available.

Vaccination rates are in fact low both in adults and in children. Such low rates seem to be connected with health professionals' attitude toward flu vaccine and their underestimation of flu impact on subjects at risk and of the benefits provided by vaccination. All efforts should therefore be made to increase knowledge on flu and its prevention.

Molecular Biology Tests

Simona Puzelli, Livia Di Trani

Several infectious agents are capable of causing respiratory symptoms in humans extremely similar to those of flu, thus turning the process needed to reach certainty of diagnosis of influenza a complex procedure. Moreover, co-circulation in humans of different flu virus types (A and B) and antigenic subtypes (A H1N1, A H3N2) raises further difficulties in the diagnosis and antigenic identification of these etiological agents.

Traditional techniques, including viral isolation in suitable substrata (embryonated chicken eggs, cellular lines), are essential to carry out a detailed antigenic characterization of all flu viruses circulating during epidemics, but they require a long time, complex procedures and protocols, and specialized laboratories. To avoid fulfilling all such requirements more sensitive methodologies have been developed, able to rapidly confirm clinical diagnosis, improving the quality of human influenza surveillance systems.

The most recent gene amplification assays, aimed at demonstrating the presence of specific viral sequences in biological samples, have high sensitivity and specificity. Their use allows also the typing and/or sub-typing of identified flu viruses.

Molecular assays are mainly based on polymerase chain reactions (PCR) carried out on retro transcribed DNA obtained from viral RNA through a reverse transcription (RT) reaction. RT-PCR, recreating the *in vivo* DNA replication principle, allows the *in vitro* DNA cyclic synthesis. This process is carried out using couples of oligonucleotides capable of recognizing and linking with highly conservative regions of genes coding viral internal type-specific and surface sub-type-specific proteins.

The gene sequencing analysis allows both to retrieve antigenic characterization data and to characterize circulating viruses from a molecular point of view. In particular, the study on flu virus molecular evolution through the phylogenetic analysis of genomic sequences allows to assess the evolution of the flu variants responsible for yearly human epidemics. It thus contributes to provide the information needed to update each year the vaccine¹.

The need of rapidly confirming diagnostic data – for example during pandemics –, the difficulties in viral isolation, the frequent lack of clinical samples, along with several other factors, brought to the development of new and more sophisticated molecular assays, such as the “real time RT-PCR” and the NASBA (*Nucleic Acid Sequence-Based Amplification*) assays. The recent development of control systems monitoring the different test phases (extraction, amplification and display of amplification results) and the introduction of internal quality controls and of standardization instruments (external quality control) increased the efficiency of these assays.

Searching recent international literature, data on the evaluation of the different molecular tests currently available in diagnostic laboratory can be analysed to assess their efficiency. RT-PCR ability of improving the surveillance and characterization of circulating flu virus stems is well documented^{2, 3, 4, 5}. Published studies report, for the most part, results of comparisons between molecular assays and traditional techniques, including isolation in cellular cultures and/or with immunofluorescence assay.

Results show that RT-PCR has higher sensitivity, rapidity and efficiency when compared with traditional diagnostic methods. For example in a study carried out in England on samples collected during a flu season and in particular during an epidemic peak, the traditional procedure of isolation in cellular cultures has been compared with a “multiplex RT-PCR” assay. The multiplex RT-PCR method uses more than one couple of oligonucleotides in a single amplification reaction, with the purpose of detecting the presence of more than one genomic segment. This study showed that 57.5% of the gathered clinical samples were positive when analysed with PCR, while only in 38.9% of samples viruses could be isolated³.

The real time RT-PCR is a more recent innovation in gene amplification assays. This new technique allows the real time measuring of amplification during the PCR exponential phase through the

emission of a fluorescent signal. Moreover, amplification and revelation are combined in a close system avoiding all passages following amplification. It thus reduces variability and risks of contamination that can sometimes impair traditional PCR results. The assay allows also to obtain quantitative results, accurately measuring the number of viral genomic copies detected in the analysed sample.

Several studies described the creation and validation of real-time RT-PCR assays with high sensitivity and specificity^{6,7}, highlighting an increase of the identification potentials if compared with traditional RT-PCR. The abilities of this new technique are even more crucial in a pandemic context.

Molecular assays are essential to obtain rapid and accurate diagnosis in case of flu pandemic, but they are also valid diagnostic methods in inter-pandemic periods considered their potential applications.

