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Sumario

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The Spanish flu and the fiction literature

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ABSTRACT

This review focuses on the fictional literature in which the Spanish flu is represented either as an anecdotal or as a historical aspect and the effect on the author or fictional character. We examine this sociocultural period in the press and mainly in Anglo-Saxon literary works and from other countries, including Spanish and Latin American literature that is not very represented in some international reviews on the subject. Also, we include books about the previous and subsequent influenza pandemics to the Spanish flu.

Keywords: Spanish flu; Influenza; pandemic; medicine in literature

La gripe española de 1918 y la literatura de ficción

RESUMEN

Esta revisión se centra en la literatura de ficción en la que la gripe española se representa como un aspecto anecdótico o histórico y el efecto sobre el autor o el personaje ficticio. Examinamos este período sociocultural en la prensa y principalmente en obras literarias anglosajonas y de otros países, incluida la literatura española y latinoamericana que no está muy representada en algunas revisiones internacionales sobre el tema. Además, incluimos libros sobre las pandemias de influenza anteriores y posteriores a la gripe española.

Palabras clave: Gripe española, gripe, Pandemia, medicina en la literatura

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INTRODUCTION

"*I had a little bird.*
Its name was Enza.
I opened up the window,
And in flew Enza."
(Old nursery rhyme)

Flu has caused global pandemics over the centuries. In the 18th century, the influenza pandemic between 1708-1709 was not fairly assessed [1]. During epidemics and pandemics in 1847–1848 and 1889–1893, it was recognized that the respiratory complications of flu could greatly elevate the death rate [2]. Another pandemic has been in 2005, the avian flu, with the emerging cultural patterns and interpretative repertoires and metaphors [3].

The Spanish flu, in 1918, killed 50-100 million people in the World and, in Spain, caused as many deaths as in the Spanish Civil War. About the Spanish flu, there are different studies, this is not an exhaustive list, in the world [4-13] and in Spain [14-17] with its spatial-temporal patterns [18].

This pandemic has been reviewed from different points of view: sociological or historical and the origin of the flu [19-21].

This review focuses on the fictional literature in which influenza is represented either as an anecdotal or as a historical aspect and the effect on the author or fictional character. In neither case it is an exhaustive review, but it focuses mainly on Anglo-Saxon literary work and from other countries, including Spanish and Latin American literature that is not very represented in some international reviews on the subject. All literature books are cited in the Tables with authors and their books in English and Spanish and we include books about the previous and subsequent influenza pandemics to the Spanish flu.

The name of influenza. The name of influenza is believed to have been used in the city of Florence in the 14th century (by Villani in 1358), considering that the disease was due to the «*influenza di freddo*» (to the cold) or «*di stelle*» (to the stars, by the astrological theories in those times) [22-23]. In 1742, Sauvage use the name «*grippe*». The terms «*gripper*» (French), «*to grip*» (English) or «*greifen*» (German) mean in Spanish «*agarrar, atrapar*».

Perhaps the abrupt way of presenting this disease on many occasions has justified the name «*grippe*», that in Spanish it was written «*grippe*» until at least 1925, and then with a single *p*. At the beginning of the Tolstoi´s book, "*War and Peace*" (1869), a novel that is the chronicles of the French invasion of Russia and the impact of the Napoleonic era on Tsarist society, Tolstoi writes that: "*On a July day in 1805... Anna Pávlovna had been coughing for a few days; it was a "grippe", as she said ("grippe" was a new word then, that very few used*").

Another word in Spanish was "*trancazo*" ("*strike with a bar*"), "*tranca*" means "*iron or wood bar*" and from this word derives "*trancazo*" that is a colloquial name for flu.

Other nicknames were *Spanish flu* or *Spanish Lady,* also *French flu.* It appears that French journalists had, initially, called it the "*American flu*"; but the fact that the American soldiers were his allies in the warlike conflict advised not to assign such a link to them; and as there were also cases of influenza in Spain, it was decided to generalize the use of this expression, which was later assumed by Germans and others [22].

Another most popular name in Madrid, was the "*Soldado de Nápoles*" ("*Naples soldier*"), a popular song in the zarzuela (popular musical genre or "*género chico*" in Spain) called *La canción del olvido* (*The forgotten song*) due both, were "*highly contagious*".

Today, there are many authors who avoid such a name (the Spanish flu) and they aptly refer to it as the "1918-1819 influenza pandemic".

The origin of the Spanish flu pandemic. There are several theories about the origin: a) the origin could be in China and after in Philippines and the USA and the army in Europe. b) English soldiers in France in 1916, the disease soon spread to other neighboring countries (England, Italy, Spain) and to more distant ones (the USA) as a consequence of the displacement of the troops [22]. c) the regular arrival of Chinese workers to Africa and Europe, throughout those years, could have been the origin of an earlier introduction (coinciding with the war). And this is a very plausible interpretation due to the circumstance that the Spanish Royal Family and the Spanish ministers suffered the flu, in the month of May 1918, and could contribute to this unjustified name [21].

The flu in the Spanish King is debated, the majority of scholars think that it was a flu. For Cervera C [24] was scarlet fever: between September and October 1918, Alfonso XIII had to interrupt this work and his conversations with Germany to stop sinking Spanish ships in the Atlantic. The "*ABC*" newspaper reported on September 30, 1918 that «*H. M. the King is sick with the flu. The attack is mild, and although his majesty has a fever, so far the ailment is of no importance*". On October 4, however, the official party pointed out a fact that indicates that the King did not suffer from the flu: a series of "*scarlet fever eruptions of normal evolution*" on his body. Skin rashes that do not fit with the usual symptoms of the Spanish flu, in the same way that the fact that ten days later the press continued to report mild fever and more skin problems does not coincide with the picture of this disease for Cervera C [24]. The first signs of scarlet fever can be flu-like symptoms, including a high temperature of 38 ºC or above, a sore throat and swollen neck glands.

It could be probable that these two theories may be both true, the flu can later in the course of the disease be complicated by scarlet fever in a percentage of patients. Scarlet fever circulating with chickenpox or influenza can be particularly dangerous. Another explanation is, although infrequently, the flu can take with an exanthematous skin rash.

The treatment and vaccines of the Spanish flu pandemic. The treatment was based in several substances and bacterial vaccines in relationship with the belief in the bacterial theory of disease: **"***Bacterial vaccines, some were derived exclusively from the Pfeiffer's bacillus, the presumed cause of influenza, were widely used, while others contained one or more other organisms found in the lungs of victims*" [25].

The treatment included "*symptomatic therapy with salicylates and quinine and codeine, for pneumoniae intramuscular or intravenous silver or platinum colloid, digitalis, alcamphor oil, or adrenaline, and bleeding*" [26].

In the *Espasa* encyclopedia (popular Spanish Encyclopedia), it was cited that "*the serums and vaccines inspired by bacterial associations are now abandoned*"; and that "*strychnine, oxygen inhalations, arsenicals, salicylates and bleeding are prescribed*" [27].

Other treatments were vapors from aromatic plants, purgatives, sweats, medicinal plants, and hydrotherapy, strong showers with alternating hot and cold water, iodine, leeches, cardenal brand water filter to trap all microbes. Marañón advocated to use a light antiseptic nasal douches twice a day [19].

Loeb L [28] found "*striking similarities between orthodox and commercial suggestions for treating influenza*" in The Lancet and the British Medical Journal between 1889 and 1919.

THE SPANISH FLU AND THE PRESS

The first reference in the Spanish press to an epidemic

outbreak in the Spring of 1918 can be found in the Madrid newspapers "*ABC*" and *"El Sol" (The Sun)*, the latter one published its first headline about the subject on 22 May 1918 [18]: *"What is the cause? An epidemic in Madrid*. In June 2 of 1918, "*The Times*" in Madrid, talked about an epidemic with the name the Spanish flu and this name began to circulate and in August the *'Journal of the American Medical Association'* dedicated its number to the "Spanish flu" [18]. An important book about the Spanish flu and the press is that of Davis RA [19].

In the Spanish press, it was the subject of attention with different comic strips that are not included in this work but that can be found in the digital newspaper archives [29a]. These comic strips remember the previous coloured engraved satires, in the Wellcome collection, such as "*An Address of thanks from the Faculty to the Right Hon.ble Mr. Influenzy for his kind visit to this country*" (by Temple West) (https://wellcomecollection.org/works/kn2xshu9) [29b].

THE SPANISH FLU AND THE RELIGION

The God punishes is a typical approach to the plagues and pandemics. This is just one example: In León, Spain, during the Spanish flu in his prayer "*Pro tempore pestilentiae*" ("*For the times of pestilence*"), the bishop: "*exhorts their parishioners to repent of their guilt because sins are the cause of scourging with that God punishes us".* Among the reasons cited by the bishop to explain the incidence of influenza are the desecration of holidays, blasphemy, obscene and immoral amusements and debauchery [29a]. And in Zamora (city in Castilla), with one of the highest mortality, there were a lots of Mass and the consequent spreading of the flu.

WHY DOES THE LITERATURE IS SCARCE IN THE INFLUENZAE?

Instead the literature of the plague (Bocaccio´s *Decamerone*, Camus´s *The plague*), or tuberculosis (such as Thomas Mann´s *The Magic Mountain*), the 1918-1919 pandemic have hardly been the subject of novel or realistic descriptions by writers. Could it be the coincidence in the time of the First World War with the most fatal stages of the pandemic that contributed to the desire not to insist more on the evocation of so many sufferings, and thus favor a deliberate forgetfulness? Stalin said: "*a single death is a tragedy; a million deaths is a statistic*", the little literature in the 1918 pandemic, perhaps was due to the "*flu overwhelmed language in ways that World War I did not*" [31]. The Spanish flu is called a "*forgotten pandemic*" [31], that's the difference for example, between literature of the Spanish flu and the literature of the World War I and the poets of the war. Or for F. Scott Fitzgerald, Gertrude Stein, Ernest Hemingway and John Dos Passos, the flu did not represent a topic in their novels, the Great War could represent the newness material to build your novels, whereas the pandemic represented historical continuity of the past plagues and this matter was not modern for their literature [32].

In the essay "*On Being Ill*" (1926), Virginia Woolf lamented that flu hadn't become a central theme in literature [33].

Susan Sontag pointed out, "*novelists tend to focus on illnesses that can be "used" as metaphors, plague with its medieval aura, cancer with its mysterious provenance, tuberculosis with its rosy-cheeked energy and Dickensian associations. These illnesses, unlike influenzae, carry built-in mythologies primed for literary appropriation*" [33].

For Hovanec [34a]. "*The flu acts as metaphor for the dehumanizing and denaturalizing aspects of modern life, which take on many forms*".

But, since Woolf first complained about the lack of novels devoted to influenza, a small body of English, Spanish -language literature and other languages about the virus has arisen, some of them in relationship with the World War I. "*The resurgence of interest in the flu during the 1930s may have been influenced by new developments in virology and influenza research*" [34a].

ENGLISH LITERATURE (TABLES 1-3)

Belling [31] divides fiction representing the pandemic in two groups: the authors with "*experienced*" disease, or autobiographical works, and those with "*registered rather than experienced*" motifs.

The first group: authors who were alive at the time ("experienced") (table 1)

The best known is Katherine Anne Porter's novella *Pale Horse, Pale Rider*.

a) At the beginning, was considered not a serious infection. On 24 June 1918, the war poet Wilfred Owen composed an ironic letter to his mother and considered the flu something of a joke: "*STAND BACK FROM THE PAGE! and disinfect yourself*" [35].

b) T. S. Eliot makes a possible reference to the Spanish flu in his poem *Sweeney among the Nightingale*: "*The person in the Spanish cape*". Elliot and Vivien (his wife) caught the disease in November 1918 and he was working in his masterpiece poem "*The waste land".*

c) D.H. Lawrence suffered influenza in 1919, the flu nearly killed him, in a town in the United Kingdom, after the end of the World War I. In his book, *The Fox*, the soldiers begin to return home, and the shadow of the Spanish flu glides in the environment.

d) F. Scott Fitzgerald. He fell ill while finishing his novel *This side of the paradise* (1920):

"—He represented Beatrice's immortality, also

Table 1 **American and British authors and their books (in chronological order) about the 1918 influenza pandemic (The Spanish flu)**

Title of book in English and Spanish (year)	Author (dates)
Letter to Susan Owen, 24 June 1918', in H. Owen and J. Bell (eds), Wilfred Owen Collected Letters (London: Oxford University Press, 1967), 560.	Wilfred Owen (1893-1918)
Sweeney among the Nightingale (Poem) (1918). Sweeney entre el ruiseñor. Not translated	T. S. Eliot (1888- 1965)
This side of the paradise (1920) A este lado del paraíso. Trad. Hernán Poblete Varas. Ed.	F. Scott Fitzgerald (1896-1940)
Three soldiers (1921) Tres soldados. Trad. Mary Rowe. Ed. Debolsillo, 2014	John Dos Passos (1896-1970)
The Fox (1922) La mariquita. El zorro. Trad. Pablo Mañé. Ed Los Libors de Plon 1980.	D.H. Lawrence (1885-1930)
One of ours (1922) Uno de los nuestros (Trad. Beatriz Bejarano del Palacio). NØrdica Ed.2013	Willa Sibert Cather (1876-1947)
The green hat (1924) El sombrero verde. Trad. Eduardo de Guzmán. Ed. Lauro 1946	Michael Arlen (1895-1956)
On being ill (1926) De la enfermedad. Trad. Ángela Pérez. Ed. Centellas 2014. Mrs. Dalloway (1925) La Señora Dalloway Trad. Andrés Bosch Alianza Editorial, 2012	Virginia Woolf (1882-1941)
Look homeward, Angel; A story of the buried life (1929) El ángel que nos mira (Trad. José Ferrer Aleu). Valdemar Ed. 2009	Thomas Wolfe (1900-1938)
Death in the afternoon (1932) Muerte en la tarde. Trad. Lola Aguado, Ed Planeta, 1993	Ernest Hemigway (1899-1961)
The doctor´s son (1935) El hijo del doctor. Not translated)	John O´Hara (1905-1970)
Pale horse, Pale rider (1936) Pálido caballo, Pálido jinete (Trad. Maribel de Juan). Círculo de Lectores Ed. 1992	Katherine Anne Porter (1890-1980)
They came like swallows (1937) Vinieron como golondrinas (Trad. Gabriela Bustelo). Libros del Asteroide Ed. 2007 Other Maxwell´s books with flu aspects are: Ancestors (1971), So Long, See You Tomorrow (1996), and Time Will Darken It (1948)	William Keepers Maxwell (1908-2000)
Letter to Lord Byron, poem in Letters from Iceland (1937) Carta a Lord Byron. Not translated The fall of Rome (1947) La caída de Roma, en Canción de cuna y otros poemas. Trad. Eduardo Iriarte. Ed. Debolsillo 2016	W. H. Auden (1907-1973)
The Big Rock Candy Mountain (1938) La montaña Big Rock Candy. Not translated	Wallace Stegner (1909-1993)
Goodbye to Berlin (1939) Adios a Berlin. Trad. María Belmonte. Ed. Acantilado 2014 The sixties. Diaries volume two: 1960-1969 Autobiografía. Not translated	Christopher Isherwood (1904-1986)
The Case of the Caretaker (1942). In: Miss Marple's Final Cases and Two Other Stories El caso de la vieja guardiana. In: Tres ratones ciegos y otras historias. Ed. Molino 1957 Hallowe'en Party (1969) (Hercule Poirot) Las manzanas. Trad. Alberto Coscarelli. Ed RBA 2011	Agatha Christie (1890-1976)
Memories of a catholic girlhood (1946) Memorias de una joven católica (trad. Andrés Bosch). Lumen Ed. 2019	Mary McCarthy (1912-1989)

Table 1 | **American and British authors and their books (in chronological order) about the 1918 influenza pandemic (The Spanish flu) (cont.)**

Title of book in English and Spanish (year)	Author (dates)
The Autobiography of William Carlos Williams (1951) Autobiografía. Not translated	William Carlos Williams (1883-1963)
Anthony Burgess, Little Wilson and Big God: being the first part of the confessions of Anthony Burgess, London, Heinemann, 1987, p. 18. Anthony Burgess, Little Wilson y el Gran Dios: Primera parte de las confesiones de Anthony Burgess. Not translated	Anthony Burgess (1917-1993)
Unity (1918). Talonbooks, Vancouver 2002. Unidad (1918). Not translated	Kevin Kerr (1968-) (Canada)
Wickett´s remedy (2005) El remedio de Wickett. Not translated)	Myla Goldberg (1971-)
This time of dying (2006) Tiempo de muerte. Not translated	Reina James (1947-)
October mourning (2006) Luctuoso octubre. Not translated	James Rada, Jr (-)
Kyrie (Messenger) (2007) Kyrie. Not translated	Ellen Bryant Voight (1943-)
The last town on earth (2007-) La última ciudad en la tierra. Not translated	Thomas Mullen (1974-)

love-affairs of numerous dead men who surely had never thought of him... if it wasn't appendicitis, influenza maybe".

e) Michael Arlen, in *The green hat*, the protagonist was inspired in the heiress Nancy Cunard, who caught the flu in 1919 with pneumonia and depression.

f) Virginia Woolf wrote an essay on flu, *On being ill*, and she describes the mental effects of disease. Her mother had died of influenza in 1895. In her diary writes: "*Influenza, which rages all over the place, has come next door.*" "*Rain for the first time for weeks today and a funeral next door; dead of influenza*". She had several bouts of influenza: in 1918 was kept in bed 8 days, in 1920, 1922, 1923 and 1925.

In her book, *Mrs. Dalloway*, there are two flu quotations: "*For having lived in Westminster—how many years now? Over twenty, —one feels even in the midst of the traffic, or waking at night, Clarissa was positive, a particular hush, or solemnity; an indescribable pause; a suspense (but that might be her heart, affected, they said, by influenza) before Big Ben strikes*".

"*Thus, when she said in her offhand way "How's Clarissa?" husbands had difficulty in persuading their wives and indeed, however devoted, were secretly doubtful themselves, of her interest in women who often got in their husbands' way, prevented them from accepting posts abroad, and had to be taken to the seaside in the middle of the session to recover from influenza*".

g) Thomas Wolfe, *Look homeward, Angel; A story of the buried*. This is his first novel, a semi autographic story, covers the span of time from Eugene's birth in 1900 to his definitive departure from home at the age of 19. The setting is a fictionalization of his home town of Asheville, North Carolina, called Altamont, Catawba in the novel. Brother´s writer died with influenza.

h) John O´Hara, in a short story *The doctor´s son*. His father worked during the flu outbreak in the Pennsylvania mining and O´Hara accompanied his father on house calls. Here, O´Hara, as the narrator, adopts a point of view of observer not such as a personal or familiar victim also dramatizes another major public health risk: the gathering of crowds [34].

i) While *Pale Horse, Pale Rider* represents the best literature of the flu and perhaps the paradigm of the Spanish flu, there was a lack the interest on it, maybe the reason is the traumatic experience just of a person [36] and without importance in comparison to the World War I. Katherine Anne Porter, the author, suffered influenza at twenty eight years old in 1918, and her father had planned in advance her funeral. Twenty years later, she published *Pale Horse, Pale Rider*, a novella in which her autobiographical protagonist, Miranda, almost dies of the flu. The story closely follows an account of Porter's own illness and recovery during the pandemic, when she was working as a reporter in Denver.

j) William Keepers Maxwell wrote *They came like swallows*. A novel about a Midwestern family that falls ill

when the flu reaches their town. Maxwell describes the fever and the sleep. Mother´s writer died by influenza and pneumonia and he caught the flu in 1918: "*My aunt put her hand on my forehead and got up from the table and took me upstairs and put me to bed because I had a high fever. And I think what happened was that I slept and slept and slept and slept*". That is revisited too in other Maxwell´s books: *Ancestors*, *So Long*, *See You Tomorrow*, and *Time Will Darken It*. Uncle Wilfred, in *They came like swallows*, insists that the flu was purposely spread by Germans in U-boats, and seems familiar for us now, with the SARS Cov-2 and China.

k) William Carlos Williams, *The autobiography of William Carlos Williams*. Poet and doctor during the time he turned to the exercise of his profession wrote that, we doctors made up to sixty visits a day. Several of us lost consciousness, one of the young people died, others were infected and we had nothing that was effective in controlling "*the potent poison that was sweeping the world*". "*The war and the influenza epidemic, in particular, provided a collective trauma, Williams infected twelve people in his immediate family, including his wife and children*" [37].

l) Mary McCarthy wrote *Memories of a catholic girlhood*. She suffered influenza at six years, in 1918, and her deceased grandmother, mother and father.

m) Anthony Burgess, in *Anthony Burgess, Little Wilson and Big God: being the first part of the confessions of Anthony* wrote: "*In early 1919 my father, not yet demobilized, came on one of his regular, probably irregular, furloughs to Carisbrook Street to find both my mother and sister dead. The Spanish Influenza pandemic had struck Harpurhey. There was no doubt of the existence of a God: only the supreme being could contrive so brilliant an afterpiece to four years of unprecedented suffering and devastation. I apparently, was chuckling in my cot while my mother and sister lay dead on a bed in the same room*".

