# INSTITUTIONAL AMYLOIDOSIS REGISTRY OF THE ITALIAN HOSPITAL OF BUENOS AIRES CEPI

**Protocol No.: 1675**

Clinical Research Area in Internal Medicine

## Manual of Procedures for the Institutional Amyloidosis Registry

Amyloidosis is a systemic disease resulting from the deposition of usually misfolded proteins in the form of amorphous fibrillar material in various tissues, potentially causing progressive dysfunction [1]. The prevalence of amyloidosis varies depending on the population and the type of amyloid. While the prevalence in the general population is unknown, estimates from the Mayo Clinic suggest it is 1 in 90,666% in the US [2]. In England, it generated approximately 0.0084% (1367/16232579) of the total hospital consultations between April 2008 and April 2009[3].

The most frequent clinical manifestations are cardiac, renal, and hepatic involvement, but these vary widely depending on the type of amyloidosis, the affected organ, and the extent of the deposits [4]. Amyloid infiltration can produce signs and symptoms that may be very similar to other rheumatological pathologies [5]. This potentially polymorphic clinical presentation may suggest underdiagnosis due to low clinical suspicion.

Records are organized systems for the systematic collection of data from a large number of patients in a fast and efficient manner, about a particular disease, at a given time [6, .].

The main difficulty with registries is ensuring the quality of their data. The main objectives of registries are [7]:

1. Understand the risk and prognostic factors of the disease.
2. Evaluate the diagnostic and therapeutic management by comparing it with current standards.
3. To advance knowledge of diseases in order to optimize the assessment, treatment and follow-up of patients.
4. Analyze the effectiveness of new therapies.
5. Study the differences between different populations.
6. Quickly estimate morbidity, mortality, and resource utilization associated with a pathological entity.
7. Examine the course of a disease
8. Formulate novel hypotheses for the subsequent performance of prospective studies.

Currently, there are registries for patients diagnosed with transthyretin amyloidosis (TAHOS) [8], and a global transplant registry for patients with familial amyloid polyneuropathy [9]. There are also indirect registries such as those for kidney transplantation, heart transplantation, and others [10].

We found no data on the prevalence, incidence, progression, or prognosis of amyloidosis in our country. There are also no current amyloidosis registries.

national or Latin American studies that could describe the behavior of this disease in our setting are essential. Because it is a chronic disease with amyloid infiltration and can produce signs and symptoms that are very similar to other rheumatological pathologies [5, 11], this potentially polymorphic clinical presentation may suggest underdiagnosis due to low clinical suspicion. Furthermore, there is no curative treatment, and some patients experience persistent symptoms despite appropriate therapy [12, 13]. Therefore, the creation of [a research group/research group/research group] is fundamental.

A monitoring system that generates data on disease progression and prognosis. Data from these registries can be used to develop new treatment guidelines and recommendations, and to inform and educate physicians on the management of this disease.

Because the Italian Hospital of Buenos Aires is a high-complexity referral center for this type of pathology and given that the hospital's prepaid health plan provides a unique opportunity for denominators to generate a population registry of its

members, we propose to create an Institutional Amyloidosis Registry.

## *Goals*

### Primary objectives

Creation of a system of**Population Registry of Amyloidosis**with prospective survey of epidemiological data, risk factors, diagnosis, prognosis, treatment, follow-up and survival.

### Secondary objectives

1. Describe the occurrence of**Amyloidosis**in the population of HIBA in the Central Hospital.
2. Describe the characteristics of the clinical presentation, evolution, and predisposing factors of**Amyloidosis.**
3. Describe epidemiological data through registry participation Latin American Amyloidosis Association.

## *Population and methods.*

## *Design*

Multicenter Cohort Study

## *Population*

The study population will consist of adults over 17 years of age diagnosed with amyloidosis.

Table 1. Participating Centers

| **City** | **Hospital** | **Regarding** |
|---|---|---|
| Montevideo, Uruguay | Hospital de Clínicas, Myeloma Unit, Department of Hematology | Eloísa Riva |
| GELAMM-registry Latin American Amyloidosis Association | | Eloisa Riva |
| Capital Buenos Aires (coordination) | Italian Hospital of Buenos Aires | Adel Aguirre-Lourdes Posadas (IP |

