

# Italian evidence-based guidelines for the management of influenza-like syndrome in adults and children

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**Summary.** Specific clinical practice recommendations for the management of influenza like-illness were developed by a national multidisciplinary panel (Guideline Development Group, GDG), and included in the update of the evidence-based clinical practice guideline: “Management of influenza-like syndrome” issued by the Italian National Guidelines System (SNLG May 2008). The methodological process included: creation of a GDG, definition of key questions, search strategies, critical appraisal of the selected studies, development and grading of recommendations. Eight clinical questions were defined regarding: rapid tests for influenza, treatment, and hospitalization criteria. Eighty studies underwent critical appraisal. The GDG develops recommendations for each key question.

*Key words:* influenza, flu, grippe, antiviral, antibiotic, guidelines.

**Riassunto** (*Linee guida italiane per la gestione della sindrome influenzale in bambini e adulti basate sulle prove di efficacia*). Raccomandazioni per la pratica clinica basate sulle prove di efficacia relative alla gestione della sindrome influenzale sono state elaborate da un panel di esperti multidisciplinare e incluse nell’aggiornamento della linea guida “La gestione della sindrome influenzale” del Sistema Nazionale Linee Guida. Il percorso metodologico ha incluso: la creazione di un panel multidisciplinare, la definizione di quesiti clinici e delle relative strategie di ricerca; la valutazione critica degli studi, la sintesi delle prove, la formulazione e la graduazione delle raccomandazioni. Il panel ha individuato otto quesiti clinici a riguardo dell’uso dei test rapidi per la diagnosi dell’influenza, uso di antivirali, antiinfiammatori e antibiotici, e alla definizioni dei criteri di ricovero. Basandosi sulla sintesi delle prove di efficacia ha elaborato le relative raccomandazioni.

*Parole chiave:* influenza, antivirali, antibiotici, linee guida.

## INTRODUCTION

Influenza-like-syndrome is largely self-limiting and lasts generally a short lapse of time, but has a strong impact on the health of population and on the commitment of resources by the National Health Systems.

Variability in the management of adults and children with influenza-like syndrome still remains, due to uncertainties in the diagnostic, therapeutic and prognostic areas.

All of these critical areas are explored in the update of the Italian national guideline “Management of influenza-like syndrome” (full text in Italian and English on the SNLG website [www.snlg-iss.it](http://www.snlg-iss.it)) released by the Italian National Guidelines System (Sistema Nazionale Linee Guida) (SNLG) in May 2008. This article summarises the SNLG guidelines for effective and safe interventions in the management of influenza-like syndrome. The SNLG recommendations are

based on systematic review of best available evidence. Recommended best practice are based on the clinical experience of the Guideline Development Group (GDG), when minimal evidence is available.

## METHODS

The recommendations were developed in the landscape of the Italian guideline elaboration process, which includes the following steps: creation of a multidisciplinary group of experts, definition of key questions and of search strategies, selection of studies through abstract, critical appraisal of the selected studies, the synthesis of the gathered evidence, and the development and grading of recommendations.

GDG included representatives of key stakeholders and experts in disciplines such as infectious diseases,

paediatrics, geriatrics, hygiene and preventive medicine, virology, pharmacology, epidemiology, pulmonary diseases, experts in guideline development, and information specialists.

A systematic review of the literature published from January 2003 to October 2007 was carried out in order to update evidence. Targeted search strategies were created for each key question. The following databases were searched: Medline, PubMed, Embase and Biosis, Cochrane Library, Cochrane Controlled Trials Register and SciSearch.

The selection of studies and their critical appraisal were performed by specifically trained personnel. The methodological checklists drawn up by the Scottish Intercollegiate Guidelines Network (SIGN, www.sign.ac.uk) were used for critical appraisal.

Recommendations were graded using the grading system (Table 1) described in the PNLG Methodological Handbook (www.snlg-iss.it).

The final document has been reviewed by professionals not involved in the drafting process (influenza and infectious diseases specialists). The GDG considered each suggestion and used it to refine the guideline draft.

## RESULTS

The GDG members drew up the following questions: 1 clinical question on the diagnosis of flu through rapid tests (Table 2); 5 questions on the indications to the

use of amantadine and rimantadine, neuraminidase inhibitors, antipyretic and non-steroidal anti-inflammatory drugs (NSAIDs), and non-conventional therapies (Table 2); and 2 questions on the indications to hospitalization in children and adults (Tables 3 and 4).