The second group: "registered rather than experienced") (table 1)

They are authors with recent historical fictions that attempt to reconstruct accounts of the pandemic such as in 2006: Thomas Mullen's *The Last Town on Earth* and Myla Goldberg's *Wickett's Remedy*.

a) Willa Sibert Cather, *One of ours* (Pulitzer Prize in 1923). She suffered influenza. The book is a contemporaneous literary accounts of the 1918 pandemic, on American soldiers aboard the fictional troop ship Anchises, bound for France.

b) Craig Dilouie, *The Thin White Line*. Fictionally documented history of an avian flu pandemic in 2012. He describes the fever and the sleep: "*...unconscious. I felt like Rip Van Winkle, sleeping through history.*"

c) Thomas Mullen, in *The Last Town on Earth*, describes the bleeding, cyanosis and the quarantine in Commonwealth, a small town in the Pacific Northwest, to keep the influenza out of the town.

d) Myla Goldberg, *Wickett's Remedy*. She describes the death of her family. Both Goldberg and Mullen describe pulmonary congestion as a creature inhabiting the lungs.

e) Ernest Hemingway, *Death in the Afternoon*. He describes a Spanish flu death choking on snot.

f) W. H. Auden wrote *Letter to Lord Byron*, poem in *Letters from Iceland*, and another poem *The fall of Rome*: "*Unendowed with wealth or pity,/ Little birds with scarlet legs,/ Sitting on their speckled eggs,/ Eye each flu-infected city*".

Auden was thinking in the Spanish flu.

g) Wallace Stegner, *The Big Rock Candy Mountain*, is a semi autographic novel. In 1916 he was trapped one day in the school due to the low temperatures.

h) Christopher Isherwood in *Goodbye to Berlin*: "*The whole city lay under an epidemic of discreet, infectious fear. I could feel it, like influence in my bones*". Christopher Isherwood's time in 1930s Berlin, describes the pre-Nazi Germany. The book was adapted into the musical and the film *Cabaret*.

In your diaries, *The sixties. Diaries volume two: 1960-1969*: "*I found Dorothy well but shaken by flu...Gerald and Michael had flu...*" (January 1962). "*...but Michael won´t let me see him because I might give Gerald flu...*" (March 1966).

i) Agatha Christie, *The Case of the Caretaker* (Miss Marple´s novel) and *Hallowe'en Party* (Hercule Poirot´s novel). Finding A. Christie in bed with influenza, her mother suggested she write down the stories she was so fond of telling. And so, began her literary career.

The Case of the Caretaker (Miss Marple cases): "*Miss Marple smiled at him wanly from pillows. 'I suppose, really, that I'm better,' she admitted, 'but I feel so terribly depressed. I can't help feeling how much better it would have been if I had died. After all, I'm an old woman. Nobody wants me or cares about me.'*

Doctor Haydock interrupted with his usual brusqueness. 'Yes, yes, typical after-reaction of this type of flu. What you need is something to take you out of yourself. A mental tonic.'"

Hallowe'en Party (Hercule Poirot novel): "*He has not got 'flu,' said Hercule Poirot. 'He has only a nasty cold. Everyone always thinks they have 'flu. It sounds more important. One gets more sympathy. The trouble with a catarrhal cold is that it is hard to glean the proper amount of sympathetic consideration from one's friends.*"

j) Others:

-Kevin Kerr, *Unity (1918)*, a theatre work about the return of the soldiers in the World War I and the presence

Table 2A | **Other English books (in chronological order) about the 1918 influenza pandemic (The Spanish flu) and flu in general**

Title of book in English (year)	Author	Plot´s place
Hero Over Here: A Story of World War I (1992)	Kathleen V. Kudlinski	World War I (Youth literature)
Gracie's Angel (The Latter-Day Daughters Series) (1996)	Launi K. Anderson	Salt Lake City, USA
A Time of Angels (1997)	Karen Hesse	USA (Youth literature)
The Flu Epidemic (1998)	JoAnn A. Grote	Youth literature
Ghost Dance (1999)	Mark T. Sullivan	-
Ponies from the Past (Pony Pals #31) (2001)	Jeanne Betancourt	USA (Youth literature)
When the War Came Home (2002)	Sarah Ell	Auckland, New Zeeland
A Doctor Like Papa (2002)	Natalie Kinsey-Warnock	Vermont, USA (Youth literature)
Marven of the Great North Woods (2002)	Kathryn Lasky	USA (Youth literature)
The Name of the Child (2002)	Marilynn Reynolds	Canada (Youth literature)
A Doctor Like Papa (2002)	Natalie Kinsey-Warnock	Vermont, USA (Youth literature)
Marven of the Great North Woods (2002)	Kathryn Lasky	USA (Youth literature)
A different sort of real: the diary of Charlotte McKenzie, Melbourne 1918-1919 (2002)	Kerry Greenwood	Melbourne, Australia (Youth literature)
When the War Came Home (2002)	Sarah Ell	Auckland, New Zeeland
The Trouble with Jeremy Chance (2003)	George Harrar	Boston, USA
Joshua's Song (2003)	Joan Hiatt Harlow	Boston, USA (Youth literature)
The Sailmaker's Daughter: A Novel (2003)	Stephanie Johnson	Suva, Fiji
The Memory Quilt: A Tale of Friends And Family Lost And Found In The Great Cloquet Fire Of 1918 (2003)	Pamela J. Erickson	USA (Youth literature)
A Bird Named Enza (2003)	Dawn Meier	Story based in the influenza 1918
Divining women (2004)	Kaye Gibbons	USA
And in Flew Enza (2004)	Sherri Fuchs	Cincinnati, USA
Voices Airy (2004)	Catherine Karp	San Diego, USA
The Serpent's Tooth (2006)	Michelle Paver	Scotland, UK
If I Die Before I Wake: The Flu Epidemic Diary of Fiona Macgregor (2007)	Jean Little	Canada in 1918
Loving and Losing (2007)	Pamela Oldfield	England
Upon the Mountains (2007)	Gale Sears	Salt Lake City, USA
The Heirs of Ravenscar (2008)	Barbara Taylor Bradford	UK
War´s end (2008)	Victoria Bowen	Australia
Hellie Jondoe (2009)	Randall Platt	USA (Youth literature)
Fire Angels (2009)	Joseph Richardson	Florida, USA
Fever Season (2009)	Eric Zweig	Montreal, Canada (Youth literature)
Pushin' Up Daisies (A Black Swan Historical Romance, #2) (2009)	Carolyn Brown	Arkansas, USA
Winnie's War (2009)	by Jenny Moss	Texas, USA (Youth literature)
Hellie Jondoe (2009)	Randall Platt	USA (Youth literature)
Fever Season (2009)	Eric Zweig	Montreal, Canada (Youth literature)
Fire Angels (2009)	Joseph Richardson	Florida, USA
The Keening (2010)	A.Lafaye	Maine. USA
Ambitious Love (2010)	Rosie Harris	Cardiff, UK
All That We Are (2010)	Elizabeth Lord	London, UK
An American Family Myth (2010)	Norine G. Johnson	Louisville, USA
Diamond Ruby (2010)	Joseph Wallace	New York, USA

Table 2B | **Other English books (in chronological order) about the 1918 influenza pandemic (The Spanish flu) and flu in general**

Title of book in English (year)	Author	Plot´s place
Wings of a Dream (2011)	Anne Mateer	Texas, USA
Like the Willow Tree: The Diary of Lydia Amelia Pierce, Portland, Maine, 1918 (2011)	Lois Lowry	Portland, Maine, USA
Home by Morning (2011)	Alexis Harrington	Oregon, USA (Youth literature)
Death and the Spanish Lady (2011)	Carolyn Morwood	Melbourne, Australia
A Bird Named Enza (2011)	Joseph J. Bakewell	USA
Palace Beautiful (2011)	Sarah DeFord Williams	Salt Lake City, USA (Youth literature)
Enza (2012)	Kristy K. James	
Foul Ball in Beantown (2012)	G.S. Rowe	Boston, USA
A Bride Sews with Love in Needles, California (2012)	Erica Vetsch	France and USA
Yesterday's Dead (2012)	Pat Bourke	-
Pandemic: Spanish Flu, 1918 (2012)	Sally Stone	New Zealand
The Flu (2012) (there is a confusion between bacteria and virus)	Jacqueline Druga	Ohio, USA
Yesterday's Dead (2012)	Pat Bourke	
Beret (2012)	Chris Womersley	Nueva Gales del Sur, Australia
Dunaway's Crossing (2013)	Nancy Brandon	Savannah, USA
Innocents into War (2013)	Murray Rowlands	New Zeeland
The Wings of Morning (2012)	Murray Pura	Philadelphia, USA
Peacetime for Alice (Our Australian Girl) (2012)	Davina Bell	Melbourne, Australia (Youth literature)
A Bride Sews with Love in Needles, California (2012)	Erica Vetsch	France and USA
In the shadow of blackbirds (2013)	Cat Winters	
An Unmarked Grave (Bess Crawford, #4) (2013)	Charles Todd	France
The Romanov Cross (2013) / La cruz de los Romanov. Trad. Valentina Reyes. Ed. Algaid, 2014.	Robert Masello	Alaska
Horrors of History: People of the Plague: Philadelphia Flu Epidemic 1918 (2014)	T. Neill Anderson	Philadelphia, USA Youth literature
The given day (2008)/ Cualquier otro día. Trad. Carlos Milla Soler y Ferrer Marrades. RBA Libros, 2014.	Dennis Lehane	Boston, USA
The Goodbye Season (2015)	Marian Hale	
In a Gilded Cage (Molly Murphy Mysteries #8) (2015)	Rhys Bowen	New York, USA
The uninvited (2015)	Cat Winters	USA
A beatiful posion (2017)	Lydia Kang	New York, USA
One for Sorrow: A Ghost Story (2018)	Mary Downing Hahn	USA (Youth literature)
Light Over Water (ebook)	Noelle Carle	Maine, USA

of the Spanish flu

-James Reina, *This time of dying* and *October mourning*

-Ellen Bryant Voight, *Kyrie*, cycle of poems, is part of the 2007 poetry compilation "*Messenger*" that gives voice to American victims of the Spanish flu.

k) Below is a short list of other writers with an experience with the Spanish flu:

-Raymond Chandler Chandler was sent to the infirmary twice in England, in July and October 1918. Each time,

Table 3 | **American authors and their books (in chronological order) about the influenza pandemic (genetic manipulation of the virus and bioterrorism)**

Title of book in English and Spanish (year)	Author (dates)	Plot
Ninth day of creation (1998) El noveno día de la creación. Not translated	Leonard Crane	Genetic manipulation of the virus and bioterrorism
The first horseman (1998) El primer jinete del Apocalipsis. Trad. Sofia Coca y Roger Vázquez de Parga. Ed. Planeta, 2001	John Case	Genetic manipulation of the virus and bioterrorism
Pandemic (2005) Pandemia. Trad. Teresa Camprodón. Ed. Plaza y Janés. 2006	Daniel Kalla	Genetic manipulation of the virus and bioterrorism
The thin white line (2008) La delgada línea blanca. Not translated	Craig DiLouie	Avian influenza pandemic
Hidden and imminent dangers (2009) Peligros ocultos inminentes. Not translated	D. W. Hardin	Avian influenza pandemic
The Jakarta Pandemic (2010/2012) La pandemia de Jakarta. Not translated	Steven Konkoly	Avian influenza pandemic
The Stand (1978) Apocalipsis. Trad. Lorenzo Cortina. Ed. DeBolsillo, 2003	Stephen King	Post-apocalyptic pandemic
Flu (2010), Fever (2011) Pandemia. Dolmen Ed.2011	Wayne Simmons	Belfast pandemic and Zombi story
Station Eleven (2014) Estación once. Traductor: María del Puerto Barruetabeña Díez. Ed. Kailas 2015	Emily St. John Mandel	Pandemic in Michigan, USA
Pandemia (2015) (in French) Pandemia. Trad. Joan Riambau Möller. Ed. Planeta, 2017	Franck Thilliez	-
The Cobra Event (1998) Operación Cobra. Trad. Javier Guerrero Jimeno. Ed. B 2001.	Richard Preston	A terrorism release of a fictional virus (not influenza) combining various qualities of different diseases upon New York City,

he recovered after six days. The digitized military records reveal two bouts with influenza during the peak of the deadly pandemic (http://www.thekeptgirl.com/2017/07/the-clews-from-raymond-chandlers-war.html).

-Arthur Conan Doyle stopped writing fiction, after losing his son with the Spanish flu, and went to spiritualism.

-Hilda Doolittle was nearly to die with the Spanish flu

-John Dos Passos perhaps saved his life, as he contracted it on a military transport while crossing the Atlantic to fight in Europe.

-Dashiell Hammett enlisted in the United States Army, and in 1918 was afflicted during that time with the Spanish flu and later contracted tuberculosis.

-W. B. Yeast took care of his pregnant wife through the illness

l) Writers died in the Spanish flu pandemic:

-Randolph Bourne, American progressive writer and public intellectual, (December 22, 1918)

-Bernard Capes, British Victorian novelist (2 November 1918)

-Stephen Sydney Reynolds, English writer, (February 14, 1919)

In tables 2A and 2B, we show a list the other authors and books, and in table 3 books in relationship with the genetic manipulation and bioterrorism.

WORLDWIDE LITERATURE (TABLE 4)

a) Johan Olof Wallin, Swedish minister, orator and poet, in his poem *The Angel of Death*: "*Those plagues of night and of desolation*".

b) Leon Tolstoi, *War and Peace*. The plot is in July 1805

c) Sforim, *Tales of Mendele*, describes the flu in Odessa 1st October 1886. In 1918, the first wave of flu affected Russia in May, but it went unnoticed except in Odessa, where

Table 4 | **Other worldwide authors and their books (in chronological order) about the influenza**

Title of book in English (Original title) and Spanish (year)	Author (dates) (country)
The Angel of Death (1838). Jefferson Publication, 2016 El angel de la muerte. Not translated	Johan Olof Wallin (1779-1839) (Sweden)
War and Peace (1869) (Voiná I mir) Guerra y Paz. Trad. Lydia Kúper. Ed Mario Muchnik 2010.	Leon Tolstoi (1828-1910) (Russia)
Tales of Mendele. The book peddler (1868-1888) - Trad. English Ted Gorelick and Hillel Halkin. Ed. Dan Miron and Ken Frieden. 1996 Historias de Mendele, el vendedor de libros. Not translated	Sholem Yankev Abramovich (Mendele Mocher Sforim) (1836-1917) (Belarus)
The red-haired girl (1908) http://www.radixlab.net/andraslasso/sites/default/files/Hungarian-Short-Stories.pdf La chica pelirroja. Not translated	Géza Csáth (1887-1918) (Hungary)
Letters to Felice (1912-1917) (Briefe an Felice und andere. Korrespondenz aus der Verlobungszeit) Cartas a Felice. Trad.: Pablo Sorozábal. Ed. NØrdica, 2013	Franz Kafka (1883-1924) (Czech Republic)
Storm of Steel (1920) (In Stahlgewittern) Tempestades de acero. Trad. Andrés Sánchez Pascual. Ed. Austral 2015	Ernst Jünger (1895-1998) (Germany)
Letter from an Unknown Woman (1922) (Brief einer Unbekannten) Carta a una desconocida. Trad. Berta Conill Purgimon. Ed. Acantilado, 2002	Stefan Zweig (1881-1942) (Austria)
The Wilko Girls' (1933) (Panny z Wilka) Las Señoritas de Wilko. Trad. Bozena Zaboklicka y José Ramón Monreal. Ed. Cátedra. 1993	Jaroslaw Iwaszkiewicz (1894-1980) (Ukrania)
Love and Death (Ai to Shi) (1939) Trad. William F. Marquardt. Twayne Publishers, New York 1958. Amor y Muerte. Not translated	Saneatsu Mushanokōji (1885-1976) (Japan)
A life Misspent (memoir) (1939) Una vida malgastada. Not translated	Suryakant Tripathi (Nirala) (1896-1961) (India)
Cevdet and sons (Not translated in English) (1982) (Cevdet Bey ve Oğulları) Cevdet Bey e hijos. Trad.Rafael Carpintero. Ed. Random House Mondadori 2013	Orhan Pamuk (1952-) (Turkey)
The club of angels (1998) (O clube dos anjos) El club de los ángeles. Trad. Juan Carlos Gentile Vitale. Ed. Plaza y Janés 2001	Luis Fernando Verissimo (1936-) (Brazil)
Moonstone – The Boy Who Never Was (2013) ("Mánasteinn – drengurinn sem aldrei var til"). El chico que nunca existió. Trad. Enrique Bernández. Ed Letras Nórdicas, 2016	Sjón (Sigurjón Birgir Sigurðsson) (1962-) (Iceland)

with the ongoing Russian civil war, it had a major problem of food shortages and the existence of gangster gangs. Due to its strategic position and suffering from different infections throughout history with quarantines since the time of Catherine the Great, Iliá Mechnikov chose Odessa in 1886 as the first center of disease control (Bacteriological Institute) of Russia with vaccinations against the rage. His assistant Yakóv Bardakh continued his work investigating anthrax, typhoid, cholera, malaria and tuberculosis. Bardakh's Jewish origin led to his dismissal and one of his students, Stefansky, was put in his place, but his fame was so great that he was the most famous doctor in southern Russia. The arrival of the Spanish flu *(ispanka)* and other infections such as cholera and typhus made Odesa a chaotic city and many did not want to listen to the rational explanations for the reason for that epidemic, so on October 1 was celebrated the first black wedding (*shvartze khasene* in Yiddish). Sforim recounts the first black wedding in his book: It was a Jewish ritual to protect themselves from deadly epidemics, consisting of looking for a boyfriend and girlfriend among the most disadvantaged in the city (crippled or destitute) and marrying them in a cemetery [20].

d) Géza Csáth, Hungary writer, in the short story *The red-haired girl*: "*I had taken to my bed. I had contracted influenza. In the evening, fever developed. At such times it is as though the air has become as dense as oil, and everything seems to be swimming in a soft warm fluid.... I saw my father hurrying to*

my bedside as soon as he was awake. He feels my pulse, examines my eyes and throat and then leaves to wash his hands... Having no appetite, I did not eat any lunch, yet my temperature went up again in the afternoon. I was gazing with tired, feverish eyes at the grey winter sky above the blank wall."

e) Franz Kafka, Czech Republic, in *Letters to Felice* (1912-1917). He contracted the flu in Prague on October 14, 1918 and while in his sickbed he witnessed the fall of the Austro-Hungarian Empire from his window. "*Getting the fever as a subject of the Habsburg monarchy and recovering from it as a citizen of a Czech democracy was certainly overwhelming, but also a little comical*" wrote his biographer. In: *Letters to Felice (18-19, XII, 12)*: "*But, my love, I am writing so calmly here and perhaps you are ill. In the next letter to Schillings Flucht you get to mention the possibility of a flu. By God, my love to whom my life belongs, take care of yourself! I confess that when I think you are sick the first idea that comes to mind is not that you are suffering, but that I may not receive news from you, and immediately, under the harassment of despair, I feel mortified by everything around me. On Tuesday the sore throat gave way to a cold, which certainly represents an improvement in these chills totally unknown to me. Do you still have migraines, though? I am seeing how after closing the last letter you go looking for aspirin and you swallow it: I get chills*".

f) Ernst Jünger, *Storm of Steel*, about the Spanish flu.

g) Stefan Zweig, *Letter from an Unknown Woman*:" *My son died yesterday. For three days and three nights I have had to fight with the death that surrounded that small and fragile life. I sat next to her bed for forty hours, while the flu stirred her poor burning body. I held cold cloths over his boiling temple and, day and night, I held his uneasy hands.*

I think I have a fever, maybe I even have the flu, which now goes door to door"

h) Jaroslaw Iwaszkiewicz, *The Wilko Girls'*, about the Spanish flu. The story of an ex-military man (Wiktor) who, after fighting in World War I, quelling the communist revolt in Russia, decided to return to his town, where he had a relationship with six sisters who each represent a different type of love. His cousin, the Polish composer Karol Szymanowski composed his opera *King Roger* in a Black Sea resort in the autumn of 1918 when he contracted the Spanish flu and composed this opera: "*a sleepless Spanish night came to mind*" [20].

i) Saneatsu Mushanokōji, member of the Japanese avant-garde Shirakaba, in *Love and death*, described the death by flu of a young´s girlfriend.

j) Suryakant Tripathi (Nirala) (first modern Hindi poet of India). In 1918 many members of Nirala´s family died of flu and there was not enough wood to cremate them. "*My family disappeared in the blink of an eye"* [20].

k) Orhan Pamuk, *Cevdet and sons*, in the 30s and flu:

"*29, Wednesday*

On Monday afternoon my fever rose to forty. I fell back into bed. Doctor Izak came. It seems like I'm having a bad flu. Than disaster being here, in bed, tied its own hands!