| | | |
|---|---|---|
| | | change 2019) |
| Autonomous City of Buenos Aires | Buenos Aires Cardiology Institute | Juan Pablo Costabel |
| Rosario, Santa Fe | Private Hospital of Rosario, Gamma Group | Carlos umont Dunayevich |
| Pilar, Buenos Aires Province | Hospital Austral | Sergio Baratta |
| Autonomous City of Buenos Aires | Hospital de Clínicas | Veronica Volberg |
| Autonomous City of Buenos Aires | British Hospital of Buenos Aires | Pablo Young |
| Autonomous City of Buenos Aires | British Hospital of Buenos Aires | Luciana León Cejas |
| Buenos Aires | Nestor Kirchner High Complexity Hospital, El Cruce | Gisela Streitenberger |
| Santa Cruz, Bolivia | Foianini Clinic | Carolina maria petit cwirko |
| Autonomous City of Buenos Aires | Favaloro | Alejandro Quiroga, Adrian Fernandez |
| Autonomous City of Buenos Aires | Anchorena | Josefina Parody |
| Montevideo, Uruguay | Galeno Clinic | Franco Leoni |
| Autonomous City of Buenos Aires | CHEMICAL | Jorge Thierer |

| | | |
|---|---|---|
| Cordoba, Cordoba | Private University Hospital of Córdoba | María Laura Martínez |

## *Scope*

The scope consists of the sectors of each senior citizens' hospital 17 years with amyloidosis from the participating centers.

The scope of the registry is the Italian Hospital of Buenos Aires. The registry will be institutional in nature, without excluding any area within the hospital setting. including the outpatient area (outpatient clinics, emergency room, demand and hospitalization in all areas of the central hospital).

In a second stage, other centers will be incorporated according to a preliminary feasibility assessment and a training program designed to train the different components.

## *Eligible population*

All patients over 18 years of age and from any health provider who have amyloidosis or are suspected of having it will be included.

# Selection criteria

## Inclusion Criteria

Patients over 18 years of age with:

**Confirmed amyloidosis**
Demonstration of amyloid deposition by Pathological Anatomy in abdominal fat, bone marrow, rectum or involved organ (e.g., kidney, liver, sural nerve)

**Clinical case compatible with Amyloidosis but not confirmed:**
Cardiac: The presence of 2 or more of these points:
Right and/or left heart failure
ECG: decreased QRS complex voltage
Echocardiogram: increased wall thickness with hyperechoic ventricular walls and increased interatrial septum thickness. No other clear cause of increased ventricular thickness (hypertension, valvular heart disease).
Cardiac MRI: increased diffuse subendocardial gadolinium uptake on late images.
Renal:
Renal involvement plus serum lambda free chains

Evidence of clonal proliferation of plasma cells. This includes serum/urinary monoclonal protein, plasma cells in bone marrow, abnormal serum light chain ratio, without evidence of amyloid deposition composed of light chain fragments by immunofluorescence or immunohistochemistry, both lambda and kappa

Blood relatives of patients with confirmed familial amyloidosis

who present with a clinical picture of polyneuropathy without an alternative cause and a confirmed mutation of the amyloidogenic protein gene

## Exclusion criteria

1. Refusal to participate in the study or the informed consent process by the patient or legal representative or refusal to consent to participate in the study in the case of minors.

## *Designs*

1. Prospective registration, with capture of consecutive cases and annual follow-up.
2. Cross-sectional descriptive studies for prevalence studies.
3. Follow-up cohort of patients with Amyloidosis or suspected Amyloidosis.
4. Retrospective cohort in the Latin American Amyloidosis Registry.5.

Data quality assessment and record validation.

## *Data capture and collection circuit*

The system for capturing evaluable patients will detect suspected or confirmed cases of amyloidosis in real time and issue an alert (see below). A list of potentially eligible patients, called the watch list, will be generated. The registry coordinator will manage this list sequentially, assigning assessments to participating physicians.

Patients meeting inclusion criteria and none of exclusion criteria will be evaluated in a standardized manner and the corresponding forms for the evaluation of the registry will be completed.

## *Data logging*

The evaluation for patient inclusion and the collection of data from the standardized interview will be carried out by specially participating physicians and uploaded to a form for each included episode.

It will be the physician's responsibility to complete all fields of the CRF. Monitors will check the completeness of each patient's record before

Provide the data to the data entry clerk. Any missing or clearly erroneous data may be completed by reassessing or re-interviewing the patient, if possible.

## *Follow-up*

A fixed schedule of annual telephone evaluations will be used. Surveillance lists will be used to detect readmissions, mortality, and new requests for re-evaluation due to a new episode of amyloidosis in the electronic medical record.