### Early assessment of influenza

(Table 2) reports the results of critical appraisal in relation to the use of rapid tests for the diagnosis of influenza.

Selected studies assessed the validity of the various marketed rapid influenza diagnostic tests, comparing their performance with the reference tests (viral culture and/or molecular biology tests). Studies reported low sensibility and specificity for rapid tests [1-4].

The quality and the type of samples affect the validity of the test (nasopharyngeal aspirates increase sensibility vs throat and nose swabs) [5]. Rapid tests resulted more sensitive in children aged less than 5 years [6, 7] and in diagnosing influenza type A more than influenza type B [8].

Tests resulted having a low positive predictive value in non-epidemic periods (low prevalence of influenza). Moreover, the inadequate sensitivity turns into a reduction in negative predictivity, *i.e.* a negative result is not enough to exclude diagnosis of influenza.

Thus GDG decided not to recommend the routine use of rapid tests due to their unsatisfactory performance.

### Treatment of influenza and influenza like-syndrome Antiviral drugs

The use of antiviral drugs in the treatment of influenza was the core topic in several systematic reviews and primary studies. However, these studies were found to be based on scarcely relevant outcomes.

Jefferson's reviews and Turner's review [9, 10] showed that amantadine shorten duration of fever by one day in adults aged 16 to 65 and in children. It was also proven to be effective in reducing the incidence of laboratory-confirmed influenza type A (RR reduction 61%, 95% CI 35%-76%) and the incidence of flu-like syndrome cases (RR reduction 25%, 95% CI 13%-36%).

However, amantadine has unpleasant side effects including nausea, anxiety, depression, insomnia and hallucinations. It tends also to induce viral resistance [9], a side effect reported also in Gravenstein's study in relation to rimantadine [11].

Oseltamivir and zanamivir were found to induce a 30-36 hours reduction of disease course in children (younger than 12) and in adults with laboratory-confirmed influenza, when administered within 48 hours from the onset of symptoms [10, 12-14].

Two studies focusing on post-exposure prophylaxis [13] showed that oseltamivir has a prophylactic efficacy among households (58%) and among contacts of cases of influenza (68%-89%), while zanamivir has a prophylactic efficacy only among

Table 1 | Levels of evidence and strength of recommendations

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 meta-analysis
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
Strenght 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

**Table 2** | Key questions, selected studies and recommendations regarding the routine use of flu rapid test, amantadine and rimantadine, neuraminidase inhibitors, antipyretic and anti-inflammatory drugs and non-conventional therapies for the treatment of influenza-like syndrome

Key questions	Studies	Recommendations
Should rapid diagnostic tests be routinely used for the management of influenza-like-syndrome in general medicine?	122 identified, 25 selected, 19 appraised, 19 included	<b>D/III</b> - 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
Should amantadine and rimantadine be used for the treatment of Influenza-Like Syndrome considered age and risk conditions?	237 identified, 58 selected, 9 appraised, 9 included	<b>D/I</b> - The routine use of amantadine and rimantadine is not recommended.
Should neuraminidase inhibitors be used for the treatment of, influenza-like syndrome considered age and risk conditions?	178 identified, 93 selected, 4 appraised, 4 included	<b>D/I</b> - The routine use of neuraminidase inhibitors for the symptomatic treatment of I-Like Syndrome is not recommended. Their use is to be evaluated in each case <b>C/I</b> - Oseltamivir is recommended only for post-exposure prophylaxis in non-vaccinated institutionalized subjects
Should antibiotics be used for the treatment of influenza-like syndrome considered age and risk conditions?	525 identified, 63 selected, 8 appraised, 8 included	<b>E/I</b> - The use of antibiotics is not recommended in non-complicated flu <b>D/I</b> - The routine use of antibiotics in the treatment of influenza-like syndrome-related sore throat is not recommended, unless symptoms are complicated by bacterial infections
Should non-steroidal anti-inflammatory and antipyretic drugs be used for the treatment of influenza-like syndrome considered age and risk conditions?	1846 identified, 22 selected, 17 appraised, 17 included	<b>C/VI</b> - 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>B/I</b> - Paracetamol and ibuprofen can be used in the treatment of fever and pain in children <b>E/III</b> - The use of acetylsalicylic acid is not indicated in children younger than 12, due to its connection with Reye syndrome <b>E/IV</b> - 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>B/I</b> - Paracetamol, ibuprofen and diclofenac can be used, if needed, for the treatment of fever and pain in adults <b>B/VI</b> - 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>B/VI</b> - Doctors prescribing antipyretic and analgesic drugs should carry out a careful anamnesis of the basic gastro-duodenal and cardiovascular damages patients could risk <b>B/II</b> - Paracetamol can be used for the treatment of fever and pain in pregnant women
Should non-conventional therapies be used for the treatment of influenza-like syndrome considered age and risk conditions?	34 identified, 6 selected, 2 appraised, 2 included	<b>D/I</b> - Studies included in the analysis are not strong enough to recommend the use of non-conventional therapies to prevent Influenza-like syndrome or to improve its clinical course