The role of laboratory diagnostics is to identify as soon as possible the first case or cases of human infection in a pandemic scenario, with the purpose of restraining the epidemic and stop or slow down viral dissemination in population. In this context, the use of rapid molecular techniques, such as real-time RT-PCR – which is able to provide extremely rapid performances, high sensitivity, specificity and excellent reproducibility – is crucial.

Bibliography

1. Puzelli S, Frezza F, Fabiani C, Ansaldi F, Campitelli L, Lin Y P, Gregory V, Bennett M, D'Agaro P, Campello C, Crovari P, Hay A, Donatelli I. Changes in the hemagglutinins and neuraminidases of human influenza B viruses isolated in Italy during the 2001-02, 2002-03, and 2003-04 seasons. *J Med Virol* 2004; 74: 629-40
2. Ellis JS, Zambon M. Molecular diagnosis of influenza. *Rev Med Virol* 2002; 12: 375-89
3. Ellis JS, Fleming D, Zambon M. Multiplex reverse transcription-PCR for surveillance of influenza A and B viruses in England and Wales in 1995 and 1996. *J Clin Microbiol* 1997; 35: 2076-82
4. Zhang W, Evans DH. Detection and identification of human influenza viruses by polymerase chain reaction. *J Virol Methods* 1991; 33: 165-89
5. Pregliasco F, Mensi C, Camorali L, Anselmi G. Comparison of RT-PCR with other diagnostic assay for rapid detection of influenza viruses. *J Med Viro.* 1998; 56: 168-73
6. Ellis JS, Smith JW, Braham S, Lock M, Barlow K, Zambon M. Design and validation of an H5 TaqMan real time one-step reverse transcription-PCR and confirmatory assays for diagnosis and verification of influenza A virus H5 infections in humans. *J Clin Microbiol* 2007; 45: 1535-43
7. Chen W, He B, Li C, Zhang X, Wu W, Yin X, Fan B, Fan X, Wang J. Real time RT-PCR for H5-N1 avian influenza A virus detection. *J Med Microbiol* 2007; 56: 603-7

Pandemic Medical Early warning Score

Giulio Cocco

The *Pandemic Medical Early Warning Score* (PMEWS) is an exclusively clinical grading system that can be used in any healthcare structure, both in general medicine and in hospitals, even without the support of laboratory analysis or diagnostic imaging. It can be also used during flu epidemics. Challen et al's¹ study describes the validation of this prognostic score. The study follows a non-selected population of adults (age > 15) with community pneumonia, a disease considered a quite faithful model of clinical situations frequent in flu epidemics. It is retrospective and is focused on a cohort of patients hospitalized from February to December 2005. The following events have been taken as reference and on their basis the significance of scores has been assessed in relation to the need of hospitalizing and to the amount of care to be dedicated to patients:

Emergency hospitalization

Hospitalization in intensive care or in sub-intensive care, or use of mechanic ventilation

Death during hospitalization

The score has been defined on the basis of data reporting the alteration of some physiological parameters (respiratory frequency, oxygen saturation, cardiac frequency, systolic pressure, temperature, state of consciousness), considered patients' age, concomitant chronic (respiratory, cardiac, renal, immunitary, metabolic) pathologies, social isolation and performance status (global psychophysical conditions).

The CURB-65, the score for predicting mortality due to pneumonia, created by the *British Thoracic Society*², has been also calculated in the same group of patients.

The PMEWS score accurately defined patients requiring hospitalization (area under ROC 0.944 curve) and patients requiring a higher level of assistance to avoid irreversible damages to vital organs (are under ROC 0.83 curve). The areas under the curve resulted definitely more precise than those obtained with CURB-65. CURB-65, on the other hand, showed higher sensitivity and specificity when assessing mortality: which is logic, considering that CURB-65 has been specifically designed to predict mortality in case of pneumonia.

The authors concluded that PMEWS is an effective "instant" prognostic flu-patients assessment system (in a pandemic scenario), allowing to identify of altered "physiological" conditions and to define the required level of assistance (hospitalization or non-hospitalization; hospitalization in intensive care, in sub-intensive care, or ordinary hospitalization). In particular, the score to be considered as a threshold on the basis of which to decide if hospitalization is needed can vary in relation, for example, to the availability of beds in hospitals during flu pandemics, selecting sensitivity and specificity values differing from those used in usual conditions.

In evaluating this study the following elements should be taken into account:

this is a retrospective study;

the study has been carried out on patients affected by a different disease (pneumonia used as proxy for a possible flu pandemic) and not specifically by influenza;

the study lasted a time span (11 months) during which no flu pandemic occurred in the interested area.