## *Loaded with data*

Data entry will be performed by the data entry clerk. Laboratory results and supplementary test results will be obtained from secondary databases using the highest quality validated source available. Administrative and inpatient data will be cross-referenced with secondary databases for patient interactions and the institutional registry.

## *Data quality and completeness*

Laboratory and administrative data will be obtained from high-quality secondary databases. The remaining data will be collected by monitors using forms designed for that purpose.

The data entry system will check for incomplete fields, which will then be sent back to the doctor for completion. This will occur after the data has been uploaded to the registry database.

Supervisors will subsequently check the data for consistency and the presence of obviously erroneous data. Any detected anomalous data will be sent back to the monitor for completion and re-entering into the database. If there is no reliable source for the data, it will be considered lost.

**Data management and workflow for incorporating data into the CEPI 7014 rare disease registry and biobank**

Retrospective data is expected. In the case of a biobank, from 16 years onwards, the current version of the biobank (currently version 3, approved 5-2024, attached) will be used for future research.

Patient recruitment will be done through a help desk request.

Research information management and/or direct reporting by interdisciplinary attending physicians will be used. Data collection will be carried out through review of electronic health records (EHRs) and/or requests to secondary databases for information management. Retrospective data on biological samples will be requested from the corresponding service (pathology, laboratory). Administrative

and inpatient data will be cross-referenced with the secondary databases of the institutional and inpatient registries.

A standardized form designed specifically for this purpose will be used to collect the information.

To ensure that the data is reliable and complete, the forms will be structured and the person responsible for collecting the data will be trained.

For follow-up, a retrospective review of the electronic health record (EHR) and/or a request to the information management help desk are planned. If contact with the patient or family member is required, the Informed Consent form will be customized with details of the contact method, such as a fixed schedule of telephone evaluations and/or email and/or REDCap and/or internal EHR messaging, depending on the Rare Disease Program unit 7014, with notification to CEPI. Surveillance lists will be used to detect events such as hospitalizations, mortality, and new requests for evaluation for new episodes in the EHR.

## Data loading and storage

The registration form will be submitted through REDCap using validation rules to minimize data entry errors. REDCap adheres to confidentiality and security protocols, with access restricted to researchers who log in with their username and password. It allows for the identification of data fields according to established standards.

The data will be stored in REDCap, a repository recommended by the Research Department and the Health Informatics Department for research. The mechanism for sharing and transferring databases will be as follows: access via passwords, with passwords sent through a different method than the database itself.A working group is planned, comprised of advanced students from the IUHI ESIN Program, a scholarship recipient (the project will be submitted for permanent funding), and the leaders of each Amyloidosis and EPF unit. The research professors will be responsible for the base and its maintenance. The corresponding task delegations will be presented with the periodic reports.

## Data validation

It is essential to ensure that the data is reliable, clean, and clear. Validation will be provided during the form design phase and subsequently for analysis. Data cleaning will be performed through frequency analysis, searching for and verifying implausible values, and identifying missing data.

## Data processing and analysis

Once the database is complete, all identifying information about the participants must be removed. When using statistical software, some variables will need to be recoded for analysis. The final data are usually stored on the hospital network with

restricted access.
The de-identification process will be carried out in accordance with HIPAA regulations, using the REDCap form's identification tool to remove identifying data so that it is not downloaded for analysis.

The possibility of using the data for other research projects derived from the registry is foreseen. These projects must be submitted to CEPI.
for its corresponding evaluation and opinion in accordance with the legal framework that regulates the investigation in CABA or Province of Bs As.

For de-identified retrospective data, including data from secondary databases and retrospective data from biological samples, the informed consent requirement established by the CIOMS guidelines is waived (see section on ethical considerations). For projects involving prospective data collection, data reuse, or the use of samples in a prospectively collected biobank, the Informed Consent process of the amyloidosis registry in effect since November 20, 2019, will be incorporated, as well as biobank version 3.

Projects associated with the Research Protocol Ethics Committee will be presented in accordance with hospital standard No. 93/23Access to data from research studies conducted at the institution

1 ***Data analysis***

Annual written reports and open oral presentations will be held at the central conference. At the hospital level, information will be disseminated on the intranet with the same frequency to ensure access within the HIBA (Hospital Interzonal de Albacete).
The presentations will include data on the evolution and development of the registry structure, data descriptions, and assessments of data quality and registry processes. The main objectives of these reports will be to implement improvements in the structure and data quality, and to generate hypotheses to be tested on the registry data.