households. However, the prophylactic administration of oseltamivir causes a significant increase in nausea, when compared to placebo (OR 1.79, 95% CI 1.10-2.93).

The GDG decided not to recommend the routine use of amantadine, rimantadine, oseltamivir and zanamivir due to the irrelevance of the outcomes considered in the selected studies, of their side effects, and of the emerging resistance phenomena. The GDG decided instead to recommend the use of oseltamivir in the post-exposure prophylaxis in non-vaccinated institutionalized patients (*Table 2*).

#### *Antibiotics*

Selected studies focused on the efficacy of antibiotics in relieving symptoms and in preventing flu-related complications.

Del Mar's review [15] reported a statistically significant efficacy of antibiotics in reducing the risk of otitis media (OR 0.23, 95% CI 0.12-0.44) and tonsillitis (OR 0.16, 95% CI 0.07-0.35), but not in reducing the risk of glomerulo-nephritis (OR 0.07 CI 95% 0.00-1.32) and sinusitis (OR 0.46, CI 95% 0.10-2.05). However it is worth noting that the studies included in that review did not report a clear discrimination between subjects with a throat swab positive culture and subjects with a throat swab negative culture. Petersen's large retrospective cohort study [16] reported a significant reduction in pneumonia after upper respiratory tract infection, mastoiditis after otitis, peri-tonsillar abscess after sore throat, and pneumonia after thoracic infection in patients of all ages after administration of antibiotics. Nonetheless, the Number Needed to Treat (NNT), to prevent one complication, was

>4000 (except cases of pneumonia after thoracic infection) due to a low prevalence of bacterial complications among flu patients.

As regards the risk of adverse events, a systematic review [17] highlighted an incidence rate higher in flu patients taking antibiotics, than in those taking placebo (RR 1.22 CI 95% 0.94-1.58). Spurling's systematic review [18] analysed the use of the delayed antibiotics (>48 hours), vs the immediate use of antibiotics and no antibiotics, as a prescribing strategy in upper respiratory tract infections. There were no significant differences between the two immediate vs delayed strategies in relation to the disappearance of symptoms (fever, cold, vomiting, pain, cough), whereas a decrease in the use antibiotics in case of delayed strategy was reported.

The GDG concluded, on the basis of the evidence gathered, that the use of antibiotics is not recommended in non-complicated flu, nor in flu-related sore throat, unless the symptoms are complicated by proven bacterial infections (*Table 2*).

#### Antipyretic and non-steroidal anti-inflammatory drugs (NSAIDs)

Children: ibuprofen and paracetamol were proven to be equally effective in the treatment of pain and fever in children [19-23]. The administration of high doses of paracetamol (generally higher than 90mg/kg/day) in children was demonstrated to increase the risk of liver diseases [24]. The combined or alternated strategies adopted in children for the administration of ibuprofen and paracetamol did not show clinically relevant benefits [20-22, 25]. However, the effects associated to the different dosages in each strategy resulted of difficult interpretation, due to the small size of the samples.

The GDG therefore, recommended paracetamol and ibuprofen in the treatment of fever and pain in children. (*Table 2*).

