



Perspectives in Research

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- Intelligent use of Medications
- Observational Study of Nosocomial Infections
Epidemiologic Surveillance in the Hospital Nacional de Geriatría y Gerontología (Geriatrics and Gerontology National Hospital) between 2008-2010
- Atrial fibrillation as a problem of public health: New options to prevent a stroke?
- Comments on the ethical aspects of an investigation with human being participation



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From the Editor

Intelligent use of Medications

Lovato-Gutiérrez Pedro, MD MPH¹

The irrational use of medication currently is a public health concern that should be shared across the health systems. Poly drug use and diagnostic exercise do not bear a relation with a therapeutic practice and the ideal patient care. A cost-effective or a cost-benefit assessment is necessary if a maximization of available resources for health technologies like drug therapeutic is to be achieved. To perform the correct drug prescription, with the exact dose and the right period remains to be the ultimate goal. The purpose of this review is to present a point of view about the intelligent use- or like some authors call it- rational use of medications. The right consolidation of these concepts can help to avoid biological alterations or disorders in the health of patients as well as saving resources in the health system.

Introduction

The irrational use of medication currently is a public health concern that should be shared across the health systems. Poly drug use and diagnostic exercise do not bear a relation with a therapeutic practice and the ideal patient care. A cost-effective or a cost-benefit assessment is necessary if a maximization of available resources for health technologies like drug therapeutic is to be achieved. To perform the correct drug prescription, with the exact dose and the right period remains to be the ultimate goal. The purpose of this review is to present a point of view about the intelligent use- or like some authors call it- rational use of medications. The right consolidation of these concepts can help to avoid biological alterations or disorders in the health of patients as well as saving resources in the health system.

Methods for Evaluation of Medication Use and Prescription

There are some examples and methodologies to evaluate the rational use and prescription of drugs^{4, 5}:

- Mean of prescribed medications per doctor appointment.
- Percentage of drug prescription using the generic name or the active ingredient.
- Percentage of doctor appointments where an antibiotic was prescribed.
- Percentage of doctor appointment where an injectable was prescribed.
- Percentage of prescribed medications taken from the essential medications lists, or taken from the basic list or basic form.

Assistance to the patient indicators such as^{4,5}:

- Average time of appointment.
- Average time of delivery.
- Percentage of medications actually delivered.
- Percentage of medications correctly labeled.
- Patient's knowledge of the correct dosage.

Facility or health service indicators, for example^{4,5}:

- Availability of the medication basic chart, basic list and form.
- Availability of therapeutic guidelines or assistance protocols.
- Availability of essential medications or priority medications.
- Availability of an active pharmaceutical committee.

Reference norms such as^{4,5}:

- Availability of therapeutic protocols agreed on or therapeutic options list.
- Pharmacovigilance norms.

important for health professionals to be informed and to take account in a constant update process. Insufficient medical information, lack of proper diagnostic means, the unnecessary multiple prescription (a certain number of medications per prescription) with the hope of accumulate efficacy and the risk of interaction are some of the elements present in the poly drug use. Below are some of its consequences:

- Additional and unnecessary cost which affects public and private funds.
 - Incorrect use of medicine by general population.
 - Higher risk of side effects (15% of incidents in Scotia, 26% in the U.S.)¹².
2. Prescription of insufficient amounts: Sometimes there is not access to the necessary medication or the access is limited. The lack of availability of medications is related to the inadequate administration which does not allow therapeutic results and, in many cases, like in the case of antibiotics, can favor the development of a bacterial resistance¹.
3. Incorrect prescriptions: This is probably the most common type of irrational prescription; either the prescribed medication is inefficient or questionable for the type of infection treated, or it is administrated under inadequate circumstances. Another form of incorrect prescription is the improper administration of antibiotics, especially for those viral respiratory infections that do not respond to antibiotics; as well as the prescription of treatments that do not relate to the diagnosis. Several studies reveal many anomalies in prescriptions; the same active ingredient was found in several medications: some of them contained antagonist substances (stimulant and sedatives) and others indicated the prescription of several vitamin preparations that contained the same ingredients^{1,8}.

General Aspects of Medication Prescription

As part of reality and in some environments there are a percentage of prescriptions provided by doctors which are far from reflecting the criteria established by the therapeutic sciences^{1, 5}. The reasons are varied and complex. Some frequent reasons are presented below:

1. Excessive prescription (polymedication or poly drug use): The number of medications per prescription increased 22% in the nineties. Developed countries report a maximum of three medications per prescription while developing countries prescribe more than three^{6, 7}. It is

Aspects of patients lack of adherence to the prescription.

A good diagnosis and proper prescription are of little use if the patient does not follow doctor's instructions. The bibliography shows that the prescription adherence rate varies from 30% to 50%¹. Some patients only take part of the prescribed medications and others do not take the right doses or use them incorrectly. A high percentage of these mistakes can harm the patient if he/she did not follow the orders prescribed; the result will be the failure of the preventive or curative treatment as well as negative effects for the patient and society. For example, in the case of antibiotics, it can cause the development of resistant strains or financial expenses due to added interventions because of the incorrect treatment. There are some factors that contribute to the adherence to doctor instructions^{4, 8}: the illness, the way the medication is administrated, the number of doses the patient has to take daily and the information provided by the professional. The adherence to instruction increases when the doctor provides ample information.

Causes which prevent the rational prescription and intelligent use of medications.

- The influence the professional training and education has in doctors in therapeutics.
- Existence of tendencies and therapeutic habits that cause certain regional or national differences.
- Lack of knowledge and improvement of the proper therapeutic use of medications.
- Inadequate development of clinical pharmacology in the university curricula which functions as a bridge between basic and therapeutic pharmacology^{1, 4}.
- Insufficient education a medicine student has on the pharmaceutical regulations, the medical

information, the cost of medications, the concept of essential medications, and the art of communicating the patient the right use of medications and the risks of self-medication in a simple language.