–He has been with the flu for ten days and it still hasn't passed. It worries me.

I hope it's not the flu ... What do they call it? Spanish, Asian or than?"

l) Sjón (Sigurjón Birgir Sigurðsson), *Moonstone – The Boy Who Never Was*. The Spanish flu

m) Sigmund Freud, who in 1920 wrote an essay entitled *Beyond the Pleasure Principle* (1920), in which he introduced the concept of the death drive alongside the sexual drive. At the time, he denied that, the death from the Spanish flu of his daughter Sophie pregnant with their third child (she died of septic pneumonia as a result of the flu), had any influence, but later admitted that perhaps it had something to do with it. The "*fear of contagion*" possibly affecting his scientific reasoning and resulting theories [38].

n) Writers died in the Spanish flu pandemic:

-French poet and proto-surrealist Guillaume Apollinaire (November 9, 1918)

-French witer Edmond Rostand, *Cyrano de Bergerac*´s author (December 2, 1918)

-Margit Kaffka, Hungarian writer and poet, (December 1, 1918)

-Ivan Cankar, Slovenian Writer, (December 11, 1918)

SPANISH AND LATIN AMERICAN LITERATURE (TABLE 5)

The authors talk about the facts: "*I caught the flu*" in their diaries and letters, while mainly about the consequences of the flu in the novels and poems. The most important Spanish writers in this period and the Spanish flu are Josep Plá, Rosa Chacel and Miguel Delibes

The first group: authors who were alive at the time ("experienced")

a) Ramón de Valle- Inclán, an Spanish playwright, poet and novelist, *Letters*: "*Letter to Don Julio Romero de Torres (a famous Spanish painter):*

... I beg your pardon that I did not write to you before thanking you. The cause has been not having Josefina, in all this time, with a health day. All this as a result of a "flu" that left her very delicate" [39].

b) Josep Plá, *The Gray Notebook*. Josep Plá´s dietary wrote between March 1918 and November 1919. Plá caught the flu that year. Spanish flu caused the faculties to close and Plá returns to his town, Palafrugell, to the family home: "*Since there is so much flu they have had to close the College... The flu continues to relentlessly kill people. In these last days I have had to attend various burials*".

There are extensive references in the text.

c) Juan Pérez Zúñiga, *The fashionable illness* (Poem). He was a writer, journalist and humorist. He wrote this po-

Table 5 | **Spanish and Latin Americans authors and their works (in chronological order) about the influenza**

Title of book in English (original tittle) and Spanish (year)	Author (dates) (country)
The search (1904). Not translated La Busca (1904). Ed. Cátedra, 2010. Other books (Not translated): Weed (1904)- Mala hierba (1904). The cape of the storms (1932) - El Cabo de las tormentas. The resources of cunning (1915) - Los recursos de la astucia. The Buen Retiro´s nights (1934)- Las noches del Buen Retiro. The Monleón´s priest(1936)- El cura de Monleón. Carnival´s follies (1937) -Locuras de carnaval (1937). Family, childhood and youth (1944)- Familia, infancia y juventud	Pio Baroja (1872- 1956) (Spain)
Letters (1908) Cartas	Ramón María del Valle- Inclán (1866-1936) (Spain)
The Gray Notebook. Trad. Peter Bush. NYRB Classics, 2014 El cuaderno gris (El quadern gris). Trad. Dionisio Ridruejo y Gloria de Ros. Ed Destino 1996 (It was written in 1918 and 1919 but the first edition was in 1966)	Josep Plá (1897-1981) (Spain)
My Last sigh (2003). Trad. Abigail Israel. Ed. University of Minnesota Press Mi último suspiro. Ed. Taurus, 2018	Luis Buñuel (1900-1983) (Spanish film director)
The fashionable illness (poem) (1918). No translated El mal de moda. In: Cosquillas. Heraldo de Madrid (newspaper), May 27, 1918.	Juan Pérez Zúñiga (1860-1938) (Spain)
The flu (comic play in three acts) (1918). Not translated El trancazo. Ed. R. Velasco, 1918 Double pneumonia (comic play in one act) (1919). Not translated Pulmonía doble. Ed. Correspondencia Militar, 1922 (third edition)	Ramón López-Montenegro (1877-1936) and Ramón Peña (Spain)
Letter of Encarna (Elena Fortún) to Mercedes, since Santander, 8th November 1918) Carta de Encarna a Mercedes, desde Santander. 8 de noviembre de 1918) In: Los mil sueños de Elena Fortún by Marisol Dorao	Elena Fortún (1886- 1952) (Spain)
Against the epidemics: People beg for the veil!. (a journalistic column in El sol Newspaper, October 24, 1918) Contra la epidemia ¡Se suplica el velo!.	Mariano de Cavia y Lac (1855-1920)
Select Greguerías (1919) (Not translated)- Greguerías selectas Other works (not translated): Social gatherings in the café Pombo (1918)- Tertulias en el café Pombo. The holy crypt of the Pombo (1924)- La sagrada cripta del Pombo. The bullfighter Caracho (1926)- El torero Caracho	Ramón Gómez de la Serna (1888-1963) (Spain)
The caciques (1920) La señorita de Trevelez; y Los caciques. De. Castalia, 1997.	Carlos Arniches (1866-1943) (Spain)
The spaces of memory (The literary work of María Teresa León). Not translated Los espacios de la memoria (La obra literaria de María Teresa León). Ed. De la Torre, 1996	Gregorio Torres Nebrera (Spain)
Epistolary Perez de Ayala and Jesús Pabón (1936-1941). Not translated Epistolario (July 5, 1941)	Ramón Pérez de Ayala (1880-1962)
My idolized son Sisi. Not translated Mi idolatrado hijo Sisi (1953). Ed. Destino, 2003.	Miguel Delibes (1920-2010) (Spain)
Epistolary (years 1957, 1961, 1964, 1965, 1966 and 1968) Epistolario. http://www.ffayala.es/epistolario/	Francisco Ayala García-Duarte (1906-2009) (Spain)
Letters. Not translated Cartas 1955-1964. Tomo 2 (Biblioteca Cortázar). Ed. Alfaguara, 2012 Hopscotch. In: Blow-Up, We Love Glenda So Much. Everymans LIB (2014) Rayuela (1963). Ed. Debolsillo, 2016 The pursuer (1959) (short story). In: End of the Game and Other Stories. PANTHEON PBK (1992) El perseguidor y otros relatos. Ed Bruguera 1980	Julio Cortázar (1914-1984) (Argentina)
How the tailor Bieito returned to hell (short story). Not translated De cómo el sastre Bieito volvío al infierno (1973), En: Antología de literatura fantástica. Ed. Valdemar, 1992.	Anxel Fole (1902-1986) (Spain)

Table 5 Spanish and Latin Americans authors and their works (in chronological order) about the influenza (cont.)

Title of book in English (original tittle) and Spanish (year)	Author (dates) (country)
Acropolis. Aims International Books Corporation, 1984 Acrópolis. Ed. Seix Barral, 1984	Rosa Chacel (1898-1994) (Spain)
The club of angels (1998) (O clube dos anjos) El club de los ángeles. Trad. Juan Carlos Gentile Vitale. Ed. Plaza y Janés 2001	Luis Fernando Verissimo (1936-) (Brazil)
The luminous novel. Not translated La novela luminosa. Ed Mondadori, 2005	Mario Levrero (1940-2004) (Uruguay)
The year of the flu and other stories. Not translated El año de la gripe y otros relatos burgaleses Ed. Burgos : Rubio Marcos, 2005	Elías Rubio Marcos (Spain)
This America of ours. Correspondence 1926-1956. Not translated Esta América nuestra. Correspondencia 1926-1956. Ed. El Cuenco de Plata 2007	Gabriela Mistral (1889-1957) and Victoria Ocampo (1890-1979) (Chile and Argentina)
Mortal flu. Not translated Gripe mortal. E. Martínez Roca 2009	Pablo Caralps (Spain)
Pandemic alert?. Not translated ¿Alerta pandémica?. Ed. Meteora, 2011	José Manuel Echevarria (Spain)
The spring epidemia. Not translated La epidemia de la primavera. Ed Suma, 2018	Empar Fernández (Spain)
Mariela. Not translated Mariela. Ed B 2019	Yolanda Guerrero (Spain)

em about the Spanish flu that makes us think about the SARS Cov-2 pandemic (different types of theories: a bacillus, causes such as works or the water, a threat coming from outside, politics, and extravagant treatments). In two different centuries the reaction to them has not changed and for this reason we include the complete poem:

"*There is no other way, gentlemen, / to talk a bit today too / of this evil, whose rigors / has all Madrid crazy. / The bacillus of the grip / has sneaked in everywhere, / like, with impudence, / we were talk yesterday. / But it is nonsense the number/ of causes that are blamed, / without rhyme or reason/ the evil that so bends us. / Many are not satisfied / if they don't blame the insane / bug to the works they do / for, the Metropolitan./ Another seriously say / that is in the water; divine/ pretext of many people to gorge themselves on wine!./ Someone, like Don Felipe, says (and not using your head) / that the grippe bug comes from a part of France/ and war has brought him. / But I don't know how./ They wouldn't have allowed, cross the border! / They also say with grace / that the tiny bug / is floating in the air / such as a zeppelin. / And you don't know who do you blame / the cause of evil Juan Creso! / Well, to the strike committee since he is in Congress. / And there are those who blame the bug/ of Lola Turrón's little toilet /, which, according to her boyfriend, / she is a filthy like herself / and she scare/ with soap and water / from the same day of/ his first communion. / And if regarding the origin / of evil lies so much today, / ¡The remedies that rule are/ its healing a charm! / People full of fear / say every nonsense .../ Ones, there is nothing better / than cod with tomato./ Others take the job, / for the good of his skin, /sleeping upside down / inside an old closet, / and others heal with gum, / and others with hard asphalt./ Me, taking the evil as a joke / prevent it with bromide./ even when to sweat / I know there is nothing better / what to do verses incessantly / when you don't have humor ...*"

d) Luis Buñuel, the Spanish film director, in his autobiography *My Last sigh*: "*During the influenza epidemic of 1919, the terrible Spanish flu that killed so many people, we were practically alone in the Residence (Buñuel and Moreno Villa*)"

e) Ramón López-Montenegro and Ramón Peña, *El trancazo* (*The flu*) (1918) and *Pulmonía doble* (*Double pneumonia*) (1919). These are two comic players in three and one act, both respectively, about the Spanish flu.

f) Elena Fortún, *Letter of Encarna (Elena Fortún) to Mercedes, since Santander, 8th November 1918).* María de la Encarnación Gertrudis Jacoba Aragoneses y de Urquijo was a Spanish author of children's literature who wrote under the pen name Elena Fortún. She became famous for Celia ("*What Celia Says*"), the first in the series of children's novels which were a collection of short stories first published in magazines in 1929. The series were both popular and successful during the time of their publications and are today considered classics of Spanish literature. "*The flu epidemic continues, and at times we are very overwhelmed and very sad and wanting to escape.*

Nothing serious happens to me, but what has been happening to me since the flu in. More and more cough, pain in

the side, more and fatigue, and, in the last week, fever and a hundred beats a minute".

"*With such a terrible pain in her side, she took her to a radiologist, and to have blood tests done, and then she was seen by Dr. Ribas Sobera, with whom Asita worked, who said she had pleurisy in her right lung*".

g) Gregorio Torres Nebrera, *The spaces of memory (The literary work of María Teresa León).* Evocation by Rosa Chacel of the figure of María Teresa León in Berlin in 1932. Rafael is Rafael Alberti, the Spanish poet: "*That girl who had developed so much beauty was there, in a hotel room, dressed elementally, typing hours and hours, during a long Rafael´s flu*"

h) Julio Cortázar, *Letter to Damián Bayón (March 18th 1956 in Paris)*: "*And that's what we were doing when Glop gives up on not accepting the cold snap (16 below zero) and catches a fierce flu, complicated by liver.*"

i) Francisco Ayala García-Duarte, in his *Epistolary*, there are 10 letters dated between 1957 and 1968 in which he writes that he has caught the flu (years 1957, 1961, 1964, 1965, 1966 and 1968)

j) Rosa Chacel, her novel *Acropolis* is a look at women and their stage of growth in a generation that lived the Spanish flu. It covers the period of the Spanish flu until the proclamation of the Second Republic ("*Segunda República*") in 1931: "*It was not enough with the date, from 15 to 18, the years of the Spanish flu that we have just gone through ... Why Spanish? Who knows, but there's no smoke without fire... And after all, whether there's no smoke without fire or not, whether or not it is Spanish, the flu, ours, the one that we live here, in our neighborhood, in our house, was Spanish, authentic. The bug has a foreign name ... "*

"*... in this Madrid life, with all its bugs. Because the one with the flu is striking and he is listened to, he is treated, but Madrid life survives by force of ignorance ...*"

"*Timothy told me something that had happened in the months of his flu... He had suffered one flu after another during the previous year and the persistence of the feverish state and other symptoms had made him fear that it was a serious lung condition*".

In the second group ("registered rather than experienced")

a) Federico García Lorca went to the Student Residence in Madrid in November 1919 but occupies it in February 1920, the delay could be due to the flu in 1919.

(https://www.granadahoy.com/ocio/Ano-Lorca-Federico-Residencia-Estudiantes-Madrid_0_1358564641.html).

b) Pio Baroja, with several books: *Weed, The resources of cunning, The nights of the Buen Retiro, The priest of Monleón, Follies of carnival,* and *Family, childhood and youth.* In *The Search*: "*Manuel, the protagonist, I do not know if because of the flu or what he fell ill with and "he was close to two weeks with a very high fever, delusional.*"

The Cape of Storms: *Juanito Vélez, a character linked to the plots and union agitations in Catalonia, he died, far from Barcelona in Tuy: "There he caught the flu and soon after, tuberculosis manifested itself with very high fevers and vomiting of blood and in a short time died. "*

c) Mariano de Cavia y Lac, Spanish journalist that in your journalistic column entitled: *Against the epidemics: People beg for the veil!,* in *El Sol* ("The Sun") newspaper (October 24, 1918), he echoes the song of the "*zarzuela*" of Barbieri "*Gloria and Wig*" (*Gloria y Peluca*): "*Do not cover your face/ pretty girl,/ that whoever hides the good/ God takes it away*" and he changed it: "*If you cover your face,/ pretty girl/ you will get rid of flu/ and scarlet fever*". He was following Professor Marchoux´s advice, in the Pasteur Institute, advocated wearing mask for the flu [19].

d) Ramón Gómez de la Serna, a Spanish writer, dramatist and avant-garde agitator especially known for "*Greguerías*" (a short form of poetry that roughly corresponds to the one-liner in comedy): *"The flu is the fog of death, that little smoke that she also throws on the harsh days of winter"*

"Some guys on the fringes of life, who seem to go down unspecified sidewalks, are household disinfectants. They pass with their big appliances on their backs talking about indifferent things to avoid the contagion of the epidemics that have just died out. They know that their path had to be secret so as not to startle the life of the street, which is neglected of all the problems and on which they are cast as shadows. They leave a wake of fallen microbes, but they are looked upon with benevolence, since they are heroic soldiers who enter the house where there has been a flu, and close the doors of the fateful rooms, and are inexorable executioners of evil in the hermetic rooms".

In *The bullfighter Caracho* (1926): "*The sensible man maintained that if those misfortunes were exorbitant it is because he had been focused with a telescope in agony and that of a tuberculosis patient or that of a carpentry officer who dies of the flu calling his mother cannot be focused in this way*").

In *Social gatherings in the café (Pombo): "Salvador sometimes has long absences. Pombo misses the little Satan who sniffs everything and is distracted from ideas by sniffing things, sensual and dissolute. It is that Salvador always has the flu, his grip is temporary, so Bartolozzi and Flu are also savior*".

"*Crespo: "If I had not said that the great Savior is Lucifer, I would say that this man is Mephistopheles, although of course Salvador is that in a very serious way with a black coat*".

He also alludes to his chronic flu in one of his characteristic humorous notes (in *The Pombo´s holy crypt*).

e) Carlos Arniches, a Spanish playwright. His prolific work, drawing on the traditions of the "*género chico*", the zarzuela and the grotesque, came to dominate the Spanish comic theatre in the early twentieth century. In this theater comedy, *The caciques*, released in Madrid on February 13, 1920, he alludes to the high mortality in old people: "*MORRONES. — There is no*

Table 6 The Spanish flu topics in the books and authors

Spanish flu topics in the books	Authors
Origin of the name	Rosa Chacel, Luis Fernando Verissimo
Superstitions	William K. Maxwell, Sforim, Juan Pérez Zuñiga
Epidemiology:	
-Crowds	John O´Hara
-Contagion (health professionals)	William Carlos Williams
-Quarantine	Thomas Mullen, Josep Plá, Miguel Delibes
Symptoms:	
-In general	Several authors: William K. Maxwell, Graig Dilouie, Thomas Mullen, Myla Goldberg, Ernest Hemingway, Géza Csáth, Orhan Pamuk, Josep Plá, Elena Fortún, Rosa Chacel, Pio Baroja
-Duration of the symptoms	Mario Levrero
-Mental effects	Virginia Wolff, Agatha Christhie
Mortality	Mainly: Anthony Burgess, Ellen Bryant Voight, Stefan Zweig, Josep Plá, Carlos Arniches
Recovery	K. Anne Porter
Desinfection	Ramón Gómez de la Serna
Face mask	Mariano de Cavia
Hand washing	Géza Csáth

abundance of the elderly with the flu; but "ou" will see later the best I have found. And the boys are picking them up for me, my wife. I have told him to pay them six pesetas for half a dozen ... I was already nine when I came; but the nine of both sexes, as "ou" wanted".

f) Ramón Pérez de Ayala, in his *Epistolary* between Pérez de Ayala and Jesús Pabón: "*I did not answer immediately because a whole month I suffered from the flu, which had me perfectly asthenic. The South American flus are very impertinent. I have not recovered yet, but I am improving*".

g) Miguel Delibes, *My idolized son Sisi*. The novel recreates the situation experienced in a province by the flu and the quarantine. The novel in three parts (the first one between 1917-1920):

"-Oh, the flu! Said Cecilio Rubes. Since when is the flu a major disease?

