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Original research

# Publication rates and characteristics of medical theses from a University Hospital in México City

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## ABSTRACT

**Background**: In medicine, as in other disciplines, a significant amount of research is first captured in the thesis of university degree candidates. Nevertheless, on many occasions the scientific rates of thesis publication are meager. The Hospital General "Dr. Manuel Gea Gonzalez" (HGMGG) is a relevant public university hospital in Mexico City; however, the characteristics, fate, and publication rates of the dissertations produced by medical residents are unknown. The objective of the present study was to examine these essential aspects in our Hospital to identify areas of opportunity to increase publishing of these research dissertations. **Material and methods**: Data from the theses presented between 1980 and 2000 were obtained from the TESIUNAM repository. Publication of theses in indexed and non-indexed biomedical journals was assessed by a search strategy using Google Scholar, SciELO, Pubmed, Scopus, Science Direct, ProQuest, Ebsco, Ovid, Imbiomed, and Lilacs databases. **Results**: Sixty-eight of 360 (18.9%) medical theses written by residents were transformed into articles published in scientific journals. Residents were the first authors on 19% (13/68) of these articles. The factors associated with the publication of a particular thesis were a prospective and analytical design; human beings as the study subjects; presentation by the Department of Pediatrics; supervisor with PhD degree, and Mexican journal with impact factor in SJR and Scopus Impact Factor. **Discussion**: A low proportion of theses publication was found in our hospital. It is necessary to implement measures to improve the rate of publication by residents.

**Key words:** publication thesis; medicine residents; scientific papers; medicine specialty.

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## RESUMEN

**Antecedentes**: En medicina una cantidad significativa de investigación se refleja primero en las tesis de los residentes. Sin embargo, en muchas ocasiones la publicación de las tesis científicas es exigua. El Hospital General "Dr. Manuel Gea González" es un relevante hospital público universitario de la Ciudad de México; sin embargo, se desconocen las características y tasas de publicación de las tesis realizadas por los médicos residentes. El objetivo del presente estudio fue examinar estos aspectos en nuestro Hospital para identificar áreas de oportunidad para incrementar la publicación mediante tesis de investigación. **Material y métodos**: Los datos de las tesis presentadas entre 1980 y 2000 se obtuvieron del repositorio TESIUNAM. La publicación de tesis en revistas biomédicas indexadas y no indexadas se evaluó mediante una estrategia de búsqueda en las bases de datos Google Scholar, SciELO, Pubmed, Scopus, Science Direct, ProQuest, Ebsco, Ovid, Imbiomed y Lilacs. **Resultados**: Sesenta y ocho de 360 (18,9%) tesis médicas escritas por residentes fueron transformadas en artículos publicados en revistas científicas. Los residentes fueron los primeros autores en el 19% (13/68) de estos artículos. Los factores asociados a la publicación de la tesis fueron un diseño prospectivo y analítico, con el ser humano como sujeto de estudio, presentación por parte del departamento de pediatría, director con título de doctorado y revista mexicana con factor de impacto en SJR y Scopus Impact Factor. **Discusión**: En nuestro hospital se encontró una baja proporción de publicación de tesis. Es necesario implementar medidas para mejorar el ritmo de publicación por parte de los residentes.


**Palabras clave:** publicación de tesis; residentes de medicina; artículos científicos; especialidad médica.

## INTRODUCTION

In Mexico, as in many countries, medical specialization is completed when the specialist trainee doctors (residents) present their thesis. However, publication in a scientific journal is unnecessary to obtain the medical degree.

Consequently, the knowledge remains in the archives of a university library, where sometimes it is difficult to consult, and its diffusion is almost null.[1]

This inaccessible information may result in many unfavorable consequences, including waste of resources and medical knowledge, unnecessary duplication of studies, and loss of scientific integrity trust.[2]

Although students know, as with any research, that a thesis should not be complete before it is shared, that there are advantages of publishing the work carried out during their years of specialization. Getting residents to publish their results is a global problem since only on a few occasions does half of the theses appear in indexed journals.[1-29] (Table 1)

**Table 1.** Some representative thesis publication rates in the world

| Author (year) | Country | No. of theses | Published | % |
|---|---|---|---|---|
| Hollmann *et al* (2015)[3] | Spain | 162 | 87 | 53.7 |
| Caan and Cole (2012)[4] | United Kingdom | 82 | 43 | 52.4 |
| Brunod *et al* (2020)[1] | France | 148 | 76 | 51.3 |
| Pitche *et al* (2007)[5] | Togo | 240 | 99 | 41 |
| Al-Busaidi *et al* (2017)[6] | New Zeland | 89 | 36 | 40.4 |
| Chassagnon *et al* (2016)[7] | France | 224 | 79 | 35.3 |
| Roudbari *et al* (2012)[8] | Iran | 313 | 96 | 30.7 |
| Sipahi *et al* (2012)[9] | Turkey | 538 | 161 | 30 |
| Dhaliwal *et al* (2010)[10] | India | 160 | 48 | 30 |
| Varela-Pinedo *et al* (2015)[11] | Perú | 399 | 114 | 28.6 |
| Baufreton *et al* (2012)[12] | France | 598 | 165 | 28 |
| Nieminen P. *et al* (2007)[13] | Finland | 256 | 61 | 23.8 |


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| | | | | |
|---|---|---|---|---|
| Ticse *et al* (2014)[14] | Perú | 199 | 47 | 23.6 |
| Nour-Eldein *et al* (2015)[15] | Egypt | 208 | 45 | 21.6 |
| Arriola-Quiroz *et al* (2010)[16] | Peru | 482 | 85 | 17.6 |
| Salmi *et al* (2001)[17] | France | 300 | 51 | 17 |
| Munung *et al* (2014)[18] | Cameroon | 130 | 22 | 16.9 |
| Koca *et al* (2016)[19] | Turkey | 1,508 | 224 | 14.9 |
| Griffin and Hindocha (2011)[20] | United Kingdom | 515 | 72 | 14 |
| Valle and Salvador (2009)[21] | Perú | 93 | 11 | 11.8 |
| Benotmane *et al* (2012)[22] | France | 2,150 | 243 | 11.3 |
| Rhyne (2000)[23] | USA | 201 | 17 | 8.5 |
| Castro-Rodríguez *et al* (2020)[24] | Perú | 1,954 | 134 | 6.9 |
| Özgen *et al* (2011)[25] | Turkey | 22,625 | 1386 | 6.1 |
| Figueredo *et al* (2002)[26] | Spain | 204 | 13 | 6.3 |
| Atamari-Anahui *et al* (2015)[27] | Peru | 398 | 20 | 5 |
| Taype-Rondán *et al* (2012)[28] | Peru | 74 | 2 | 2.7 |

The causes reported in the scientific literature related to this problem are multiple,[29-31] and the actions implemented to improve the publication rate have not proven to reverse them (stimulation training and promotional activities of investigation, the obligation to present a thesis to obtain the academic degree, research methodology courses during residency, training advisors who actively publish, help to adapt the format of the thesis to that of a scientific article).

Furthermore, the low rate of thesis publication has worsened because universities allow students to obtain degrees through options other than preparing and presenting a thesis.[29]

The Hospital General "Dr. Manuel Gea Gonzalez" (HGMGG) is a public general hospital in the south of Mexico City; it is surrounded by the most important hospitals that belong to the National Health Institutes of our country, offering several medical specialties for the thousands of patients seeking medical care. HGMGG is also an important university hospital in the country, because it hosts up of 17 medical and nursing subjects to university students, from different careers such as Medicine, Dentistry, Nursing, and Nutrition. Approximately 335 residents of Mexico and other countries in Central and South America receive training annually at the hospital.[32]

Given that the rate of thesis publications in the HGMGG is still being determined, the present study's objective was to analyze how frequently research carried out by residents appears in scientific journals and the characteristics mentioned in the material and methods section.

## MATERIAL AND METHODS

### Timeframe and case selection

We conducted a single-center retrospective cohort study over 20 years (1980 and 2000). The search for theses and articles consisted of three stages.

### First stage:

The theses were retrieved from the open access repository of the Universidad Nacional Autónoma de Mexico, known as TESIUNAM (https://tesiunam.dgb.unam.mx/F/XSGYNI5G2AMXX9EYVBKBHAYKXXLEE1C771TQN65JTXXS4MYJ9P-04173?func=file&file_name=find-b), which is the web site where these documents are stored for public consultation. We obtain the title of the thesis and the year of publication, the name and sex of the resident, the supervisor or supervisors, and the corresponding medical specialty, the type of study carried out, and the material and methods used. In addition, the degree of the supervisor(s) was obtained from the publicly available National Registry of Professionals database (https://cedulaprofesional.sep.gob.mx/cedula/presidencia/indexAvanzada.action)

### Second stage:

We check if a thesis resulted in a corresponding scientific publication in the indexed and non-indexed journals. An

exhaustive search was carried out, without time limit, in Scholar Google, SciELO, Pubmed, Scopus, Science Direct, ProQuest, Ebsco, Ovid, Imbiomed, and Lilacs, using the names and surnames of the thesis supervisor (s) and the resident. Whenever possible, one of the researchers contacted the thesis directors via email to confirm whether all the theses they had supervised were those that were in the repository or if they had any more, and whether they published other articles from the theses found and those not found.

### Third stage:

We analyzed published articles from the thesis to gather the following information: the year of publication of the article. Also, we confirmed that the title, the name of the Hospital, and the material and methods coincided with those described in the thesis.
Finally, the order of authorship by the tutor and the resident in the publication and the type of journal (indexed or not, national or international. language and impact factor) where the article was published were registered.

### Statistical analysis

A database was created in Excel and analyses were performed with the Statistical Package for the social sciences (SPSS) software (version 22.0). Descriptive statistics were used to analyze the data (means, medians, standard deviation, and percentages as appropriate), and comparisons were conducted using the Chi-square test, odds ratio, and confidence intervals.

In all cases, a value of $p<0.05$ was considered significant. The analyses were performed with the Statistical Package for the social sciences (SPSS) software (version 22.0).

## RESULTS

### Theses

We found three hundred and sixty-seven theses in TESIUNAM; the contacted supervisors added none. Seven were not included, three due to a lack of the supervisor's name (s), and four due to the absence of the theses' full text in the catalog. A total of three hundred and sixty theses were included in the study, with an average of 17± 15 per year (range 0 to 59). In the years 1981 and 1985 no theses were found in the repository and in the year 2000 the greatest number was found. Each of the theses was writen by a resident, and 315 (87.5%) had one supervisor. A total of 102 supervisors participated, who directed from one (mean 4, median 2).

Almost a quarter of the theses found in the repository belongs to the Department of Pediatrics [74/360 (21%)], and one hundred ninety-seven theses (55%) were presented by residents of the four specialties considered basic in our country (Pediatrics, General Surgery, Gynecology, and Internal Medicine)

According to what was mentioned in the materials and methods section of the theses, it was found that 208 theses (58%) were descriptive and 152 (42%) analytical. Likewise, 251 (70%) were prospective, 104 (29%) retrospective, and five (1%) ambispective, of which 65% (234) were performed with human subjects.

### Articles and Journals

Sixty-eight out of 360 (18.9%) medical theses written by residents were transformed into articles published in indexed and non-indexed journals (average of 3.2 articles per year; range, 0-15), sixty-five were found in the bases consulted and three added by the contacted supervisors.

Fifty-seven (84%) of the theses were published in Mexican journals and eleven (16%) in international journals, 40 of 68 (59%) papers were published in indexed journals, and the median impact factor was 0.158 (range 0.056-15.487). Ninety percent of articles (61/68) were published in Spanish (57 in México and 4 in Spain). The four journals in which most articles in Spanish were La Revista Mexicana de Pediatría with ten papers (16%), seven in the Boletin Médico del Hospital Infantil de México (12%), five in Dermatología Revista Mexicana, and five in Gynecology and Obstetrics of Mexico (8.2% each respectively in these papers). Only 19% of the residents were first authors (13/68), 56% (38/68) were second authors, and 7% (5/68) of them did not appear in the published documents. On the other hand, the supervisors were the first author in 78% (53/68) of the published articles.

The median delay between thesis presentation and paper publication was 12 months (range 6-120 months). In the comparative analysis, significant differences were found for the publication of the theses. When they were carried out in the Department of Pediatrics, the study was analytical and prospective, when it was carried out on human beings, the director had a doctorate, when the publication was carried out in national journals, in Spanish, were indexed and had some impact factor (Table 2).


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**Table 2. Characteristics of the theses in relation to their subsequent publication**

| | | Total (%) | Published (%) | Not published (%) | $X^2$ | OR (CI) | p-value |
|---|---|---|---|---|---|---|---|
| **Number of theses** | | **360** | **68 (18.9)** | **292 (81.1)** | | | |
| Sex of resident | Male | 212 (59) | 35 (17) | 177 (83) | 1.91 | 0.69 (0.405-1.17) | NS |
| | Female | 148 (41) | 33 (22) | 115 (78) | | | |
| Sex of supervisor | Male | 295 (82) | 53 (18) | 242 (82) | 0.91 ( | 0.73 (0.381-1.40) | NS |
| | Female | 65 (18) | 15 (23) | 50 (77) | | | |
| Medical specialty | **Pediatrics** | **74 (20.5)** | **31 (42)** | **43 (58)** | **32.2** | **4.85 (2.73-8.64)** | **< 0.001** |
| | Gynecology and Obstetrics | 45 (12.5) | 6 (13) | 39 (87) | 1.04 | 0.63 (0.25-1.55) | NS |
| | Surgery | 49 (14) | 4 (8) | 45 (92) | 4.26 | 0.34 (0.12-1.0) | NS |
| | Plastic surgery | 39 (11) | 6 (15) | 33 (85) | 0.27 | 0.79 (0.32-1.96) | NS |
| | Internal Medicine Dermatology | 30 ( 8 ) | 1 (3) | 29 (97) | 5.20 | 0.14 (0.02-1.01) | NS |
| | Other | 26 ( 7 ) | 9 (35) | 17 (65) | 4.52 | 2.47 (1.05-5.81) | NS |
| Number of supervisors | One | 315 (87.5) | 60 (19) | 255 (81) | 0.041 | 1.09 (0.48-2.46) | NS |
| | More than one | 45 (12.5) | 8 (18) | 37 (82) | | | |
| Academic level of supervisor | Specialist | 283 | 43 | 240 | 11.79 | 0.37 (0.21-0.66) | NS |
| | Subspecialist | 21 | 7 | 14 | 3.04 | 2.28 (0.88-5.88) | NS |
| | Master´s degree | 32 | 10 | 22 | 3.50 | 2.12 (0.95-4.71) | NS |
| | **PhD** | **22** | **8** | **14** | **4.670** | **2.65 (1.06-6.59)** | **0.03** |
| Study design | Descriptive | 208 (58) | 31 (15) | 177 (85) | 5.11 | 0.54 (0.32-0.93) | NS |
| | **Analytic** | **152 (42)** | **37 (24)** | **115 (76)** | **5.11** | **1.84 (1.08-3.13)** | **0.024** |
| Data collection | **Prospective** | **251 (70)** | **57 (23)** | **194 (77)** | **7.90** | **2.62 (1.31-5.22)** | **0.005** |
| | Retrospective | 104 (29) | 11 (11) | 93 (89) | 6.60 | 0.41 (0.21-0.82) | NS |
| | Ambispective | 5 (1) | 0 (0) | 5 (100) | 1.18 | 0.81 (0.77-0-85) | NS |
| Material | **Human beings** | **234 (65)** | **55 (23.5)** | **179 (76.5)** | **16.78** | **2.67 (1.40-5.11)** | **0.002** |
| | Histopathological samples | 24 (6.7) | 7 (29.2) | 17 (70.8) | | | |
| | Clinical records | 76 (21.1) | 4 (5.3) | 72 (94.7) | | | |
| | Animal model | 17 (4.7) | 2 (11.8) | 15 (88.2) | | | |
| | Documentary review | 9 (2.5) | 0 (0) | 9 (100) | | | |
| Journal´s characteristics | **Mexican** | ----- | **61 (90)** | ----- | **360** | ----- | **< 0.001** |
| | Foreign | ----- | 7 (10) | ----- | | ----- | |
| | **Spanish** | ----- | **58 (85)** | ----- | **360** | ----- | **< 0.001** |
| | English | ----- | 10 (15) | ----- | | ----- | |
| | **With impact factor** | ----- | **40 (59)** | ----- | **360** | ----- | **< 0.001** |
| | Without impact factor | ----- | 28 (41) | ----- | | ----- | |

## DISCUSSION

In the present study, the articles that appeared in both indexed and non-indexed journals, showed a thesis publication rate of 18.9%, but if only the indexed journals are taken into account, the publication rate drops to 11.1%. This low publication rate is consistent with studies carried out in Peru,[16,21,24,27,28] France,[17,22] Cameroon,[18] Turkey,[19,25] the United Kingdom,[20] the USA,[23] and Spain,[26] but it is much below the value of 30% considered very satisfactory by some authors.[32]

This low rate of scientific article production is also consistent with the report by Oboku *et al*.[33] who found that the average publication in low and middle-income countries is only 7%, which translates into Latin American participation of less than 1% of world scientific production.[34] One of the possible causes of this low production at the international level is that even though most scientific journals in Latin America and the Caribbean are open access, few of them are found in recognized databases,[35] which would explain why despite ten databases were used to search for the publications of the residents' theses, three articles were not found in them and were provided by the supervisors; this fact has already been highlighted by several authors, although none used the number of databases data used in this study. Despite this, Brazil and Mexico lead scientific production in the region.[36]

On the other hand, our study revealed that the probability of a thesis being published is more significant if the study is prospective, analytical, and the study subject are human beings, which is in opposition to the findings of Taype-Rondán *et al*. in Peru,[28] who found that most of the theses published as original articles were descriptive and cross-sectional, despite the fact that, in the present study, the cross-sectional design was used in 58% of all theses.