- Expensive medications which do not add any therapeutic value, and sometimes have lower efficacy.
- Lack of use of international common denomination (ICD) in the prescription of medications.
- A better control by health authorities to avoid the free sale of medication that requires a doctor prescription.
- Lack of pharmaceutical and pharmacological information centers to notify of any adverse drug reaction (ADR).
- Lack of permanent regulation of pharmaceutical advertising, since it is one of the factors that influence the most a doctor prescription. This advertising should remain ethical and truthful.
- Honesty in the medication advertising must be universal, without tolerating different patterns for developed and developing countries.
- Information related to therapeutic forms financed by incorrect advertising and the wrong distribution to doctors. This information should be adapted from authorized texts since the surveillance of this published information is limited or non-existent.
- Lack of availability of periodic pharmaceutical or pharmacotherapeutic bulletins for doctors and health professionals issued by health authorities about adverse reactions^{1, 4}.
- The role of pharmaceutical professionals is very important since they are the authorized informant to patients during the delivery of medications.
- Sometimes the patient stops using the medication once he/she starts feeling better.
- Self-medication is a phenomenon which occurs in almost every society and tends to increase on developed countries; and although it has its positive and negative aspects, the policy about this topic is still insufficient.

How can we rationalize the use of medication?

The problem of rational use of medication pertains to all of us. Health authorities, universities, the pharmaceutical industry, medical staff and consumers. Most attempts to control the prescription and use of medications have been directed towards regulatory and legal measurements or persuasion. Here are some of them:

- Medication control: control organizations should make sure that the medication marketing is regulated and satisfies the basic population needs. This authorities should verify accomplishment with quality requirements, safety, efficacy and price.
- Drugstore control over medication dispensation requiring physician prescription.
- Promotion of essential medications prescription in an institutional level and the use of an international common denomination on those prescriptions.
- To update the therapeutic form of the institution according to the Basic Chart or Basic Form of medications.
- To adopt, when possible measures to improve the practice of prescription through the elaboration of protocols or therapeutic guidelines; without this meaning the adoption of therapeutic behaviors which do not relate with the reality of most persistent illnesses. Some private and government medical insurances in the United States and France exercise a qualitative control over the prescriptions or sets in advance maximum amount of medications that can be delivered¹. The limit of prescriptions can be found in the therapeutic form of each facility. These restrictions, although

efficient, do little for those doctors who believe they control their freedom to prescribe. The creation of a pharmacologic and therapeutic surveillance committee which works in an institutional level, allowing the identification of prescription errors or irrational prescription; and the systematic notification, recording and evaluation of adverse reaction to medication⁹.

- To add basic clinical pharmacology aspects to the university curricula as well as in the practice of the profession in the form of updates. There is a gap between pharmacology and its application in the therapeutic practice. This would represent the most profitable way to rationalize the prescription practice.
- The importance of different information sources, knowledge and practice of the National Form of medications must be explained to medicine students. They must understand the economy of prescription and the education to the patient about the rational use of medication.
- Pharmacists must inform about the use of prescribed medications and about the risk of self-medication. They should be updated in clinical, hospital and informative pharmacology.
- The advertising of medication should be based on ethical criteria inspired on the recommendations of the WHO. These criteria, among others, should be the following^{1, 11}:
 1. Obligation to use only information approved by health authorities.
 2. Advertising which arouses fear, anxiety, or the expectation of infallible therapeutic results should not be allowed. Advertising which insinuates supposed recommendations from dentistry or medicine professionals should be avoided.

3. Information about prohibited, withdrawn, under strict restrictions or not approved medication due to safety reasons should be spread out.❖

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Observational Study of Nosocomial Infections Epidemiologic Surveillance in the Hospital Nacional de Geriatría y Gerontología (Geriatrics and Gerontology National Hospital) between 2008-2010.

Leandro Gustavo, MD ^{1,2}

Abstract

Introduction: The nosocomial infections are a problem for the Public Health with a high cost of assistance and an increase on the morbidity and mortality. The WHO mentions an incidence of 5 and 10% (1). The main nosocomial infection for the general population is the urinary tract infection, being the Escherichia coli the most common agent involved. The objective of this study was to characterize the nosocomial infections in the Hospital Nacional de Geriatría y Gerontología (Geriatrics and Gerontology National Hospital) in the years 2008-2010 with the purpose of knowing the current situation of a specialized care center.

Methodology: An observational descriptive study of the nosocomial infections which occurred during 2008, 2009 and 2010 was carried out. People over 60 years old, admitted in the Hospital Nacional de Geriatría y Gerontología (Geriatrics and Gerontology National Hospital), who did not present an infection nor were they in an incubation period at the moment of admission, but developed it after 48 hours of admission from January 2008 to December 2010 were taken as case definition. The information was retrieved from the database of the Infections and Statistics Committee. Relative and absolute frequencies, rates and proportions for the types, services and agents were calculated. The programs used were Microsoft Office Excel 2007 and the Surveillance Epidemiology System base of the institution (SISVE).

Results: 6336 discharged patients, 904 nosocomial infection events and an incidence rate of 14.8% were registered. The average age was 82.1 years and most cases were female. The infections of the upper respiratory tract were the main nosocomial infection, being caused mainly by the *Staphylococcus aureus*. During the time of the study there was an outbreak of diarrhea caused by *Clostridium difficile*. Most cases occurred in the acute geriatric unit.

Conclusions: The rates found are not in the references indicated by WHO for the general population, but there are not specific data for the studied population. The infections of the upper respiratory tract were the most common nosocomial infection, being *Staphylococcus aureus* the most frequent agent.

Key words: nosocomial infection, types, microorganisms, services, geriatrics.

Introduction

The nosocomial infections are a challenge to the Public Health worldwide due to the high financial cost resulting from its care and complications, extending the hospital stay, increasing the morbidity and mortality, and due to its effect in the quality of life of the patients and their families. These have caused the nosocomials infections to be considered a true increasing problem in the public health. The World Health Organization has found an incidence of 8.7% ¹ in developed and developing countries; however, reports go from 1%, like in the north of Europe to 40% in the African continent ². The most common nosocomial infections are urinary tract (36%), surgical site infections (20%), pneumonia (11%) and blood infections (11%) ³. Regarding the deaths associated with these infections, the descendent order is pneumonia, bacteremias, urinary tract and surgical site.

In the context of nosocomial infections, there are selected pathogens which have emerge as a threat to the public health: Methicilíne-resistant *Staphylococcus aureus* meticilínevancomicina-resistant *Enterococcus*, Extended-Spectrum beta-lactamase gram negative bacilli and *Clostridium difficile*.

The measures designed to prevent nosocomial infections, which go from the cheapest but most effective ones like hand washing to the complex and expensive ones such as isolation systems, are elements to try to decrease the events; however, the controversy lays on the lack of compliance of the hospital personnel to the most basic ones.