Valentine said:

- This one right now is not a joke, Mr. Rubes. It is a flu that does not go away with two days of bed and an aspirin seal".

h) Julio Cortázar, *Hopscotch (Rayuela)*: "*I will explode from an intestinal occlusion, the Asian flu, or a Peugeot 403...*"

Julio Cortázar, *The pursuer (El perseguidor*) (short story): "*You had the flu. Your better now?*

It wasn´t flu. The doc arrived and right away began telling me he liked jazz..."

i) Anxel Fole, *How the tailor Bieito returned to hell* (short story):

"*the gravedigger, seeing that the tailor apparently dead of the flu, rises, exhorts him to return to hell:*

-Don't you see that I'm alive?

-Alive? You died of the flu complicated with pneumonia. Or do you want to know more than the doctor who issued you the death certificate?"

j) Luis Fernando Verissimo, *The club of angels*. Spanish flu or bird flu:

"*When someone asked about Samuel's parents, he replied that they had died of the Spanish flu. And if someone remembered that it was impossible, since the Spanish flu epidemic had reached Brazil at the beginning of the century, he said: "Then it was Asian flu, I did not ask for documentation*".

k) Mario Levrero, *The luminous novel*: "*Many years ago, a relative dentist expressed in my presence the theory of that flu lasting three, seven or twenty-one days. The numbers are too cabalistic to trust them too much*".

l) Elías Rubio Marcos, *The year of the flu and other stories*. Book about the causes that motivated the depopulation in Ochate (Treviño County, Spain), during the Spanish Flu.

m) Gabriela Mistral and Victoria Ocampo, *This America of ours. Correspondence 1926-1956*. Correspondence, where the flu contagion is counted

"*I stay in bed with my second flu..*"

n) Others:

- Pablo Caralps, *Mortal flu*. Use of a Spanish influenza strain, its spread and create one vaccine and two influenza drugs

-José Manuel Echevarria, *Pandemic alert?*. A new flu virus in a pandemic in Guatemala.

- Empar Fernández, *The spring epidemia*. The Spanish flu

- Yolanda Guerrero, *Mariela*. Spanish nurse in Paris, in 1918

Finally, in table 6 we correlate the Spanish flu topics and the authors.

In conclusion, we show the different literary works about the Spanish flu and an extensive list of them. All these works show the wrong idea of Virginia Woolf complained about the lack of novels devoted to influenza and we have contextualized the works with the historical situation of the Spanish flu.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

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Revisión exploratoria

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Revisión exploratoria sobre series de casos de coronavirus (SARS-CoV, MERS-CoV y SARS-CoV-2) y sus resultados obstétricos y neonatales

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RESUMEN

Antecedentes. La aparición de nuevas enfermedades infecciosas, como el COVID-19, supone un reto en el seguimiento de la gestación y la prevención de complicaciones obstétricas y neonatales. La revisión exploratoria tiene el objetivo de revisar la información disponible en mujeres embarazadas infectadas por los coronavirus MERS-CoV, SARS-CoV, SARS-CoV-2 para evaluar las similitudes y diferencias en las características clínicas de las madres y los resultados neonatales.

Métodos. Realizamos una búsqueda bibliográfica (revisión exploratoria) acorde a las pautas de PRISMA entre marzo y abril del 2020 en las bases de datos de MEDLINE, SciELO, y CUIDEN y el Centro de Información sobre el COVID-19 de Elsevier.

Resultados. Analizamos 20 artículos con un total de 102 casos: 9 de MERS-CoV, 14 de SARS-CoV y 79 de SARS-CoV-2. La fiebre (75,5%) y la neumonía (73,5%) resultaron ser los síntomas más frecuentes en las gestantes infectadas. Las complicaciones obstétricas más frecuentes fueron la amenaza de parto prematuro (23,5%) y la cesárea (74,5%). No se documentó ninguna transmisión vertical en los neonatos.

Conclusiones. Los tres coronavirus producen una neumonía con sintomatología muy similar, resultando más leve en el caso de SARS-CoV-2. A pesar de las complicaciones obstétricas documentadas, los resultados neonatales son favorables en su mayoría. Es preciso aumentar el conocimiento para mejorar y prevenir las complicaciones obstétricas y neonatales de estas infecciones en mujeres embarazadas.

Palabras clave: Coronavirus, MERS-CoV, SARS-CoV, SARS-CoV-2, Síndrome Respiratorio Agudo Severo (SARS), Síndrome Respiratorio de Oriente Medio (MERS), COVID-19, Mujeres Embarazadas

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Scoping review of coronavirus case series (SARS-CoV, MERS-CoV and SARS-CoV-2) and their obstetric and neonatal results

ABSTRACT

Background. The appearance of new infectious diseases, such as COVID-19, poses a challenge in monitoring pregnancy and preventing obstetric and neonatal complications. A scoping review has the objective to review the information available in pregnant women infected with the MERS-CoV, SARS-CoV, SARS-CoV-2 coronaviruses to assess the similarities in terms of and differences in the clinical characteristics of the mothers and neonatal outcomes.

Methods. We carried out a bibliographic search (scoping review) according to the PRISMA guidelines between March and April 2020 in the MEDLINE, SciELO, and CUIDEN databases and the Elsevier COVID-19 Information Center.

Results. We analyzed 20 articles with a total of 102 cases.9 of MERS-CoV, 14 of SARS-CoV and 79 of SARS-CoV-2. Fever (75.5%) and pneumonia (73.5%) were the most frequent symptoms in infected pregnant women. The most frequent obstetric complications were the threat of premature delivery (23.5%) and caesarean section (74.5%). No vertical transmission was documented in any of the infants.

Conclusions. All three coronaviruses produce pneumonia with very similar symptoms, being milder in the case of SARS-CoV2. Despite documented obstetric complications, neonatal outcomes are mostly favorable. Increased knowledge is needed to improve and prevent obstetric and neonatal complications from these infections in pregnant women.

Keywords: Coronavirus, MERS-CoV, SARS-CoV, SARS-CoV-2, Severe Acute Respiratory Syndrome (SARS), Middle East Respiratory Syndrome (MERS), COVID-19, Pregnant Women.

INTRODUCCIÓN

A lo largo de los últimos veinte años, se ha producido el aumento y una rápida expansión de ciertas enfermedades infecciosas debido a la extraordinaria conectividad que define a nuestra civilización global [1]. Algunas de ellas, el Síndrome Respiratorio Agudo Severo (SARS) (2003), la gripe H1N1 (2009), el Ébola (2014) o el Zika (2015) afectan especialmente a las mujeres gestantes, ya que pueden producir una pérdida del embarazo o daños congénitos graves [2,3].

En diciembre del 2019, emergió un agrupamiento de casos de neumonía en la ciudad de Wuhan (provincia de Hubei, China), con una exposición común en un mercado que fue cerrado el día 1 de enero de 2020. Una semana después se identificó como agente causal del brote un virus de la familia *Coronaviridae* que posteriormente fue denominado SARS-CoV-2. La enfermedad causada por este nuevo virus ha sido denominada por consenso internacional COVID-19, cuyo primer caso en España se produjo en La Gomera el 31 de enero. Posteriormente, el 11 de marzo, la Organización Mundial de la Salud declaró el estado de pandemia [4-7].

De los siete tipos de coronavirus que infectan a los humanos, tres de ellos, MERS-CoV, SARS-CoV, SARS-CoV-2, pueden generar un cuadro de síndrome respiratorio severo. El primero en aparecer fue el SARS-CoV identificado en China (2003) que se extendió por 26 países y ocasionó cerca de 8000 casos. El segundo, conocido como MERS-CoV y que producía el Síndrome Respiratorio del Medio Oriente (MERS) se identificó en Arabia Saudita en 2012 produciendo 2500 casos [6]. Finalmente, el SARS-CoV-2 es el responsable de la actual pandemia en todo el mundo [8].

Las mujeres embarazadas constituyen un grupo de especial riesgo y vulnerabilidad para las enfermedades de origen infeccioso [9], debido a tres factores: su mayor compromiso cardio-respiratorio al avanzar la edad gestacional (sobre todo en el tercer trimestre) [10], la inmunosupresión secundaria a la gestación [11], y las limitaciones en los tratamientos por el posible daño al feto en cada trimestre de embarazo) [12].

Hasta la fecha el virus respiratorio más común que ha afectado a las mujeres embarazadas es el virus de la gripe estacional [13,14] generando mayor morbilidad y muerte durante los periodos epidémicos [10]. Este incremento de las complicaciones en la salud de las mujeres embarazadas, también se ha observado con los coronavirus que produjeron el SARS y el MERS [15]. En el estudio realizado por Lam et. al.[16] las mujeres embarazadas con SARS-CoV experimentaron un peor curso clínico en comparación con las mujeres no embarazadas, presentando insuficiencia renal y coagulopatía intravascular diseminada, además de mayores ingresos en la Unidad de Cuidados Intensivos (UCI). También se observó que si la tasa de mortalidad tras infección por SARS-CoV se incrementaba un 10% en la población general, en las mujeres embarazadas lo hacía un 25% más [17]. Tanto el SARS-CoV como el MERS-CoV han dado lugar a urgencias obstétricas como la hemorragia preparto [18], los partos prematuros [19], el Desprendimiento Prematuro de Placenta Normalmente Inserta (DPPNI) [20] e incluso el fallecimiento de la gestante [21].

El SARS-CoV-2 está infectando a mujeres embarazadas, lo que hace interesante realizar una revisión exploratoria para conocer en qué manera las está afectando y si existen similitudes o diferencias entre los casos clínicos y su evolución obstétrica en las gestantes con diagnóstico confirmado de SARS-CoV, MERS-CoV y SARS-CoV-2, lo que constituye el objetivo de esta revisión.

MÉTODOS

Se ha llevado a cabo una revisión exploratoria [22] con objeto de conocer en gestantes su sintomatología general asociada a las infecciones por coronavirus, sus posibles complicaciones obstétricas y sus resultados neonatales.

Para la elección de documentos se establecieron los siguientes criterios de inclusión: artículos originales sin importar el idioma en el que estuvieran escritos, texto completo, población de mujeres embarazadas, casos únicos o múltiples generados por la infección viral durante el embarazo ocasionado por coronavirus (SARS-CoV, MERS-CoV y SARS-CoV-2) y calidad de la revista mediante factor de impacto publicado en la Web of Science (WoS), y excluyendo los que no cumplían los criterios inclusivos de mujeres embarazadas y coronavirus conjuntamente.

Se exploraron como fuentes de información las bases de datos: MEDLINE, SciELO y CUIDEN. Dada la situación de pandemia de la COVID-19, se han puesto distintas fuentes bibliográficas en acceso abierto sobre la literatura científica disponible sobre coronavirus, por lo que seleccionamos el recurso de Elsevier para explorarlo a través de su Web de Centro de Información sobre el COVID-19 accesible en https://www.elsevier.com/connect/coronavirus-information-center.

Se estableció una estrategia de búsqueda (tabla 1) utilizando combinaciones mediante operadores booleanos de OR y AND de los siguientes términos controlados localizados en Desc y MeSH: "coronavirus", "SARS-CoV", "MERS-CoV", "sindrome respiratorio agudo grave", "severe acute respiratory syndrome" "sindrome respiratorio de Oriente Medio", "middle east respiratory syndrome", "embarazada" y "pregnant women" y "pregnant woman". En formulario libre de las mencionadas fuentes bibliográficas y en algunos casos en el campo de "título/abstract" de MEDLINE usamos libremente los términos "COVID 19", "COVID-19", "COVID19", "2019-nCov", "2019nCov", "SARS-CoV2", "SARS-CoV-2". La búsqueda bibliográfica comprendió desde el año 2003 hasta la actualidad (abril 2020) y se realizó entre el 2 de marzo y el 14 de abril del 2020.

Posteriormente se seleccionaron y clasificaron los estudios, así como sus variables bibliométricas, de contenido y de calidad. Para evaluar la calidad metodológica, elegimos la herramienta de evaluación critica de JBI para series de casos como los utilizados en el trabajo de Murad et. al.[23] en función de los dominios de selección, verificación, causalidad e informes. Se utilizó una plantilla para extraer los siguientes datos:

autor, año de publicación, país, tipo de diseño de los estudios, objetivo y población. Los datos fueron extraídos y volcados a la plantilla por dos investigadores del equipo. Se observó una considerable heterogeneidad entre los estudios y factores como el sesgo de publicación y el informe selectivo de los resultados que no pudieron explicarse. Para la comunicación de resultados se siguieron las pautas de la Declaración PRISMA [24,25].

RESULTADOS

Las fuentes bibliográficas consultadas inicialmente arrojaron un total de 162 artículos reducidos a 157 tras eliminar las referencias duplicadas. La lectura de título y resumen condujo a la exclusión de 87 artículos porque no mencionaban conjuntamente a las mujeres embarazadas con coronavirus. De los 70 artículos leídos a texto completo, se seleccionaron 20 artículos finales y se descartó el resto porque no cumplían con todos los criterios de inclusión, tal como se muestra en la figura 1 del PRISMA.

La mayoría de los 20 artículos seleccionados proceden de China (9), seguidos de Corea (2), Arabia Saudí (2), EE. UU. (2), Japón (2), Honduras (1), Emiratos Árabes (1) y Jordania (1). Los diseños de estudios son de tipo "series de casos" (12), "reporte de un caso" (7) y uno tipo "caso-control" (1). La población elegida estaba compuesta de mujeres embarazadas, aunque hay cuatro que además incluían a neonatos (tablas 2 y 3) [8, 12, 17, 18 , 20, 21, 26-39].

La muestra final recogió casos de 102 gestantes, con una media de edad de 31,2 (DE±4,5) años; 79 gestantes correspondían a casos de SARS-CoV-2; 14 gestantes correspondían a casos de SARS-CoV y 9 gestantes a casos de MERS-CoV. La mayoría de las infecciones se detectaron durante el segundo y tercer trimestre (32 semanas ±10 semanas), exceptuando siete casos de SARS-CoV en los que la infección se produjo durante el primer trimestre y que acabaron en un aborto espontáneo o voluntario. En la tabla 4 se describen los datos comparativos sobre las tres enfermedades, resaltando la fiebre con un 89,5% (IC 95%: 82,6-96,3) y la neumonía con un 81,5% (IC 95%: 72,7-90,2) los síntomas comunes de los tres coronavirus. Además, se observó que la Amenaza de Parto Prematuro (APP) con un 26,6% (IC 95%: 8,9-44,2) y la cesárea con 85,4% (IC 95%:77,5-93,3) fueron las complicaciones obstétricas más frecuentes.

Sintomatología general asociada a la patología. Como se aprecia en la tabla 5 [8, 26-34], la fiebre en un 85,9% (n=55) de los casos y la tos en un 32,9% (n=26) fueron los síntomas más característicos de las gestantes que enfermaron por SARS-CoV-2, resultando ocasional, la aparición de diarrea con un 8,9% (n=7). La neumonía fue padecida por 75,7% (n=53) de las gestantes y esta fue de carácter leve en la mayoría de los casos, ya que solo 4,3% (n=3) de las gestantes precisaron de ventilación mecánica e ingreso en UCI. En este último dato cabe destacar que en el artículo de Zhu et. al. [26] no especifica qué gestantes tuvieron neumonía y si alguna de ellas precisó o no de ventilación asistida.

En relación con el SARS-CoV (tabla 6) [17, 18, 36, 38], la fiebre y la mialgia aparecieron en el 100% (n=14) de los casos estudiados. Todas las gestantes, desarrollaron neumonía y un 42,9% (n=6) precisaron recibir ventilación mecánica en UCI.

Tabla 1 Estrategias de búsqueda empleadas

Base de datos	Estrategia de búsqueda
MEDLINE	((((((((((((((((((((((((coronavirus[MeSH Terms]) OR coronavirus[Title/Abstract]) OR COVID 19[MeSH Terms]) OR COVID 19[Title/Abstract]) OR COVID-19[MeSH Terms]) OR COVID-19[Title/Abstract]) OR COVID19[MeSH Terms]) OR COVID19[Title/Abstract]) OR 2019-nCoV[MeSH Terms]) OR 2019-nCoV[Title/Abstract]) OR 2019nCoV[MeSH Terms]) OR 2019nCoV[Title/Abstract]) OR SARS-CoV[MeSH Terms]) OR SARS-CoV[Title/Abstract]) OR SARS-CoV-2[MeSH Terms]) OR SARS-CoV-2[Title/Abstract]) OR SARS-CoV2[MeSH Terms]) OR SARS-CoV2[Title/Abstract]) OR MERS-CoV[MeSH Terms]) OR MERS-CoV[Title/Abstract]) OR Severe acute respiratory sindrome[MeSH Terms]) OR Severe acute respiratory sindrome[Title/Abstract]) OR Middle East Respiratory Syndrome[MeSH Terms]) OR Middle East Respiratory Syndrome[Title/Abstract]
SciELO	CORONAVIRUS [Todos los indices] and EMBARAZADA [Todos los indices] CORONAVIRUS [Todos los indices] and PREGNANT [Todos los indices] COVID [Todos los indices] and PREGNANT [Todos los indices] COVID [Todos los indices] and EMBARAZADA [Todos los indices]
CUIDEN	CORONAVIRUS AND embarazada COVID 19 AND embarazada COVID 19 AND pregnant COVID 19 AND pregnant women COVID 19 AND pregnant woman
Elsevier	("COVID-19" OR Coronavirus OR "Corona virus" OR "2019-nCoV" OR "SARS-CoV" OR "MERS-CoV" OR "Severe Acute Respiratory Syndrome" OR "Middle East Respiratory Syndrome") AND (PREGNANT WOMAN OR PREGNANT WOMEN)

Respecto al MERS-CoV (tabla 7) [12, 20, 21, 36, 37, 39], destaca la fiebre en el 100% (n=9) de los casos, la tos y la disnea que se produjo en el 87,5% (n=7) como síntomas más característicos. El 100% de las gestantes estudiadas padecieron neumonía, pero solo la mitad precisaron de ventilación mecánica.

Complicaciones obstétricas de las gestantes. Las complicaciones obstétricas en las mujeres que pasaron el COVID-19 durante la gestación son escasas, destacando que se produjo la APP en el 24,3% (n=18) y el Riesgo de Pérdida de Bienestar Fetal (RPBF) en un 18,9% (n=14) como urgencias obstétricas más frecuentes. De estos datos destaca que no se produjo ningún fallecimiento entres las infectadas por SARS-CoV-2.