*Adults:* two RCTs comparing ibuprofen vs diclofenac, and acetylsalicylic acid vs paracetamol in adults, reported equal efficacy of these drugs against influenza-like symptoms and did not show differences in terms of adverse events [26, 27].

Adverse events associated to the use of the antipyretic and NSAIDs were detected by a multicentre case-control study [28] where ketorolac, piroxicam, indomethacin, ketoprofen, naproxen and acetylsalicylic acid were associated to a higher risk of upper gastrointestinal bleeding even at low doses. The risk resulted increased in patient with a history of peptic ulcer and/or upper gastrointestinal bleeding. A meta-analysis [29] assessing the efficacy and safety of Coxibs vs traditional NSAIDs (ibuprofen, diclofenac and naproxen), showed that diclofenac and ibuprofen increase the risk of cardiovascular adverse events and so do Coxibs when taken in a high dosage and for a long period of time (more than 1 month); naproxen, on the contrary, was found not to be associated to this risk.

The GDG placed high value on the potential adverse effects of these drugs, on the basis of the information gathered, including the recent guidelines issued by the American Heart Association [30]. A special consideration of the benefits and harms for patients at higher risk of adverse outcome, such as those with a history of peptic ulcer/gastrointestinal bleeding and those at increased absolute cardiovascular risk (recent bypass surgery, infarction, unstable angina, presence of factors indicating high risk of ischemia), guided the definition of the recommendations (*Table 2*).

#### Complementary/alternative therapy

Two systematic reviews were included into the guideline to answer the question about the efficacy of complementary/alternative therapies [31, 32]. One systematic review of seven RCTs analyzed the efficacy and safety of Oscilloccocinum-like formulations and homeopathic mixtures of inactivated viruses and bacteria [31]. No evidence of efficacy was gathered. Adverse events were associated to the use of homeopathic mixtures of inactivated viruses and bacteria.

The other systematic review [32] including two trial about chinese herbs, showed some efficacy of Ganmao capsules vs amantadine and no differences between E Shu You vs ribavirin. The GDG decided not to recommend the use of non-conventional therapies to prevent influenza-like syndrome or to improve its clinical course due to the weakness of the available evidence (*Table 2*).

### CLINICAL HOSPITALIZATION CRITERIA IN FLU-LIKE SYNDROME

As a rule, to define a characteristic as "hospitalization criterion", people with that characteristic should be prospectively proven to have a more favorable outcome if hospitalized, when compared to other subjects in the same conditions but treated at home. Unfortunately, no studies with such design are present in literature. Several descriptive studies have been instead gathered, retrospectively investigating all factors associated to the decision of hospitalizing patients.

#### *Hospitalization criteria in adults*

The included studies are case series, where physiological and clinical data are collected to assess the severity of influenza-like syndrome and to establish in adults the need of hospitalization.

A clear relationship has been underlined between indication to hospitalization of flu-patients and age  $\geq 65$ , comorbidities and poor socio-economical conditions [33, 34]. Two of these studies analysed the reliability of prognostic scores. Challen's study [33] described the Pandemic Medical Early Warning Score (PMEWS) applied in all subjects older than 18 years. Hak's study [34] described instead a prognostic score specific for elder people (age  $\geq 65$ ). The PMEWS resulted 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 scores 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 examinations [33]. Finally, hospitalization rates are higher in patients with cancer and in pregnant women, specially if they are in the last 3 months of pregnancy [35, 36].

The GDG therefore was guided in developing recommendations, by a special consideration of the underlying conditions of patients. Thus, concomitant pathologies should be taken into account since such conditions may expose patients to a more severe disease course (Table 3).

#### **Clinical hospitalization criteria in children**

The included studies showed an association between co-morbidities and indication to hospitalization. The Advisory Committee of Immunization Practice [37] defines the following risk classes in children, taking into account pre-existing co-morbidities: 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.

A main criterion to hospitalize children with influenza is the presence of complications like pneumonia or respiratory insufficiency. Strong evidence is available in literature supporting the hospitalization of children showing cyanosis, severe dehydration, neurological symptoms, bronchiolitis, sepsis [38].

The recommendations are shown in (Table 4). Some pathologies and treatments were taken into account in assessing the need of hospitalizing a child with flu, as such conditions may expose patients to a more severe disease course.