Interestingly, it was identified that the resident as a first author was considerate in only 19% of those published, which contrasts with the general premise by which the name of the principal investigator, in this case, the resident, is almost always mentioned first. This outcome may be due to the fact that this aspect is not a rule and is poorly standardized,[37] even though there are recommendations on the order of appearance of the authors in publications with more than one author.[38] Another possibility that can explain this phenomenon is the little interest of the residents in the publication of their thesis, and when all the work is done, the supervisor is noted as the first author.

## CONCLUSIONS

In HGMG, it is necessary to increase the level of evidence of the studies carried out by residents, as well as to promote their publication in high-impact English-language journals in order to substantially improve their dissemination and the rate of publication of articles. Additionally, it is necessary to carry out actions aimed at improve the interest of the residents interested in publishing their own thesis before his/her presentation and obtaining the university degree, such as trying to adapt as much as possible the requirements of the documents demanded by the Universities with those of the journals. Alternatively, to encourage thesis publication, residents and their supervisors could be included in incentive programs or assisting with the publication of their work, even when they are no longer within the Hospital. Finally, training potential supervisors in the preparation of works and lines of research with greater impact, as well as in the way of obtaining financing, both for the development of the project and for the publication of its results, would undoubtedly promote an increase in the publication of research theses.

As a limitation of the present study, there is a high probability that some theses were not found in the repository because either the residents did not submit their thesis to the University or because we did not include all the names of the residents who completed their studies in this period and only appeared the theses in which the name of the Hospital was included. Furthermore, not contacting all the thesis directors could modify the actual rate of publications coming from residents' theses. However, even with these limitations inherent in the experimental design approach used, valuable information was obtained.

Currently, data collection is being carried out between the years 2000 and 2020, as well as a multicenter study in several universities and hospitals in the country.

## CONFLICT OF INTEREST

The authors declare that they are free of any conflict of interest.

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Original research

# Zinc supplementation in patients with cirrhosis and dysgeusia: Randomized Clinical Trial

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## ABSTRACT

**Background**: Dysgeusia has been identified as part of liver cirrhosis (LC). Since zinc (Zn) is involved in taste and LC pathophysiology, this study aimed to evaluate the effect of zinc supplementation in patients with LC. **Methods**: Double-blinded randomized clinical trial, controlled with placebo in patients with LC. The intervention consisted of 100mg/day of Zn for six months. Improvement of dysgeusia was evaluated according to changes in perception (PT) and recognition (RT) thresholds of five flavors evaluated by ascending molar dilutions method. Differences were assessed by determining the size and the magnitude of effects, interpreted according to Common Language Effect Size, and determining the number needed to treat (NNT). **Results**: 50% (n=17) of patients were male, with a median age of 57 [51-63] years. After six months, 28 patients accomplished the follow-up; in patients who receive Zn, we observed a PT at a lower molar concentration in salty (1.0 [IQR 1.0-14.7] M vs. 12 [IQR 1.0-12] M, improvement probability 58% (NNT=6)), sweet (1.5 [IQR 1.5-3.5] M vs. 3.5 [IQR 1.5-4.0] M, improvement probability 57% (NNT=6)), sour (0.48 [IQR 0.48-0.48] M vs 0.48 [IQR 0.48-2.44] M, improvement probability 65% (NNT=3)) and umami (0.40 [IQR 0.40-0.40] M vs 0.70 [IQR 0.70-0.80] M, improvement probability 74% (NNT=2)) tastes compared to placebo group. With respect to RT, patients who received Zn, recognition of umami taste was observed at a lower molar concentration (0.70 [IQR 0.40-1.17] M vs 0.90 [0.70-1.1] M, improvement probability 59% (NNT=5)) compared to placebo. **Conclusion**: Patients supplemented with GZn show an improvement probability of PT higher than 55% for salty, sweet, sour, and umami tastes. Meanwhile, the improvement probability of RT for umami taste is 59%.

**Key words:** taste disorders; cirrhosis; zinc; liver.

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## RESUMEN

**Antecedentes**: La disgeusia se ha identificado como parte de la cirrosis hepática (CH). Ya que el zinc (Zn) está involucrado en la fisiología del sabor y la CH, el objetivo de este estudio fue evaluar el efecto de la suplementación con Zn en pacientes con CH y disgeusia. **Métodos**: Ensayo clínico aleatorizado, doble ciego, controlado con placebo de 34 pacientes con CH. La intervención consistió en 100mg/día de gluconato de Zinc (GZn) durante 6 meses. La mejoría de la disgeusia fue evaluada con la concentración en que se detectaron los umbrales de percepción (UP) y reconocimiento (UR) de cinco sabores. Para evaluar las diferencias, se determinaron los tamaños de efecto y la magnitud de estos con interpretación de acuerdo con los Common Language Effect Size (expresado en porcentaje) y determinando el numero necesario a tratar (NNT). **Resultados**: El 50% (n=17) fueron hombres con mediana de edad de 57 [IQR 51-63] años. Posterior a los 6 meses, 28 pacientes cumplieron el seguimiento; en los pacientes que recibieron Zn se observó UP a menor concentración en los sabores salado (1.0 [IQR 1.0-14.7]M vs 12 [IQR 1.0-12]M, con una probabilidad de mejoría de 58% (NNT= 6)), dulce (1.5 [IQR 1.5-3.5]M vs 3.5 [IQR 1.5-4.0] M, probabilidad de mejoría de 57% (NNT=6)) , ácido (0.48 [IQR 0.48-0.48]M vs 0.48 [IQR 0.48-2.44]M, probabilidad de mejoría de 65% (NNT=3)) y umami (0.40 [IQR 0.40-0.40]M vs 0.70 [IQR 0.70-0.80]M, probabilidad de mejoría de 74% (NNT=2)) en comparación con el placebo. Los pacientes que recibieron Zn presentaron UR del umami en menor concentración respecto al placebo (probabilidad de mejoría 59% (NNT=5)). **Conclusión**: Los pacientes suplementados con GZn durante seis meses, presentan probabilidades de mejoría del UP de los sabores salado, dulce, ácido y umami mayores al 55%, mientras que la probabilidad de mejoría del UR del sabor umami es del 59%.


**Palabras clave:** alteraciones del gusto; cirrosis; zinc; hígado.

## INTRODUCTION

Liver cirrhosis (LC) is the final stage of chronic liver diseases, characterized by four pathophysiological mechanisms independent of the initial cause of liver damage: necrosis of hepatocytes with loss of liver parenchyma and inflammation, fibrogenesis, changes in cell growth and vascular alterations.[1] The epidemiology of LC is challenging to estimate due to the multifactorial etiology and access to health systems according to the economic development of each country; on the other hand, the prevalence may be underestimated due to the asymptomatic phase of the disease. According to 2021 published data, LC is the 11th cause of death worldwide, with 1.32 billion deaths per year.[2]

Dysgeusia is defined as an impairment in perception (PT) or recognition (RT) thresholds of basic flavors (salty, sweet, sour, bitter, and umami),[3] and it has been associated with a direct impact on quality of life (QoL), weight loss and malnutrition.[4] Despite the importance of dysgeusia, its effect is commonly underestimated until its presentation.[5] Dysgeusia is recognized as part of the natural history of liver diseases, with a prevalence of 40%;[6-8] taste disorders are associated, majorly, with zinc deficiency, although the cause of LC and pharmacological treatment could have a role in the presence of dysgeusia in patients with cirrhosis.

Since the 1970s, zinc has been identified as a key player in human taste perception,[9] however, its physiology has not been fully described. Zinc is also implicated in liver function, therefore, hepatic injury is related to zinc liver function impairments, including taste perception and recognition.

Despite the clinical relevance of dysgeusia and zinc deficiency in LC patients, evidence related to epidemiology and clinical impact needs to be clarified; the reported prevalence of dysgeusia comes from small studies with variable methodology and performed in single cirrhosis etiology.[10-13] Therefore, this clinical trial aims to evaluate zinc supplementation in improving dysgeusia in patients with cirrhosis.

## MATERIAL AND METHODS

### Trial design

This is a double-blinded randomized clinical trial controlled with a placebo of two parallel groups with a 1:1 allocation ratio.

### Eligibility criteria of participants

Adult patients (18-70 years old) with an LC diagnosis who attended Medica Sur Foundation for hepatic disease surveillance, patients with and without comorbidities, were


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included. Exclusion criteria: patients with hepatic encephalopathy at the time of evaluation, patients with zinc supplement consumption, patients with neurological impairment, patients with common cold, allergic rhinitis or buccal infections, and patients with active alcohol consumption. After clinical confirmation of LC diagnosis, eligible patients were invited to participate in this trial. Patients who presented adverse effects higher than grade 214 related to supplementation and patients who did not accomplish a six-month follow-up were eliminated.

## Setting

Recruitment was made by an open invitation to patients diagnosed with LC who attended medical surveillance at Fundación Clínica Médica Sur.

## Interventions

Once LC was confirmed, dysgeusia was evaluated by ascending dilutions method15 at baseline and after six months to identify PT and RT of five basic tastes: salty, sweet, sour, bitter, and umami. The substances used for the five tastes were dissolved in distilled water in eight ascending concentrations (Supplementary 1). The solutions were prepared every week and stored at 4ºC; at the time of testing, 5 ml of each solution was poured into a Falcon tube at room temperature, and each box was labeled with a letter and number according to concentration taste. The order in which eight solutions for each taste were presented was identical for all subjects. PT was identified as the number of dilutions in which the patient tasted dilution different from water; meanwhile, RT was defined as the number of dilutions in which the patient could identify the taste. For diagnosis of dysgeusia, dilutions were compared with normal values previously established in the Mexican population [16]; patients who perceive or recognize tastes in different dilutions of these values were diagnosed with dysgeusia.

Patients diagnosed with dysgeusia were randomized into two groups: Zinc supplementation (100mg of Zinc Gluconate (ZnG)) and Placebo (100 mg of dextrose), and they were provided a bottle with 30 capsules, then instructions for consumption of capsules were explained (1 capsule/24 hrs). In both groups, patients received nutritional consulting adequate to LC (including adequate protein and fiber consumption), at baseline. Patients were evaluated monthly to identify possible adverse effects and clinical evaluation of liver disease. At baseline and after six months, serum zinc was determined.

Nutritional risk was evaluated by Subjective Global Evaluation16 and Royal Free Nutrition Priorizating Tool17 at baseline and after six months. Quality of life was assessed by the Liver Disease Quality of Life Questionnaire (Spanish version)18 at baseline and after six months. Macro and micronutrient consumption were evaluated with the SNUT19 questionnaire at baseline and after six months.

## Outcomes

The primary outcome was the improvement of PT and RT according to the difference in the number of dilutions identified at baseline and after six months. Nutritional risk, liver decompensation, quality of life, macro and micronutrient consumption, and serum zinc levels were secondary outcomes.

## Sample Size

After twelve months of population analysis, the prevalence of dysgeusia in patients with cirrhosis was determined at 80%. This intervention aims to decrease the prevalence of dysgeusia in LC patients, considering 85% of statistical power and 5% alpha two-sided, with 1:1 proportion between groups, 13 patients were required in each group for reject the null hypothesis of failure ratio in intervention and control group are equal. Considering a 10% loss, we obtained a final sample size of 29 patients.

## Randomization

A random sequence table was generated using a computer-based- number generation. A study external person generated the sequence. Capsules and bottles were identical, placed in two boxes, and allotted in an external office. At the inclusion moment, treatment was assigned according to a random sequence for an external person not involved in the clinical evaluation of patients. At every monthly assessment, the patient delivered the monthly bottle, and at this moment, leftover capsule counting was made.

## Blinding

During inclusion and evaluation, all researchers and patients were blinded to the group assigned to each patient.

## Statistical analysis

Only patients who accomplished the six-month follow-up were considered for statistical analysis. Variable distribution was determined by the Shapiro-Wilks test, resulting in non-parametric distribution; therefore, descriptive analysis for continuous data was presented as median and interquartile ranges. Meanwhile, categorical data were presented as numbers and percentages. A p-value <0.05 was considered statistically significant.

For the primary outcome, median differences of dilutions were evaluated by the Mann-Whitney U test and the Cohen d test calculated effect sizes. Differences in LC decompensation and nutritional risk after six months were evaluated by the Chi-square test. Median differences in macro and micronutrient consumption, quality of life domains, and Zn serum levels were evaluated by the Mann-Whitney U test and effect sizes (Cohen d).

## Ethical considerations

All procedures were performed according to the Helsinki Declaration; all patients signed a Consent Informed Form. The protocol was approved by Comité de Ética en Investigación de Médica Sur S.A.B. de C.V. (2013-EXT-16) and by Comité de Investigación de la Universidad Anáhuac.

## RESULTS

A total of 34 patients were randomized, sixteen in the ZnG group and eighteen in the placebo group. Figure 1 presents the study flow diagram. 50% (n=17= of patients were male, with median age of [IQR 51-63] years. Hepatitis C Virus infection was the primary etiology of LC (41.2%, n=14), followed by abuse of alcohol consumption (26.5%, n=9). According to LC status, the median of MELD was 11 [IQR 9.7 – 12.2]; at baseline, the presence of ascites was the most prevalent decompensation. There were no differences in baseline characteristics of patients (Table 1).