Respecto al SARS-CoV, un 41,7% (n=5) tuvieron un aborto durante el primer trimestre, por ello no tenemos datos de las complicaciones obstétricas. En el resto de gestantes, la infección se produjo cuando aún no habían llegado a término,

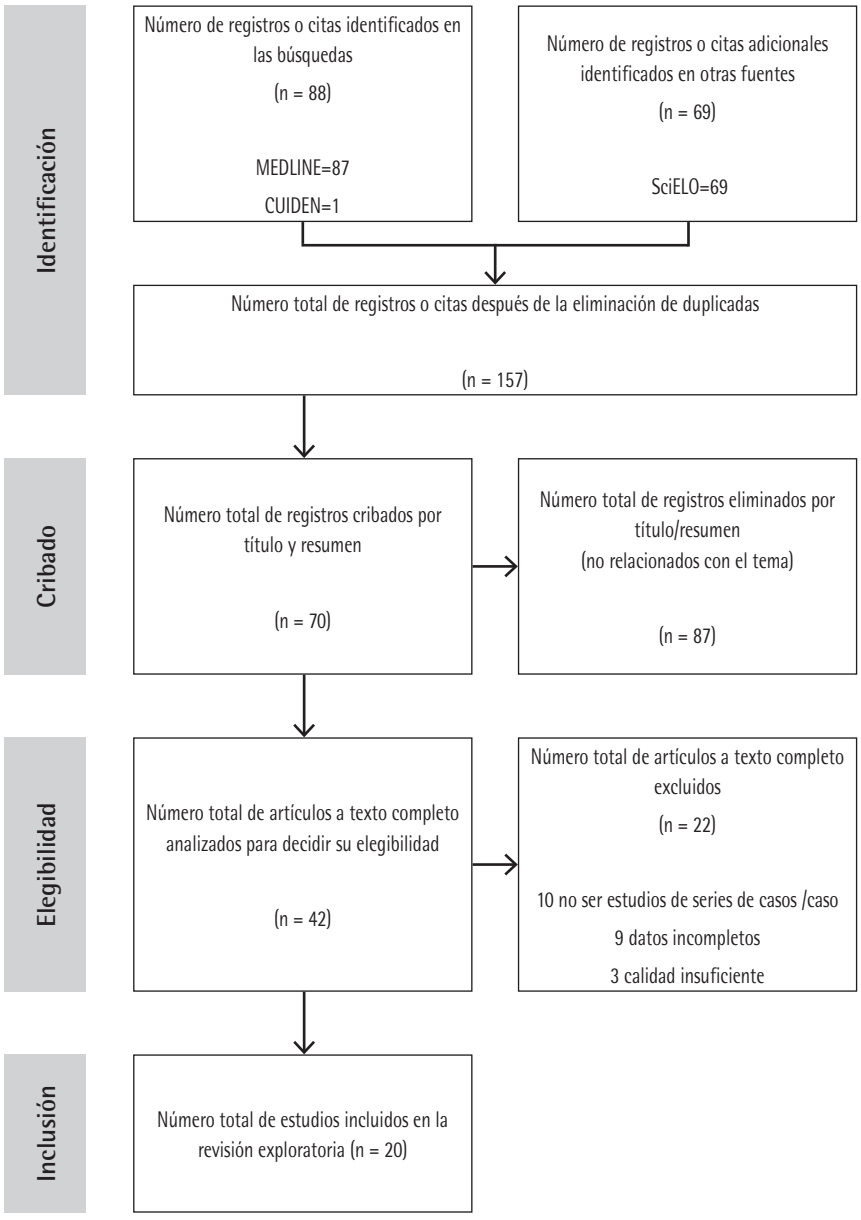

Figura 1 | **Diagrama de flujo selección tipo PRISMA revisión exploratoria**

Tabla 2 **Estudios incluidos en la revisión sobre SARS-CoV-2.**

Autor	País Año	Periodo de estudio	Diseño de estudio	Objetivos	Población
Chen [8] et al.	China 2020	No reportado	Serie de casos	Describir los casos clínicos de bebés nacidos de mujeres embarazadas con infección por SARS-CoV-2.	Mujeres embarazadas y Neonatos
Zhu [26] et al.	China 2020	20 enero - 5 febrero	Serie de casos	Analizar retrospectivamente las características clínicas y los resultados de 10 neonatos de madres con infección confirmada	Mujeres embarazadas y Neonatos
Chen [27]et al.	China 2020	20 enero - 10 febrero	Serie de casos	Evaluar a las mujeres embarazadas infectadas por SARS-CoV-2 y proporcionar ayuda para la prevención y el tratamiento clínico en China.	Mujeres embarazadas
Zambrano [28] et al.	Honduras 2020	19 marzo	Reporte de un caso	Informar de casos sobre mujeres embarazadas afectadas por el COVID-19 de América Central.	Mujeres embarazadas
Liu [29] et al.	China 2020	8 diciembre - 25 febrero	Serie de casos	Describir las características epidemiológicas, clínicas, del embarazo y los resultados perinatales de todas las pacientes embarazadas hospitalizadas diagnosticadas con COVID-19 en China	Mujeres embarazadas
Chen [30] et al.	China 2020	20 - 31 enero	Serie de casos	Evaluar las características clínicas de COVID-19 en el embarazo y el potencial de transmisión vertical intrauterina.	Mujeres embarazadas
Liu [31] et al.	China 2020	20 enero - 10 febrero	Serie de casos	Describir las manifestaciones clínicas y las características de la neumonía por SARS-CoV-2 en 15 mujeres embarazadas	Mujeres embarazadas
Wang [32] et al.	China 2020	6 febrero	Reporte de un caso	Presentar un caso clínico de una mujer embarazada de 30 semanas con COVID-19 dando a luz a un bebé sano sin evidencia de enfermedad.	Mujeres embarazadas
Zhang [33] et al.	China 2020	30 enero - 17 febrero	Caso-Control	Estudiar el efecto de COVID-19 sobre los resultados del embarazo y el pronóstico neonatal en la provincia de Hubei.	Mujeres embarazadas
Yu [34] et al.	China 2020	1 enero - 8 febrero	Serie de casos	Aclarar las características clínicas y los resultados obstétricos y neonatales de pacientes embarazadas con SARS-CoV-2 en Wuhan, China.	Mujeres embarazadas

por ello el 71,4% (n=5) padecieron una APP. Las hemorragias preparto ocurrieron en un 57,1% (n=4) y fueron de distinto origen, una fue por Placenta Previa (PP) [36, 38] y las otras tres una Coagulación Intravascular Diseminada (CID) [18, 36]. Una de las complicaciones más graves que produjo la neumonía por SARS-CoV fue la co-infección por sepsis y neumonía bacteriana que se produjo en el 57,1% (n=4) de las gestantes. El 21,4% (n=3) de las gestantes fallecieron.

Entre las diagnosticadas por MERS-CoV, destacan tres complicaciones: la hemorragia preparto que se presentó en el 22,2% (n=2), la hipertensión arterial previa a la infección y la APP en un 11,1% (n=1) respectivamente. La hemorragia que se dio en dos gestantes, una fue por DPPNI y la otra no se especificó [20, 35]. Fallecieron el 33,3% (n=3) de las gestantes estudiadas.

Fin de parto, resultado neonatal y transmisión vertical. Las gestantes adquirieron la infección por SARS-CoV-2, durante el tercer trimestre [36 semanas (DE±3)] y el 89,0% (n=66) terminó en cesárea. Se registró una muerte fetal, de un lactante cuya madre empeoró durante la estancia hospitalaria y precisó ventilación mecánica [29]. El 98,6% (n=73) de los neonatos tuvieron un Apgar superior a 8 tanto al minuto como a los cinco minutos de vida. No se documentó ninguna transmisión vertical al recién nacido. Los datos de transmisión vertical se obtuvieron mediante el análisis microbiológico del líquido amniótico, la sangre de cordón umbilical o la placenta. No se disponen de algunos datos, porque el diagnostico positivo de infección materna a SARS-CoV-2 fue posterior al nacimiento o por no consentimiento paterno para la realización de las pruebas [8]. La transmisión del SARS-CoV-2 a través de la leche materna no se produjo en ningún caso, pero solo se realizó el análisis en el 5,9% (n=6) de las puérperas [30] y algunas gestaciones no habían finalizado cuando se publicaron los trabajos [29, 31].

Respecto al SARS-CoV, un 85,7% (n=6) de las gestantes que se infectaron durante el tercer trimestre acabaron en cesárea. Ningún bebé murió, aunque un 57,1 % (n=4) tuvieron un Apgar al minuto inferior a 7, que consiguieron estabilizar a los 5 minutos (Apgar superior a 7). No se registró transmisión vertical tras el análisis microbiológico del neonato, líquido amniótico, sangre de cordón o placenta [17, 18]. La transmisión por leche materna tampoco fue detectada [36, 38].

El MERS-CoV afectó a gestantes en segundo y tercer trimestre [22 – 38 (29±6)]. El 55,6% (n=5) de las gestaciones terminó mediante cesárea. Se produjeron dos muertes prenatales y una a las cuatro horas del nacimiento [20, 21] y sólo se registró el Apgar en dos casos [12, 35]. La transmisión vertical tampoco se constató en ninguno de los seis casos analizados

Tabla 3 **Estudios incluidos en la revisión sobre SARS-CoV y MERS-CoV.**

Autor	País Año	Periodo de estudio	Diseño de estudio	Objetivos	Población
Malik [12] et al.	Emiratos Árabes 2016	Noviembre 2013	Reporte de un caso	Presentación de un caso clínico de una mujer embarazada con MERS-CoV que recibió terapia con ribavirina-peginterferón-α	Mujeres embarazadas
Wong [17] et al.	Japón 2004	Febrero - julio 2003	Serie de casos	Evaluar el embarazo y los resultados perinatales de mujeres embarazadas con síndrome respiratorio agudo severo en Hong Kong.	Mujeres embarazadas
Shek [18] et al.	Japón 2003	Marzo 2003	Serie de casos	Presentación de 5 casos clínicos de bebés nacidos vivos de mujeres embarazadas con SARS-CoV.	Mujeres embarazadas y Neonatos
Payne [20] et al.	Jordania 2014	Abril 2012	Serie de casos	Investigar la epidemiologia entre los sobrevivientes de un brote de infección por MERS-CoV en Jordania.	Mujeres embarazadas
Assiri [21] et al.	Arabia Saudita 2016	Mayo 2014 - julio 2015	Serie de casos	Describir los 5 casos de mujeres embarazadas de Arabia Saudí con infección por MERS-CoV.	Mujeres embarazadas
Jeong [35] et al.	Corea 2017	Mayo 2015	Reporte de un caso	Presentar un caso clínico de una embarazada de Corea con resultado positivo de la reacción en cadena de la polimerasa MERS-CoV	Mujeres embarazadas
Robertson [36] et al.	EE. UU. 2004	Febrero 2003	Reporte de un caso	Presentación de un caso clínico confirmado por laboratorio de síndrome respiratorio agudo severo en una mujer embarazada.	Mujeres embarazadas
Park [37] et al.	Corea 2016	No reportado	Reporte de un caso	Presentación de un caso clínico confirmado de MERS-CoV en la República de Corea en una mujer en la semana gestacional 35 + 4.	Mujeres embarazadas
Stockman [38] et al.	EE. UU. 2004	Marzo 2003	Serie de casos	Presentación del caso clínico de una mujer embarazada con afección de SARS-CoV, y seguimiento 1 mes después del nacimiento.	Mujeres embarazadas y Neonatos
Alserehi [39] et al.	Arabia Saudita 2016	Abril 2012	Reporte de un caso	Presentación de un caso clínico de la infección por MERS-CoV en una mujer embarazada que adquirió la infección durante el último trimestre.	Mujeres embarazadas

[21, 35, 37, 39]. En dos casos se analizó la transmisión a través de la leche materna con resultandos negativos [35, 37, 39].

DISCUSION

Un siglo después de la pandemia por Influenza A/H1N1 conocida como "gripe española" y causante de más de 40 millones de fallecimientos, la pandemia por SARS-CoV2 ha emergido con una fuerza inusitada poniendo a prueba la capacidad de respuesta de los sistemas sanitarios [40], con la desventaja de que no existe por el momento disponibilidad de vacunas o tratamientos específicos para las infecciones por coronavirus [15].

Era conocido que los coronavirus, SARS-CoV y MERS-CoV, causaban complicaciones graves durante el embarazo, por lo que las observaciones extraídas de los casos podrían ser útiles para la toma de decisiones clínicas y preventivas en el nuevo SARS-CoV-2. Los resultados arrojan similitudes y diferencias, pero todos coinciden en el aumento de morbi-mortalidad en la mujer gestante en comparación con la no gestante [13, 15, 18-20, 41].

La mayor parte de gestantes infectadas por SARS-CoV2 se encontraban en el tercer trimestre de embarazo, probablemente porque existía un gran número de pacientes asintomáticas [31]. En una reciente publicación [42] se realizó a todas las mujeres en trabajo de parto un examen de detección al ingreso mediante una prueba nasofaríngea, resultando que la mayoría positivas a SARS-CoV-2 no presentaban ningún síntoma de la enfermedad.

El monitoreo de todas las gestantes desde el inicio es importante, dado que en otras infecciones como la gripe o el SARS, estas patologías se relacionaron con abortos espontáneos [11], Restricciones del Crecimiento Intrauterino (RCIR) [18] y APP [14].

El manejo de las gestantes con SARS-CoV-2 debe correr a cargo de un equipo multidisciplinar que permita mantener el control materno-fetal y detectar el inicio de una posible APP [26, 29, 30, 43]. En esta revisión, una cuarta parte de las gestantes con SARS-CoV-2 desarrollaron una APP, con las siguientes consecuencias de bajo peso fetal e ingreso en neonatos [26, 28-30, 32, 33], aunque no están directamente relacionados con el virus sino por lo general, consecuencia de patología materna o RPBF. En segundo lugar, una quinta parte documentaron anormalidades en el registro cardiotocográfico

Tabla 4 **Comparativa entre SARS-CoV-2, SARS-CoV y MERS-CoV**

	SARS-CoV-2 n/N (%) N=79	SARS-CoV n/N (%) N=14	MERS-CoV n/N (%) N=9	TOTAL CORONAVIRUS n/N (%) [IC 95%] N=102
Edad	22 – 41 (31±4)	24- 44 (31±6)	27 – 39 (33±4)	
SA nacimiento	26 – 41 (36±3)	3 – 38 (19±15)	22 – 38 (29±6)	
Sintomatología General Gestante				
Fiebre	55/64 (85,9%)	14/14 (100%)	8/8 (100%)	77/86 (89,5%) [82,6-96,3]
Mialgia	15/64 (23,4%)	14/14 (100%)	1/8 (12,5%)	30/86 (34,9%) [17,8-51,9]
Diarrea	7/79 (8,9%)	2/14 (14,3%)	0/8 (0,0%)	9/101 (8,9%) [0,0-27,5]
Tos	26/79 (32,9%)	11/14 (78,6%)	7/8 (87,5%)	45/101 (44,5%) [29,9-59,0]
Disnea	11/79 (13,9%)	6/14 (42,9%)	7/8 (87,5%)	24/101 (13,9%) [0,0-27,7]
Neumonía	53/70 (75,7%)	14/14 (100%)	8/8 (100%)	75/92 (81,5%) [72,7-90,2]
UCI / VM	3/70 (4,3%)	14/14 (100%)	4/8 (50,0%)	21/92 (22,8%) [4,8-40,7]
Complicaciones Obstétricas				
HTA	6/74 (8,1%)	0/7 (0,0%)	1/9 (11,1%)	7/90 (7,6%) [0,0-27,2]
RPM	9/74 (12,1%)	1/7 (14,3%)	0/9 (0,0 %)	10/90 (23,4%) [0,0-49,6]
Coinfecciones	1/74 (1,3%)	4/7 (57,1%)	0/9 (0,0 %)	5/90 (8,9%) [0,0-33,9]
RPBF	14/74 (18,9%)	2/7 (28,5%)	0/9 (0,0 %)	16/90 (17,8%) [0,0-36,5]
APP	18/74 (24,3%)	5/7 (71,4%)	1/9 (11,1%)	24/90 (26,6%) [8,9-44,2]
Hemorragias	3/74 (4,0%)	4/7 (57,1%)	2/9 (22,2%)	9/90 (10,0%) [0,0-29,6]
RCIR	0/74 (0,0%)	2/7 (28,6%)	0/9 (0,0 %)	2/90 (2,2%) [79,1-85,3]
Muerte materna	0/79 (0,0%)	3/14 (21,4%)	3/9 (33,3%)	6/102 (5,8%) [0,0-26,4]
Fin de parto				
Parto vaginal	8/73 (11,0%)	1/7 (14,3%)	4/9 (44,4%)	13/89 (14,6%) [0,0-33,8]
Cesárea	65/73 (89,0%)	6/7 (85,7%)	5/9 (55,6 %)	76/89 (85,4%) [77,5-93,3]
Resultado neonatal				
Vivo	73/74(98,6%)	7/7 (100%)	6/9 (66,7%)	86/90 (95,5%) [91,1-99,8]
Muerto	1/74 (1,4%)	0/7 (0,0%)	3/9 (33,3%)	4/90 (4,4%) [0,0-24,5]
Test de Apgar (1' y 5')				
5-9	0/57 (0,0%)	2/7 (28,6%)	0/2 (0%)	2/66 (3,0%) [0,0-26,7]
5-7	0/57 (0,0%)	1/7 (13,3%)	0/2 (0%)	1/66 (1,5%) [0,0-25,3]
6-8	0/57 (0,0%)	0/7 (0,0%)	1/2 (50%)	1/66 (1,5%) [0,0-25,3]
8-9	5/57 (8,8%)	0/7 (0,0%)	0/2 (0%)	5/66 (7,6%) [0,0-30,8]
7-8	2/57 (3,5%)	1/7 (13,3%)	0/2 (0%)	3/66 (4,5%) [0,0-27,9]
8-10	1/57 (1,7%)	0/7 (0,0%)	0/2 (0%)	1/66 (1,5%) [0,0-25,3]
9-9	0/57 (0,0%)	1/7 (13,3%)	0/2 (0%)	1/66 (1,5%) [0,0-25,3]
9-10	30/57 (52,6%)	2/7 (28,6%)	1/2 (50%)	33/66 (50,0%) [32,9-67,0]
10-10	15/57 (26,3%)	0/7 (0,0%)	0/2 (0,0%)	15/66 (22,7%) [1,5-43,9]
Transmisión				
Vertical	0/66 (0,0%)	0/7 (0,0%)	0/6 (0,0%)	
Leche materna	0/6 (0,0%)	0/2 (0,0%)	0/2 (0,0%)	

SA= Semanas de Amenorrea; VM= Ventilación Mecánica; RPM= Rotura Prematura de Membranas; RPBF= Riesgo de Pérdida de Bienestar Fetal APP= Amenaza de Parto Prematuro; RCIR= Restricción del Crecimiento Intrauterino.

con RPBF [26, 30] y en el grupo de gestante a término se observó Rotura Prematura de Membranas [33].

La sintomatología común de los tres coronavirus fue la fiebre, con el SARS-CoV-2 y el SARS-CoV la aparición de mialgia y con el MERS-CoV la tos [30, 31]. La fiebre se produjo durante el postparto en algunas gestantes y la sintomatología respiratoria fue leve. La neumonía como patología coincidente entre los tres, fue más leve en el caso del SARS-CoV-2 [44].