#### **DISCUSSION**

This review summarizes the recommendations included in the clinical practice guideline: "The management of influenza-like syndrome" drawn up by the Italian National Guidelines System (SNLG).

The strength of this guideline is the transparent, evidence-based approach and its dealing with flu-like syndrome as it appears to health professionals in every day clinical practice: a condition with blurred borders, presenting uncertainties in the diagnosis, treatment and prognosis. Rapid tests

**Table 3** | Key questions, selected studies and recommendations about the hospitalization criteria/indications in adults

Key question	Studies	Recommendations
What are the hospitalization criteria/indications in adults, elder people and pregnant women with influenza-like syndrome?	476 identified, 20 selected, 5 appraised, 5 included	<p><b>B/V</b> - 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</p> <p>Pregnant women Subjects aged 65 or older than 65</p> <p><i>Clinical criteria</i></p> <p>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 <math>\geq 30</math> breaths/min, diastolic pressure <math>\leq 60</math>mmHg or systolic pressure <math>&lt; 90</math> mmHg, pulse <math>\geq 125</math>/min, body temperature <math>&lt; 35</math> or <math>\geq 40</math> °C, alterations of the mental status (disorientation, stupor), signs of extra pulmonary sites of infection</p> <p><i>Laboratory data</i></p> <p>white cells <math>&lt; 4000</math>/ml or <math>&gt; 30\ 000</math>/ml or absolute neutrophil number <math>&lt; 1000</math>/ml; PaO<sub>2</sub> <math>&lt; 60</math>mmHg or PaCO<sub>2</sub> <math>&gt; 50</math>mmHg; signs of altered renal function: creatinine <math>&gt; 1.2</math>mg/dl; unfavorable radiographic evolution and/or pneumonia with multiple hotbeds, presence of cavitation or pleuric effusion; hematocrit <math>&lt; 30\%</math> or hemoglobin <math>&lt; 9</math>g/dl; signs of sepsis or of organ damage, such as metabolic acidosis or alterations in blood coagulation; arterial PH <math>&lt; 7.35</math></p> <p><b>GCP/Good Clinical Practice</b> - 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</p>

**Table 4** | Key questions, selected studies and recommendations about the hospitalization criteria/indications in children

Key question	Studies	Recommendations
What are the hospitalization criteria/indications in children with influenza-like syndrome?	370 identified, 22 selected, 11 appraised, 11 included	<p><b>D/IV</b> - There are no absolute indications to hospitalization based exclusively on age</p> <p><b>D/V</b> - 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:</p> <ul style="list-style-type: none"> <li>- dehydration to be treated orally;</li> <li>- infants younger than 3 months with low birth weight or premature;</li> <li>- slight respiratory distress</li> </ul> <p><b>C/V</b> - Hospitalization in children with flu should be considered but not necessarily carried out in the following cases:</p> <ul style="list-style-type: none"> <li>- family unable to manage the situation</li> <li>- economic or social conditions not guaranteeing domiciliary assistance</li> <li>- episodes of non-complicated fever convulsions following the first one (ceased before reaching the hospital)</li> <li>- respiratory frequency &gt; 60/min or saturation O<sub>2</sub> &lt; 92% (NB: respiratory frequency varies with age)</li> <li>- 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):</li> <li>- asthma (patients needing a daily therapy with corticosteroids or bronchodilators or cromons or antileucotriens)</li> <li>- chronic pulmonary diseases (ex. Cystic fibrosis)</li> <li>- cardiopathies</li> <li>- immunosuppression (patients with a story of neoplastic pathologies, vasculitis and collagen-related diseases, congenital or acquired immunodeficiency or immunosuppressive therapy &gt; 2 weeks)</li> <li>- hemoglobin-related diseases</li> <li>- chronic renal disorders <ul style="list-style-type: none"> <li>• diabetes mellitus</li> <li>• congenital metabolic defects</li> <li>• long-term therapy with salicylates (ex. ARI, S. Kawasaki)</li> <li>• neurological and neuromuscular pathologies causing respiratory difficulties</li> </ul> </li> </ul> <p><b>A/III</b> - Hospitalization in children with flu is strongly recommended mainly if they show the following symptoms:</p> <ul style="list-style-type: none"> <li>• signs of respiratory distress</li> <li>• cyanosis</li> <li>• RF &gt; 70/min or O<sub>2</sub> Saturation &lt; 90%</li> <li>• severe dehydration</li> <li>• convulsions (first episode) or neurological symptoms</li> <li>• bronchiolitis &lt; 3 months</li> <li>• altered state of consciousness</li> <li>• Signs of septicemia (at least two among: paleness, hypotony, hypotension)</li> <li>• cyanogenetic cardiopathies</li> </ul>