The Hospital Nacional de Geriatría y Gerontología (Geriatrics and Gerontology National Hospital) is a specialized center

which treats people over 60 years old; it has 140 beds distributed in an admissions area for acute cases and/or study, a rehabilitation area, and an Intermediate Care unit for those cases with a higher haemodynamic risk.

The objective of this study is to characterize the nosocomial infections in the Hospital Nacional de Geriatría y Gerontología (Geriatrics and Gerontology National Hospital) in the years 2008-2010 with the purpose of knowing the current situation of a specialized care center.

Methodology

An observational descriptive study of the nosocomial infections which occurred during 2008, 2009 and 2010 in the Hospital Nacional de Geriatría y Gerontología "Dr. Raúl Blanco Cervantes" (Geriatrics and Gerontology National Hospital) was carried out. People over 60 years old, admitted in the Hospital Nacional de Geriatría y Gerontología (Geriatrics and Gerontology National Hospital), who did not present an infection nor were they in an incubation period at the moment of admission, but developed it after 48 hours of admission from January 2008 to December 2010 were taken as case definition.

The study covers all the cases reported in the hospitalizations service including the Geriatrics services, Intermediate Care and Rehabilitation. The cases where reported through the Health Ministry Epidemiology Surveillance form to the Infections and Statistic Committee.

The information was retrieved from the discharge database of the hospital, medical records, VE01 forms and the database of the Infections and Statistics Committee. Relative and absolute frequencies, rates and proportions for

the types, services and germs were calculated. The programs used were Microsoft Office Excel 2007 and the Surveillance Epidemiology System base of the institution (SISVE).

Results

From 2008 to 2010, 6336 released patients, 904 nosocomial infection events and an incidence rate of 14.8% were documented (Chart 1).

CHART 1: HOSPITAL DISCHARGE AND NOSOCOMIAL INFECTIONS DISTRIBUTION PER YEAR FROM 2008 TO 2010 AT HOSPITAL NAC. DE GERIATRÍA Y GERONTOLOGÍA. (GERIATRICS AND GERONTOLOGY NATIONAL HOSPITAL)

Year	2008	2009	2010	Total
No. Egresos	2158	1974	2204	6336
No. Eventos	179	356	405	940
Tasa Incidencia	8.3	18.6	18.4	14.8

Source: CIIH-HNGG

The available information regarding the age was obtained from the years 2009 and 2010; there is not a real database for 2008. The average age during 2009 was 81.7 with a range between 62 and 102 years old; while in 2010, the average age was 82.6 years old with a range between 61 and 99 years old. The femininity ratio for the years studied was 1.15, 1.34 and 1.06 respectively.

There is an increase in the number of infections as the years go by. In general the two conditions with more incidences are the inferior respiratory tract (37.6%) and the urinary tract (33.3%). There was an increase in the number of gastrointestinal tract in the year 2009 due to

an outbreak of diarrhea caused by Clostridium difficile (Chart 2).

CHART 2: NOSOCOMIAL INFECTIONS DISTRIBUTION ACCORDING TO THE SITE FROM 2008 TO 2010 AT HOSPITAL DE GERIATRÍA Y GERONTOLOGÍA (GERIATRICS AND GERONTOLOGY NATIONAL HOSPITAL).

Year	2008	2009	2010	Total
VRTI	79	111	163	353
UTI	65	85	163	313
GITI	30	152	32	214
Skin and Mucous	3	6	46	55
Bacteremia	2	2	0	4
Bones	0	0	1	1
TOTAL	179	356	405	940

Source: CIIH-HNGG

VRTI: Viral Respiratory Tract Infection

UTI: Urinary Tract Infection

GITI: Gastrointestinal Tract Infection

According to the distribution of events in the different hospitalization services in the period studied, it was found that most cases occurred in the sections of Geriatrics 1 and 2, followed closely by Geriatrics 3. A total of 7.3% of cases happened at the Intermediate Care Unit (Chart 3).

CHART 3: NOSOCOMIAL INFECTION DISTRIBUTION BY ADDITION SERVICE FROM 2008 TO 2010 AT HOSPITAL DE GERIATRÍA Y GERONTOLOGÍA (GERIATRICS AND GERONTOLOGY NATIONAL HOSPITAL).

Year	2008	2009	2010	Total
1 y 2	44	161	76	281
3	44	64	141	249
4	42	62	90	194
5 y 6	30	34	83	147
ICU	19	35	15	69
Total	179	356	405	940

Source: CIIH-HNGG

CHART 4: NOSOCOMIAL INFECTIONS DISTRIBUTIONS BY ISOLATED GERM ACCORDING TO THE SITE OF INFECTION FROM 2008 TO 2010 AT HOSPITAL DE GERIATRÍA Y GERONTOLOGÍA (GERIATRICS AND GERONTOLOGY NATIONAL HOSPITAL).

GERM	Respiratory Tract	Urinary Tract	Gastrointestinal Tract	Total
Clostridium difficile	1	0	213	214
Staphylococcus aureus	113	43	0	156
Escherichia coli	33	103	0	136
Klebsiella pneumoniae	61	50	0	111
Pseudomonas aeruginosa	59	23	0	82
Proteus mirabilis	0	34	0	34
Acinetobacter baumanii	21	3	0	24
Enterococcus faecalis	0	13	0	13
Total	288	269	213	770

Source: CIIH-HNGG

Regarding the germs causing the main nosocomials infections, we found that *Escherichia coli* is the main cause of the urinary infections, *Staphylococcus aureus* of respiratory tract infections and *Clostridium difficile* of gastrointestinal tract (Chart 4).

Analysis

The incidence found in this study is larger than the one reported worldwide, which is justified since it is a risk population not only because of the age, but also because of the multiple comorbidity, severity of the illnesses and decrease of the immunological system, which increments the patient's susceptibility. There are not specific international reports of specialized care centers.

The main nosocomial infection found was the respiratory tract infection, well above what is reported in literature which is the urinary tract infection. This is explained to a great extend in the fact that the cases correspond to patients with

neurological conditions such as cerebrovascular disease, dementia, neurological dysphagia, which predisposes them in a great extend to a development of respiratory tract infections.

The percentage of urinary tract infection is similar to the one reported worldwide, most of them related to the use of urinary catheter.