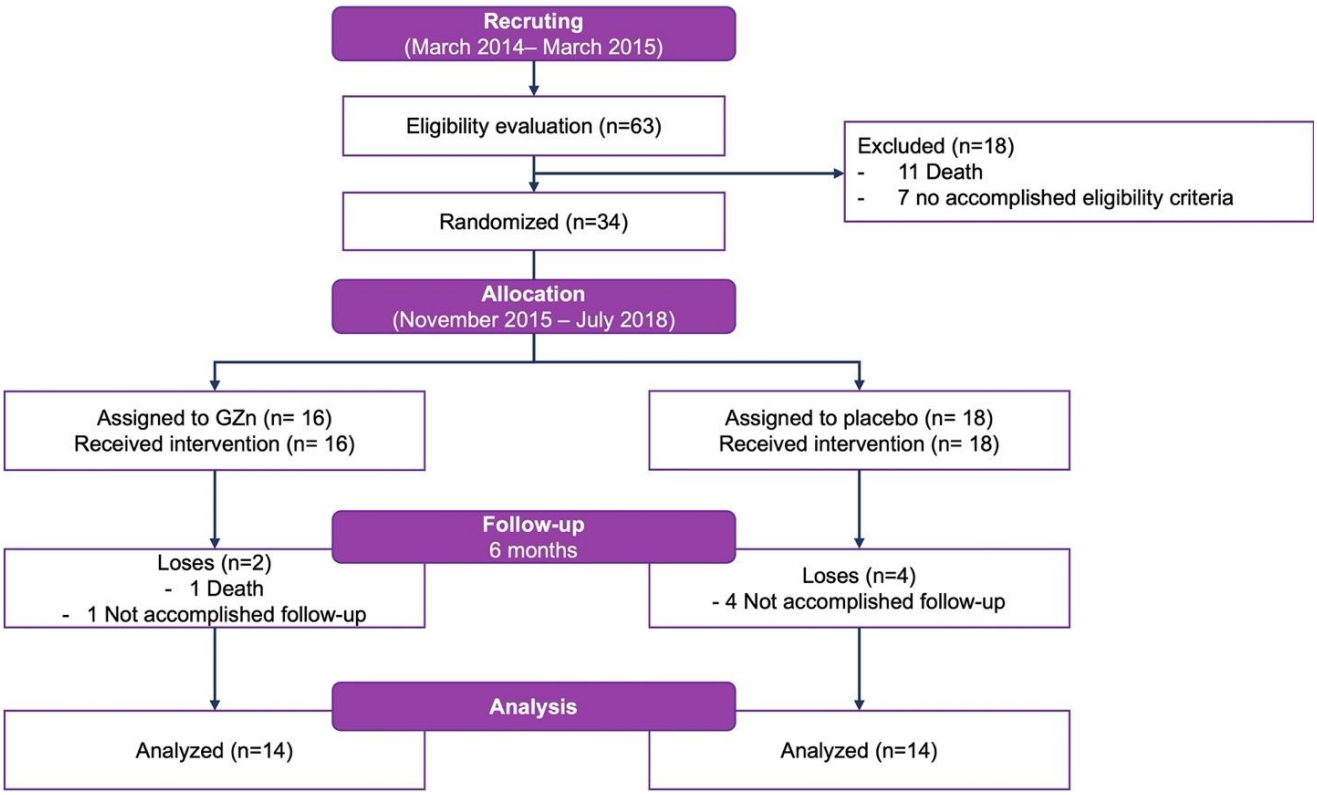


**Figure 1.** Study Flow Diagram.


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**Table 1.** General characteristics of patients included

| Characteristic | General n=34 % (n)/M [IQR] | ZnG n=16 % (n)/M [IQR] | Placebo n=18 % (n)/M [IQR] | p* |
|---|---|---|---|---|
| | | **General** | | |
| **Male** | 50% (17) | 50% (8) | 50% (9) | 1.00 |
| **Age (years)** | 57 [51-63] | 55[49-64] | 57[54-61] | 0.48 |
| **BMI (kg/m²)** | 27[24.-28.8] | 27.1[23.9-28.7] | 26.4[23.6-31.1] | 0.41 |
| **DM** | 41.2% (14) | 25% (4) | 55.6% (10) | 0.92 |
| **Hypertension** | 20.6% (7) | 25% (4) | 16.7% (3) | 0.68 |
| **Smoking** | 41.2% (14) | 50% (8) | 33.3% (6) | 0.48 |
| **Serum Zn** | 60.5 [46.7-70.2] | 61[44.5-70.7] | 58.5[47-70.2] | 0.73 |
| | | **Liver cirrhosis characteristics** | | |
| **Etiology** | | | | |
| **Alcohol** | 26.5% (9) | 18.8% (3) | 33.3% (6) | |
| **NAFLD** | 8.8% (3) | 0 | 16.7% (3) | |
| **HCV** | 41.2% (14) | 50% (8) | 33.3% (6) | 0.30 |
| **Autoimmune** | 17.6% (6) | 25% (4) | 11.1% (2) | |
| **Other** | 5.9% (2) | 6.3% (1) | 5.6% (1) | |
| **MELD** | 11 [ 9.7 – 12.2] | 10 [9.2-11-7] | 11 [9.5-13] | 0.41 |
| **Ascities** | 38.2% (13) | 31.3% (5) | 44.4% (8) | 0.49 |
| **Variceal Bleeding** | 20.6% (7) | 6.3% (1) | 33.3% (6) | 0.09 |
| | | **Taste disorders** | | |
| **PT Dysgeusia** | 76.5% (26) | 68.8% (11) | 83.3% (15) | 0.42 |
| **RT Dysgeusia** | 85.3% (29) | 75% (12) | 94.4% (17) | 0.16 |

* p value represents difference significance between ZnG group and placebo group. BMI body mass index; DM diabetes mellitus; Zn zinc; NAFLD non-alcoholic fatty liver disease; HCV Hepatitis C virus; MELD Model of End-stage Liver Disease; PT perception threshold; RT recognition threshold.

76.5% (n=26) of the patients presented at least one dysgeusia in PT, while 85.3% (n=29) presented dysgeusia in RT. Regarding nutritional risk, according to SGA, most patients were malnourished or at risk of malnutrition (61.8%, n=21). On the other hand, the risk of malnutrition measured by the Royal Scale was (41.2%, n=14). Zinc consumption was within the recommended daily intake ranges for Mexican patients.[20]

Regarding QoL, the global median was 4.7 [IQR 4.2-5.3], with the lowest scores observed in the domains of fatigue 4.2 [IQR 3.4-5.4] and worry 4.3 [IQR 3.4-5.8]. Regarding the median consumption of the intervention, the overall median consumption was 17,700 [IQR 17,250 – 17,900] mg, with no differences between the group that received the supplement (17,600 [IQR 17,350 – 17,925] mg) and the placebo group (17,800 [IQR 17,000 – 17,850] mg) (p=0.44, Mann-Whitney U).

## Dysgeusia improvement

According to the evaluation of the PT of each flavor, after six months of intervention, patients who received ZnG perceived sweet, sour, and umami tastes at a lower concentration.; That is, they needed a smaller amount of the stimulus to be able to perceive it; however, the effect size of the salty and sweet flavors was small, while the sour and umami flavors presented intermediate and large effect sizes respectively. According to the interpretation of the magnitude of the effect sizes, after six months of intervention

with ZnG, the probability of improvement in the UP of salty tastes is 58.1%, and sweet taste is 57.8%, with an NNT of 6 patients, while the probability of improvement in the UP of the acid taste is 65.3% and 74.4% for the umami taste, with NNTs of 3 and 2 patients, respectively. No significant differences were observed in bitter taste (Table 2). In RT evaluation, differences were only observed in RT of the umami taste, similarly at a lower concentration in the patients who received ZnG, with a small effect and probability of improvement of 59.5% (NNT=5). (Table 2)

**Table 2.** Differences in perception and recognition thresholds after six months of intervention

| Taste | ZnG M [IQR] | Placebo M [IQR] | p* | Effect size | CLEs | NNT |
|---|---|---|---|---|---|---|
| | | **Perception Threshold** | | | | |
| **Salty** | 1.0 [1.0-14.7] | 12 [1.0 - 12] | 0.59 | 0.29 | 58.12% | 6.1 |
| **Sweet** | 1.5 [1.5-3.5] | 3.5 [1.5-4.0] | 1.00 | 0.28 | 57.85% | 6.3 |
| **Bitter** | 89 [89-89] | 89 [89-93] | 0.07 | -0.31 | 41.32% | NA |
| **Sour** | 0.48 [0.48-0.48] | 0.48 [0.48-2.44] | 0.32 | 0.56 | 65.39% | 3.2 |
| **Umami** | 0.40 [0.40-0.40] | 0.70 [0.70-0.80] | 0.59 | 0.93 | 74.46% | 2.0 |
| | | **Recognition Threshold** | | | | |
| **Salty** | 1.0 [1.0-23] | 12 [9.2 - 12] | 0.16 | -0.07 | 58.12% | 6.1 |
| **Sweet** | 3.5 [2.5-7.5] | 3.5 [3.0-4.0] | 0.67 | -0.42 | 57.85% | 6.3 |
| **Bitter** | 89 [89-93] | 93 [89-93] | 0.25 | -0.02 | 41.32% | NA |
| **Sour** | 0.48 [0.48-0.96] | 0.48 [0.48-2.44] | 1.00 | 0.17 | 65.39% | 3.2 |
| **Umami** | 0.70 [0.40-1.17] | 0.90 [0.70-1.1] | 0.44 | 0.34 | 74.46% | 2.0 |

* p value represent significance of median difference. Effect size was evaluated by Cohen d. M median IQR interquartile range. CLES Common Language Effect Size. NNT number needed to treat.

## Liver cirrhosis decompensation

After six months of intervention, MELD did not show significant differences between the ZnG group (10.0 [IQR 9.7-10] and placebo (10.0 [IQR 9.2-12.2]), p=0.64 (null effect size). Regarding LC decompensations, 35.7% (n=5) of patients in the placebo group presented variceal bleeding (p= 0.04), and 50% (n=7) developed hepatic encephalopathy (p=0.005). Only one patient (2.9%) died after six months of follow-up (ZnG group).

## Nutritional risk

Regarding nutritional risk evaluation by SGA, patients who received ZnG did not show significant differences after six months of intervention; on the contrary, patients in the placebo group significantly improved nutritional status according to this indicator, increasing the proportion of well-nourished patients compared to the baseline evaluation (14.2% vs. 54.2%, p=0.01). The nutritional risk assessment using the Royal Free Tool did not show significant differences in any groups.

## Macro and micronutrient consumption

Regarding the consumption of macro and micronutrients, no significant differences were observed in the consumption of kilocalories, proteins, carbohydrates, and lipids. According to micronutrient consumption, in patients who received ZnG, lower consumption of fiber (19.2 [15.8-21.3] vs. 22.8 [18.8-23.2]) and vitamin B6 (1.5 [1.3-1.5] vs. 1.7 [1.4-1.7]) was observed, with a small effect size and a probability of change of 60% and NNT of 4 patients for both cases. Sucrose (17.9 [16.8-27.1] vs. 30.1 [22.7-33.3]) and vitamin C 120 [72.4-152.4] vs. 168.9 [143.4-169.3]) consumption also showed a reduction in patients receiving


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ZnG, with an intermediate effect size and a probability of change of 66.6% (NNT=2) for sucrose and 64.8% (NNT=4) for sucrose consumption of vitamin C.

## Quality of life

According to QoL, after six months of intervention, statistically significant differences were observed in the worry domain, obtaining a higher score in patients who received GZn (6.0 [IQR 5.2-6.4] vs. 4.4 [IQR 2.9-5-5], p=0.007). However, the effect size was -1.01 (Adverse). Global QoL did not show significant differences.

## Serum Zinc levels

Regarding the effect of ZnG supplementation on serum Zinc concentration, this was significantly lower in patients who received placebo compared to those who received ZnG (52 [IQR 45.5-58.2] mg vs. 64 [IQR 60- 76.2] mg, p=0.007), however, when evaluating the effect size, it had a value of -1.08 (Adverse). (Figure 2)

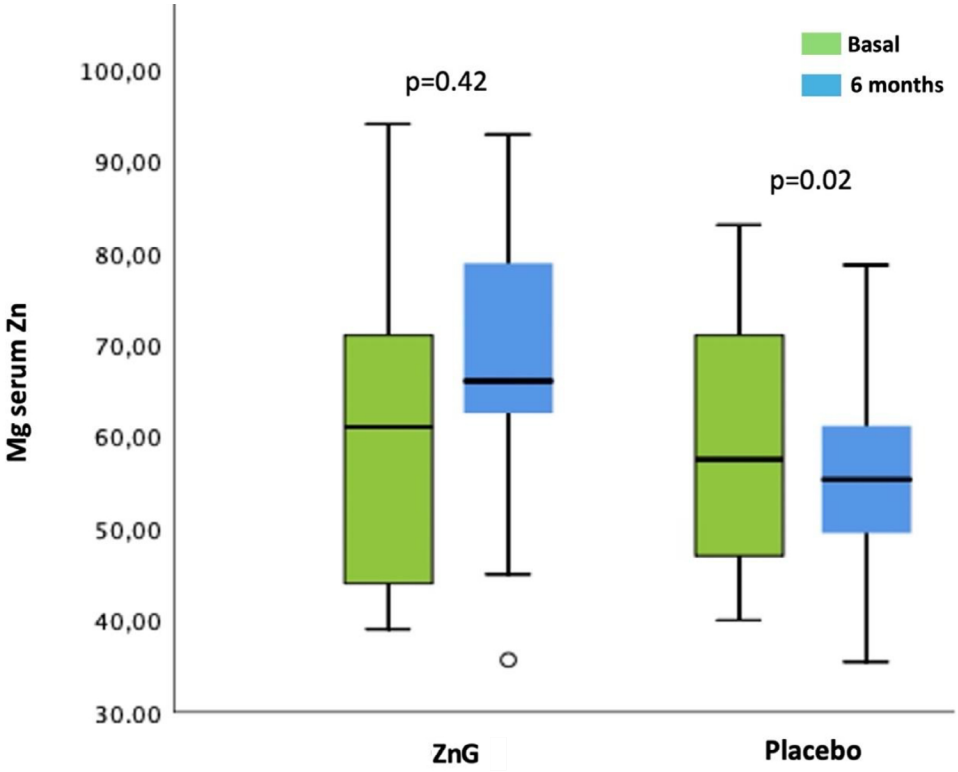


**Figure 2.** Differences in serum levels of Zinc.

## Adverse effects

The presence of fatigue (71.4% (n=20), nausea (57.1% (n=16)), and skin rash (53.6% (n=15) were the most frequent; no significant differences were observed between groups. Only in one patient, the intervention was suspended for one month due to the presence of nausea > grade 2. This patient was assigned to the placebo group.

## DISCUSSION

To our knowledge, this is the first study that objectively evaluates taste perception and recognition changes in patients with cirrhosis and proposes a therapeutic intervention. In patients who received supplementation with 100 mg/day of ZnG for six months, it was observed that at the end of the follow-up, they presented earlier PT in salty, sweet, sour,

and umami tastes compared with patients who received placebo. Regarding RT, this early detection of the umami taste was only observed in patients who received ZnG.

The importance of these changes lies in the fact that sweet, bitter, and umami tastes are the most important for the acceptance of foods since they are responsible for pleasant taste sensations, which is why monosodium glutamate is increasingly used as an additive in Western food.[21] However, in this study, no significant differences were observed in bitter taste. Improvement in taste perception is directly related to the individual's well-being since it has been shown that the organoleptic properties of foods represent the primary reason individuals desire to eat.[8,22]

Even dysgeusia in patients with LC has been observed as part of the disease; it is an underdiagnosed entity, and few studies evaluate this condition despite being reported in more than 30% of patients.[8] In our population, at baseline, the prevalence of dysgeusia was higher in salty and umami tastes, which showed changes after supplementation. These observations coincide with the study carried out by Madden *et al*.,[23] in which it was observed that patients with cirrhosis perceived and recognized the salty taste at higher concentrations compared to healthy volunteers (UP 16 [IQR 1-50] mMol vs 11[IQR 1-60] mMol, p=0.004; UR 72 [IQR 1-800] mMol vs. 60 [IQR 1-800], p=0.009). The umami taste was not evaluated in this study. Although they assessed dysgeusia with different dilutions of each flavor, the standardized method published by Amerine & Pangborn[15] was not used. Another important observation of this study was that those patients who needed higher concentration to taste perception or recognition were patients with restrictive diets, mainly in sodium. Hyponatremia is common in patients with cirrhosis, and it has been identified that the main factor is the deficiency in the consumption of this micronutrient due to excessive or unnecessary restrictions, as well as changes in fluid consumption.[24]

According to cirrhosis decompensation, most patients were in decompensated stages at baseline, mainly due to a history of ascites, variceal bleeding, or second decompensation events; no patient presented hepatorenal syndrome. Regarding the average MELD score (11.3), our patients had a three-month mortality risk of less than 6%. When the effect of ZnG supplementation on liver decompensation was evaluated, patients who did not receive ZnG had a higher prevalence of hepatic encephalopathy. Zn supplementation has been considered as an intervention for hepatic encephalopathy. According to a meta-analysis, which evaluated a total of 233 patients, it was observed that Zn supplementation improves the score of neuropsychometric tests for the evaluation of hepatic encephalopathy (standard difference from the mean: –0.62; 95% CI –1.12 to –0.11).25 In another meta-analysis, it was observed that when Zn supplementation is combined with lactulose for more than three months, this intervention could also improve the scores of the tests used for diagnosis (standard difference of the mean: -0.97; 95% CI: - 1.75 to - 0.19). Supplementation with ZnG could be why only seven patients presented episodes of encephalopathy over six months in the group that received this intervention. Although the consumption of nutrients has been associated with decompensation of the disease, 26 supplementation with ZnG did not show significant differences in the frequency of consumption of macro and micronutrients; on the other hand, the supplementation of a single nutrient is insufficient to improve the nutritional status of patients and the decompensation of cirrhosis that is dependent on HVPG.