Statistical analyses will be performed by a team of physicians trained for this purpose. Continuous variables will be expressed using summary measures and measures of central tendency, selected according to the distribution of each particular variable. Qualitative variables will be expressed as proportions. Statistical tests will be selected according to the hypotheses and the characteristics of the data, as appropriate.

The following will be calculated using the data recorded upon registration:

Annual incidence/prevalence of amyloidosis in the HIBA population, crude, specific by sex and age group (age groups will be established by decade of

life).

Case descriptions:

- **Demographics:**age, sex, place of origin
- **Symptoms:** Frequencies of each of the symptoms with which the cases present themselves
- **Diagnosis:**frequency of each of the diagnostic methods used.
- **Therapeutic:**Frequency of use of each of the initial therapies, frequency of associated complications, duration of treatments

Multiple logistic regression. Known risk factors and those under investigation will be included.

**With the tracking data:**

Survival analysis of these patients within the Italian Hospital. (Cox regression) Known and potential prognostic factors will be considered.

## Budget

The registry is based on the systematic collection of observational data; therefore, it does not alter in any way the costs associated with patient evaluation, diagnosis, hospitalization, or treatment. These expenses will continue to be covered by each patient's individual insurance plan.

Registration fees cover administrative and staff expenses. Administrative expenses include stationery costs, including all registration forms for each case. Both costs are covered by the Internal Medicine Department of the Hospital Italiano de Buenos Aires.

The staff of the Amyloidosis Registry includes the Physicians, the Coordinator, the Data Entry, and the Area Supervisors.
The fees and schedules for the Monitor Coordinator, Data Entry, and Supervisors will be agreed upon later.

Currently, it does not have direct funding. For BIOBANCO, the EPF samples were identified as strategic institutional samples. Amyloidosis samples will be incorporated through the institutional amyloidosis registry 1675 and the rare disease registry 7014.

## Ethical considerations, data confidentiality and security

Participation in the registry will be voluntary in all cases and certified through the oral informed consent process. There are many examples in the literature of disease registries that use oral consent. When the patient is unable to express their consent, it will be requested from their legal representative or a suitable family member [13-16].

At all times, the protection of the patient's identity and data will be observed in accordance with current legal regulations, specifically the National Law on the

Protection of Personal Data 25.326 (Habeas Data), and in accordance with international regulations on disease registration and the protection of personal and private data, as established by the 18th World Medical Assembly in Helsinki (1964), where applicable. The right to opt out of registration will be respected at all times, and this will not imply any type of discrimination, differential treatment, or mistreatment.

All documents or forms containing patient data from the registry are confidential and will be kept under lock and key with access restricted to authorized personnel of the institutional Amyloidosis registry.
The head of the department and the hospital director are aware of the protocol

In the case of other centers in the country, the principal investigator at each center will be responsible for presenting the proposal to their committee and requesting approval. The amendment for approval of the Protocol and additional centers will be submitted to CEPI, and the principal investigator at each center will be responsible for submitting the regulatory material requested by CEPI in order for it to be accepted.

The HIBA Committee has no jurisdiction over centers in other countries, and the protocol must go through the regulatory procedures corresponding to that center and country.

## 6. Ethical considerations for incorporating data into the register of rare diseases CEPI 7014 and biobank

This research will be conducted in compliance with ethical principles in accordance with the regulatory standards for human health research at the national and international levels, in accordance with the regulatory standards for human health research at the national level (Resolution of the Ministry of Health of the Nation 1480/2011 and Law 3301/09 of CABA), the Declaration of Helsinki of the World

Medical Association and all its amendments, and respecting the ICH E6 Standards of Good Clinical Practice.

All data from the study will be treated with maximum confidentiality, with restricted access only for personnel authorized for the purposes of the study in accordance with current legal regulations National Law on the Protection of Personal Data 25.326/00 (Habeas data Law) and Law 26.529/09.

**Retrospective data - waiver of consent**

Given that, as stated in Chapter 10 of the International Ethical Guidelines for Health-Related Research Involving Human Subjects CIOMS/2017, this research: 1-would not be feasible or viable to carry out without such a waiver or modification, given that it will involve a retrospective review of medical records or anonymized retrospective biological samples, and informed consent is not feasible to obtain, and within the framework of Law 26.689 on rare diseases, which establishes the creation of a national network and promotes the creation of a National Registry of people with a rare disease; 2-it has significant social value given that there is limited information on the clinical-epidemiological and anatomopathological characteristics of this population, given that amyloidosis is a rare disease; and 3-it entails only minimal risks for the participants, given that the data will be presented in a grouped and de-identified form; we request a waiver of the requirement to obtain informed consent.