A relevant fact is the increase in the incidence of gastrointestinal tract infection in 2009 due to an outbreak of diarrhea caused by *Clostridium difficile*, which had a great significance.

The spread of infections was greater in the acute admission rooms and lesser in the intermediate care unit proportional to the number of beds, differing with what has been published which means that the elderly represents a different risk because the complexity of his/her comorbidity.

Similar to the literature, the main agent associated with the urinary tract infection was *Escherichia coli* well above the other bacterias.

Regarding the respiratory tract infections, *Staphylococcus aureus* is the main agent, followed by *Enterobacterium* which is very similar to what has been reported worldwide.

Conclusions

The rates found are not in the references indicated by WHO for the general population, but there are not specific data for the studied population.

The infections of the lower respiratory tract were the most common nosocomial infection, being *Staphylococcus aureus* the most frequent agent identified. In second place we have the urinary tract infections caused by *Escherichia coli* which is the main germ identify for this infection. An outbreak of diarrhea due to *Clostridium difficile* was identified in 2009.

The acute services are the places in the hospitals where the most number of cases was found. Keeping strategies are recommended to prevent nosocomial infections because of the consequences it could have for the user and the health system.

The population seen at the hospital is considered a risk population due to the comorbidity and the immunological changes that help the development of infections in this age group; therefore, a special care must be provided when assisting these people.

The report of nosocomial infections by health personnel, which is the responsible of assisting these users, must be improved.

It is advisable to continue with future national studies in regards of nosocomial infections, but focusing on the geriatric population. ♦

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Atrial fibrillation as a problem of public health: New options to prevent a stroke?

Ana Marcela Salazar, MD^{1,2}

Introduction

LAtrial fibrillation (AF) is a public health problem worldwide. In the next 40 years, AF prevalence would have doubled, and for the year 2050, only in the United States, approximately 6 million people will suffer AF.

This condition represents the most frequently treated type of cardiac dysrhythmia; it affects disproportionately an elderly population, and its incidence intensifies with each ten years increase in age (around 9% of the population over 80 years-old suffer AF). It affects primarily males (prevalence of 1.1% vs 0.8%). AF has been related to an increase in mortality, heart failure exacerbations and strokes²⁻¹⁰.

Its prevalence increases with age, in a general population it is of 0.4-1% and a 9% in people older than 80 years old. It has been estimated that 2.2 million people in the Americas and 4.5 million in the European Union suffers paroxysmal or persistent AF. The average age is 75 years old and approximately 70% are between 65 to 85 years old. The prevalence between men and women is similar, but approximately 60% of the patients with AF over 75 years old are women. AF is less common in African-American patients than in Caucasians with heart failure⁴.

According to Miyasaka et al., it has been estimated that in 2050, there will be 12.1 million adults with AF in the United States, assuming there is not increase in the AF

incidence per age after the year 2000. If there is a continuous increase in the incidence, it has been projected that by 2050 there will be 15.9 millions of Adults with AF in the United States¹⁰. (Figure 1)

Specifically, the AF increases to 5 times the risk of suffering a cardioembolic stroke (around 4.5% per year) and it has been associated with systematic embolism (0.8% per year) and death¹¹⁻¹⁴.

It is a supraventricular tachyarrhythmia characterized by a disorganized atrial activation with a deterioration of the atrial and ventricular mechanical function. It can occur isolated or in association with other arrhythmias, most commonly with atrial flutter or atrial tachycardia¹.

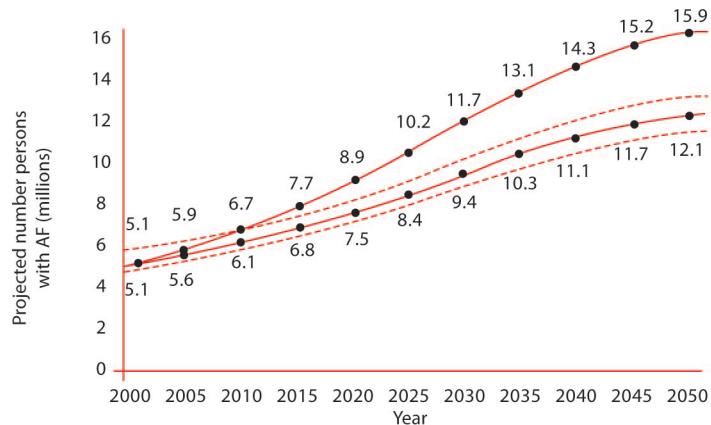
The beginning and perpetuation of a tachyarrhythmia requires the presence of triggers and substrate for its continuation.

The AF is related to very well classified risk factors which will be described in Chart 1.

Classification of Atrial Fibrillation

There are several classification systems proposed for AF. It can be classified as recurrent, paroxysmal, persistent, permanent, valvular, nonvalvular, primary and secondary.

FIGURE 1. PROJECTED NUMBER OF PEOPLE WITH AF IN THE U.S. FROM 2000 TO 2050



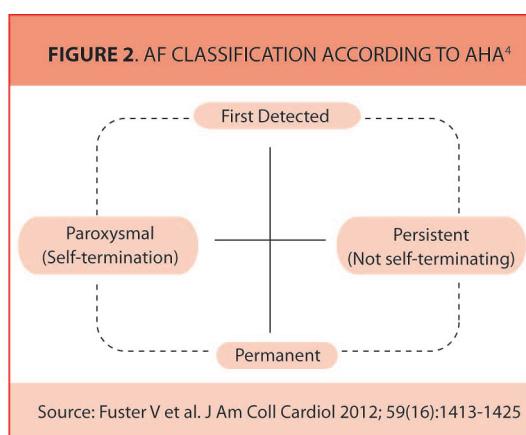
Source: Miyasaka Y et al. Circulation. 2006; 114: 119–2510

CHART 1. AF PREDISPOSING FACTORS¹

Aging	Loss and isolation of the age-dependent auricular myocardium. Associated conduction disorders.
Hypertension	Incidence and complication risk factor.
Heart Failure	Present in 30% of patients with AF.
Valvulopathy	In 30% of patients
Cardiomyopathies	Increased risk of AF, especially on young patients.
Atrial Septal	10-15% of AF patients.
Ischemic Cardiopathology	Present in more than 20% of the AF population.
Thyroid Dysfunction	It could be the only cause for AF and it can predispose the patient to complications.
Obesity	In 25% of AF patients.
Diabetes Mellitus	It is found in 20% of AF patients.
Chronic Lung Disease	Present in 10-15% of AF patients.
Sleep Apnea	Due to increments in the pressure and auricular size.
Chronic Kidney Disease	Present in 10-15% of AF patients.