Since most patients were in decompensated stages of liver disease, the prevalence of malnutrition is expected to be high. The risk of malnutrition, like dysgeusia, is an entity considered part of the natural history of the disease, but it is also underdiagnosed due to the variability of methods to identify it. Therefore, prevalence data varies between 10 to 100% of patients, depending on the diagnostic instrument and stage of the disease.[26] In our population, after six months of intervention, the proportion of well-nourished patients increased in the placebo group, with no significant differences observed in the group of patients who received ZnG; despite this favorable result, although not related to the ZnG group, prevalence of patients at risk or malnutrition was higher than 10%, this in combination with the decompensated stage of our patients, increases the risk of infections, delay in the list of transplantation for potential candidates, prolonged hospital stays and mortality.[27] However, it must be considered that malnutrition in these patients is due to different factors such as long fasting periods, inflammation, dysbiosis, malabsorption, alterations in nutrient metabolism, and hypermetabolism of the disease; on the other hand, the decrease in food intake is related to the presence of ascites, sodium restriction, micronutrient deficiency, loss of appetite and portal hypertension.[26]

QoL in patients with LC is associated with the presence of malnutrition and decreased food consumption, as well as the stage of the disease and the presence of dysgeusia.[28-30] As mentioned above, hyponatremia is common in patients with LC. Ahluwalia *et al*. evaluated the effect of correcting hyponatremia on the QoL of patients with LC after 14 days of supplementation, demonstrating that the correction of hyponatremia improved the global quality of life scores (3.4±1.1 vs 3.8 ±1.2, p=0.04) according to specific questionnaire for chronic liver diseases.[31] Hyponatremia is associated with the characteristics of the diet and food perception,


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so improving the perception of salty taste could contribute to improving or correcting hyponatremia with a direct impact on quality of life.

Regarding serum Zn levels, patients who received ZnG maintained serum levels in normal ranges at the end of the intervention, while patients in the placebo group significantly decreased serum Zn levels; once again, when evaluating the effect size, this change was not clinically relevant. Serum Zn levels in both groups remained in the range of 54 to 70 mg/dL, in which it has been shown that the manifestation of symptoms associated with deficiency is mild to moderate.[32]

In adverse effects evaluation, these were lower than those reported in studies of Zn supplementation in patients with liver diseases,[11-13] demonstrating the safety of supplementation with 100 mg/day of ZnG. Although these symptoms were higher than 50%, it cannot be determined if the intervention is the cause since both the pharmacotherapy and the natural history of the disease are strongly associated with these symptoms.

Despite our favorable results in the primary outcome, the secondary objectives did not show significant changes. On the other hand, patient losses during follow-up were high. This may be due to the medical care scheme for these patients which was by open invitation without being a captive population with strict follow-up. According to decompensation, it is essential to highlight that at the end of the intervention, the patients who presented episodes of encephalopathy were not eliminated from the study, which could affect the result of the perception and recognition of flavors. However, at the time of final evaluation, it was ensured that no patient presented overt encephalopathy. Although mortality was low, the outcome of patients who did not complete follow-up is unknown. On the other hand, pharmacological treatment and LC etiology could be related to the presence or severity of dysgeusia.

## CONCLUSION

Patients supplemented with ZnG show an improvement probability of PT higher than 55% for salty, sweet, sour, and umami tastes. Meanwhile, the improvement probability of RT for umami taste is 59%. The probability of decreased sucrose, fiber, vitamin C, and B 6 consumption is higher than 60% in patients supplemented with ZnG. There are no significant differences in QoL and plasma Zn levels in patients receiving ZnG compared to placebo.

## CONFLICT OF INTERESTS

None.

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Review Article

# Dendritic cells in the treatment of HIV, cancer and systemic lupus erythematosus

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## ABSTRACT

Vaccines have been one of the best weapons against diseases that have affected humanity for years, their development has allowed the eradication of important epidemics such as smallpox in 1980. Previously, complete microorganisms, or parts of them, were used to fight a disease. Nowadays vaccines make use of more sophisticated components such as genetic material and/or viral vectors. However, although technology in vaccine development has increased considerably in recent years, there are still limitations for the treatment of diseases caused by viruses such as HIV and complex diseases that are difficult to address such as systemic lupus erythematosus and cancer. This article briefly describes an overview of such diseases and the current trend of directing the immune response by vaccinating cells, not people. The importance of dendritic cells and the new technologies that have emerged in recent years are highlighted.

**Key words:** cancer; dendritic cells; immune system diseases; systemic lupus erythematosus; vaccines; HIV.

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## RESUMEN

Las vacunas han sido una de las mejores armas en contra de enfermedades que han afectado a la humanidad durante años, su desarrollo ha permitido la erradicación de importantes epidemias como la viruela en 1980. Anteriormente, se hacía uso de microorganismos completos o partes de ellos para combatir una enfermedad. Hoy en día las vacunas usan de componentes más sofisticados como material genético y/o vectores virales. Sin embargo, aunque la tecnología en el desarrollo de vacunas ha aumentado considerablemente en los últimos años, aún existen limitaciones para el tratamiento de enfermedades causadas por virus como el VIH y enfermedades complejas difíciles de abordar como el lupus eritematoso sistémico y el cáncer. Este artículo describe brevemente una visión general de tales enfermedades y la tendencia actual de dirigir la respuesta inmunitaria mediante la vacunación de células, no de personas. Se destaca la importancia de las células dendríticas y las nuevas tecnologías surgidas en los últimos años.


**Palabras clave:** cáncer; células dendríticas; enfermedades del sistema inmune; lupus eritematoso sistémico; vacunas; VIH.

## INTRODUCTION

For many years, humanity has been struggling against different infections that have caused millions of deaths around the world. However, researchers have found the perfect weapon to protect people from them, with the development of vaccines. The impact has been so important that diseases such as smallpox have been eradicated.[1,2] It is estimated that vaccines save between 3.5 and 5 million lives each year[3] however, their progress has been limited in some cases, for example on diseases caused by the HIV virus, and other more complex pathologies such as systemic lupus erythematosus and cancer. These pathologies, although in some cases have a unique and well-defined causal agent, still have no cure. But why is it hard to develop a vaccine to withstand these pathologies? As an example, HIV due to its high capacity to produce a high rate of mutations, generating a great diversity of sequences at the time of its retrotranscription, especially in the coding of its envelope proteins (env), allows the virus to scape from therapeutic targets.[4] This is why HIV has been treated through pharmacological schemes which only minimize symptoms such as Pre-Exposure Prophylaxis (PrEp),[5] Post-Exposure Prophylaxis (PEP)[6] and Antiretroviral Treatment (ART)[7] since they decrease the transmission of the virus and increases the life expectancy of undetectable seropositive patients. Nonetheless, several studies have shown that prolonged use of these drugs can affect different organs such as the liver and kidneys.[8]

Talking about complex pathologies like cancer, the approach is even more challenging and difficult since it involves different non-isolated etiological agents that represent an important hurdle on the development of vaccines. In these cases, why is it hard to produce a vaccine? The answer is quite complicated since it depends on tumor variability; one tumor can have different origins for example, one organ has multiple cell types and depending on the localization of the cell, the tumor behaves differently.[9] We must also consider mutations which makes cancer be subcategorized into different subgroups and finally a genetic variation could affect the same signaling pathway for example in colorectal cancer; the MAP kinase pathway can be altered by mutations in the EGFR gene but also by mutations in KRAS or BRAF.[10] Therefore, addressing all the variables that promote cancer makes it difficult to eliminate the problem with a single vaccine.

Finally, in Systemic Lupus Erythematosus (SLE) how can we address this pathology with a vaccine? There is a way to do it which will be discussed in more detail later. The management of the disease focuses on achieving remission or, at least, on decreasing symptoms[11] because its manifestation is different for most patients, becoming refractory in many cases. The treatment of patients with SLE is based on the use of immunomodulatory drugs such as hydroxychloroquine (HCQ) and glucocorticoids (GC) and others like prednisone, nonsteroidal anti-inflammatory drugs (NSAIDs), which cause gastrointestinal problems,[12] and antimalarials; as well as the use of monoclonal antibodies such as belimumab and rituximab.[11]

## VACCINE DEVELOPMENT OVERVIEW

Historically, vaccines were developed due to the need to protect the population against deadly disease-causing pathogens The first attempts to develop a vaccine involved the inoculation of dried pustules, mixed with specific plants, from smallpox patients to healthy people[13] and it was not until the 18th century in Europe that Edward Jenner inocu-


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lated a preparation of infected tissues to an 8-year-old boy against rabies, becoming the first person to be vaccinated.[14] As mentioned above, it was enough to take fragments of infected tissue, make a preparation and inoculate it to say that it was already protected against the disease; However, over the time, the way of making vaccines began to change. Between the 19th and 20th centuries, Robert Koch's postulates promoted the development of vaccines beginning with the first microorganisms that could be isolated. Time after, Louis Pasteur developed a vaccine against fowl cholera and rabies, which consisted of a 13-dose schedule with a gradually increasing concentration of live virus.[15] Later it was no longer necessary to include the entire microorganism but only parts of them (protein or conjugated subunits and polysaccharides) capable of generating immunity and incapable of causing disease (see Figure 1). Examples include the pneumococcal polysaccharide vaccine that protects against pneumonia or the bivalent vaccine against HPV. Progress allowed for a deeper understanding the pathogen genome through sequencing and editing techniques, which would later be great tools for the Research and Development of therapeutic targets. That is the case of mRNA vaccines against SARS-CoV-2. In spite of the technology presented by the development of these vaccines, there is still a long way to go in order to understand the complexity of this issue.[16]

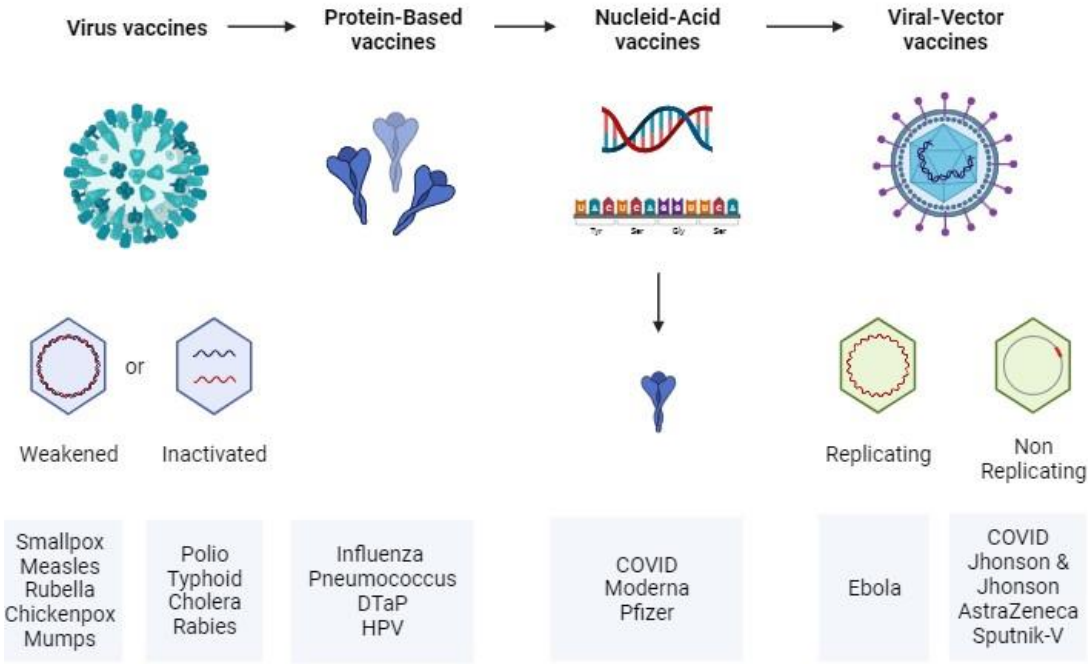


**Figure 1.** Evolution of vaccine development. More representative examples of the different types of vaccines that exist, some use complete viruses (live or attenuated), specific proteins or genetic material, as well as viral vectors (replicating and non-replicating).

## THE APPROACH TO COMPLEX PATHOLOGIES NOWADAYS

So great has been the impact of vaccines that they are now being used to combat diseases such as HIV, cancer and SLE by different methods, for example, the most recent studies on HIV vaccines includes the RV144 vaccine or "Thai trial" which has achieved 31.2% of protection. This study is currently in phase III, but its results were made public in 2009 with a participation of more than 16,000 patients and were based on a "sensitization-booster" regimen consisting of the use of a recombinant vaccine using a canarypox vector that sensitizes and induces T lymphocyte-mediated responses,[17] and a second vaccine that boosts B lymphocyte-mediated activity based on the presentation of recombinant surface proteins.[18] There are also other vaccines still

being studied, such as RV305 and RV306 in Thailand[19] and HVTN 097 and HVTN 100 in South Africa.

In the case of cancer, there are only 2 vaccines approved by the Food and Drug Administration (FDA) which are HPV and hepatitis B.[20] Nonetheless, a type of therapeutic vaccines called immunotherapy has been developed that includes the use of monoclonal antibodies and checkpoint inhibitors like atezolizumab, avelumab, dostarlizumab, durvalumab, ipilimumab, pembrolizumab, among others. Also used are nonspecific immunotherapies such as cytokines, interferons, interleukins and bacillus Calmette-Guérin (BCG) and therapies with oncolytic viruses like Talimogen laherparepvec (Imligic) or T-VEC.[21] Other types of techniques include nanodevices and nanoparticles of silver, gold, zinc or titanium oxides, carbon nanotubes and nanoclays used in melanoma, breast cancer, non-small cell lung cancer, etc.[22,23] Some other vaccines include target antigens that have not been effective in activating strong T-lymphocyte responses. Examples include PANVACTM-VF against pancreatic cancer, Allovectin-7 against recurrent melanoma, abagovomab against epithelial ovarian cancer, tecemotide against non-small cell lung cancer and vitespen against resectable glioblastoma.[24]

In SLE it seems like there is no vaccine approach for the management of this disease by vaccines, however, there are several practical guidelines to treat it that have not been very effective since they are not adapted to all individuals and their effects are heterogeneous and only control symptoms in specific cases such as pregnancy or other specific situations. It should be noted that even within different ethnic groups the behavior of SLE varies with respect to documented clinical manifestations such as neuropathies and myelitis in Latin American population and glomerulonephritis in crossbreed people.[25] Another point to consider is the treatment prescribed to patients, which depends on the degree of organic or multiorgan involvement. It is considered severe when patients report thrombocytopenia, retinal vasculitis, optic neuritis, hemolytic anemia, severe myositis among other life-threatening conditions, and mild when it affects a minor organ such as mucous membranes, joints and/or serous membranes.[26,27]

That is why medication seems to be the only alternative like methylprednisolone succinate and prednisone with vitamin D and calcium supplementation as GC, hydroxychloroquine and/or chloroquine as antimalarials, Rituximab, cyclosporine, methotrexate, azathioprine, cyclophosphamide and/or mycophenolic acid as immunosuppressants have been used.[28] Additionally, most of the studies are focused on analyzing the risk of applying one or several vaccines in patients with this autoimmunity, their implications, safety and efficacy.[29,30,31]

## IMPORTANCE OF DENDRITIC CELLS IN VACCINATION

During vaccination, one of the primary mechanisms is the induction of inflammation due to tissue damage and proinflammatory cytokines triggered by adjuvants.[32] Inflammation activates several mechanisms that induce a cascade of events including activation of polymorphonuclear cells, complement activation and chemotaxis of antigen presenting cells (APC) including dendritic cells (DC) to the site of damage to process the pathogen. These lasts cells are considered the bridge between innate and adaptive immunity, and it has been shown that, depending on the type of microorganism and the interaction of APC with naive T lymphocytes, the latter will be able to differentiate into helper T lymphocytes (Th) producing mainly IL-21, IL-22 and IL-17. In addition, these events also induce the differentiation of follicular effector T lymphocytes (Tf) indispensable for the differentiation of B lymphocytes into antibody-producing cells.[33]

DC are also capable of producing varieties of cytokines essential for such differentiation and carry out various effector functions in the inflammatory process, which has led them to be targets of study in the development of vaccines. The interesting thing is that there are different types and the rationale behind the use of these cells in vaccines depends on the type of DC used. The classification depends on their nature and mechanism of action. For example, there are conventional dendritic cells (cDC) type 1 (cDC1) and type 2 (cDC2) or plasmacytoid dendritic cells (pDC) producing IFN type 1. In humans, cDC1 can induce cytotoxic T cell responses and are able to stimulate naive CD4+ lymphocytes, they are also thought to be potent inducers of regulatory T cells, although their mechanism is uncertain. cDC2 carry out mechanisms similar to cDC1, but in smaller numbers. Regarding pDC in mice located in the spleen are divided into 2 types based on CD4 expression, they are characterized as essential machines in viral infections due to an increase in MHC-II and stimulatory molecules such as CD80, 86 and 40 in addition to producing high amounts of type 1 and 3 IFN. pDC are also divided into 2 and promote the production of cytokines in response to viruses and promote a strong activation of T lymphocytes and antiviral immunity.[34] In the inflammatory process, DC are crucial due to the chemotaxis they carry out through CRR7-dependent lymphoid and non-lymphoid tissues, epigenetic reprogramming such


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as DNA methylation, histone modification and non-coding RNAs they produce, which play an important role in the development of innate immune cells. They assist in metabolic remodeling involving enzymes, sensors or intermediates that involve cell migration. Also, it has been studied that CCR7 promotes migration from peripheral tissues to lymphoid tissues through four signaling pathways, the first pathway is PI3K/AKT, PI3K exerts function in immune cell modulation and chemotaxis, CRR7 induces the activation of PI3K and subsequently AKT kinase through FAS which induces the production of CXC and CC chemokines by DC through the ERK pathway. The second pathway involved is MAPK/NF-KB which is critical for TLR-induced DC maturation through IL-1, IL-6 and TNF which are crucial in inflammatory processes. The third pathway is HIF-1α which is key in the migration and inflammation of DC for their cytoskeletal rearrangement and finally the last pathway is IRF which has been showed that in mice a deficiency of IRF shows reduced expression of CCR7 and therefore defective migration.[35] All these processes and signaling pathways ensure DC as an alternative in the treatment of complex diseases.