The plan is to collect retrospective data for the amyloidosis registry, the Rare Diseases Registry (7014), and the National Ministry of Health's Rare Diseases Registry via SISA, which contains general information about the individual, the diagnosis, data from the healthcare facility, and the treating professional. This health data is combined with other data also managed through SISA.Citizen's Record, which centralizes the various records associated with the same person



in a single and individual repository, because the law on rare diseases requires mandatory reporting.

**Prospective data**

In the case of projects that include prospective data collection, the Informed Consent process of the current amyloidosis registry (20-11-2019) will be incorporated.

**Data for the biobank**

The comprehensive consent form for BIOBANCO version 3 explicitly outlines the collection of biological samples to promote science as a common good, respecting patients' rights and the rights of citizens. The ethical and legal regulations

considered in this informed consent form are: National Law 25.326 on data protection, National Law 26529 on patients' rights, Resolution 1480 - Guide for Health Research of the Ministry of Health of Argentina (2011), the UNESCO Declaration on the Protection of Genetic Data and Declaration on Bioethics and Human Rights, the World Medical Association's Declaration of Helsinki (2008 version), and the CIOMS Guidelines (2009). For biobanking, the current version of the biobank (currently version 3, approved 5-2024) will be used for individuals aged 16 and over.


**1. Gorevic, P.D., An overview of amyloidosis, in UpToDate, P.H. Schur and P.L. Romain, Editors. 2010, UpToDate: Waltham, MA.**

**2. Prevalence and Incidence of Amyloidosis. Volume,**

**3. Primary diagnosis: 3 character, 2008-09. www.hesonline.nhs.uk. 2009, UK: Hospital Episode Statistics HESonline - The Health and Social Care Information Centre.**

**4. Simmons, Z. and C.S. Specht, The neuromuscular manifestations of amyloidosis. J Clin Neuromuscul Dis. 11(3): p. 145-57.**

**5. Prokaeva, T., et al., Soft tissue, joint, and bone manifestations of AL amyloidosis: clinical presentation, molecular features, and survival. Arthritis Rheum, 2007. 56(11): p. 3858-68.**

**6. Dyke, C.K. and R.M. Calif, National and regional registries: what good are they? Eur Heart J, 2000. 21(17): p. 1401-3.**

**7. Alpert, J.S., Are data from clinical registries of any value? Eur Heart J, 2000. 21(17): p. 1399-401.**

**8. THAOS: TTR Amyloidosis Patient Registry 2010 [cited 2010.**

**9. Herlenius, G., et al., Ten years of international experience with liver transplantation for familial amyloidotic polyneuropathy: results from the Familial Amyloidotic Polyneuropathy World Transplant Registry. Transplantation, 2004. 77(1): p. 64-71.**

**10. Roig, E., et al., Outcomes of heart transplantation for cardiac amyloidosis: subanalysis of the spanish registry for heart transplantation. Am J Transplant, 2009. 9(6): p. 1414-9.**

**11. Fujishima, M., et al., Amyloid arthropathy resembling seronegative rheumatoid arthritis in a patient with IgD-kappa multiple myeloma. Intern Med, 2003. 42(1): p. 121-4.**

**12. Chin, K.M. and L.J. Rubin, Pulmonary arterial hypertension. J Am Coll Cardiol, 2008. 51(16): p. 1527-38.**

**13. Consensus statement on the management of pulmonary hypertension in clinical practice in the UK and Ireland. Heart, 2008. 94 Suppl 1: p. i1-41.**

**14. Lizzi, A., G. Almada, and L. Clara, Practical Measures for the Control of Hospital Infections. 2002, Capital Federal Buenos Aires. Argentina: Infection Control Committee of the Italian Hospital of Buenos Aires. Preventio Foundation.**

**15. Hulley, S.B. and R.S. Cummings, Designing Clinical Research. An epidemiologic aproach. 1988, Baltimore, USA: Williams & Wilkins.**

**16. Bennett, S., et al., Data Management for Suveys and Trials. 1996, Llanidloes, Powys: Brixton Books. 17.**

**Olson, J.E., Data Quality. The accuracy dimension. 2003, San Francisco, USA Morgan Kaufmann Publishers.**

**18. Malone, T.W., K. Crowston, and G.A. Herman, Organizing Business Knowledge: The MIT Process Handbook. 2003, Massachusetts, United States of America: The MIT Press.**

**19. Amin, S.G., Control charts 101: a guide to health care applications. Qual Manag Health Care, 2001. 9(3): p. 1-27.**