Source: Camm et al. Rev Esp Cardiol 2010; 63(12):1483.e1-e83

In the recurrent AF the patient presents two or more episodes, paroxysmal AF is the one that ends spontaneously, persistent AF is the one that stays steadily for more than seven days as observed in Figure 2.



The nonvalvular AF: in the absence of rheumatic mitral disease or prosthetic valve. The AF could be secondary to myocardial infarction, heart surgery, pericarditis, myocarditis, pulmonary thromboembolism, hyperthyroidism, pneumonia, etc.

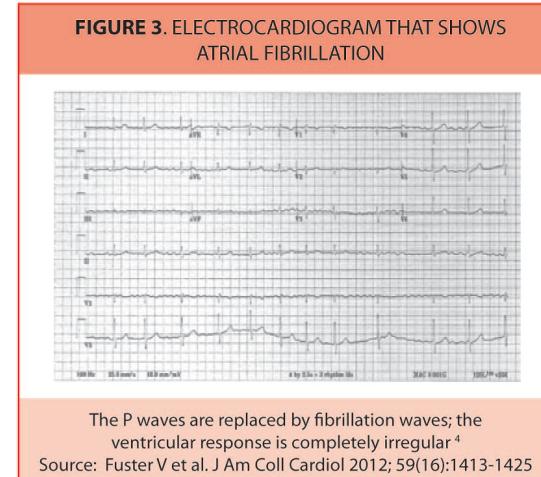
The AF progresses from short and infrequent episodes to strong and prolonged attacks; with time, most patients acquire more persistent forms.

In the Isolated Atrial Fibrillation (IAF) there is not clinical evidence of a cardiopulmonary disease (including Arterial Hypertension); generally, it occurs in young people under 60 years old and it has a favorable prognosis⁴. It has a very low risk of cerebral vascular accident, calculated in 1.3% at 15 years of age.

Diagnosis of AF

Electrocardiographically, the AF presents the following characteristics: irregular RR intervals

which do not follow a repetitive pattern, there are not definite P waves, the auricular cycle length tends to be variable and generally is higher than 300 bpm. (Figure 3)¹



The most frequent anatomopathological changes in AF are fibrosis and loss of atrial muscle mass¹. The histological exam of the atrial tissue reveals fibrosis marks juxtaposed to normal atrial fibers, which are responsible for the inconsistencies in the conductions. It is difficult to distinguish between the changes produced by the atrial fibrillation and those caused by a heart disease, but fibrosis precedes the beginning of AF⁴.

Clinically, up to 40% of patients can be asymptomatic, the main symptoms are: anxiety, palpitations, dyspnea, dizziness, weakness and fatigue. The AF can initially manifest itself as an ischemic cerebral vascular accident (CVA) or as a transitory ischemic attack⁴.

The European Guidelines for the management of atrial fibrillation 1 recommends, as first step to establish a diagnosis, to perform a 12-lead ECG; in some occasions, when the ventricular rhythm is fast, the Valsalva maneuver, a carotid massage or the intravenous administration

of adenosine can help to expose auricular activity¹.

When arrhythmia or other symptom is suspected, a Holter monitoring or other external system to record episodes should be considered.

To diagnose the condition, it is important to have a detail clinical history and the physical exam can show findings like irregular pulse and irregular jugular venous pressure.

It is very important to perform tests such as thyroid function, complete blood counts, serum creatinine determination and proteinuria analysis, blood pressure determination and diabetes mellitus tests^{1,4}.

A transthoracic echocardiogram is standard to diagnose, it allows the identification of valvular pathology, atrial and ventricular size, function of the left ventricle and pericardial disease, although it cannot exclude the presence of thrombus in the left atrium. The transesophageal echocardiogram is not part of the initial standard investigation that is done to the patient; it can be useful to detect thrombus in the left atrium, and it provides structural and cardiac functioning images. It is more sensitive and specific to detect sources and potential mechanism of cardiogenic embolism.

Atrial Fibrillation and Stroke

The AF is responsible of 15-20% of ischemic cerebrovascular accidents (CVA), which is defined as an acute cerebral focal ischemic episode with a length over 24 hours; the hemorrhagic stroke occurs 13% and the ischemic stroke 87%. It can also cause transitory cerebral ischemia episodes, which is defined by neurological symptoms and signs with less than 24 hours length, and it does not produce permanent neurological damage.

According to the Clinical Practice Guidelines, published in 2011 by the European Society of Cardiology, AF increases 5 times the risk of CVA and 1 out of 5 CVA is claimed to be caused by this arrhythmia. When AF is associated with ischemic CVA, it is very often fatal, and patients who survive become disabled¹.

In patients with AF, the atrial appendage predisposes to blood stasis, this is the most common place for the thrombus formation; the AF causes dilation in the left atrium extending the potential to stasis. The atrium wall presents edema and fibrinous transformation; monocytes stimulate the tissue factor and abnormal concentrations of prothrombin^{1,2}, and Vwf and dimer D increments, promoting a prothrombotic state.

Moreover, there is evidence that ischemic cerebrovascular accidents associated with AF are more serious than the ones produced by other etiologies. (Figure 4)²⁰

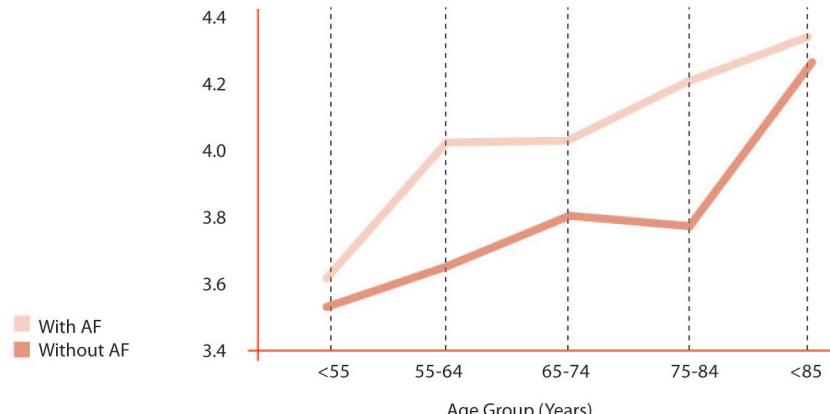
The simplest method to evaluate CVA risk is the CHADS2 classification (Chart 2), which came out from the criteria of AF Investigators and Stroke Prevention in Atrial Fibrillation (SPAF) and it is based in a score system in which 2 or 1 points are assigned according to each condition. In patients with a ≥ 2 score, a chronic oral anticoagulant treatment is recommended, unless it is contraindicated.