Tabla 5 **Características clínicas de las madres diagnosticadas de SARS-CoV-2 y resultados neonatales**

	SARS-CoV-2										
	Chen et al [30] N=9	Liu et al. [29] N=13	Wang et al [32] N=1	Zhu et al. [26] N=8	Chen et al. [27] N=5	Zambrano et al. [28] N=1	Yu et al. [34] N=7	Liu et al. [31] N=15	Zhang et al. [33] N=16	Chen et al. [8] N=4	TOTAL n/N (%) N=79
Edad	26-40 (26±10)	22-36 (29±4)	28	25- 39 (32±4)	29-31 (28±1)	41	30- 34 (31±1)	23 - 40 (32±5)	(29±3)	23 – 34 (29±5)	22 – 41 (31±4)
SA nacimiento	36 -39 (36±4)	33 – 38 (35±1) [c]	30	33 – 39 (35±3) [d]	39-40 (39±0)	32	37- 41 (39±1)	12 – 38 (32±8) [c]	(38±1)	37 – 39 (37±1)	26 – 41 (36±3)
Sintomatología General Gestante											
Fiebre	7/9	10/13	1/1	9/9	5/5	1/1	6/7	13/15	NA	3/4	55/64 (85,9%)
Mialgia	3/9	0/13	0/1	0/9	0/5	1/1	0/7	9/15	NA	2/4	15/64 (23,4%)
Diarrea	1/9	0/13	0/1	1/9	0/5	0/1	1/7	1/15	3/16	0/4	7/79 (8,9%)
Tos	3/9	2/13	0/1	4/9	1/5	1/1	1/7	9/15	3/16	2/4	26/79 (32,9%)
Disnea	1/9	3/13	1/1	0/9	0/5	0/1	1/7	1/15	3/16	1/4	11/79 (13,9%)
Neumonía	9/9	1/13	1/1	n/c	0/5	0/1	7/7	15/15	16/16	4/4	53/70 (75,7%)
UCI / VM	0/9	1/13	1/1	n/c	0/5	0/1	0/7	0/15	1/16	0/4	3/70 (4,3%)
Complicaciones Obstétricas											
HTA	2/9	0/10[c]	0/1	0/9	1/5	1/1a	0/7	0/11 [c]	1/16	0/4	6/74 (8,1%)
RPM	2/9	1/10 [c]	0/1	3/9	0/5	0/1	0/7	0/11 [c]	3/16	0/4	9/74 (12,1%)
Coinfección	1/9	0/10 [c]	0/1	0/9	0/5	0/1	0/7	0/11 [c]	0/16	0/4	1/74 (1,3%)
RPBF	2/9	3/10 [c]	1/1	6/9	1/5	0/1	0/7	0/11 [c]	1/16	0/4	14/74 (18,9%)
APP	4/9a	6/10 [c]	1/1	5/9	0/5	1/1	0/7	0/11 [c]	1/16	0/4	18/74 (24,3%)
Hemorragias	0/9	0/10 [c]	0/1	2/9	0/5	0/1	0/7	1/11 [c, f]	0/16	1/4f	3/74 (4,0%)
RCIR	0/5	0/10 [c]	0/1	0/9	0/5	0/1	0/7	0/11 [c]	0/16	0/4	0/74 (0%)
Muerte Materna	0/9	0/13	0/1	0/9	0/5	0/1	0/7	0/15	0/16	0/4	0/79 (0%)
Fin de parto											
Parto vaginal	0/9	0/10 [c]	1/1	2/9	3/5	1/1	0/7	1/11 [c]	0/16	1/4	8/73 (11,0%)
Cesárea	9/9	10/10 [c]	1/1	7/9	2/5	0/1	7/7	10/11 [c]	16/16	3/4	65/73 (89,0%)
Resultado neonatal											
Vivo	9/9	10/10 [c]	1/1	9/10	5/5	1/1	7/7	11/11 [c]	16/16	4/4	73/74 98,6%)
Muerto	0/9	1/10 [c]	0/1	0/10	0/5	0/1	0/7	0/11 [c]	0/16	0/4	1/74 (1,4%)
Test de Apgar (1' y 5')											
5-9						NA			NA		0/57 (0%)
5-7						NA			NA		0/57 (0%)
6-8						NA			NA		0/57 (0%)
8-9	2/9			3/10		NA			NA	3/4	5/57 (8,8%)
7-8				1/10		NA			NA	1/4	2/57 (3,5%)
8-10	1/9					NA			NA		1/57 (1,7%)
9-9						NA			NA		0/57 (0%)
9-10	6/9		1/1	5/10		NA	7/7	11/11 [c]	NA		30/57 (52,6%)
10-10		9/10[c]		1/10	5/5	NA			NA		15/57 (26,3%)
Transmisión											
Vertical	0/6[b]	0/10 [c]	0/1	0/10	0/5	0/1	0/3 [b,e]	0/11 [c]	0/16[g]	0/3 [h]	0/66 (0%)
Lactancia materna	0/6 [b]	NA	NA	NA	NA	NA	NA	NA	NA	NA	0/6 (0%)

SA= Semanas de Amenorrea; VM= Ventilación Mecánica; RPM= Rotura Prematura de Membranas; RPBF= Riesgo de Pérdida de Bienestar Fetal APP= Amenaza de Parto Prematuro; RCIR= Restricción del Crecimiento Intrauterino. NA= No hay datos

[a]No relacionado con COVID-19; [b]No testado en algunos pacientes; [c]Los embarazos evolucionaron, sin resultado neonatal; [d]Un embarazo gemelar; [e]Un positivo a las 36 horas; [f]Placenta previa; [g]RN desarrollaron neumonía postparto (n=3); [h]No consentimiento para realizar la prueba

Tabla 6 **Características clínicas de las madres diagnosticadas de SARS-CoV y resultados neonatales**

	SARS-CoV		
	Wong et al. [17] Shek et al. [18] N=12	Robertson et al.[36] Stockman et al.[38] N=2	TOTAL n/N (%) N=14
Edad	24- 44 (31±6)	36 – 38	24- 44 (31±6)
SA nacimiento	3- 12 (5±3) 26 – 37 (31±4)	38 – 36	3 – 38 (19±15)
Sintomatología General Gestante			
Fiebre	12/12	2/2	14/14 (100%)
Mialgia	12/12	2/2	14/14 (100%)
Diarrea	2/12	0/2	2/14 (14,3%)
Tos	9/12	2/2	11/14 (78,6%)
Disnea	4/12	2/2	6/14 (42,9%)
Neumonía	12/12	2/2	14/14 (100%)
UCI /VM	4/12	2/2	6/14 (42,9%)
Complicaciones Obstétricas			
HTA	0/5 [a]	0/2	0/7 (0%)
RPM	0/5 [a]	1/2	1/7 (14,3%)
Coinfecciones	4/12[b]	0/2	4/7 (57,1%)
RPBF	1/5 [a]	1/2	2/7 (28,5%)
APP	4/5 [a]	1/2	5/7 (71,4%)
Hemorragia	3/12 [c]	1/2[d]	4/7 (57,1%)
RCIR	2/5 [a]	0/2	2/7 (28,6%)
Muerte materna	3/12	0/2	3/14 (21,4%)
Fin de parto			
Parto vaginal	1/5 [a]		1/7 (14,3%)
Cesárea	4/5 [a]	2/2	6/7 (85,7%)
Resultado neonatal			
Vivo	5/5 [a]	2/2	7/7 (100%)
Muerto	0/5 [a]	0/2	0/7 (0%)
Test de Apgar (1' y 5')			
5-9	2/5 [a]		2/7 (28,6%)
5-7	1/5 [a]		1/7 (13,3%)
6-8			0/7 (0%)
8-9			0/7 (0%)
7-8		1/2	1/7 (13,3%)
8-10			0/7 (0%)
9-9		1/2	1/7 (13,3%)
9-10	2/5 [a]		2/7 (28,6%)
10-10			0/7 (0%)
Transmisión			
Vertical	0/5 [a]	0/2	0/7 (0%)
Leche materna	NA	0/2	0/2 (0%)

SA=Semanas de Amenorrea; VM= Ventilación mecánica; RPM= Rotura Prematura de Membranas; RPBF= Riesgo de Pérdida de Bienestar Fetal APP= Amenaza de Parto Prematuro; RCIR= Restricción del Crecimiento Intrauterino. NA= No hay datos
[a]Solo 5 pacientes llegaron a 2º o 3º trimestre; [b]Neumonía bacteriana y sepsis; [c]Coagulación Intravascular Diseminada (CID); [d]Placenta previa (PP)

Tabla 7 **Características clínicas de las madres diagnosticadas de MERS-CoV y resultados neonatales**

	MERS-CoV					
	Jeong et al.[35] Park et al. [37]	Alserehi et al.[39]	Assiri et al. [21]	Malik et al. [12]	Payne et al. [20]	TOTAL n/N (%)
	N=1	N=1	N=5	N=1	N=1	N=9
Edad	39	33	27 – 34 (30±6)	32	39	27 – 39 (33±4)
SA nacimiento	37	32	22 – 38 (28±7)	32	23	22 – 38 (29±6)
Sintomatología General Gestante						
Fiebre	1/1	1/1	5/5	1/1	1/1	9/9 (100%)
Mialgia	1/1	0/1	1/4 [b]	0/1	1/1	1/8 (12,5%)
Diarrea	0/1	0/1	0/4 [b]	0/1	0/1	0/8 (0%)
Tos	0/1	1/1	4/4 [b]	1/1	1/1	7/8 (87,5%)
Disnea	1/1	1/1	3/4 [b]	1/1	1/1	7/8 (87,5%)
Neumonía	1/1	1/1	5/5	1/1	NA	8/8 (100%)
UCI / VM	0/1	1/1	3/5	1/1	NA	4/8 (50,0%)
Complicaciones Obstétricas						
HTA	0/1	0/1	1/5	0/1	0/1	1/9 (11,1%)
RPM	0/1	0/1	0/5	0/1	0/1	0/9 (0 %)
Coinfecciones	0/1	0/1	0/5	0/1	0/1	0/9 (0 %)
RPBF	1/1	0/1	0/5	0/1	0/1	0/9 (0 %)
APP	0/1	0/1	0/5	0/1	1/1	1/9 (11,1%)
Hemorragias	1/1 [a]	0/1	0/5	0/1	1/1	2/9 (22,2%)
RCIR	0/1	0/1	0/5	0/1	0/1	0/9 (0 %)
Muerte materna	0/1	0/1	2/5	1/1	0/1	3/9 (33,3%)
Fin de parto						
Parto vaginal	0/1	0/1	3/5	0/1	1/1	4/9 (44,4%)
Cesárea	1/1	1/1	2/5	1/1	0/1	5/9 (55,6 %)
Resultado neonatal						
Vivo	1/1	1/1	3/5	1/1	0/1	6/9 (66,7%)
Muerto	0/1	0/1	2/5[c]	0/1	1/1	3/9 (33,3%)
Test de Apgar (1' y 5')						
5-9		NA	NA		NA	0/2 (0%)
5-7		NA	NA		NA	0/2 (0%)
6-8		NA	NA	1/1	NA	1/2 (50%)
8-9		NA	NA		NA	0/2 (0%)
7-8		NA	NA		NA	0/2 (0%)
8-10		NA	NA		NA	0/2 (0%)
9-9	1/1	NA	NA		NA	0/2 (0%)
9-10		NA	NA		NA	1/2 (50%)
10-10		NA	NA		NA	0/2 (0%)
Transmisión						
Vertical	0/1	0/1	0/4[d]	NA	NA	0/6 (0 %)
Leche materna	0/1	0/1	NA	NA	NA	0/2 (0 %)

SA=Semanas de Amenorrea; VM= Ventilación Mecánica; RPM= Rotura Prematura de Membranas; RPBF= Riesgo de Pérdida de Bienestar Fetal APP= Amenaza de Parto Prematuro; RCIR= Restricción del Crecimiento Intrauterino. NA= No hay datos

[a]Desprendimiento de Placenta Normoinserta; [b]En uno de los casos solo especifica que tuvo fiebre y neumonía; [c]Un neonato murió a las 4 horas; [d]No se realizó por muerte neonatal 24 semanas.

El fallo en la función respiratoria, que en algunos casos precisa la intubación endotraqueal e ingreso en UCI tiene implicaciones para la salud materno-fetal [45]. Con los antecedentes de los que disponemos en otros coronavirus, debemos monitorizar los casos de SARS-CoV-2, ya que la tasa de letalidad por SARS-CoV ascendió al 25% y para el MERS-CoV a un 27% [17, 21, 35].

Todas las gestantes infectadas por MERS-CoV y SARS-CoV desarrollaron una neumonía, precisando ingreso en UCI la mitad de las pacientes con MERS-CoV y la totalidad de las pacientes con SARS-CoV [12, 17, 36]. La coinfección producida en gestantes con neumonía por SARS produjo más mortalidad materna asociada [18]. En el caso de las gestantes con COVID-19 algo más de la mitad desarrolló neumonía, pero esta fue más leve, requiriendo ingreso en UCI pocos casos [30, 31, 33]. Por lo tanto, la neumonía materna genera en todos los coronavirus resultados obstétricos adversos como APP, RCIR o muerte fetal intrauterina. Durante la pandemia de gripe de 1918, las complicaciones más frecuentes fueron el aborto espontáneo y la APP. Entonces se observó que más de la mitad de las gestantes con gripe y neumonía asociadas, no llegaron a término [46].

En la muestra de gestantes con SARS-CoV-2 la forma principal de fin de parto fue la cesárea en un (89,0 %) [8, 29, 30, 33, 34] porcentaje coincidente con la muestra del SARS-CoV y en menor medida con el MERS-CoV, que tuvo partos vaginales casi en la mitad de los casos [20, 21]. Este elevado porcentaje de cesáreas es motivo de preocupación, ya que la mayoría son electivas y no siempre estuvieron justificadas [47].

La transmisión vertical de la infección se produjo a través de la placenta intraútero o durante el desarrollo del parto. El riesgo de ingestión de secreciones cervicovaginales es superior en el parto vaginal, por lo que este podría ser uno de los factores que podría explicar la no transmisión al feto en los casos de COVID-19. Por tanto, el riesgo de no transmisión vertical no puede confirmarse, aunque en la mayoría de las pruebas realizadas tras el parto en las gestantes con SARS-CoV-2, no se evidenció infección neonatal [29, 31, 48]. En el estudio de Yu et. al. [34], la prueba de ácido nucleico en la garganta de un recién nacido fue positiva a las 36h del nacimiento, aunque no se especifica el modo de contagio, ya que todas las gestantes de la muestra se encontraban en el último trimestre. En otro estudio Chen et. al. [8]. cuatro de los casos resultaron negativos, aunque en dos de ellos se desarrolló una erupción al nacer que desapareció a los pocos días.

Se ha demostrado que la transmisión a profesionales o personal del entorno cercano es posible [49]. Los lactantes de madres positivas a SARS-CoV-2 no estaban infectados al nacimiento, aunque solo se documentaron en 6 casos [30] y no desarrollaron la sintomatología característica de sus madres (disnea, fiebre o mialgia) [8]. Con los otros dos coronavirus, tampoco hubo constancia de infección a través de la lactancia materna, pero en el caso del SARS-CoV en sangre del cordón umbilical y en leche materna aparecieron anticuerpos, lo que hace pensar en una posible inmunidad pasiva [36, 38]. Sin embargo, esta inmunidad pasiva se ha documentado recientemente en un estudio con madres infectadas con SARS-CoV-2, que habla sobre la transferencia de anticuerpos (IgA) en leche materna.[50]. La inmunidad a través de la placenta (sobre todo en el tercer trimestre) y de la leche materna [51] sugiere que se podría permitir a las mujeres infectadas el amamantamiento, manteniendo medidas de protección como higiene de manos y mascarilla facial [52].

Independientemente, del tipo de parto, ya sea por cesárea o vaginal, las valoraciones del Apgar de los recién nacidos de madres con COVID-19, son en todos los casos superiores a 8 (al 1 min y 5 min) [27, 34]. Con los otros dos coronavirus, existen valoraciones inferiores [21].

La muerte intrauterina solo se documentó en un caso de SARS-CoV-2 [29] y ningún caso de mortalidad fetal [30, 31] a diferencia del MERS-CoV en un tercio de los casos [16, 20, 29].

Con todo lo expuesto, existen todavía lagunas en el conocimiento sobre las consecuencias para la madre y el feto, pero los antecedentes clínicos de otros coronavirus nos hacen pensar que existen más complicaciones durante la gestación (APP, RCIR, hemorragias del tercer trimestre, hospitalizaciones), el parto (RPBF, cesáreas electivas y urgentes) y en el recién nacido (prematuridad, dificultades respiratorias al nacimiento) [26,35,53]. Sin embargo, es muy alentador que las últimas revisiones muestren una evolución muy favorable de las mujeres enfermas por COVID-19, con una tasa de mortalidad materna muy baja o casi nula, con un solo caso [54-56].

Señalamos como limitación de esta revisión que todos los artículos son de tipo observacional, retrospectivos de series de casos o de reporte de un caso, en los que la fuente de datos fueron las historias clínicas, por lo que no es posible establecer relación de causalidad. Nuestro estudio compara los tres coronavirus como la revisión realizada recientemente por Di Mascio et .al. [57], pero difiere en el mayor número de casos analizados de SARS-CoV-2 y la muestra de los casos de MERS, los trabajos de Jeong et. al. [35] y Park et. al. [37] no han sido analizados por separado, por tratarse de la misma gestante.

A pesar de las limitaciones, en estos momentos de emergencia sanitaria por un nuevo agente infeccioso, este tipo de estudios (revisión exploratoria) [58] pueden representar la mejor evidencia disponible para informar de la práctica clínica y sus resultados orientar futuras investigaciones.

Con las limitaciones propias de un acontecimiento que está en constante evolución, puede afirmarse que las gestantes infectadas por alguno de los tres coronavirus producen una neumonía con sintomatología muy similar, resultando más leve en el SARS-CoV-2. Las complicaciones obstétricas son frecuentes y atribuibles a que la infección se produce cuando la gestación aún no ha llegado a término. Aun así, los resultados neonatales son favorables en su mayoría, destacando que no se encuentra evidencia de transmisión vertical al final del embarazo. Será necesario seguir documentando casos de gestantes infectadas, para aumentar el conocimiento y minimizar los efectos indeseables en este grupo de población vulnerable.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflictos de intereses.

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The situation of infection in the elderly in Spain: a multidisciplinary opinion document

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ABSTRACT

Infection in the elderly is a huge issue whose treatment usually has partial and specific approaches. It is, moreover, one of the areas where intervention can have the most success in improving the quality of life of older patients. In an attempt to give the widest possible focus to this issue, the Health Sciences Foundation has convened experts from different areas to produce this position paper on Infection in the Elderly, so as to compare the opinions of expert doctors and nurses, pharmacists, journalists, representatives of elderly associations and concluding with the ethical aspects raised by the issue. The format is that of discussion of a series of pre-formulated questions that were discussed by all those present. We begin by discussing the concept of the elderly, the reasons for their predisposition to infection, the most frequent infections and their causes, and the workload and economic burden they place on society. We also considered whether we had the data to estimate the proportion of these infections that could be reduced by specific programmes, including vaccination programmes. In this context, the limited presence of this issue in the media, the position of scientific societies and patient associations on the issue and the ethical aspects raised by all this were discussed.

Key-words: Infection in the elderly, elderly, aged, nursing homes, Urinay tract infection, pneumonia, burden of infection, vaccines, ethics.

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Situación de la infección en el anciano: un documento multidisciplinar de opinión

RESUMEN

La infección en los ancianos es un tema enorme que suele recibir enfoques muy específicos pero parciales. Además, es una de las áreas en las que la intervención podría tener más éxito para mejorar la calidad de vida de los pacientes mayores. En un intento de dar el mayor enfoque posible a este tema, la Fundación de Ciencias de la Salud ha convocado a expertos de diferentes áreas para elaborar este documento de opinión sobre la situación de la infección en los ancianos, tratando de comparar las opiniones de médicos expertos, enfermeras, farmacéuticos, periodistas, representantes de asociaciones de ancianos y terminando con los aspectos éticos que plantea el problema. El

formato es el de la discusión de una serie de preguntas preformuladas que fueron discutidas entre todos los presentes. Empezamos discutiendo el concepto de "anciano", las razones de la predisposición a la infección, las infecciones más frecuentes y sus causas, y la carga laboral y económica que suponen para la sociedad. También preguntamos si teníamos datos para estimar la proporción de estas infecciones que podrían ser reducidas por programas específicos, incluyendo programas de vacunación. En este contexto, se discutió la baja presencia de este problema en los medios de comunicación, la posición de las asociaciones científicas y de pacientes sobre el problema y los aspectos éticos que todo esto plantea.

Palabras clave: Infección en la vejez, ancianos, asilos, infección del tracto urinario, neumonía, carga de la infección, vacunas, ética.

INTRODUCTION

The ageing of the population in more developed societies is an incontrovertible fact. In the face of the indisputable success in achieving a longer life for a large proportion of the population, questions arise as to the viability of social protection systems.