## DENDRITIC CELLS AND HIV

Speaking of cell-based vaccines, it is important to consider that some studies have focused on the characterization of CD4+ and CD8+ T lymphocyte epitopes, as well as the quantification of interleukins (IL) produced upon vaccine delivery with ex vivo-trained DC loaded with IFNα together with LIPO-5 peptides containing Gag, Nef and Pol sequences in HIV patients treated with ART. According to the authors, vaccination induced the expansion of IFNγ-secreting CD4+, IL-2 and IL-13 and generated proliferation of IFNγ-producing CD8+, perforin and granzyme A and B, signifying a control in viral replication, as stated by Surenaud M, *et al*.[36] (see Figure 2). Another publication supporting the above work starts from the same principle, which seeks, on the one hand, to develop strategies based on the optimization of CD8+ T lymphocytes that have been implicated with protective effects in clinical trials and, on the other hand, argue that T lymphocyte responses are also enhanced in preclinical trials.[37]

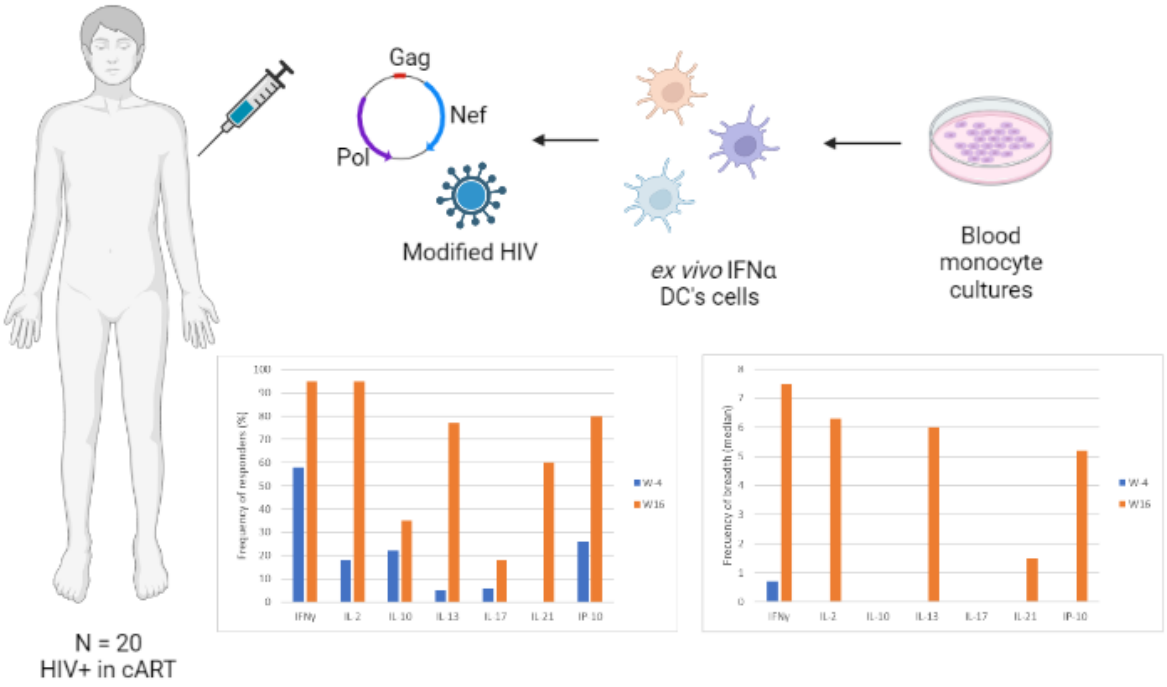


**Figure 2.** Design of a dendritic cell vaccine for the treatment of HIV-1. A cell culture of differentiated monocytes is performed on dendritic cells loaded with IFNα and exposed to a modified HIV virus for the immunization of seropositive patients treated with antiretroviral therapy (ART). Modified from: PLoS Pathog. 2019; 15(9):E1008011.47.

## DENDRITIC CELLS AND CANCER

In cancer this is one of the most interesting fields. Cells have been used, for example, in carcinoma a vaccine composed of autologous Th17-inducible monocyte-derived DC (moDC) pulsed with folate receptor alpha (FRα) epitopes has been developed which promotes increased ovarian cancer remission period. Nagai *et al*.[38] used an adherent population of peripheral blood polymorphonuclear cells stimulated with Wilms tumor gene 1 peptide and mucin 1. In melanoma a monocyte-derived vaccine with tumor lysate has been developed that has worked, but also affects the positive regulation of PDL-1 expression, likewise another electroporated moDC vaccine with mRNA encoding CD40 ligand, CD70 and a CATLR4 (TriMiXDC-MEL) has been developed as monotherapy and in conjunction with Ipilimumab. However, autologous natural myeloid DC loaded with HLA-A*0201-restricted melanoma-associated peptides (gp100 and tyrosinase) have also been used. In glioma, a vaccine called DCVACS®-L has been developed with a cDC loaded with glioblastoma lysates. Another based on α1-type DC pulsed with 5 synthetic peptides and cytokines, and finally Wan *et al*.[39] showed a positive effect on patients using DC. In sarcoma, vaccines with moDC containing tumor antigens have been shown to be safe. However, certain combinations of anticancer drugs are counterproductive, such as temozolomide + irinotecan and a combination (pazopanib + topotecan + cyclophosphamide) negatively affected DC maturation. Similarly, the use of DC loaded with tumor lysate with imiquimod and gentamicin has been studied. Finally, in lymphoma, moDC in the presence of IFNα and GM-CSF (IFN-DC) has shown promising results.[40]

It is important to note that there are still great challenges in the development of this type of vaccine. Interestingly, although DC vaccines have been shown to be effective, there is a study which argues that DC vaccines have not shown efficacy other than provenge, or also called APC 8015 and sipuleucel-T, approved in 2010 by the FDA for the treatment of metastatic prostate cancer. But why have they failed? Although the answer is complicated, there are several alternatives that could improve this type of vaccines, for example it has been seen that most vaccines tend to use only moDC, but it has also been noted that cDC1 could be promising due to the cross presentation of tumor antigens and the use of the vaccine combined with other immunotherapies and not only as monotherapy.[41] Another alternative is the use of hematopoietic stem cells to generate cDC1 and/or induced pluripotent stem cells. In vivo DC-targeted vaccines consisting of administering tumor antigens to host-specific DC subsets using Abs against specific DC receptors some examples include anti-CTLA with DC vaccines using a human monoclonal anti-DEC-205 Abs fused to NY-ESO-1 led to a much higher rate of complete partial response than the 15% observed for anti-CTLA-4 in monotherapy. Another strategy is the use of pDC and finally using DC-derived exosomes (exosDC) as they have been found to be more resistant to tumor-mediated immunosuppression.[41]

It has also been observed that the use of DC has positive anticancer effects, specifically in different types of cancer-causing solid tumors. Two main approaches have been proposed (See Figure 3), the first method consists of isolating cancer cells that are lysed and exposed to DC that will recognize tumor antigens or implement neoantigens, which consists of developing new antigens using omics sciences as stated by Harari A, *et al*.[42] The other method is based on in situ vaccination of DC in the tumor proposed by Castiello L, *et al*.[43] This promotes a faster and more direct arrival of APCs to the tumor and, therefore, the CD8+ mediated cytotoxic effect is activated more rapidly.


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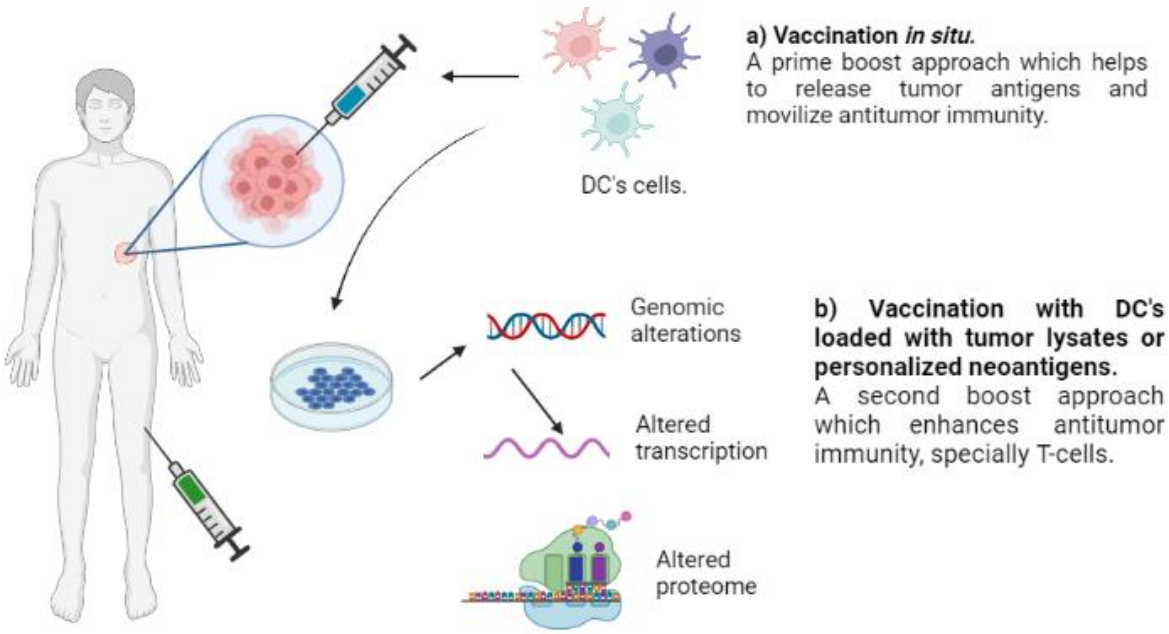


**Figure 3.** Dendritic cell vaccine approaches for cancer treatment. The first is based on the in situ vaccination of dendritic cells that activate the immune response to various non-metastatic tumor masses and a second approach that is based on the principles of omics sciences and the prediction of new tumor antigens.

## DENDRITIC CELLS IN SLE

This field has observed an important relationship between DC cells and autoreactive T and B cells. Preclinical and clinical studies have shown that it is possible to induce tolerogenic DC cells that have a positive impact on tolerance mechanisms; these mechanisms have already been described and this implies their use in vaccines.[44,45] This largely depends on the subtype and the location of the CDs. Regarding conventional DC (cDC), inadequate processing and presentation are believed to lead to the activation of autoreactive CD4+ and CD8+, while in plasmacytoid DC (pDC) the high levels of IFNI and TLR9 expression of the cells B promote the development of autoantibodies. Finally, the role of follicular DC (fDC) in SLE is poorly known. It is believed that fDC are relevant in the protection of B cells; However, poor elimination of these promotes the development of autoantigens and, therefore, the incitement of this disease, as described by Seitz HM, *et al*.[46] Therefore, approaches for the treatment of this disease are aimed at process of peripheral tolerance of T and B cells through tolerogenic DC; that is, those that express low levels of costimulatory molecules (MHC II, CD83, etc.) and high levels of immunomodulators that suppress the activity of T lymphocytes (IL-10, PDL-1, TGF-β, etc.). Tolerogenic CD can be induced by various molecules such as vitamin D3, dexamethasone, neuropeptides such as vasoactive intestinal peptide and rapamycin, radiation, among other processes. The induction mechanisms have already been described by Švajger U, *et al*.[47] (see Figure 4).

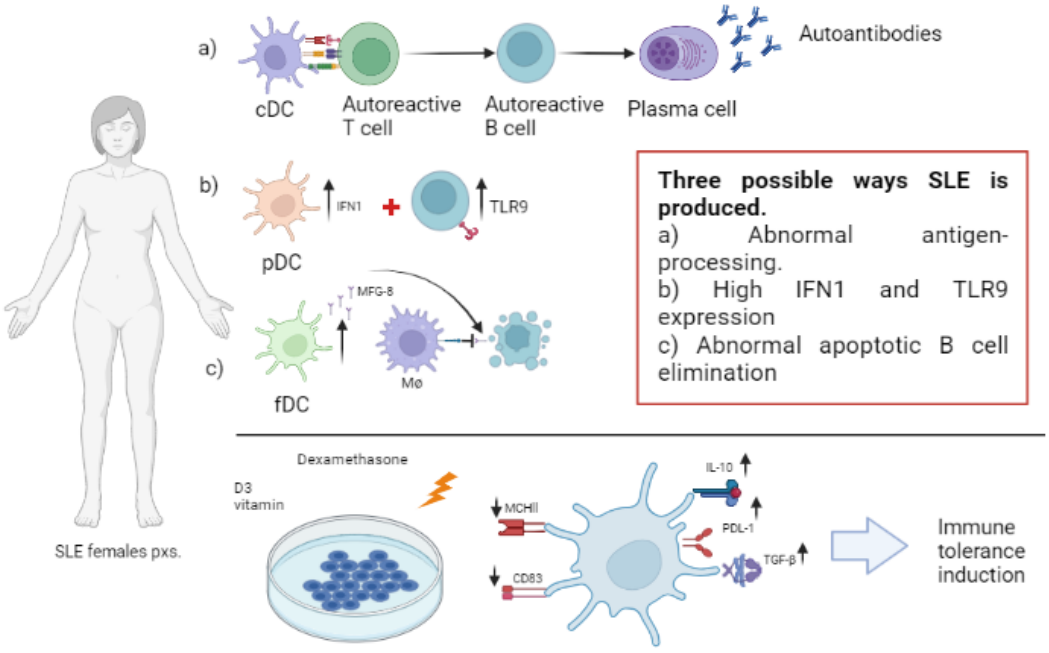


**Figure 4.** An approach to inducing peripheral dendritic cell tolerance for the treatment of systemic lupus erythematosus. Highlights at the top are the 3 possible ways in which SLE occurs depending on the type of CD, as well as the induction at the bottom of tolerogenic CD by various molecules and its therapeutic implications.

## DISCUSSION

According to the World Health Organization (WHO), vaccines represent a form of protection against a disease, without suffering from it. This is a very effective and reliable alternative for acquiring immunity and generating response memory. However, the number of studies in the literature with this new approach is usually quite large and diverse.

Global HIV mortality rates range from 53% in women and girls to approximately 41% in men and boys since 2010.[48] In Mexico, the number of deaths by age is more concentrated in people aged 30-40 years, with 1718 deaths compared to men and 337 women. On the other hand, HIV cases by year of diagnosis have decreased dramatically due to the use of antiretrovirals, having a total of 6560 in 2021.[49] Although reported cases have been decreasing considerably over time, it is important to note the emergence of viral resistance to current drugs.[50]

Regarding cancer, figures date a population-dependent mortality rate of about 7.2% in Latin America and the Caribbean, 7% in North America, 19.6% in Europe, 58.3% in Asia, 7.1% in Africa and finally 0.7% in Oceania.[51] In Mexico, mortality rates for malignant tumors are estimated by decennial group and sex, 51% in women and 49% in men. Alarmingly, cancer deaths are increasing over the previous month and years, having a January to August rate of 4.65 in 2019 and 4.73 in 2020 per 10,000 population. The leading cause of death from malignant tumors in men and women aged 0-29 years is leukemia. In men aged 30 to 59 years, the most common malignant tumors are colon, rectum and anus. From 60 years of age onwards, the most common tumor is the prostate. While in women aged 30 to 60 years and older it is given by breast cancer.[52] However, it is important to decide and evaluate in which cases it is feasible, since in many cases it is counterproductive to puncture a tumor due to the release of cancer cells to other parts of the body. As we have seen above, there are more alternatives that have maximized the effectiveness of cancer vaccines.