CHART 2. CHADS 2 CRITERIA TO ESTABLISH THE EMBOLIC RISK ON AF PATIENTES.¹

CHADS2 CRITERIA	SCORE
Stroke or ischemic cerebral vascular accidents	2
Age > 75 years	1
Hypertension	1
Diabetes Mellitus	1
Heart Failure	1

Source: Camm et al. Rev Esp Cardiol 2010; 63(12):1483.1e-e83

FIGURE 4. SEVERITY OF STROKE ASSOCIATED WITH AF



Source: Dulli Da et al. Neuroepidemiology 2003; (22)2: 118-123²⁰

Other method is CHA2DS2-VASc (Chart 3); based on a score system that gives 2 or 1 points to each of the following conditions. This method expands CHADS2 taking into account additional CVA factors that could influence the decision of using anticoagulant or not.

AF and anticoagulant treatment to prevent strokes

According to the European Guidelines mentioned before, the CHADS2 criteria should be used as a first simple tool, easy to remember, to evaluate the risk of CVA, especially adapted for primary care doctors and non-specialists. For patients with a ≥ 2 classification, a chronic oral anticoagulant treatment with adjusted doses is recommended¹.

CHART 3. CHA2DS2-VASC CRITERIA TO ESTABLISH THE EMBOLIC RISK ON AF PATIENTES.¹

RISK FACTOR	SCORE
Congestive Heart Failure/ Left Ventricular Dysfunction	1
Hypertension	1
Age > 75 Years	2
Diabetes mellitus	1
Cerebral Vascular Accident/AIT/ Thromboembolism	2
Vascular disease	1
Age 65-74 years	1
Sex category (meaning female)	1
Maximun score	9

Fuente: Camm et al. Rev Esp Cardiol 2010; 63(12):1483.1e-e83

For patients with a CHADS2 classification of 0-1 or when a more detailed CVA risk evaluation is needed, a comprehensive approach based on the risk factors which incorporates additional risk factors like thromboembolism is recommended. An approach based on the risk factors can also be expressed as a CHA2DS2-VASc score system. In patients with a CHA2DS2-VASc classification of 1 (for example, women < 65 years old) a treatment with an aspirin instead of an oral anticoagulant can be considered¹.

According to the Guidelines for the Management of Patients with AF from the American College of Cardiology:

- An antithrombotic therapy is recommended for those patients with AF, except for those with Isolated AF or contraindications⁴.
- The selection of the antithrombotic agent has to be based on the absolute CVA risk and bleeding in each patient.
- Anticoagulation with a Vitamin K antagonist is recommended for patients with more than one moderate risk factor (age > 75 years, hypertension, heart failure, diabetes mellitus and an ejection fraction of 35% or less)⁴.
- A daily 81-325mg aspirin is recommended as an alternative of Vitamin K antagonist for those patients with a low risk or for those with contraindications for oral anticoagulants.
- The AF pattern does not generally influence the method or degree of anticoagulant therapy.
- The use of anti-arrhythmic drugs does not necessarily reduce the need of anticoagulation.
- The risk of thromboembolism increases after a cardioversion.
- The anticoagulant therapy is recommended for all AF patients, except Isolated AF or when the patient has a contraindication.
- The selection of the anticoagulant depends on the risk factors for stroke and bleeding.

The AHA/ACCF/HRS Guidelines recommend anticoagulation with warfarin for patients with paroxysmal and persistent AF with stroke and systemic embolism as risk factors. Despite the benefits of the warfarin, only around 25-50% of AF patients receive it, due to the risk of bleeding, the need of monitoring, the dose variability and the interactions with other medications and food⁴.

An oral anticoagulation is recommended for all patients, male or female over 75 years, over 65 years old with diabetes mellitus or coronary disease, over 65 years old with heart failure, patients with rheumatic heart disease or prosthetic heart valve and thromboembolism history⁴.

Vitamin K Antagonists

Vitamin K Antagonists have a slow onset action; at the beginning, it produces a hypercoagulability state; therefore, a concurrent treatment with heparin is necessary.

It is associated with multiple adverse reactions such as: gastrointestinal bleeding, severe bleeding and intracranial hematomas. The risk of bleeding is increasing in patients with a history of stroke, kidney failure or anemia. Interaction with multiple drugs like: atorvastatin, antibiotic esomeprazole (chloramphenicol, clarithromycin, tetracyclines, penicillin G, metronidazole), NSAIDs, paracetamol and aspirin. The patient should avoid eating: broccoli, cabbage, spinach, green leaves, liver, green tea and vegetable oils.

CHART4. PHARMACOLOGIC CHARACTERISTICS DIRECT THROMBIN INHIBITORS AND XA FACTOR INHIBITORS.

	DABIGATRAN ETEXILATE	RIVAROXABAN	APIXABAN	EDOXABAN
Mechanism of action	Selective direct FIIa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor	Selective direct FXa inhibitor
Oral bioavailability, %	6.5	80-100	50	62
Half-life, h	12-17	5-13	8-15	6-11
Renal elimination, %	85	66 (36 unchanged and 30 inactive metabolites)	27	50
Time to maximum inhibition, h	0.5-2	1-4	1-4	1-2
Potential metabolic drug interactions	Inhibitors of P-gp: verapamil, reduce dose; dronedarone: avoid Potent inducers of P-gpt: avoid	Potent inhibitors of CYP3A4and P-gp*: avoid	Potent inhibitors of CYP3A4 and P-gp*: avoid	Potent inhibitors of P-gp*: reduce dose Potent inducers of P-gp: avoid
		CYP3A4 and P-gp: usewith caution	CYP3A4 and P-gp: usewith caution	

Source: Adapted from De Caterina R et al. J Am Coll Cardiol 2012; 59(16): 1413-25 3

New Oral Anticoagulants

The new anticoagulants present remarkable advantages over Vitamin K antagonists including predictable anticoagulant effects, little interaction with other drugs and food, and there is not a need to monitor. Besides, they have pharmacologic properties which increase the number of eligible patients for oral anticoagulant treatment. (Table 2)³

Dabigatran etexilate

Dabigatran is a direct oral thrombin inhibitor; it is excreted unchanged mainly in the urine; therefore, the plasma concentrations increment in patients with mild renal failure.