**20. Evans, J.R. and W.M. Lindsay, Quality Management and Control 1995, Mexico City, Mexico: Grupo Editorial Iberoamérica.**

**21. Fuentes, N., et al. Hyponatremia associated with thiazide consumption in the patient population of a health plan. in XVII NATIONAL CONGRESS OF MEDICINE. 2009. Autonomous City of Buenos Aires.**

**22. Millán Ramos, C., et al. Quality Indicators of the Institutional Registry of Thromboembolic Disease (RIET). in XVI National Congress of Medicine - SAM 2007 2007. Autonomous City of Buenos Aires, Argentina.**

**23. Alcalde San Miguel, P., Quality. 2007, Madrid, Spain: Thomson Paraninfo.**

**24. Mukerjee, D., et al., Prevalence and outcome in systemic sclerosis associated pulmonary arterial hypertension: application of a registry approach. Ann Rheum Dis, 2003. 62(11): p. 1088-93.**

**25. National Law 25 326: Personal Data Protection Law. October 4, 2000, Sanctioned by the Senate and Chamber of Deputies of the Argentine Nation meeting in Congress.**

**26. Ruiz Morales, A. and L.E. Morillo Zárate, Clinical Epidemiology: Applied Clinical Research. 2004, Bogotá DC, Colombia: Editorial Médica Panamericana.**

**27. ICMJE. Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication. 2006 February 2006 [cited June 24th, 2006]; http://www.icmje.org/#author].**



**28. Rubin, L.J., Primary pulmonary hypertension. N Engl J Med, 1997. 336(2): p. 111-7.**

**29. NEJM. AUTHOR CENTER 2006 [cited June 24th, 2006]; http://authors.nejm.org/index.asp].**

**30. Gu, Q., et al., Antihypertensive medication use among US adults with hypertension. Circulation, 2006. 113(2): p. 213-21.**

**31. Collins, F.S., Shattuck lecture--medical and societal consequences of the Human Genome Project. N Engl J Med, 1999. 341(1): p. 28-37.**

**32. Annas, G.J., Rules for research on human genetic variation--lessons from Iceland. N Engl J Med, 2000. 342(24): p. 1830-3.**

**33. Elias, S. and G.J. Annas, Generic consent for genetic screening. N Engl J Med, 1994. 330(22): p. 1611-3.**

**34. Snider, G.L., Diagnosis of chronic obstructive pulmonary disease, in UpToDate version 13.2 B.D. Rose, Editor. 2005: Wellesley, MA.**

**35. Diagnosis and classification of diabetes mellitus. Diabetes Care, 2008. 31 Suppl 1 p. S55-60.**

**36. Sabate, J.M., et al., High prevalence of small intestinal bacterial overgrowth in patients with morbid obesity: a contributor to severe hepatic steatosis. Obes Surg, 2008. 18(4): p. 371-7.**

**37. Goldberg, E. and S. Chopra, Diagnostic approach to the patient with cirrhosis, in UpToDate version 13.2 B.D. Rose, Editor. 2005: Wellesley, MA.**

**38. Garcia-Tsao, G., et al., Portal pressure, presence of gastroesophageal varices and variceal bleeding. Hepatology, 1985. 5(3): p. 419-24.**

**39. Johansson, P.L., S. Safai-Kutti, and J. Kutti, An elevated venous haemoglobin concentration cannot be used as a surrogate marker for absolute erythrocytosis: a study of patients with polycythaemia vera and apparent polycythaemia. Br J Haematol, 2005. 129(5): p. 701-5.**

**40. Congenital heart defects. 13/08/2009 NCBI.**

**41. Lung Disease, Interstitial. 2009, NCBI.**

**42. Brennan, P., et al., Validity and reliability of three methods used in the diagnosis of Raynaud's phenomenon. The UK Scleroderma Study Group. Br J Rheumatol, 1993. 32(5): p. 357-61.**

**43. Jarvik, J.G., et al., Surgery versus non-surgical therapy for carpal tunnel syndrome: a randomised parallel-group trial. Lancet, 2009. 374(9695): p. 1074-81.**

**44. Cossio, P., et al., Internal Medicine. 6th edition ed. 1997, Buenos Aires, Argentina: CTM.**

**45. Barbera, J.A., et al., [Standards of care in pulmonary hypertension. Consensus Statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) and the Spanish Society of Cardiology (SEC)]. Arch Bronconeumol, 2008. 44(2): p. 87-99.**