Finally, in the case of SLE, it is difficult to find statistics both in Mexico and in other parts of the world. Interestingly, even in the United States there are no exact figures for this disease. However, in Mexico, Dr. Rocío Catana Hernández estimates that for every 10 people who suffer from SLE, 9 are women whose highest prevalence has been between 20 and 40 years per 100,000 from 2014 to 2017.[53]


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Now, why are these diseases relevant? In the first instance, they are diseases that have no cure. Secondly, their high incidence worldwide makes them a clear example that requires more research and more therapeutic alternatives. Finally, because the treatments currently used generate overwhelming side effects for patients leading to great detachment from them. In cancer it is important to mention that there are still great challenges when developing vaccines due to the various methods that cancer cells have to suppress and evade the immune system; and finally in SLE a vaccine would cause a lot of confusion and controversy, since the main objective of vaccination is to enhance and reinforce the immune system, which would be counterproductive. However, tolerance is a topic that has been studied and that may be a therapeutic target for the development of a candidate vaccine that can modulate this response,[54] since it has been observed that there are cells capable of performing this function, such as dendritic cells. In this sense, knowing the benefits of cell vaccines is of utmost importance since the amount of information found in the literature, as mentioned above, turns out to be very wide and varied. Therefore, it is important to publicize the new approach to the modern era.

This is the reason why the new trend in vaccinology implements the use of cells within its preparations, specifically DC, and this is partly since these diseases, being more complex, are more difficult to study. Therefore, this type of "vaccines" would help avoid a more heterogeneous response and address the problem in a more targeted way. However, classical mechanisms are still used to develop new vaccines which creates a challenge for researchers and pharmaceutical industries related to cell-vaccine development. In this sense, also in autoimmune diseases this idea allows us to address the problem in a more efficient way, since being multifactorial it can be derived from one, several or a combination of variables. This allows us to rescue the "danger model" described by Matzinger P. where in this theory the immune system is not only capable of distinguishing between its own and that of others but is more focused on activate on what causes "harm".[50] This new way of manufacturing vaccines focuses more on regulating the damage generated and reducing the effects of the disease. Finally, this work demonstrates that the study of vaccinology is constantly evolving. However, it is essential to think about pharmacovigilance aspects that include cost-benefit, best route of administration, dose, stability, possible events attributable to vaccination and immunization (ESAVIS), storage among other details that may affect the course of development of this type vaccines in the future.

## CONCLUSION

The new trend in vaccinology makes use of cells as possible targeted therapies in diseases that still have no cure. The new approaches involve vaccinating cells, not people. In this regard, the importance of implementing DC in vaccines is desirable, since they are capable of modulating the immune response to damage.

## CONFLICTS OF INTEREST

The authors declared that they had no conflicts of interest.

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Review Article

# Neonatal Respiratory Distress Disorders: comparative pathologies review and diagnosis suspicion algorithm proposal

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## ABSTRACT

Respiratory pathologies, along with congenital cardiac diseases, represent the main etiologies of neonatal disorders. Neonatal respiratory distress syndrome embraces several pathologies that share respiratory impairment as its main clinical manifestation. Epidemiological and risk factors for respiratory disorders, such as weeks of gestation accomplished before birth and maternal comorbidities, have been identified during the last decades. However, similar acute clinical manifestations, as well as laboratory and radiological findings, lack comprehension, which might lead to an incorrect diagnosis and delayed optimal treatment. Hyaline membrane disease, transient tachypnea of the newborn, and meconium aspiration syndrome represent the three most frequent types of neonatal respiratory distress syndrome. In this paper, we describe the risk factors and pathophysiology of each disease and compare clinical manifestations, as well as laboratory and radiological findings between them. For this purpose, we analyzed a key termed based literature review which include Systematic Reviews, Metanalysis, case reports and book chapters as well as private hospitals epidemiologic statistic reports. Finally, we present a differential diagnosis algorithm which can be used to identify which respiratory distress syndrome the newborn manifests and consequently give prompt and optimal treatment.

**Key words:** neonatal respiratory distress syndrome; hyaline membrane disease; transient tachypnea of the newborn; meconium aspiration syndrome; differential diagnosis.

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## RESUMEN

Las patologías respiratorias junto con las cardiopatías congénitas representan las principales etiologías de las enfermedades neonatales. El síndrome de distrés respiratorio neonatal engloba varias patologías que comparten la insuficiencia respiratoria como principal manifestación clínica. Durante las últimas décadas se han identificado factores epidemiológicos y de riesgo para trastornos respiratorios, como semanas de gestación cumplidas antes del nacimiento y comorbilidades maternas; sin embargo, la similitud de manifestaciones clínicas así como la mala comprensión de hallazgos de laboratorio y radiológicos puede conducir a un diagnóstico incorrecto y retrasar el tratamiento óptimo. La enfermedad de la membrana hialina, la taquipnea transitoria del recién nacido y el síndrome de aspiración de meconio representan los tres tipos más frecuentes de síndrome de dificultad respiratoria neonatal. En este trabajo se describen los factores de riesgo de cada enfermedad, la fisiopatología, y de igual forma, se comparan las manifestaciones clínicas así como hallazgos de laboratorio y radiológicos entre ellos. Finalmente, presentamos un algoritmo de diagnóstico diferencial que puede utilizarse para identificar qué síndrome de dificultad respiratoria presenta el recién nacido y, en consecuencia, ofrecer un tratamiento óptimo y oportuno.


**Palabras clave:** síndrome de dificultad respiratoria neonatal; enfermedad de la membrana hialina; taquipnea transitoria del recién nacido; síndrome de aspiración meconial; diagnóstico diferencial.

## INTRODUCTION

Neonatal respiratory distress syndrome (NRDS) is a medical term that encompasses acute pathologies manifesting as respiratory distress in newborns.[1] These diseases exhibit certain clinical and pathological characteristics, such as an onset within the first 72 hours of extrauterine life, inadequate pulmonary distention, varying degrees of cyanosis, pulmonary hypertension, and a strong correlation with the week of gestation in progress at the time of birth.[1,2] While there are several diseases that can cause this syndrome, its incidence and potential complications have led the literature to focus on the description of three main pathologies: Hyaline membrane disease (NRDS Type 1), Transient tachypnea of the newborn (NRDS Type 2), and Meconium aspiration syndrome (NRDS type 3).[3]

Hyaline membrane disease (HMD) is primarily caused by deficient production and poor quality of pulmonary surfactant. Transient tachypnea of the newborn (TTN) results from a delay in the reabsorption of fetal lung fluid. Lastly, Meconium aspiration syndrome (MAS) occurs when newborns produce meconium while still in the uterus, leading to its aspiration and intrapulmonary deposition.[2,3] Despite the different pathophysiological mechanisms, without optimal and timely detection and treatment, pulmonary incapacity, incomplete alveolar distension, and hypoperfusion can lead to respiratory acidosis and pulmonary hypertension. These conditions can lead to extrapulmonary consequences affecting organs such as the heart, kidney and brain, significantly compromising both present and future proper functioning and development.[1,3]

Epidemiology of these diseases varies depending on prenatal support and care programs in each country, nevertheless, it is clear that worldwide the incidence of this syndrome has a negative proportional relation with the weeks of gestation of the newborn, particularly in NRDS types 1 and 2.[2] Different guidelines that consider clinical manifestations and imaging criteria serve as orientation resources for the diagnosis of each type of syndrome.[1] In this paper, we present a comparative review of NRDS types 1, 2 and 3 epidemiology, risk factors and pathophysiology, and propose a differential diagnosis algorithm that can be used as a synthesized information resource that aids in the comprehension of this syndrome and the practical decision-making.

## METHODOLOGY

In order to retrieve actualized information about Neonatal Respiratory Syndromes, we performed a key words/terms based search on PUBMED, Cochrane and Google Scholar online servers. *Neonatal Respiratory Distress Syndrome, Hyaline Membrane Disease, Transient Tachypnea of the Newborn, Meconium Aspiration Syndrome,* and *Differential diagnosis* were used to mark off our research. English or Spanish written Systematic Reviews, Metanalysis, case reports and book chapters published over the last 10 years were selected for this paper. Any other sources published before 2013 or written in a language besides English or Spanish were excluded. We obtained more than 50 different publications matching our searching criteria, 22 were excluded for having been published before 2013, 6 were excluded because they were written in languages

not included in our inclusion criteria, and 1 was excluded for being a Spanish transcription of an already included English-written article. Finally, we selected a total 21 publications for the making of this paper.

## RESULTS

### Hyaline Membrane Disease (NRDS Type 1)

HMD is one of the most common respiratory disorders in newborns, especially in preterm newborns. This condition is caused by a deficient quantity and quality of pulmonary surfactant due to an immaturity of type two pneumocytes, leading to acute respiratory distress.[4] Despite epidemiological efforts to estimate the approximate incidence of HMD, data remains uncertain since it largely depends on the rate of preterm births in each country or region studied. However, it is clear that this disease primarily affects newborns born before 37 weeks of gestation (WOG), and its occurrence is inversely proportional to the number of WOG completed prior to birth. International estimates allow us to calculate the probability of suffering from HMD; newborns between 31 and 36 WOG have a 10 to 20% chance of developing HMD, 20-40% for newborns at 28-30 WOG, 50-70% for those at 26-27 WOG and 80 to 95% probability for newborns between 24 and 25 WOG.[5] Additional risk factors associated with HMD include male sex, Caucasian ethnicity, twin pregnancy, fetal hydrops, poorly controlled diabetes in the mother, and maternal hypothyroidism.[1]

HMD has its pathophysiological basis in the deficiency of pulmonary surfactant, a surface-active agent composed of lecithin, sphingomyelin, phosphatidylglycerol, and apoproteins. This surfactant fulfills essential functions for adequate pulmonary activity, such as decreasing alveolar pressure, stabilizing alveoli, optimizing gas exchange, maintaining functional respiratory residual capacity, and serving as an anti-edematous and protective agent against infections.[3,5] Pulmonary surfactant is produced by type two pneumocytes starting from the 20th WOG. However, lung maturation, as well as the correct production and functioning of the surfactant, do not occur until 34th WOG. At birth, especially in preterm infants, the absence of surfactant and the lack of maturation of its components cause poor alveolar expansion and an imbalance in the oxygen uptake, leading to the establishment of SDRRN.[6,7] Poor gas exchange results in respiratory acidosis and pulmonary vasoconstriction, damaging endothelial integrity and promoting the leakage of protein exudate, as well as the formation of hyaline membranes. Alveolar atelectasis commonly forms, leading to the generation of perfused but not ventilated lung areas. This, in turn, induces pulmonary hypertension with a right-to-left shunt. Finally, the high concentration of oxygen received by the failing lungs can damage lung epithelium and aggravate the deficiency of surfactant.[7]

Clinical manifestations include acute respiratory distress, tachypnea, intercostal shots, nasal flaring, progressive cyanosis, grunting, xiphoid retraction, and poor response to oxygen. These patients usually have high Silverman Anderson scale results and decreased on the APGAR scale due primarily to poor respiratory function.[6]

Pregnancy monitoring plays an essential role in fetal development. Timely detection of problems, such as the threat of preterm labor or any other situation that may predispose to fetal distress, is important for the correct prophylaxis of conditions such as NRDS type 1. In this case, when a situation involving fetal distress is encountered, the use of corticosteroids, which accelerate the maturation of type 1 and 2 pneumocytes, is recommended.[8] The constant concern remains as to which steroid should be applied in these cases, but the two most widely accepted for this therapy are betamethasone and dexamethasone, since they are the steroids that suffer least from placental metabolism by 11 beta-hydroxysteroid dehydrogenase.[9] A consensus of experts comprised of European neonatologists who convene every 3 years to develop updates on the latest techniques for the management and prevention of premature or at-risk infants, mention that a cycle of prenatal corticosteroids administered to pregnant patients at risk of preterm birth improves survival, reduces the likelihood of developing NRDS, necrotizing enterocolitis, and ventricular hemorrhage. Furthermore, it appears to have no adverse effects on the mother or the newborn. On the other hand, it has been observed that these prenatal steroids reduce mortality in patients with pregnancies at 22 WOG and even in patients with pregnancies at 34-36 WOG. It has been shown that prenatal steroid administration decreases the risk of short-term respiratory morbidity. It has also been observed that the optimal time between the initiation of steroid administration and childbirth should be between 24 hours and 7 days, as beyond this timeframe, the beneficial effects begin to diminish.[10]

### Transient Tachypnea of the Newborn (NRDS Type 2)

TTN, also known as pulmonary maladaptation, is a benign, non-infectious respiratory distress condition primarily caused by a delay in the reabsorption of fetal lung fluid.[1] This disease is considered the second type of the NRDS and


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is the most common presentation of respiratory distress in term newborns.[3] Its incidence worldwide is approximately 11% of live newborns, but in Mexico, it is estimated to affect 0.3-2% of term or late preterm newborns. However, it constitutes up to 50% of cases of respiratory distress admitted to pathological nurseries or neonatal intensive care units. Risk factors include birth by cesarean, maternal gestational diabetes or asthma, male sex, being small for gestational age and macrosomia.[11,12]

TTN possesses a multifactorial pathophysiology that combines pre- and post-natal conditions leading to respiratory distress. Excess lung liquid, electrolyte imbalances (mainly sodium and chloride ions), alveolar edema, as well as fluid in lymphatics and interstitium, result in hypoxemia, hypercapnia, air entrapment, and, finally, compensatory taquipnea.[9] Generally, in the final weeks of gestation, fetal lungs produce lung liquid and surfactant at an approximate rate of 5 ml/kg/h, generating an internal lung pressure of 1 to 2 mmHg greater than the amniotic fluid. This pressure differential is essential for normal lung development. At the time of birth, lung liquid needs to be cleared out and reabsorbed so lungs can function as an air reservoir and oxygen interchange chamber. The main mechanism for doing so is Na+ uptake across the airway epithelium (by Na+ channels previously activated by fetal epinephrine and glucocorticoids), which reverses the osmotic gradient leading to airway liquid reabsorption.[1,12] Absence of mechanical squeezing of vaginal delivery (which diminishes alveolar pressure natural birth increase) as well as a prolonged time lapse between birth and first breath are considered as factors that negatively impact TTN.[3]

Clinical manifestations of TTN include respiratory distress, which might be present since birth or begin in the next 2 hours. The main finding is evident tachypnea, typically with a respiratory rate above 60, which can even reach 100-120 breaths per minute. Other occasional findings can include cyanosis, tachycardia, and barrel-shaped chest.[8,13] The common duration of TTN is usually 48 hours until resolution of the clinical picture. Various treatments have been proposed to support correct resolution, which have been evaluated by different reviews published in Cochrane. These treatments include fluid restriction, administration of furosemide, salbutamol, and even epinephrine. However, it has been observed that none of these have been reported as effective. Finally, an agreement has been reached that the treatment is based on supportive measures such as oxygen therapy, suspension of enteral feeding, and the initiation of intravenous fluids. Additionally, assisted ventilation might be needed, although the percentage of cases requiring it is very low. As mentioned earlier, the condition will resolve within 48-72 hours, but it is highly likely that the newborn will need to be admitted to a neonatal intensive care unit.[13,14]

## Meconium Aspiration Syndrome (NRDS type 3)

MAS is a cause of NRDS commonly found in patients born between weeks 38 and 42 of gestation, particularly in undeveloped countries. At the same time, 3-12% of those born with Meconium-stained amniotic fluid (MSAF) will develop MAS. According to Monfredini and others, this number could be up to 52% in those beyond the 42 WOG.[15]