It is approved in the United States for the prevention of strokes and thromboembolism in AF patients with a dose of 150mg twice a day. RE-LY trial included 18133 patients with AF diagnosis with at least one risk factor for stroke and an average age of 71.5 years. It compared Dabigatran etexilate 150mg bid or 110mg bid with an adjusted dose of warfarin (INR 2-3) during 2 years. In this trial, strokes and systematic embolism occurred, in one year, 1.71% in patients treated with warfarin, 1.54% in those treated with Dabigatran 110mg and 1.11% in patients treated with Dabigatran 150mg.

Serious bleeding was present 3.57% in patients treated with warfarin, 2.87% in those who used Dabigatran 110mg and 3.31% in those

trated with Dabigatran 150 mg. Dabigatran presented more cases of dyspepsia and discontinuation of treated in 1 year³.

Rivaroxaban

Rivaroxaban is an oral, reversible and selective Xa Factor inhibitor which is administrated once a day and it is metabolized in the liver. In the ROCKET-AF trial, there was a participation of 14264 patients with AF diagnosis and at least one risk factor for stroke and an average age of 73 years. Rivaroxaban 20mg each day was compared against an adjust dose of warfarin (INR 2-3). The study demonstrated that rivaroxaban is as good as warfarin to prevent stroke and systematic embolism; there was no significant difference in the risk of serious bleeding³.

Apixaban

Apixaban is an oral, highly selective, direct Xa Factor inhibitor. The usual recommended dose to prevent AF is 5mg twice a day³. AVERROES trial had the participation of 5599 patients from 522 centers in 36 countries; the average age was over 50 years, with persistent and permanent AF diagnosis with at least one risk factor for stroke. In this study, the prevalence of stroke, thromboembolism, severe myocardium infarct, death from vascular disease and severe bleeding was less with apixaban than with aspirin. Also, for every 1000 patients treated with apixaban during 1 year, it prevents 21 strokes, 33 cardiovascular hospitalizations and 9 deaths, with only 2 severe bleedings².

The ARISTOTLE trial included 18201 patients with AF and at least one risk factor for stroke and it compared apixaban 5mg with an

adjusted dosis of warfarin. The apixaban reduced significantly the risk of stroke and systemic embolism in 21% compared with warfarin, in 31% the risk of severe bleeding and in 11% the risk of mortality. For every 1000 patients treated in 1.8 years with apixaban in comparison with warfarin, it prevents 6 strokes, 15 severe bleedings and 8 deaths⁵.

Edoxaban

Edoxaban is also an oral, selective and direct Xa Factor inhibitor. The usual dose is 30 mg once a day or 60mg once a day. Its use to prevent stroke in patients with atrial fibrillation, compared with warfarin, is being studied in the ENGAGE AF-TIMI 48 trial. This is a phase III, randomized, double blind and double simulation study with a non-inferiority design, which has the goal to include 21,107 subjects with no valvular AF and with a CHADS2 >2 classification.

The results of this trial are expected for the second half of 2012.

Conclusions

It is clear that atrial fibrillation is a problem for public health, especially for the complications it might have, particularly stokes, and it is necessary to look for new therapeutic alternatives to try to prevent these conditions.

According to the article by De Caterina et al. based on the individual results found on new oral anticoagulants trials, apixaban has features which exceed warfarine and aspirin in the prevention of stroke for AF patients, with a balance efficacy and safety profile. Dabigatran has proven to be more effective than warfarin

and aspirin; however, it is associated with specific adverse effects like dyspepsia and gastrointestinal bleeding.

On the other hand, rivaroxaban has also exceeded warfarin and aspirin in efficacy; however, it still needs to prove its safety because, from these three agents, this one has presented more bleeding problems in clinical trials³.

An indirect comparison carried out by Lip et al did not show significant differences in efficacy between apixaban, dabigatran and rivaroxaban. Only a direct comparison trial will reveal the differences in efficacy and safety between the new anticoagulants⁷.

The availability of 3 new medications as an alternative to prevent strokes in patients with no valvular atrial fibrillation is a very important step towards a better forecast of the results and a better quality of life for those patients³.

It is also important to consider the cost of these new medications from the patient's perspective, although it seems their cost-effectiveness for society can be reasonable compared with other medications which have been recently accepted in different health systems.

We are definitely facing a new era of new oral anticoagulants. These ones present remarkable advantages over traditionally used Vitamin K antagonists, like the ones previously mentioned in this review. Since these new oral anticoagulants possess pharmacologic properties which increase the number of AF patients eligible for anticoagulant treatment, it makes us consider a change of paradigm in the way we currently prevent strokes in AF patients, which it is already being reflected in guidelines of clinical management of different organizations and associations worldwide. ♦

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Comments on the ethical aspects of an investigation with human being participation.

Bustos- Montero Daniel, MD ^{1,2}

When research activities, with human subjects participating in them, are discussed, great concerns rise regarding the ethical implications these studies entail. Unmistakably, today's society has seen the need of creating regulations aimed at promoting the protection of the subjects of the investigations, while allowing the implementation of projects.

It is here where the question on how an investigation should be carried out to be considered ethically acceptable arises. Usually, if we would ask the question what makes an investigation with human subjects ethical? Researcher, bioethicists and healthcare professionals alike would have answered, without even thinking, that the presence of an informed consent would be enough to achieve the moral requirement of investigations.

However, in 2000, Emanuel Ezequiel very wisely describes in his article "What makes a clinical investigation ethical?" seven (7) key elements in the research field that must be achieved in all research activities, he describes these elements in the following way: (Pag. 24)

These 7 elements, far from being an aseptic form of facing the ethical dilemmas that an

investigation which involves human subjects can cause, represent a guideline to execute studies in an approved ethical manner, although they need to be adjusted and calibrated according to the circumstances of each investigation³⁻¹⁵.

However, this guideline could present discrepancies in 3 ways:

- a) differences in the interpretation of each requisite;
- b) the need of additional requirements and
- c) the way they are applied in the development of each particular investigation¹.