By 2030, over 25% of the population will be classed as elderly and their quality of life will depend, to a large extent, on avoiding preventable diseases such as Infectious Diseases.

It is a well-known fact that the elderly constitutes a risk group for distinct types of infectious diseases, whose diagnosis and treatment are hindered by several factors. Around this fundamental fact, however, we find a lack of answers to simple questions about the size of the problem, its epidemiology, the capacity of the social response to it and the need to plan useful preventive measures to minimise risk and reduce costs.

For this reason, the Health Sciences Foundation, which has Prevention as one of its main objectives, has organised a discussion and opinion meeting on the Infectious Diseases situation in the elderly in Spain, aiming to answer a series of questions accepted by all the participants.

This document attempts to reflect the main issues discussed, the documentation provided and the conclusions reached by the group. The document does not intend to provide any recommendations or therapeutic guidelines, but simply to contribute data to the debate on Infection in the elderly population, particularly in Spain, and to point out some possible solutions to it.

This meeting was held months before the COVID-19 epidemic that has certified many of our concerns.

The final document has been approved by all participants and represents their joint opinion.

MATERIAL AND METHODS

The questions were chosen by the coordinators and accepted by all the speakers.

The document edited in a first draft was sent to all co-authors for their corrections and amendments. The final document has been reviewed by all the authors.

We will now review the questions posed, the arguments made and the conclusion reached for each one.

What do we mean when we talk about the elderly? How many are there in Spain? How many will there be in the near future?

Presentation:

The WHO publishes reports on ageing and health, or old age and its consequences, on a regular basis, at least since the 60's. Cited here are a few more. We reproduce a paragraph in full [1, 2] "Today, for the first time in history, most people can aspire to live beyond the age of 60. In low and middle-income countries, this is largely due to the significant reduction in mortality in the early stages of life, especially during childbirth and infancy, and in mortality from infectious diseases. In high-income countries, the sustained increase in life expectancy today is mainly due to the decline in mortality among older people". The report focuses on a redefinition of healthy ageing based on the notion of functional capacity: the combination of the individual's intrinsic capacity, relevant environmental characteristics and the interactions between the individual and these characteristics.

In Spain, according to data from the National Institute of Statistics[3], 18.7% of the population is currently over 65. That's about 8.7 million people. If we focus on those over 85, they currently account for 6% of the total population (about 2.8 million). Forecasts for 2031 put the number of people over 65 years old at 12 million (26.2% of the population) and those over 85 at 3.9 million (8.5% of the population). Thus, between 1960 and 2031, the number of people over 65 will have increased by a factor of 5 (from 2.5 to 12 million), and the percentage will have increased by a factor of 3 (from 8.2 to 26.2 %), while the number of people over 80 will have increased by a factor of 10 (from 370,000 to 3.9 million) and the percentage will have increased by a factor of 6 (from 1.2 to 8.5 per %).

Once the figures have been established, it is necessary to clarify that, according to the Dictionary of the Royal Spanish Academy of Language (DRAEL), "old" is "that person of age, commonly one who has turned 70". However, age is a purely theoretical value to distinguish a person as "old" or "elderly". Taking the age of 65 as the threshold for the onset of old age dates back to the late 19th century, when less than 10% of those born reached that age. Today, more than 90% of people reach the age of 65, so this age limit is shifting towards older ages.

Nowadays the concept of "old" is more related to "function" than to age. Thus, the DRAEL defines health as "that state in which the organic being normally exercises all its functions". Therefore, one of the most relevant aspects in considering a person "old" is that they need help to carry out the activities of daily life (bathing, dressing, feeding, moving, etc.). We can find totally independent people in their 80's and others with a high degree of dependency in their 60's.

Therefore, the "elderly" is an enormously heterogeneous group in aspects such as the prevalence of chronic diseases (ischaemic heart disease, hypertension, diabetes, COPD, etc), the need for consumption of drugs and the existence or non-existence of physical, mental (dementia, depression) and social (loneliness, isolation, poverty) problems.

Conclusion:

- **The definition of elderly is artificial and refers to any person over a certain age (which can be set at 65, 70 or older) who has serious limitations in the exercise of their physical, mental or social functions.**
- **In our society, currently, almost 20% of the population would meet a definition of elderly based exclusively on the criterion of age, but it is estimated that, with this criterion, the percentage in Spain will be greater than 25% by the year 2031.**

What are the reasons for the elderly person's predisposition to infection?

Presentation:

The changes that take place throughout the ageing process favour the existence of infections. The simplest explanation is that with age the numerator of the aggression/defence equation increases (greater arrival of microorganisms that are also more virulent) and the denominator decreases (less defence capacity on the part of the organism). We can therefore divide the causes of the elderly person's predisposition to infection into those that depend on the microorganisms and those that depend on the host's defence mechanisms.

There is no evidence that the microbiota of the elderly is quantitatively different from that of younger populations, nor necessarily more aggressive. However, it is an incontestable fact that previous infections, antimicrobial treatments, the greater ease of microorganism acquisition and living in proximity to other elderly people, can predispose the elderly to colonization and subsequent infection by multi-resistant microorganisms, with the presence of "superinfections", with a worse response to antimicrobials and increased resistance to them.

In terms of host defence mechanisms, there are many factors that make the elderly more labile. Mechanical barriers, for example, are the first element of defence, but they deteriorate progressively throughout the ageing process, facilitating the entry of microorganisms. The skin and mucous membranes experience physiological losses and often also those resulting from local or systemic diseases. The most important changes are: thinning, with loss of epithelial and mucosal cells, worse hydration and vascularization, loss of elasticity, decrease in mucous gland secretions of antimicrobial peptides, worse healing, loss of cellular macrophages in the skin (Langerhans cells) and immobility with increased local pressure in certain areas.

In the respiratory system, there is a decrease in the number of cilia and a slowing down of their activity, a reduction of alveolar macrophages, a decrease of the cough reflex and greater difficulty in eliminating secretions. In the digestive tract it is common to find diverticuli in the mucosa that act as microorganism reservoirs. Also, losses in secretory function with a tendency to gastric achlorhydria, but, above all, motor function which at oesophageal level, can favour aspiration phenomena. In the urogenital system there are usually alterations arising from pregnancy, childbirth, previous surgeries and local manipulations that make the free flow of urine difficult. In this vein, it is worth adding the frequency of subjecting the elderly to diagnostic or therapeutic examinations that may favour infections.

In addition to the deterioration of mechanical barriers, there are losses in non-specific defence mechanisms. These include limitation to increase blood flow and vascular permeability at the infection entry points. The ability to mobilise polymorphonuclear leukocytes rapidly and the agility of phagocyte function is also impaired. Chemotactic capacity decreases from the age of 70, as does the capacity for the intracellular destruction of microorganisms. Ageing is associated with a chronic, progressive, nonspecific, low-level pro-inflammatory state, for which the English literature has coined the term "inflammageing", which favours an environment conducive to infection and further limits the possibilities of an effective response to it.

The deterioration of adaptive immunity ("immunosenescence") associated with the ageing process has been known for years and affects both innate and acquired immunity [4-6]. Immunosenescence includes qualitative losses in T-lymphocyte subpopulations with decreased activity of CD-4 helpers, cytotoxic CD-8s and a limitation in generating T-cell growth factor. Ageing determines a tendency to invert the CD4/CD8 T-cell ratio. The number of dendritic cells decreases with age and the response of NK cells to stimulating cytokines is limited. It also increases the activity of CD-8 suppressors. B-lymphocytes are limited in their ability to produce antibodies and to respond to external antigens. Furthermore, there is an increase in the production of autoantibodies and circulating immune complexes.

A third group of factors that add to the microorganisms and the individual are environmental and social factors, such as hygiene neglect, poverty, isolation and a sedentary lifestyle. The fact of living in nursing homes and the increase in hospitalisations favours an insufficiently quantified environmental exposure [7].

Conclusion:

There are multiple factors that explain the higher incidence of infections in the elderly. The clearest are those that have to do with alterations of the defensive barrier mechanisms. Immunosenescence is a complex concept involving various alterations in the immunity of the elderly.

What are the main clinical syndromes of infection in the elderly?

Presentation:

The frequency and even the aetiology of infections af-

fecting the elderly vary depending on the clinical environment (home, nursing home, hospital) and the functional status of the patient. In older, independent and healthy people, respiratory conditions caused by viruses or bacteria prevalent in the community, Urinary Tract Infections (UTIs), whether catheter-related or not, and intra-abdominal infections (cholecystitis, diverticulitis) are common. In contrast, in institutionalised elderly people, UTIs related to the bladder catheter, aspiration pneumonia, skin and soft tissue infections and those of the Gastro-Intestinal Tract (GIT) predominate. In hospitalised elderly people we have to consider nosocomial pneumonia, intravascular catheter associated infections and *C. difficile* infections as the most prevalent [8-14].

There is limited data analysing the comparative overall frequency of the different syndromes. In elderly people living in nursing homes, UTIs (at least 30-40% of healthcare-associated infections), respiratory infections, skin and soft tissue infections and those of the GIT predominate [15]. In a recent Spanish multicentre descriptive study, conducted in 49 Emergency Departments, 11,399 patients were included, of whom 4,255 (37.3%) were at least 65 years old. Compared to younger adults, older patients (mean 78.8 years) had respiratory, urinary and intra-abdominal infections more often, while there was no difference in the frequency of other syndromes [16]. These data are confirmed in Chinese studies that analyse elderly patients attending Emergency Departments and also show a significantly higher incidence of respiratory and urinary infections [17, 18].

In the case of UTIs, the relative prevalence is influenced by the gender of the patient. Thus, for long-term care facility (LTCF) residents and in hospitalised elderly people, UTI is the number one cause of infection and is the second most common in older women living in the community [19]. The incidence in men ranges from 0.05/person year (1/20) in men aged 65-74 and reaches 0.08 (1/12) in men over 85. In women, the incidence of UTI increases with menopause (0.07 per person/year: 1/14), increasing to 0.13 per person-year (1/7.5) after age 85 [20]. In indwelling catheter-wearing patients, the incidence of UTIs is 3.2 cases per 1,000 catheter days, compared to only 0.57 per 1,000 days for all residents (x18). Urinary tract bacteraemia was 3-39 times more common in patients with permanent urinary catheterization [20] and UTI is also the most frequent cause of community-acquired bacteraemia in the elderly (40-57%).

With respect to respiratory infections, the annual incidence of Community Acquired Pneumonia (CAP) ranges from 8-18.2 episodes per 1,000 people over 65 years of age and represents 30-40% of hospitalisations in this age group [21]. In Japan, 96% of deaths from pneumonia occur in patients over 65 years of age. The risk of CAP is 4 times higher in those over 65 compared to those under 45 and 10.8 times higher in those over 85 compared to adults aged 50-64. Viral infections are also common in this age range, as we will see later.

Conclusion:

The most prevalent infections in the elderly depend on their situation. In independent elderly people, the most common infections are respiratory conditions caused by viruses or bacteria prevalent in the community, urinary tract infections and intra-abdominal infections. In contrast, in institutionalised elderly people, bladder catheter-related UTIs, aspiration pneumonias, skin and soft tissue infections, and infections of the gastrointestinal tract predominate.

Which microorganisms are most common? How does the problem of multi-resistance impact on the elderly?

Presentation:

It is important to remember that infections in the elderly may be caused by a greater variety of microorganisms than in the younger population, so it is essential to obtain samples for culture before administering empirical antimicrobial treatment [8]. Thus, for example, while the vast majority of UTIs in young patients are caused by *E. coli*, in the elderly their relative importance is less. In the case of pneumonia, there is a higher incidence of Gram-negative bacilli (GNB) and as far as meningitis is concerned, they are rarely of viral aetiology, while we must consider GNB and *Listeria monocytogenes*.

In a Spanish study, including 333 elderly patients (mean age 81.6 years), with UTIs, the most frequently isolated microorganisms were *E. coli*, (67%), *Enterococcus faecalis* (15%), *Klebsiella pneumoniae* (10%) and *Pseudomonas aeruginosa* (9%). In up to 8% of cases, more than one microorganism was isolated in the urine. The frequency of bacteraemia was higher with *E. coli* and lower with *E. faecalis* and *P. aeruginosa* and bacteraemia was not associated with a worse prognosis [22]. The frequency of multi-resistance increases with age and comorbidity. In this Spanish study, the proportion of Extended-Spectrum Beta-Lactamase (ESBL) producing *E. coli* and *K. pneumoniae* isolates was 20.1% and 36.3%, respectively. In the previously mentioned study of patients attending the Emergency Department, the elderly accumulated more risk factors for multi-resistance ($p < 0.001$) and suffered from septic syndrome more frequently ($p < 0.001$) [16].

There are few studies that analyse the overall aetiology of respiratory infections in older patients, and most work focuses on describing specific populations or groups of pathogens. The aetiological affiliation rate of respiratory infections in the elderly is very low (<30%), and this is due, among other things, to the difficulty many patients have in producing sputum and to the high frequency of empirical treatment [21]. If we analyse the aetiology of CAP, the most frequent pathogen is *S. pneumoniae* (20-80%), followed by *H. influenzae* (3-39%), respiratory viruses (3-30%), *Legionella spp.*(1-17%) and GNB (3-14%). It is also necessary to remember the importance of viral pathogens in this population, since the prescription rate of unnecessary antimicrobials is very high in them (46% of the elderly with viral symptoms) [23]. In a study conducted in China, in 6 sentinel hospitals, it was observed that 31.64% of elderly patients with respiratory infection had a viral aetiology (41.8% among extra-hospital infections and 25.7% among

nosocomial infections) [24]. The most common cause was influenza (14% of all patients studied). RSV is also a significant pathogen in this population [25, 26].

The most important cause of GIT infection in the elderly is *Clostridioides difficile*. *C. difficile* (C-diff) infection is currently the most prevalent nosocomial infection, affecting in more than 70% of the episodes patients over 65 years of age [27]. Moreover, it is in this population that C-diff causes the highest morbidity and mortality, with an increase in C-diff-related mortality from 5.7 to 23.7 deaths per million population per year from 1999 to 2004 [28] in patients with an average age of 84 years having been described in the USA. It is interesting to note the safety of using the same therapeutic options in elderly patients, including faecal microbiota transplantation [29, 30].

Conclusion:

The microorganisms causing infection in the elderly are qualitatively the same as in the population of other age groups, although there are quantitative variations. Depending on the type of infection there is a greater predominance of infection by Gram-negative bacilli. Underlying diseases, and the aforementioned treatments increase the risk of infection by multi-resistant bacteria.

Where do they get these infections? What proportion are acquired in nursing homes? At home? In hospital? -

Presentation:

In addition to the hospital and home environment, the elderly can acquire infections elsewhere, and in particular in other care units. This is the reason why, almost 20 years ago (2002), the term "Health care-associated infection" began to be used, which is not only limited to hospitalized patients, but also extends the concept to patients in contact with the health system (home care of patients with high comorbidity and complexity; Day Care Centres; Major Outpatient Surgery Units; Outpatient Dialysis Centres; Community Health Centres for chronic or convalescent patients).

To a great extent, it is in Nursing Homes where patients with more comorbidities, polypharmacy consumption, a high degree of dependency and a high prevalence of invasive devices (bladder catheter, nasogastric tube, percutaneous gastrostomy) will be treated. In addition, the environment can facilitate the transmission of microorganisms between residents and healthcare personnel, as well as between residents. For all these reasons and the excessive or inappropriate use of broad-spectrum antibiotics, either empirically or prophylactically, Multi-Drug-Resistant (MDR) infections can be generated. Implementation of effective preventive measures in this population is very difficult to organise.

In the United States of America, it is estimated that approximately 1.5 million people live in nursing homes and suffer between 1.6 and 3 million episodes of infection annually [31]. The prevalence of infections in these residences is estimated at 10% of the residents [32] and the incidence of new infections is estimated at between 4 and 5 episodes per 1,000 days of stay in the residence [33, 34]. The figures rise to 11 for those with some kind of prosthetic material [35].

We have several European HALT studies (Healthcare-associated infections and antimicrobial use in long term care facilities), with participation from 24 countries, including Spain, with a prevalence of infection of 4.7% and 5% at two different times [36-38].

A French multi-centre study, conducted in 578 nursing homes with 445,000 beds, shows an infection prevalence of 11.23% [39].

The first data on infection in nursing homes in Spain come from the EPINGER study, conducted in community health centres in Catalonia, which reported a prevalence of 6.5%, although it should be pointed out that in Catalonia the concept of the community health centre would include medium-long term patients, while in the rest of the Spanish autonomous communities this concept would be limited to nursing homes [40]. In another study, conducted by San Sebastian's Fundación Matía, an infection prevalence between 6.44% and 4.80% was reported [41].

Data derived from the VINCat study in Catalonia show a prevalence of healthcare-associated infection in long-term care centres of 10.2%, with a great diversity, depending on the type of care unit (subacute 22.3%, palliative 18.7%, convalescent 11.7%, long stay 8.1%)[42].

Home is the most recommendable place for the healthy elderly to live, and even for the elderly patient, with healthcare falling to Primary Care professionals, although sometimes with the collaboration of some hospital resources.

The Ministry of Health, Social Services and Equality has for the first time published the results of the Primary Care Clinical Database (BDCAP), a tool that allows for a more precise and systematized knowledge of the main health problems in Spain dealt with by the doctors on the healthcare frontline. Thanks to this register, a detailed picture of the health problems of the Spanish population is available from Primary Care [43]. In this database, infections appear among those over 64 years old with an elevated frequency of 634.1 cases a year per 1,000 people (569.9‰ men and 682.7‰ women). The most frequent correspond to the respiratory system (317 cases/1000 persons/year), followed by urinary tract infections with (84.4 cases/1000 persons/year) and clear female predominance.

Finally, nosocomial infections are those that occur in hospitalized patients and are present more than 48 hours after admission. They are acquired by transmission from the environment, from other patients or from healthcare personnel. They are considered to be the most preventable cause of serious adverse events in hospitalised patients [44]. In general, these infections are related to invasive diagnostic or therapeutic procedures (urethral catheterization, surgical procedure, vascular catheter, invasive mechanical ventilation), all of which have in common the disruption of the host's own defences by a device or an incision, allowing the invasion of

microorganisms that are part of the patient's usual microbiota (endogenous microbiota), or selected by the selective antibiotic pressure (secondary endogenous microbiota), or by one found in the hospital environment (exogenous microbiota).

To understand the main epidemiological data on hospital infections, the EPINE study (Estudio de Prevalencia de las Infecciones Nosocomiales en España (Study on the Prevalence of Nosocomial Infections in Spain)) was developed. This is a multi-centre system for monitoring nosocomial infections, based on the production of an annual prevalence study, which has been conducted since 1990 in a large group of hospitals in Spain and was promoted by the Spanish Society of Preventive Medicine, Public Health and Hygiene. Its methodology guarantees a homogeneous and systematic collection of information, which allows us to understand the prevalence of Healthcare-Associated Infections (HAIs) at a national level, by Autonomous Regions and hospitals. Since 2012, every 5 years the EPINE study has been produced jointly with the European study (in 2012 and 2017) under the coordination of the ECDC [45].

Based on the latest data published, in November 2017 (313 hospitals and 61,673 patients), a prevalence of nosocomial infection in patients over 65 years of age of 6.07% (infections acquired during the current admission), 7.45% (infection acquired during the current or previous admission) and 8.76% (the total, including the centre's own or imported) has been reported. It should also be noted that this register shows that in 22% of patients over 65 years of age admitted for an infection, the infection had been acquired in the community (patient's home).

Conclusion:

The home, nursing homes and community health centres, healthcare centres other than hospitals and the hospital itself are often the places where the elderly acquire infections. The studies reviewed allow us to estimate a prevalence of infection of between 4 and 10% in nursing homes in Spain, depending on their complexity, and between 6 and 9% in hospitalised elderly people. In Primary Care and in the Residential environment, there is no homogeneous epidemiological record of this problem.