One of PMEWS' advantages is to be extremely simple: the score can be defined in a short time in any location, at home, in a medical office, in hospital triages and emergencies. The CURB-65 is also sometimes used to decide if hospitalization is needed even in case of flu pandemic. It requires laboratory analysis and is not particularly effective in identifying patients needing hospitalization or in identifying the level of care patients need during hospitalization.

Even the SOFA (*Sequential Organ Failure Assessment*)³ has been validated to be eventually used in course of flu pandemic to assess the need of hospitalizing specific patients, but it requires a series of laboratory analysis.

A specific triage for hospitalization in course of flu pandemic has also been designed by the Canada's Medical Association⁴. The system is based on clinical-anamnestic data, but it defines only

if intensive care is needed, accurately predicting both the indication to intensive care and the criteria to exclude a patient from intensive care. This system is based on experts' opinions, without any statistic validation of sensitivity and specificity. Defining objective and effective criteria supporting and speeding up the decision of hospitalizing specific patients during a flu pandemic is important for health economy, to increase reliability in doctors and in health professionals' decision choices. A score system based on simple physiological data, such as PMEWS, seems appropriate to this purpose, requiring a short time and no expenses. Using this score during a flu epidemic and not a flu pandemic, requires a further validation, with prospective criteria, on patients affected by flu during an epidemic.

Bibliography

1. Challen K, Bright J, Bentley A, Walter D. Physiological-social score (PMEWS) vs. CURB-65 to triage pandemic influenza: a comparative validation study using community-acquired pneumonia as a proxy. *BMC Health Services Research* 2007; 7: 33
2. Lim WS, van der Eerden MM, Laing R, Boersma WG, Karalus N, Town GI, Lewis SA, Macfarlane JY. Defining community acquired pneumonia severity on presentation to hospital: an international derivation and validation study. *Thorax* 2003; 58: 371.
3. Cabre L, Mancebo J, Solsona JF, et al. Multicenter study of the multiple organ dysfunction syndrome in intensive care units: the usefulness of Sequential Organ Failure Assessment scores in decision making. *Intensive Care Med* 2005; 31: 927
4. Christian MD, Hawryluck L, Wax RS, Cook T, Lazar NM, Herridge MS, Muller MP, Gowans DR, Fortier W and Burkle FM. Development of a triage protocol for critical care during an influenza pandemic. *CMAJ* 2006; 175: 11

Avian flu

Epidemiology and surveillance

Pietro Crovari

The avian flu epidemic started in South East Asia in 2003 and was caused by a subtype highly pathogenic A H5N1 virus. This epidemic needs to be taken into consideration in the history of infectious epidemics for its importance and peculiarity.

The flu-related disease affecting chickens and home-bred birds (turkeys, geese, etc.) is long known: two Italian vets, Centauri and Savonuzzi (1900), described it and called it “fowl plague” even before the individuation of the etiological agent.

However, it is the first time that avian flu affects for so long a time so many wild and home-bred birds of a high number of Asian, European and African Countries, turning in “endemic” in some of them, with epidemic recurrence.

Two types of risk should be mainly considered in relation to human health.

The first one is a concrete risk. It regards populations living in those Countries in which the avian flu epidemic is widespread, in particular breeders, vets and persons living in agricultural zones or having direct contact with living chickens and butcher them. Avian A H5N1 virus has in fact been proven to be transmittable from chicken to humans, crossing the “species barrier” usually dividing human and animal flu. This eventuality is until now extremely rare. The number of defined cases of avian-to-humans transmission are 350, from December 2003 to 15 January 2008, against several millions of infected chickens. The fact that the infectious spreading stopped after the first steps, that is, that there was no human-to-human transmission, is to be underlined. Most of cases of avian virus A H5N1 infection in humans, however, showed a severe clinical course and a mortality > 50%.

The second avian flu-related risk factor is the A H5N1 virus adaptation to humans. A H5N1 would turn into a “new” human flu virus, if it were capable of being transmitted from human to human, and would cause a pandemic.

The whole world population, lacking a natural immunity to this virus, could be infected by the disease and the situation would be similar to that of 1957 outbreak of the new A H2N2 virus that originated the so called “Asian” pandemic. The A H1N1 virus stem, that in 1918 caused the “Spanish” pandemic and continued circulating for the next 39 years, was, in that occasion, replaced by the new virus.

Experts agree that the most efficient mechanism A H5N1 could use to adapt to humans is “recombination”, that is, the exchange of genetic material between avian virus and human virus that would give birth to a virus having partly human genes and partly avian genes. Both viruses responsible for the 1957 and 1968 pandemics were the result of the same mechanism.