As Emanuel EJ et al states, these requirements are like a constitution, where each one of them can be reinterpreted, refined and reviewed with the changes science can undergo and the experience. What is for sure is that all of them should be considered in every case to ensure that an investigation, wherever it might take place, is ethical. ♦

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FIGURE 1: REQUIREMENTS TO DETERMINE IF AN INVESTIGATION IS ETHICAL

REQUIREMENT	EXPLANATION	JUSTIFYING ETHICAL VALUE	EXPERTISE FOR EVALUATION
Social or scientific Value	Evaluation of a treatment, intervention or theory that will improve health and well-being or increase knowledge.	Scarce resource and non-exploitation	Scientific knowledge; citizen's understanding of social priorities.
Scientific Validity	Use of scientific principles and methods, including statistical techniques, to produce reliable and valid data	Scarce resource and non-exploitation	Scientific and statistical knowledge; knowledge of conditions and population to assess feasibility.
Fair subject selection	Selection of subjects so that stigmatized and vulnerable individuals are not targeted for risky research and the rich and socially powerful not favoured for potentially beneficial research.	Justice	Scientific knowledge; ethical and legal knowledge
Favourable risk-benefit ratio	Minimization of risk; enhancement of potential benefits; risks to the subject are proportionate to the benefits to the subject and society	Nonmaleficence, beneficence and nonexploitation	Scientific knowledge; citizen's understanding of social values.
Independiente Review	Review of the design of the research trial, its proposed subject population, and risk-benefit ration by individuals unaffiliated with the research.	Public accountability; minimizing influence of potential conflicts of interest	Intellectual, financial and other wise independent researchers; scientific and ethical knowledge.
Informed consent	Provision of information to subjects about purpose of the research, its procedures, potential risks, benefits and alternatives, so that the individual understands this information and can make a voluntary decision whether to enroll and continue to participate.	Respect for subject autonomy	Scientific knowledge; ethical and legal knowledge
Respect for potential and enrolled subjects	Respect for subjects by: <ol style="list-style-type: none"> Permitting withdrawal from study; Protecting privacy through confidentiality; Informing subjects of newly discovered risks or benefits; Informing subjects of results of clinical research, Maintaining welfare of subjects 	Respect for subject autonomy and welfare	Scientific knowledge; ethical and legal knowledge; knowledge of particular subject population.

Source: Emanuel EJ et al. JAMA 2000;283:2701-2711

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PRODICI Activities

Bustos-Montero Daniel, MD^{1,2}

During the year 2011-2012, Pfizer Program for the Development of Investigation and Science (PRODICI) supported the implementation of several activities aimed at improving the research capacity in Central America and the Caribbean. Among these, the following stand out:

- Course Introduction to Research Ethics, April 29th-30th, 2011, Universidad Latina, San José, Costa Rica.
- Course Introduction to Research Ethics, June 9th-10th, 2011, Universidad Católica de Honduras, Campus San Pedro Sula.
- Course Fundamental concepts of Human Research, November 4th-5th, 2011, San Salvador, El Salvador.
- Course Introduction to Research Ethics, February 9th-10th, 2012, Blue Science Foundation, Dominican Republic.

For 2012 period, and through the Continuing Education Collaboration Program PRODICI is supporting the following training activities,

motivating professional from the region to achieve new academic goals. In this way, this program will benefit the following people:

- Dr. Enrique Giraldo Ho (Panama), Rheumatology Fellowship, Hospital Belvitge, Universidad de Barcelona, Spain.
- Dr. Fabricio Arguedas Monge (Costa Rica), Oncologic and Reconstructive Pathology Fellowship, Hospital Italiano, Buenos Aires, Argentina.
- Dr. Marlene Hurley (Panama), Fellowship in the Liaison Psychiatric Department, Hospital de la Universidad Javeriana, Bogotá, Colombia.
- Dr. José Pablo Muñoz Espeleta (Costa Rica), Fellowship in the Orthopedic Department at Arnold Palmer Children´s Hospital, Orlando, Florida, United States.

Also, through the Central American and Caribbean Fund for the Promotion of Health Research, PRODICI collaborated in 2011 with the research "" Prevalence of dementia and associated factor on the elderly on influence

areas for doctors working in the social service) conducted by Dr. Manuel Sierras Santos, researcher of Unidad de Investigación Científica (Scientific Research Unit), Facultad de Ciencias Médicas (Medical Science School), Universidad Nacional Autónoma de Honduras. This research is still under development and its results are expected to support the development of health strategies for the elderly population in Honduras.

In 2012, PRODIC will be collaborating with the execution of the following investigations:

- Glycosylated hemoglobin levels and its relation with the degree of erectile dysfunction in male patients in Jamaica

Principal investigator: Dr. Belinda Morrison, University of West Indies, Jamaica.

- Establishment of protocols for cell and molecular level evaluation for the induction and chemoprophylaxis of skin cancer using a in-vitro photocarcinogenicity model

Principal Investigator: Dr. Miguel Rojas, Instituto Tecnológico de Costa Rica.

- Depresion in Vascular Dementia
Principal Investigator: Dr. Rose Nina, Centro Médico Bellas Artes, Dominican Republic.

With this, PRODIC continues its mission to promote a research based culture in Central American countries and the Caribbean.

For more information about the requirements to apply for these funds as well as the deadlines for these applications, visit our webpage www.pfizercac.com, medical information section, PRODIC link.

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Reading Suggestions

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2012 CONFERENCE
EUROPEAN SOCIETY OF CARDIOLOGY

Munich, Germany
August 25th-29th, 2012
www.escardio.org

ADVANCING ETHICAL RESEARCH CONFERENCE
PUBLIC RESPONSIBILITY IN MEDICINE AND RESEARCH

San Diego, California, U.S.
December 04th-06th, 2012
www.primr.org



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Manuscripts presented for publication on this journal must adjust to the ethical considerations and technical criteria established on the "Uniform Requirements for Manuscripts submitted to Biomedical Journals", developed by the International Committee of Medical Journal Editors.

Next, essential elements that must be included in the articles:

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- **Title:** Must include all the necessary information for its electronic retrieval. There should not be any abbreviations.
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- **Short title:** maximum 40 characters (including letters and spaces), on the footer of this section.
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Conflict of Interest Page:

Consists of a declaration of all potential conflicts of interest that the authors could have. To make this declaration, the form located at the following address may be used: http://www.icmje.org/coi_disclosure.pdf.

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