are not recommended, since their performance is unsatisfactory in primary and secondary care, due to their low positive predictive value during inter-epidemic seasons, and their low negative predictive value during epidemic seasons. 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. Uncertainties in the treatment make less useful their use, even if the selected rapid test is considered among the most reliable.

The hospitalization criteria for both adults and children were drawn up on the basis of data taken from the most recent case-series studies and guidelines. Most of the evidence was therefore indirect and did not allow the elaboration of precise answers to the questions concerning the appropriateness of

hospitalization. Thus, the GDG drew up the recommendations articulating available evidence with context variables, and with the clinical expertise of each member of the GDG.

Recommendations concerning the treatment were developed taking into consideration the quality of evidence, the relevance of the outcomes and the balance between benefits and harms for individual patients. Thus, high-quality studies did not imply strong recommendations if the GDG judged that the outcomes were not clinically relevant, or harms outweighed the benefits.

Following these rules, the GDG decided not to recommend the routine use of antiviral drugs (amantadine, rimantadine, neuraminidase inhibitors) in the treatment of influenza-like syndrome.

The effectiveness of neuraminidase inhibitors, in particular, was noted to be basically related to two

variables: laboratory-confirmed diagnosis of influenza, and early administration (within 48 hours from the onset of symptoms and ideally during the first 12 hours). The concept of early administration was considered non-realistic in everyday clinical practice for the following reasons: first, because of the specific clinical characteristics of influenza like-syndrome, i.e non-severe symptoms at the onset; second, because of the setting in which general practitioners act, that is, a place where laboratory tests to confirm diagnosis are not available. Rapid tests should not be used since their performance is unsatisfactory. Thus, GDG judged inappropriate the routine prescription of neuraminidase inhibitors by general practitioners.

The question regarding the use of antibiotics in the treatment of flu-like syndrome has been handled with the same attitude, that is, evaluating the methodological quality of the studies in relation to the importance of the outcomes and the balance between benefits and harms. The GDG highlighted the effectiveness of antibiotics in reducing complications. Risks for this outcome resulted to outweigh benefits. It was noted, in fact, that the number of subjects to be treated to prevent 1 complication was considerably high (NNT > 4000) as well as the risk of adverse events associated with the use of antibiotics (RR 1.22 IC 95% 0.94-1.58). This risk is currently increasingly recognised [39-40].

Therefore, the GDG decided not to recommend antibiotics in non-complicated flu-like syndrome and limit their prescription to sore throat due to proven bacterial infection.

The balance between benefits and harms was also investigated to answer the question on the effectiveness and safety of antipyretic/anti-inflammatory drugs. The scarce power of clinical trials in

the detection of adverse events emerged. Hence the need to combine data from the clinical trials identifying benefits with data coming from observational studies specifically designed for safety.

Furthermore, some issues concerning the directness of the results from the RCTs, that is, their applicability to the considered patients, were raised in answering to the question on the effectiveness of antipyretic and anti-inflammatory drugs. The recommendations for the use of such drugs in the treatment of flu-like syndrome, in fact, have been necessarily drawn up on the basis of evidence from studies testing them in patients with chronic inflammatory diseases. Therefore, the directness of evidence, that is, how they can be generalized to "acute" clinical contexts, evidently requires caution, and the importance of the GDG's judgement should be underlined.

Finally, the GDG stressed the need of taking into consideration co-morbidities and polytherapies, both frequent conditions, mainly in elder patients. Therefore, diversified recommendations have been drawn up, including the requirement of a preliminary assessment of the individual patients' baseline risk for cardiovascular diseases and gastro-duodenal diseases, before prescribing anti-inflammatory and antipyretic drugs. Once more, the inadequacy of a too simplified clinical evaluation of the disease/condition is clear, thus the importance of an holistic approach to patients, aimed at reducing the distance between research and daily clinical practice.

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