Luckily, this mechanism has not been triggered in the almost two years during which avian virus (H5N1) and human virus (A H3N2; A H1N1) co-circulated, but the risk still exist. Another suggested mechanism is subsequent virus mutations with the selection of a H5N1 variation more and more capable of replicating in humans.

The researchers who recently resuscitated the Spanish virus affirm that the A H1N1 virus, thwt was responsible for the most widespread and severe human influenza pandemic, was born in 1918 through this same mechanism.

The risk is hypothetic, but its consequences would have a strong health and social impact.

Such consequences justify the alert status and the containment measures international bodies (WHO, EU, ONU, etc.) are applying.

However, a pandemic would be for the fist time faced not being fully disarmed:

we have an organized and worldwide-disseminated surveillance system that allows the real-time monitoring of virus evolution, thanks also to the new molecular biology diagnostic techniques; the “inverse genetic” approach allows the creation of new viral stems for the production in a short time of pre-pandemic vaccines and in a relatively short time also of pandemic vaccines;

influenza-specific antiviral drugs (zanamivir, oseltamivir) are available and can be used both for therapy and for a targeted prophylaxis;

the National Health System is organized to face both issues related to prevention and issues related to healthcare even during emergencies such as a flu pandemic;

the social system, from Civil Protection to volunteer organization, can play a crucial role in containing the social disruption consequent to pandemics;

The ability a Country has to use such resources could allow the containment of all pandemic-related damages and to reduce complications, hospitalizations and deaths rates defined through mathematic models based on previous pandemics.

The World Health Organization has recently drawn up the following document on these issues: *Clinical Management of human infection with avian Influenza A (H5N1) virus* (15.8.2007).

It is not known if avian flu A H5N1 virus will maintain unvaried its pathogenic characteristics once adapted to humans.

Prevention

Pietro Crovari

The individual prevention of infection is behavioural: it is based on avoiding contacts with dead birds.

Avian flu virus infection appears to be a professional disease mainly affecting bird-breeder and vets. Specific recommendations to minimize risks of introducing A H5N1 virus in farms and to protect workers are available.

The efficacy of antiviral drugs in post-exposure prophylaxis is not proven. The OMS, in absence of evidences, does not prevent the use of neuraminidase inhibitors for this indication. OMS' recommendation is to take 75 mg/day of oseltamivir for at least 7 days starting from the last exposure. Prophylaxis should be started as soon as possible and not later than 48 hours after exposure.

Avian flu A H5N1 virus vaccines are not currently marketed. Their development is one of the activities included in the pre-pandemic vaccination strategy, and vaccines are currently in an advanced phase of the registration process.

Clinical presentation and pathogenesis

Giampiero Carosi

Avian viruses react in a significantly different way in human body than A H3N2 and A H1N1 viruses.

1. They are responsible for a disseminated disease instead of a disease localized in the upper respiratory tract: viruses are isolated from blood, faeces, cerebrospinal fluid, liver. This dissemination is the cause of the clinical course of multi-organ failure in a high number of cases.
2. Lungs are highly affected due to some avian-subtype-specific receptors, in lung alveoli, that human subtypes do not have. This explains why lungs are constantly affected.
3. The viral charge found in the respiratory tract is sensibly higher and persist longer.
4. Cytokines production in the respiratory tract, directly reflecting the tissue inflammatory damage, is directly proportional to viral charge. A very frequently observed clinical condition associated with ARDS (Acute Respiratory Distress Syndrome) can be explained by the cytokine cascade.

Human avian flu appears to be, on the basis of the cited characteristic, a very severe disease currently associated with a 60% mortality rate.

Studies based on the serological identification of specific antibodies in exposed subjects showed that even if the infection course can also be asymptomatic, asymptomatic infection is rare.

Therapy

Giampiero Carosi

Neuraminidase inhibitors, among currently available drugs, are effective *in vitro* against A H5N1 virus stems. Oseltamivir is the only antiviral drug recommended in case of human avian flu infection. 25 subjects affected by avian flu have been treated with oseltamivir: 19 deceased and survival rates are not significantly higher in treated subjects than in non-treated subjects. However, these data could also be explained by the following factors:

the treatment with oseltamivir in the cited cases was started too late. Some indications suggest that starting the therapy within 5 days from the onset could improve prognosis (but therapy should be anyways started within 48 hours);

studies in animals suggest that the required dose of oseltamivir for the treatment of avian flu viruses is higher than the standard dose for human subtypes;

oral formulation appears to be sub-optimal in patients with severe diseases in intensive care units, even if no pharmacokinetic studies are currently available.