MAS possesses a multifactorial pathophysiology.[3] The first important factor is antenatal inflammation/infection. It is recognized that the presence of endotoxins, bacteria, and inflammatory mediators in MSAF causes an increase of intestinal peristalsis and meconium aspiration by the fetus. Another physiopathology factor is the mechanical airway obstruction, which will be caused most of the times by meconium plugs.[8] Those meconium plugs lead to a high resistance and air trapping whose intensity depends on the consistency and quantity of the meconium-stained liquid. In fact, this factor has been considered the most common physiopathology mechanism of MAS. Mechanical airway obstruction could be partial or total. If the obstruction is partial, hyperinflation will be caused because of valve effects.[15] On the other hand, if the obstruction is total, patchy areas of atelectasis can be caused. The third factor in the pathophysiology of MAS is the inactivation of pulmonary surfactant due to the presence of meconium fatty acids. This inactivation leads to atelectasis, resulting in ventilation-perfusion mismatch. Despite not being completely understood, it is known that meconium can alter the surfactant function through direct toxicity on type II pneumocytes.[15,16]

Finally, there is an activation of the inflammatory cascade due to chemotactic action for neutrophils substances contained by meconium, this activates the complement, has a vasoactive function and is a source of pro-inflammatory mediators as well.[12] Nowadays it is not well known the cellular mechanism that causes the activation of the inflammatory cascade, however, it is known that meconium induces inflammation and apoptosis, besides that, it can cause chemical pneumonia during the first 48 hours of life of the newborn. Moreover, persistent pulmonary hypertension has been identified in 15-20% of MAS patients and has been associated with pulmonary vasoconstriction, capillary hypertrophy and pulmonary hyperexpansion.[16,17]

Timely diagnosis of NRDS is essential for a quick medical response and a better prognosis, for this intention there exist several general newborn state scales, however there is one that particularly helps in the detection of respiratory pathologies.[2] The Silverman Anderson scale is a tool that allows us to identify respiratory signs and symptoms thereby determine the severity of distress present in the neonate, as presented in Figure 1. It evaluates 5 respiratory distress signs and grades them in a scale from 0 to 2 depending on the severity. A higher score indicates a more severe respiratory problem while lower scores suggest a more respiratory functional newborn.[18]

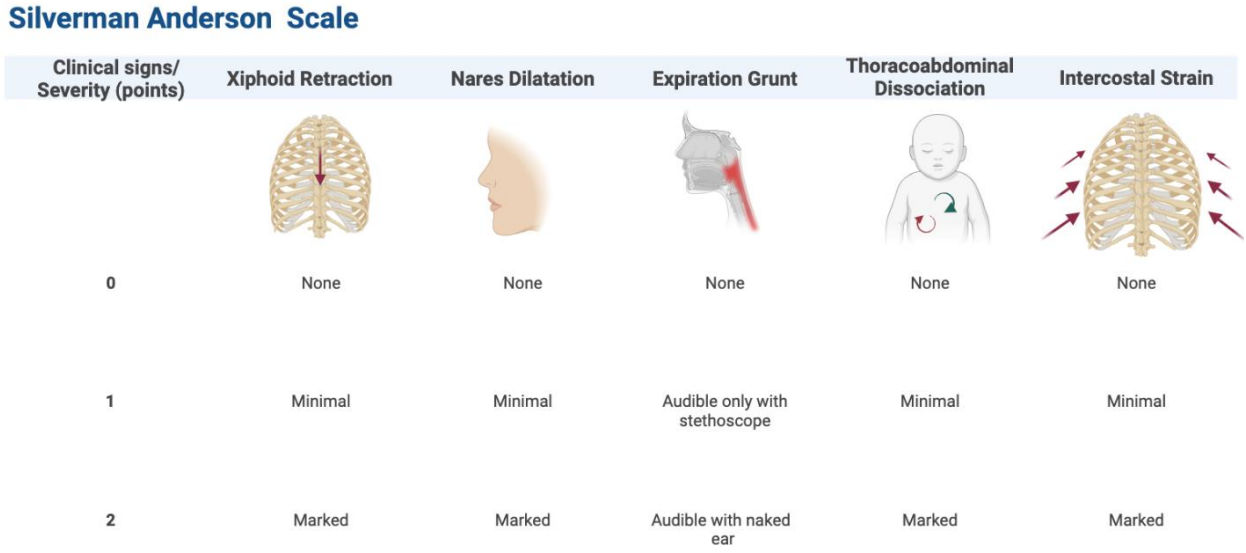


**Figure 1.** Silverman Anderson scale recreation.

## Differential diagnostic approach

The first step in the diagnosis is suspicion. As mentioned before, the main risk factor involved in any type of NRDS is the week of gestation at birth. Clinical manifestations can sometimes be shared between pathologies, mainly tachypnea, respiratory retractions, and progressive cyanosis.[2] Thus, additional laboratory tests and imaging information are frequently required to confirm or rule out a possible diagnosis. Hypoxemia, hypercapnia, and clear respiratory acidosis are common gasometrical findings, particularly in HMD and MAS. These results can be absent or slightly notable in TTN. However, when TTN or MAS is suspected, blood culture and a complete blood count can be requested to identify possible infections.[1,3]

Radiological imaging (chest X-ray) is of great support not only for confirming diagnosis but to identify damage extent and severity. Accentuated radiopacity, fine granular infiltrate, as well as a "ground glass" pattern are characteristic of HMD, while intercostal space overdistension, vascular plot reinforcement and pulmonary fissures effusions are more commonly seen in TTN. Lastly, diffuse opaque collections, as well as vascular plot reinforcement can be seen in MAS radiographs.[19] Table 1 summarizes risk factors, clinical manifestations, laboratory, and imaging findings presented so far. Nevertheless, it's important to emphasize that there are no 100% pathology specific signs and that due to their pathophysiology complexity, any manifestation (clinical or paraclinical) can be present in any type of NRDS.


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**Table 1.** Comparison of NRDS Type 1,2 and 3 risk factors, clinical manifestations, and laboratory and radiological outcomes

| | Hyaline Membrane Disease | Transient Tachypnea of the Newborn | Meconium Aspiration Syndrome |
|---|---|---|---|
| **Risk Factors** | • Preterm child (less WOG, higher incidence)<br>• Male sex<br>• Caucasian ethnicity<br>• Twin pregnancy<br>• Fetal hydrops<br>• Poorly controlled diabetic mother/ hypothyroid mother | • Cesarean delivery<br>• Prolonged time lapse between birth and first breath<br>• Mother with gestational diabetes or maternal asthma<br>• Male sex<br>• Macrosomia | • Post term child<br>• Been born in an undeveloped country<br>• Been born with Meconium-stained amniotic fluid (MSAF) |
| **Clinical Manifestations** | • Start 4-6 hours after birth<br>• Taquipnea (above 60 bpm)<br>• Nasal flaring<br>• Respiratory grunting<br>• Intercostal retraction<br>• Xiphoid retraction<br>• Progressive cyanosis<br>• Poor response to oxygen<br>• Decreased vesicular murmur<br>• Altered pulse (if there is persistence of ductus arteriosus) | • Start 2-6 hours after birth<br>• Marked taquipnea (above 100 bpm)<br>• Nasal flaring<br>• Intercostal retraction<br>• Xiphoid retraction<br>• Slight cyanosis | • Cyanosis<br>• Encephalopathy<br>• Heart failure<br>• Poor peripheral perfusion<br>• Reduction of urine output.<br>• Tachypnea<br>• Nasal flaring<br>• Respiratory retractions |
| **Laboratory Findings** | • Hipoxemia<br>• Hypercapnia<br>• Clear respiratory acidosis | • Hipoxemia<br>• Slight hypercapnia<br>• Slight respiratory acidosis (might be absent)<br>• *Blood count and culture might be requested | • Hipoxemia<br>• Respiratory acidosis<br>• *Blood count and culture might be requested |
| **Radiological Findings** | • Accentuated radiopacity<br>• Fine granular infiltrate<br>• “Ground glass” pattern | • Intercostal space overdistension<br>• Vascular plot reinforcement<br>• Pulmonary fissures effusions<br>• Reticulogranular pattern<br>• Notable pleural liquid at bases might be present | • Diffuse cottony alveolar condensations<br>• “Honeycomb” pattern<br>• Chest hyperinflation<br>• Possible neumotrax |

Similar clinical manifestations between NRDS types 1,2 and 3 might produce confusion and difficulty for reaching a successful diagnosis, hence, the importance of a sequential differential diagnosis strategy is crucial. Figure 2 represents our diagnostic suspicion algorithm. It considers gestation week at time of birth as the main risk factor for these diseases and clinical manifestations, serving not only as a staring point once the baby has been born, but as information needed before birth to prevent and have all the necessary materials for a quick response. As seen in section B, once the baby has been born, respiratory distress suspicion starts with clinical manifestations, onset time can lead to an specific type of NRDS, however we suggest that laboratory tests, particularly gasometry is performed to confirm oxygenation disturbance as well as to identify and treat potential metabolic and hydroelectrolyte imbalance. Finally, we suggest the usage of chest radiography if diagnosis is still unclear or, if MAS is suspected, localize potential sites of lung injury or meconial collection.

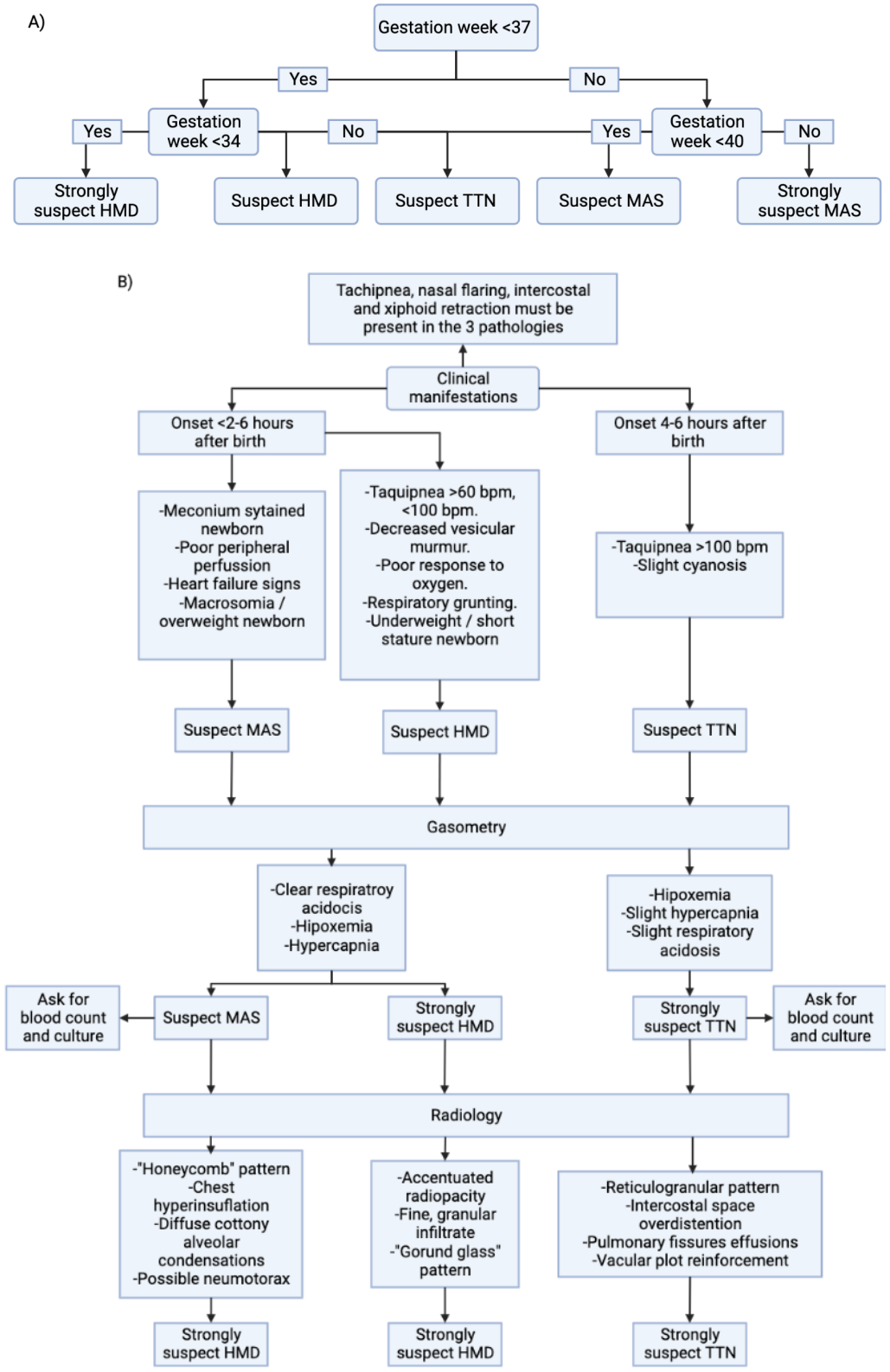


**FIGURE 2.** Differential NRDS diagnosis suspicion algorithm. A) Algorithm based on gestation week at time of birth. B) Algorithm based on clinical manifestations, and laboratory and radiological outcomes.


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## Possible treatment routes

Once a specific type of NRDS has been identified, prompt treatment care is crucial for limiting respiratory distress etiology and avoiding potential complications. For HMD, guidelines indicate exogen pulmonary surfactant administration. Natural exogen surfactant (derived from cattle or pig) are preferred over synthetic surfactant (mixture of tensioactive agents and phospholipids).[1] It is important to highlight that for HMD, the best treatment is prevention, intramuscular betamethasone or dexamethasone administration serve as fetal lungs maturing promoter and can be used 72 hours before an inevitable premature birth.[4] Regarding TTN, a systematic review studied the use of diuretic therapy as a potential medication to help the lung fluid clearance, the review included two randomized groups comparing furosemide with placebo and showed no changes in the severity of symptoms or the duration of hospital stay.[14] Similarly, other clinical studies concluded that there is not enough evidence to determine the efficacy of beta-agonists in the management of TTN.[12] It is necessary to provide respiratory support or administer oxygen to maintain oxyhemoglobin saturations between 90 - 95%.[17]

As for MAS, all patients should be admitted to the neonatal intensive care unit where they have to receive parental nutrition, keep normothermia (36.5-37.5ºC) and correct the acidosis keeping blood pH in the range 7.25–7.40 and PaCO2 in the range 40–55 mmHg.[17] In the possible scenario of respiratory failure, intubation is indicated to maintain saturation between 92-97%. Although meconium is sterile, it is prone to over-infection in areas of the lung not adequately ventilated, however the use of prophylactic antibiotics is not recommended.[20] Finally, it is important to remark that newborns that suffer continued respiratory distress should be monitored persistently in case they need supplemental oxygen. The oxygen must be applied when the SpO2 is <90%. Newborns with signs of increased work of breathing and/or persistent tachypnea may require continuous positive airway pressure (CPAP) with the objective to maintain functional residual capacity (FRC) and oxyhemoglobin saturations in their normal parameters.[13,21]

## CONCLUSION

Neonatal respiratory distress syndrome encompasses several pathologies, characterized by inadequate respiratory function, impaired gas exchange, and potential lungs and multisystemic complications. HMD, TTN, and MAS are the most studied presentations of this syndrome, and significant signs and symptoms are shared among these pathologies. However, clear risk factors, laboratory findings, and radiological signs can help differentiate respiratory distress presentations. The use of a differential diagnosis algorithm can ease the identification of specific NRDS being presented, leading to prompt and appropriate treatment. The algorithm we present recognizes WOG at time of birth as the main risk factor for any NRDS, moreover, it includes a step-by-step method which starts with clinical suspect, and uses laboratory and radiologic studies to confirm the diagnosis as well as to promptly identify and treat potential hypoxia complications.

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Case Report

# Asymmetrical Septal Hypertrophy diagnosed by MRI: a case report

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## ABSTRACT

Asymmetrical septal hypertrophy (ASH) is defined as an increase in ventricular wall thickness greater than 15 mm that is not associated with any other pathology. It is a condition that, in most cases, is caused by a mutation in one of the genes associated with the proteins that form the sarcomere. In this article, we present a case of ASH in a 43-year-old adult. After manifesting tachypnea, dyspnea, and cutaneous pallor, followed by a syncopal episode, the individual seeks medical attention. During the medical evaluation, an electrocardiogram (ECG) is performed, revealing bradycardia at 48 beats per minute and an inverted T wave in leads DI, AVL, V3, V4, V5, and V6. The diagnosis is confirmed through cardiac magnetic resonance imaging, which shows hypertrophic cardiomyopathy with non-obstructive ASH of 27.22 mm. Consequently, it is decided to initiate pharmacological treatment with propranolol, and the patient is still awaiting a surgical timeframe for the placement of an implantable cardioverter-defibrillator (ICD).

**Key words:** asymmetric septal hypertrophy; sarcomere; sudden death; syncope.

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## RESUMEN

La hipertrofia septal asimétrica (HSA) se define como un aumento del grosor en la pared ventricular mayor a 15 mm que no está asociado a otra patología. Es una enfermedad que en la mayoría de los casos, tiene como etiología alguna mutación en uno de los genes asociados a las proteínas que forman el sarcómero. En el presente artículo presentamos un caso de HSA en un adulto de 43 años. Después de manifestar taquipnea, disnea y palidez cutánea, seguido de un síncope, acude a revisión. Durante la evaluación médica, se realiza un electrocardiograma (ECG) en el que se observa una bradicardia de 48 latidos por minuto y una onda T invertida en DI, AVL, V3, V4, V5 y V6. El diagnóstico se confirma mediante resonancia magnética cardiaca, que muestra una miocardiopatía hipertrófica con HSA no obstructiva de 27.22 mm. En consecuencia, se decide iniciar un tratamiento farmacológico con propranolol y se encuentra actualmente a la espera de tiempo quirúrgico para la colocación de un desfibrilador cardioversor implantable (DCI).


**Palabras clave:** hipertrofia septal asimétrica; sarcómero; muerte súbita; síncope.

## INTRODUCTION

Cardiomyopathy is defined as a myocardial defect, in which the heart muscle is functionally and structurally abnormal, in the absence of coronary artery disease, valvular disease, hypertension, and congenital heart disease. There are 3 types of hypertrophic cardiomyopathy; ASH, apical hypertrophy and concentric hypertrophy (Figure 1).[1-2]

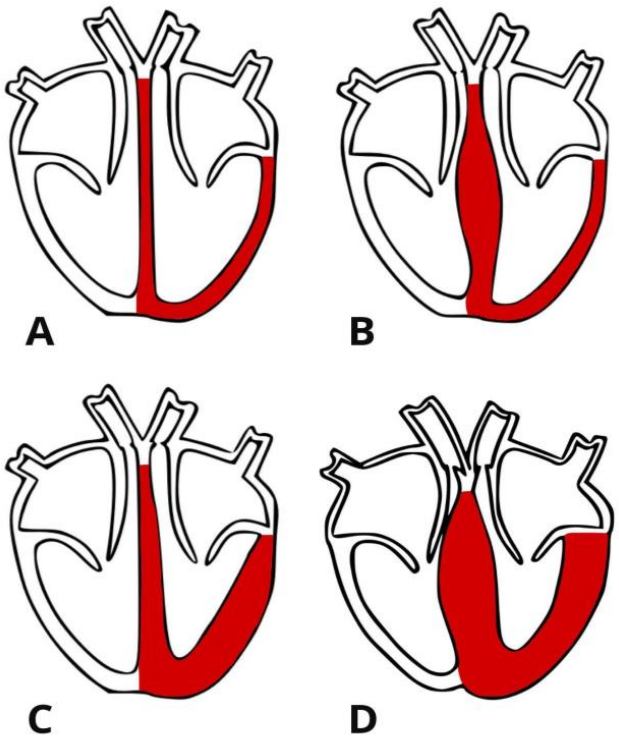


**FIGURE 1.** Types of hypertrophic cardiomyopathy. This figure shows 3 different types of hypertrophic cardiomyopathy. The first drawing (A) corresponds to a normal heart without thickening in the septum or left ventricle. The second drawing (B) demonstrates ASH, the septum is thickened while the ventricle is not. The third drawing (C) shows an apical hypertrophy where the lowest part of the septum begins to thicken along with the ventricular wall. The last drawing (D) shows a concentric hypertrophy in which both septum and left ventricle are thicker.


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ASH is defined as an increase in the thickness of the left ventricular wall (>15 mm thick), which may be accompanied by morphophysiological changes in myocardial cells and/or the mitral valve, not associated with another cause.[3] It is considered to have a classic pattern of autosomal dominant inheritance. The etiology in up to 70% of cases is due to a mutation in one of the 14 genes that produce sarcomeric proteins such as troponin I and T, MYH7, or MYBPC3;[4] up to 10% of cases will be due to other genetic mutations, including diseases like amyloidosis, mitochondrial diseases, nemaline myopathy, Pomp disease, among others.[5-6]

Depending on the location of the hypertrophy and the thickness of the ventricular wall, the clinical presentation of patients may vary, ranging from asymptomatic individuals to those with diastolic dysfunction, myocardial ischemia, mitral regurgitation, dyspnea, palpitations, asymptomatic murmurs, syncope, stroke secondary to atrial fibrillation, and even sudden death.[3]

It is important to carry out an appropriate diagnostic approach since it has a worldwide prevalence of 1 in 500 individuals in general and is the number one cause of sudden death in professional athletes and adults under 30 years of age.[7] In Mexico there are no national statistics. However, at the Ignacio Chávez National Institute of Cardiology, a prevalence of 0.16% was found among the individuals treated there.[8] Diagnosis is typically conducted through a medical history combined with a physical examination and is confirmed through imaging tests. When there is a suspicion based on the physical examination, an ECG can be requested, as it is the most sensitive routine test, while a Holter electrocardiogram can be requested for risk stratification for sudden death. A 2D echocardiogram is the initial study to evaluate ventricular wall hypertrophy, as well as a magnetic resonance imaging for better visualization.[9]

The treatment will be divided into three categories: pharmacological agents, invasive therapies (such as right ventricular pacing, septal ablation with alcohol and myectomy) and physical conditioning as an adjuvant to modify and address cardiovascular risk factors while reducing morbidity and mortality.[10] Depending on each patient's characteristics and clinical presentation, they may be candidates for one treatment over the other, with the primary goal being to reduce symptoms and improve the general quality of life.

Sudden mortality events (such as sudden cardiac death) are the principal complications, these occur at an incidence of 0.5-1.5% per year in adults and 2% per year in children and adolescents. However, patients with invasive treatment (as an ICD) have a better long-term prognosis that is similar to their peers in the general population. Showing the importance of a correct diagnosis and an early treatment.[9]

## CASE REPORT

A 43-year-old male was admitted to the emergency room of our institution due to syncope while urinating on the previous day, recovering consciousness after 3 minutes. Before the event, he presented tachypnea, dyspnea, and pale integuments. He denies having a similar event before and symptoms at the moment. In his family history these factors are relevant: a mother with systemic hypertension and a father with type 2 diabetes mellitus.

His medical record highlights smoking, stopped 16 years ago (2 cigarettes per day for a period of 3 years), with a smoking index of 0.3. He denies other important antecedents. During the medical examination only a slow heart rate was found, without murmurs or other added phenomena. His vital signs revealed bradycardia of 47 beats per minute and stage 2 hypertension with values of 170/100 mmHg. His Body Mass Index (BMI) was 27.3, which places him in the overweight category.

A 12-lead ECG was taken (Figure 2), which showed sinus bradycardia of 48 beats per minute and T wave inversion in DI, AVL, V3, V4, V5 and V6, demonstrating high lateral subepicardial ischemia. No alterations were found in laboratory studies. The cardiology department then decides his admission to the Coronary Care Unit for study protocol of his sinus bradycardia.

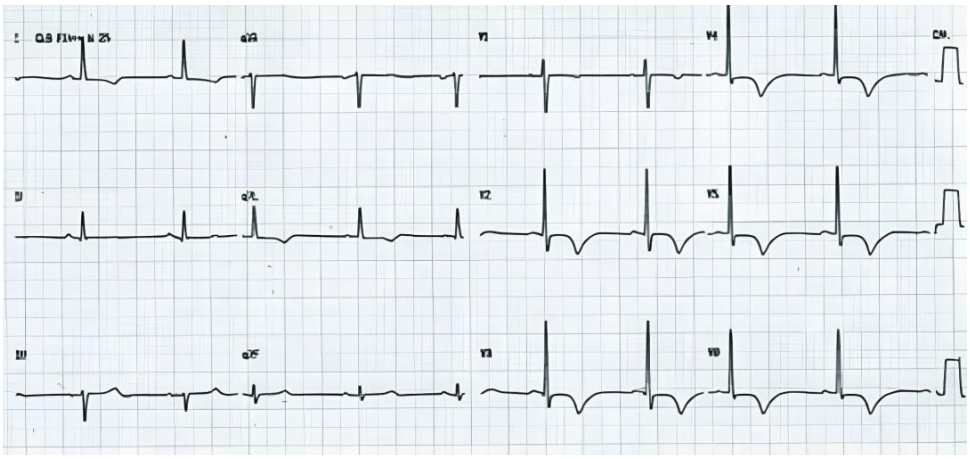

**FIGURE 2.** 12-lead electrocardiogram performed on the patient. This image corresponds to the ECG performed in the emergency room on the patient. Sinus bradycardia and T wave inversion in DI, AVL, V3, V4, V5 and V6 are shown, demonstrating high lateral subepicardial ischemia.

In the Coronary Care Unit a cardiac MRI was performed (Figure 3), which revealed the presence of hypertrophic cardiomyopathy with nonobstructive ASH of 27.22 mm. Likewise, an echocardiogram was performed, confirming the diagnosis and showed mild diastolic dysfunction, without pulmonary hypertension and left ventricular ejection fraction (LVEF) 76%.

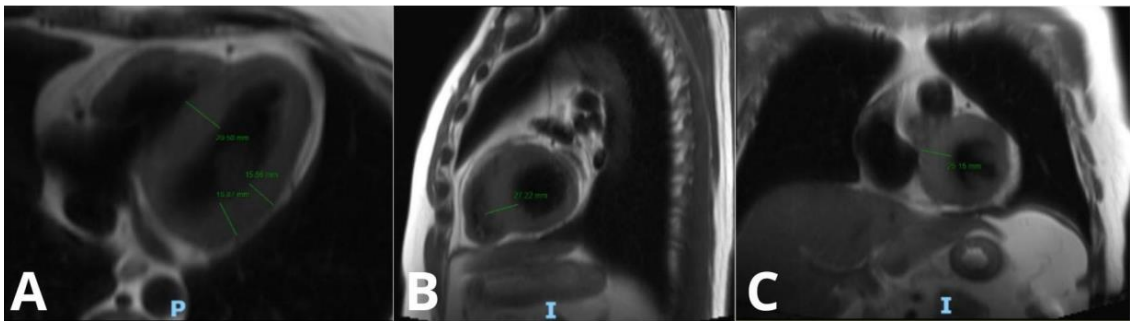


**FIGURE 3.** Cardiac magnetic resonance with cine sequence with gadolinium. This figure shows three different views of a cardiac magnetic resonance of the patient where cardiomyopathy is seen. In the transversal view (A) it is observed that the left ventricle and the septum are greater than 15 mm and that the septum has a greater measure than the left ventricle. The sagittal plane (B) shows an ASH of 27.22 mm. The coronal view (C) shows mild hypertrophy of the posterior wall of the left ventricle, accompanied by ASH.


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Due to his clinical improvement and timely diagnosis, this patient was discharged after 3 days of his admission to the unit with pharmacological treatment based on propranolol at a dose of 4 mg/kg/day and an appointment with the cardiology department to assess the placement of an ICD, which is still pending. Additionally, it was suggested to perform low-intensity aerobic exercise such as walking for 30 minutes 3 to 5 days a week, avoiding fatigue.

## DISCUSSION

ASH is characterized by abnormal thickening of the ventricular muscle of the interventricular septal wall. It mainly develops in the initial phase of left ventricular hypertrophy, but is also associated with valvular heart disease, obesity, and congenital heart disease. Therefore, patients develop symptoms of dyspnea and heart failure (orthopnea, angina pectoris, fatigue, syncope and palpitations).[11] ASH is typically seen in patients with hypertrophic cardiomyopathy and in patients with high blood pressure.[12] It has an incidence of 1% in the United States, its pathophysiology is due to a relative decrease in the posterior thickness of the left ventricle that causes compensatory hypertrophy of the interventricular septum. Left Ventricular Remodeling Is Associated with Coronary Artery Diseases.[13]

It is associated with sudden death in young athletes due to the presence of ventricular fibrillation and its timely diagnosis is important, making the identification of risk factors and their stratification important. This is achieved with the patients' symptoms and with imaging studies according to the criteria of the American College of Cardiology/American Heart Association (ACC/AHA), however, a large percentage of patients are asymptomatic, and their diagnosis is incidental.[3]

On physical examination, a harsh midsystolic murmur may be heard over the lower left sternal border that radiates to the apex. The intensity of this murmur increases with the valsalva maneuver. If suspected, it is recommended to perform a 12-lead ECG, reporting growth of the left ventricle, alteration of the ST segment (depression or slight elevation), narrow and deep Q waves from V3 to V6, inversion of T waves in V5 and V6. Another study is the two-dimensional echocardiogram and a cardiovascular magnetic resonance that allows the identification of myocardial fibrosis, the diagnosis is confirmed with hypertrophy of the left ventricle of 15 mm in adults and excluding any other cause.[3,14-15]

Medical therapy is the first line of treatment for these patients, with the goal of improving symptoms and reducing obstruction. Non-vasodilator beta blockers (Metoprolol, propranolol, bisoprolol and nadolol) are the first line medications; they are safe drugs that improve symptoms, but they improve the obstructive process very little. In case of intolerance, the guidelines recommend the use of non-dihydropyridine calcium channel blockers (diltiazem and verapamil) and in case of intolerance, the use of disopyramide is suggested due to its negative inotropic effect, improving obstruction and symptoms.[16]

Another type of treatment is alcohol septal ablation, which is a minimally invasive procedure to correct left ventricular outflow tract obstruction in patients with hypertrophic obstructive cardiomyopathy, which does not improve with medical treatment. This procedure consists of causing a controlled myocardial infarction in the basal portion of the interventricular septum by applying alcohol injection to reduce obstruction and improve the symptoms of the patients. This procedure consists of causing a controlled myocardial infarction in the basal portion of the interventricular septum by applying alcohol injection to reduce obstruction and improve the symptoms of the patients and hemodynamics.[16-17]

Septal reduction therapy has been shown to be effective in reducing obstruction and is recommended for use in patients with left ventricular outflow tract obstruction > 50 mmHg, exertional syncope, and severe symptoms. It consists of the reduction of the septum through minimally invasive surgical myomectomy, demonstrating a septal reduction of up to 11 mm and improving the functional class of the patients.[16-17]

In recent years, a new drug called Mavacamten has been developed, with its main mechanism of action being a selective inhibitor of β-cardiac myosin ATPase through allosteric binding,[18] leading to a decrease in actin-myosin bridges. This results in Mavacamten's ability to reduce cardiac contractility by decreasing the force generated by sarcomeres. Its usage depends on the left ventricular ejection fraction (LVEF), and discontinuation is advised when it is less than 50%.[19]

Despite receiving approval from the Food and Drug Administration (FDA) last year,[20] Mavacamten is still under investigation. However, clinical results are promising; in the three studies conducted so far (PIONEER-HCM, EXPLOREER-HCM, and VALOR-HCM), Mavacamten has demonstrated safety and effectiveness in patients with obstructive hypertrophic

cardiomyopathy who were already receiving conventional treatment. It was able to decrease the aortic vestibule, improve left ventricular filling, enhance exercise capacity, and increase quality of life by reducing symptoms, while imaging parameters and biomarkers improved significantly.[21-23]

Despite these promising results, further studies are necessary to clarify all aspects, improve the drug's safety profile, and potentially establish it as a new line of treatment for patients with any type of hypertrophic cardiomyopathy.

The prognosis of patients with ASH depends on the time of diagnosis, the extent of the heart injury, and the comorbidities that the patients present. It is reported that these patients reduce their life expectancy by up to 12 years less compared to a healthy person, because they present a greater risk of developing atrial fibrillation or ventricular arrhythmias, which is why it is required to follow up with an ECG every 1-2 years to prevent complications. Medications and lifestyle changes are the main treatments for ASH. Regarding lifestyle changes, it is recommended to avoid excessive alcohol consumption, avoid dehydration, regular physical activity and reduce the weight of patients.[3,5,13]

## CONCLUSION

Although ASH is a common cardiovascular disease, its clinical variation makes its diagnosis difficult. Likewise, a large percentage of patients remain asymptomatic, causing error in the incidence of the disease. The importance of an early diagnosis lies in the risk of sudden death, so it is important to do a complete history, including family cardiac background and previous episodes of syncope. Physical examination is crucial, highlighting the importance of cardiac auscultation. Complementary tests such as ECG and echocardiogram are essential in patient risk staging and in treatment choice. In our case, we highlight the importance of an early diagnosis and the patient's best treatment based on beta blockers and the implantation of an ICD.

## CONFLICT OF INTEREST

The authors declare there are no conflicts of interest.

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