What proportion of severe infections in the elderly require hospitalisation? By whom are they treated?

Presentation:

In the United States of America, patients over 65 years of age account for almost 40% of total adult admissions and the cost of these hospitalisations represents nearly 50% of the total cost for hospitalisation, although those over 65 years of age account for less than 20% of the total adult population [46, 47]. Those over 65 years of age are admitted to hospital three times more often than those between 45 and 65 years of age, and those aged 85 or over account for 9.2% of all hospital discharges, although they represent only 1.8% of the population as a whole.

Infectious diseases are the second cause of such admissions (16.2%), only surpassed by cardiovascular diseases (28.6%). Pneumonia and sepsis are the most common infections causing admission in this population [48]. The elderly population also has longer hospital stays (5.5 days for those over ≥65) than those between 45 and 64 (5.0 days) and those between 15 and 45 (3.7 days) [49].

The elderly are treated by virtually every unit in a hospital but it is worth mentioning that those over 65 years of age represent 40% of those admitted to Intensive Care Units [50]. The other group of interest is that of specialised geriatric units, not available in all hospitals, which have been shown to improve the functional status of patients and reduce the number of discharges to long-term care homes [51].

In a study by Saliba et al., conducted in Israel [52], out of a total of 81,077 hospital admissions in the elderly between 2001 and 2010, the proportion of admissions due to infectious diseases rose from 16.9% in 2001 to 19.3% in 2010. Globally, the most frequent infections causing admission were: those of the Lower Respiratory Tract (LRT) (41.0%), followed by the UTIs (21.4%), Upper Respiratory Tract (10.2%) and hepatobiliary (9.8%).

In Spain we do not have precise answers to the questions asked. The proportion of serious infections in the elderly requiring hospitalisation depends on several factors: type of infection, severity of infection and other factors such as the degree of frailty of the elderly, their place of residence and their ability to receive care at home. The environment and the resources available also influence the hospitalisation decision. However, in our environment, most serious infections in the elderly will require hospitalisation for at least a few hours.

In Spain, serious infections in the elderly can be treated by different professionals depending on the type and severity of the infection, and the environment in which it occurs. A high percentage are treated by "generalists" hospital specialists, or geriatricians. Where infectious disease specialists are available they are of course involved in their management, either in beds in their own departments or as consultants. They can also be treated by specialists of the affected organ such as orthopaedic surgeons in the case of infections of prosthetic material, or vascular surgeons in the case of infections of vascular ulcers. And if, in the end, hospital admission is not decided, the patient is cared for by the primary care team.

As an example, we have collated the urinary tract infections treated at the Hospital General Universitario Gregorio Marañón between 2015 and 2018. When UTI is the main diagnosis that motivates admission (about 700 cases a year) about 90% of cases are cared in the Medical Departments. When it comes to secondary diagnosis (about 2,000 cases per year), the Internal Medicine and Geriatrics Departments take care of about 75% of the cases.

Preventive programmes, such as flu vaccination programmes, reduce the need for hospitalisation for respiratory infections by nearly 30%, both inside and outside Spain [53-55].

Conclusion:

- **It has not been possible for us to answer precisely the question about hospitalisation figures for infection in the elderly in Spain. Data from outside Spain allow us to estimate that infection is the second cause of admission in patients over 65 years old and that pneumonia and other causes of bacterial sepsis are the main reasons, particularly sepsis of urinary origin.**
- **Only a minority of the elderly admitted for infection are treated in specific geriatric units and most are admitted to general medical departments.**

What is the workload represented by elderly patients in Hospital Emergency Departments?

Presentation:

The number of visits to Hospital Emergency Departments (ED) has been increasing progressively for decades. This increase is greater in the elderly, whose population accounts for 15-25% of all visits to the hospital [56]. The incidence and impact of infection in the ED is estimated quite reliably. In Spain it is 14.3%, 21% in the USA and around 30-40% in countries such as Nicaragua and Mexico [57].

The elderly are characterised by a higher probability of atypical presentation of diseases, of suffering from multiple diseases and of consuming many drugs. With regard to emergency care, this implies a more complex clinical evaluation, which translates into a greater request for additional tests and consultations with other specialists, longer stays in the ED (extended periods under observation and in SSUs), as well as a greater probability of admission, discharge with undetected or untreated problems and return visits to the ED [58]. All this entails a high risk of adverse episodes [58] and a significant impact on healthcare pressure, resulting in a negative effect on ED saturation [59, 60].

Likewise, the prevalence of the frail elderly in the community varies according to the diagnostic criteria. In a study conducted on elderly people admitted to the observation room of an ED in a Spanish tertiary hospital, it was verified that only one of them did not have any fragility criteria and on admission almost half of them suffered significant dependence [61]. The detection of the high-risk or fragile patient is fundamental for these Departments, for decision-making and in particular for discharge directly from the Emergency Department.

We could highlight that in the recent work of the INFUR-SEMES group, in a study conducted in 49 Spanish EDs, 31.7% of infections occurred in patients over 70 years old. Of these, 36% were urinary and 51.2% were lower respiratory. In conclusion, when compared with a similar study, conducted twelve years earlier, an increase in the prevalence of infections is observed, with an older patient profile, comorbidity, risk factors for MDR microorganisms and septic syndrome [62]. The latter almost always presents itself as an acute confusional syndrome, which implies a complex differential diagnosis.

Moreover, in our opinion, in these departments, emergency assessment should not be focused only on the isolated episode for which the patient consults, but the particulars of the elderly person, their functional, mental and social situation should be taken into account. This is a huge workload for the ED.

Finally, we should bear in mind that the training of ED physicians on these issues is limited [63] as a direct consequence of the self-training of current professionals, which is not always complete, and the lack of a regulated medical specialty in the ED.

Conclusion:

In Spain, between 15 and 25% of Emergency Department visits occur in the elderly. Elderly people come in 14.5% of the time for infections and one third of the infections seen in the Emergency Departments occur in the elderly. The population over 65 years of age who attend the Emergency Department often have multiple pathologies and clinical manifestations of infection that may be atypical.

How much of infection in the elderly is resolved in primary care? How much of the vaccination is done at the primary care clinic?

Presentation:

In the Spanish National Health Service, emergency activity accounts for a total of 47.2 million consultations per year, of which 26.5 million are attended to in primary care (PC) (outpatient or home), with an average attendance of 0.6 people/year [64]

One-third of emergency consultations in PC are related to infections [65]. In the older patient, infections are more frequent and serious, associated with greater morbidity and mortality [65-67].

Among the elderly, the rate of infection reaches 634.1 cases per thousand people per year. The most frequent correspond to the respiratory system (317 cases per thousand), particularly those of the upper respiratory tract, followed by acute bronchitis and bronchiolitis and pneumonia [65, 67-69]. In second place are UTIs, mainly affecting women (114.8 cases per thousand compared to 44.2 per thousand for men) [67]. These are followed by skin and soft tissue infections [69]. Most of these cases are dealt with in Primary Care and only those more serious situations and of uncertain diagnosis are referred.

In 75%-80% of cases, CAP is diagnosed in PC [65, 70] and *Streptococcus pneumoniae* is the cause of two-thirds of these cases. Invasive forms of pneumococcal disease (IPD) are less common, occur in patients with certain risk factors and have high mortality rates [70].

The vast majority of vaccination programmes in Spain are carried out in primary care, but the vaccination schedule for older people is neither complete nor promoted as it should be.

Conclusion:

The infection rate in the elderly exceeds 500 episodes per 1,000 sick people per year. Primary care handles the vast majority of these episodes and refers only the most serious cases.

Primary care is responsible for the vaccination programme for elderly people who attend to request it. The vaccination schedule for older people is neither comprehensive nor proactively promoted.

What does infection in the elderly entail in terms of days of hospitalisation, financial expenditure and death?

Presentation:

To approximate data/figures for variables such as "days of hospitalisation, economic expenditure and death" in a field as broad as "infection in the elderly" is enormously complicated. It must be taken into account that the infectious pathology is very varied and that it can affect people with different locations (community, community health centre or the hospital itself) and conditions. For example, with reference to nursing homes, Lim et al. estimate 4 episodes of infection for every 1,000 cumulative days spent in the home in a small group in Australia [71], while much more extensive North American data report 12% of nursing home residents having an infection at the time of the study [32]. This leads to estimates of between 1.64 and 3.83 million episodes of infection per year [31] with annual costs of no less than US$ 1 billion, prior to 2000.

In a study conducted in Brazil, the cost of an infection in the elderly requiring admission is estimated at 28,714 Brazilian reals (€ 6,305). Patients are admitted for a median of 24 days compared to a median of 9 days for elderly people admitted for non-infectious causes [72]. Of that cost, only 5% is attributable to the purchase of antibiotics.

In a multinational clinical trial on skin and soft tissue infections comparing linezolid with vancomycin, involving 1,200 individuals, 22.7% of the patients were over 65 years of age. The length of hospital stay in elderly patients was 6.8 days in patients receiving linezolid versus 10.3 days in those receiving vancomycin. The average cost of hospitalisation was $4,510 in 2002 compared to $6,478 for those treated with vancomycin.

There is a greater volume of data for community-acquired pneumonia (CAP) [73-76]. The cost of CAP varies greatly depending on where the treatment takes place. A Spanish study [77] found a cost of only € 196 in the case of an outpatient, compared to €1,153 for pneumonia requiring hospitalisation. The costs were higher for subjects ≥65 years.

Mortality increases significantly in the older patient (25%) with respect to the general population (10%). It is worth noting a publication in Spain with a sample of 2,049 subjects, where mortality due to pneumonia is more clearly related to the age group than to the aetiological agent [78].

Conclusion:

We have not found precise data calculating overall days of hospitalisation, mortality rates and the cost of infection in the elderly. Data are only obtained for specific types of infections and in certain situations (nursing homes), but there is no doubt that the figures are very high.

To what extent do you think that infection in the elderly is preventable? What proportion could be avoided with proper vaccination?

Presentation:

In an article published by Umscheid et al. [79], not specifically addressing to the elderly field, it is estimated that 65%-70% of cases of catheter-related bacteraemia or catheter-associated urinary tract infection and 55% of pneumonias from mechanical ventilation or skin and soft tissue infections could be prevented in the hospital environment using the methodology currently available.

An infection control programme for older patients includes methods for surveillance and recording of infections, recording and management of multi-resistant microorganisms, outbreak contingency plans, isolation policy and standard precautions, hand hygiene programmes, ongoing education of employees, resident health plans, audits and plans for reporting incidents to health authorities [80]. This set of resources is not available to most of the world's elderly.

A group of experts, gathered in a Delphi study on infection prevention measures in patients admitted to institutions for the elderly, agreed on 302 recommendations [81] but unfortunately the level of evidence on the effectiveness of each of them is very limited.

Data on the reduction of different infections by different measures are extremely scattered and limited. Some examples are the reduction by 53% of periprosthetic infections with antibiotic prophylaxis [82], a 60% reduction in episodes of influenza with the physical separation of the young and the elderly, [83] or a 48% reduction in episodes of pneumococcal pneumonia with the 23-valent vaccine [84].

Makris et al. [85] conducted a study to test the effect of an infection control programme in 8 institutions for the elderly in the United States of America. They divided the centres into test centres (4) and control centres (4) and studied the incidence of infections in both groups before and after the programme was introduced. In the year prior to the intervention, test sites experienced 743 infections (incidence density rate, 6.33) and control sites 614 infections (incidence density rate, 3.39). In the intervention year, the test centres reported 621 infections, a decrease of 122 infections (incidence density rate, 4.15), while in the control centres, the number of infections increased slightly to 626 (incidence density rate, 3.15). The greatest reduction in infections at the testing centres was in upper respiratory tract infections ($P = 0.06$). The intervention programme consisted mainly of implementing environmental cleanliness, hand washing programmes and educational talks.

Therefore, and speculatively, we dare to estimate that a

high quality infection control programme in nursing homes could reduce infection rates by up to 50%. But even if we estimate much lower figures, the impact on morbidity, mortality and the economy of such programmes would be enormous and would certainly outweigh their implementation costs.

With reference to the second part of the question, the possibility of reducing the problem with vaccines, the data are again scattered and studied for different vaccines individually. In addition, information on the elderly must often be inferred from data on the general population. We refer readers to a recent review on the subject[86].

Below is some data on the impact of vaccines of particular interest to the older population. Gross et al. [87] in a meta-analysis of 20 cohort studies estimate the effectiveness of influenza vaccination at 56% in preventing respiratory infections, 53% in preventing pneumonia, 50% in preventing hospitalisations and 68% in preventing deaths.

In the case of Zoster, the vaccine's efficacy is estimated at more than 90% with minimal adverse effects [88]

Different pneumococcal vaccines have different impacts on the incidence of Invasive pneumococcal disease (IPD) infection. A systematic review shows reductions in IPD incidence ranging from 61% as a combined effect of the use of PCV7, PCV10 and PCV13 in those over 65 in Canada [89] to a 21% reduction as an effect of the use of PCV7 and PCV13 in Israel [90].

With these data it is possible to imagine the added protection that adequate vaccine coverage would provide. An estimated 50,000 Americans die each year from vaccine-preventable diseases, and 99% of those who die are adults [86].

Increased provision of medical care in large care homes (e.g. those with more than 200-250 beds) could reduce the referral of many elderly residents to hospital emergency services. This provision of medical care would not necessarily be very complex and would cover both simple diagnostic material and the possibility of establishing and carrying out pharmacological therapeutic courses at the centre itself, the prescription of which in most cases still requires medical staff from outside the centre. It would be a way to reduce costs, lessen the burden on the elderly and reduce the overload on hospital emergency departments.

Conclusion:

It is impossible to give a precise answer to the questions asked, but it seems reasonable to assume that with appropriate prevention programmes, acquired infections in institutionalised elderly people could be reduced by up to 50%. Strict adherence to a vaccination programme for the elderly would have an enormous impact on reducing suffering, death and economic waste.

What data exist on the effectiveness of educational measures on the incidence of infection in the elderly?

Presentation:

Clearly no one disputes the usefulness of ongoing education in many aspects of life and particularly in the reduction of nosocomial infections. That said, the literature review on the impact of educational programmes on nosocomial infection is irregular, fragmented and often difficult to assess. Published studies generally include education as part of intervention programmes in which other measures are included, making it difficult to assess the role of education in isolation. It is also common to talk about the success or failure of an educational programme without detailing what the programme is, what content it has, how it has been implemented and how many people have accessed it.

To complicate matters, in the case of the elderly, we have at least three different areas: home, nursing homes and institutions for the elderly and hospitals. In the first, the educational scope is very general and imprecise and is based on the public health and vaccination campaigns that are usually received not only by the elderly population but by the population in general. In the hospital field, we must assume that the literature produced on the impact of educational measures in the different syndromic entities generally includes the elderly population, but does not specifically differentiate it. Most of the limited existing information, which we can consider specific to older people, is that generated in nursing homes and institutions that implement these programmes.

A study conducted in the USA on 2,514 randomly selected nursing homes [91] asked the homes for information on 34 points related to infection control programmes. Most of those responsible for control programmes, when they responded, claimed to have not only that responsibility but others as well (54%) and also to have no specific training in infection prevention (61%). There was great variability in practices carried out in each residence and 36% acknowledged having received an official citation for deficiencies in such control. Those residences cited for deficiencies had a statistically lower proportion of staff trained in infection control. This is therefore an area with clear opportunities for improvement.

In a systematic review on non-pharmacological infection prevention in long-term care facilities, only 24 papers were selected, the majority of which were randomised studies (67%) and the most common reason was prevention of pneumonia (66%). 54% showed favourable results for the interventions, but the studies had many potential biases [92-99].

From these studies the 5 main quality markers in infection control in a nursing home were deduced, namely: percentage of long-term patients with pressure ulcers, urinary tract infection, bladder catheter, and vaccinated against influenza and pneumococcal infection.

Conclusion: Without casting doubt on the effectiveness of educational measures in the control of nosocomial infection in general, existing data on the elderly population is very limited, fragmented and generally concentrated in the world of nursing homes.

What are the great scientific societies doing and what can and should they do to reduce these problems?

Presentation:

Scientific societies are professional associations that bring together generally specific groups (doctors, nurses, technicians, etc.) that essentially seek to defend the professional interests of their members. Until now, it has not been common for groups of patients affected by different diseases under the thematic umbrella of each society to participate in them. In Spain their impact and political credit is variable.

Among the most important objectives of most of these societies are such issues as training programmes for professionals, aspects related to the health education of the population in their particular field of competence, research grants, the preparation - sometimes in collaboration with societies of another related specialty - of specific diagnostic and therapeutic protocols, publications and congresses focussed on these topics, and a wide range of other activities, including health policy recommendations to the corresponding administrations that have a direct bearing on the issues discussed here.

Membership of societies is also not uniform, and often it is the more "senior" components of the profession that are most highly represented in them.

Their role, in our opinion, is to continue to improve the teaching, care and research produced in the societies' chosen fields in favour of patients, exercising ever greater mediation between the demands of patients and healthcare administration [100]. All societies must go far beyond issuing guidelines and therapeutic recommendations [81, 101-109].

In our view, scientific societies dealing with diseases of the elderly should promote, in the field of infectious diseases, among others, the following topics:

1.- Encourage a proportionate share of its members to subspecialise in infectious diseases.

2.- Coordinate and direct multidisciplinary teams specifically dedicated to the infection in the elderly and its prevention.

3.- Participate more actively in specific programmes to reduce infections in the elderly, both at the nursing home level and at home and in hospital.

4.- Implement vaccination campaigns in the elderly, taking particular advantage of admission to long-stay centres or hospital as opportunities to vaccinate.

5.- To design and disseminate educational projects on infection prevention practices for the elderly in their different environments.

6.- Put pressure on health authorities to carry out a large national programme to reduce infection in older people.

7.- To include in the training programme of residents in Geriatrics, a rotation in Infectious Diseases and Microbiology as an essential part of the curriculum.

8.- Create scientific and professional alliances with societies specifically dedicated to infection. By way of an example, in Spain, this occurs among specialists in Microbiology and Infectious Diseases and Intensive Care specialists.

9.- Specifically promote research aimed at preventing infection in elderly patients.

10.- Introduce much more active involvement of patient associations in their management structures.

What we say about societies primarily dedicated to the elderly, can be similarly assumed and applied to societies primarily dedicated to Infectious Diseases and Microbiology.

Conclusion:

The role of the scientific societies dedicated to Geriatrics and Infectious Diseases is to promote alliances in the common field of infection, in aspects of care, teaching and research. They need to look less to the interests of their members and be more proactive in promoting the interests of the patients they serve and incorporate patient associations more into their structures.

What capacity do scientists have to influence politicians? Is Parliament sensitive to these problems?

Presentation:

Capacity, understood as the possibility or potential for influence, is qualified by two variables. Firstly, for offering free and truthful scientific information at the service of the community. And secondly, for facilitating the adoption of the best possible political decisions with consistency and realism.

The rapprochement between professionals in the scientific and political fields must be adjusted to the interest of citizens, who can act as the third pillar in a transparent relationship model and as guarantor of equity befitting a democratic system of government [110]. While scientific experts advise and inform, it is the responsibility of politicians to make decisions and promote efficient measures to the benefit of the population. A complementary characteristic inherent to the scientific task is to exercise a dissemination action of the activity itself, in understandable terms and through accessible and reliable systems [111]. The configuration of platforms within scientific societies and the growing number of independent agencies advising political power represent a reality that aims to bring the contributions of science closer to the systems of governance [112].

In our country, the main function of the Congress of Deputies is legislative, which entails the approval of laws. The Constitution recognises the legislative initiative of the Government, the Congress of Deputies, the Senate, the Assemblies of the Autonomous Communities and the People's Legislative Initiative on the proposal of no less than 500,000 citizens, subject to the provisions of an Organic Law.

These Bills are known in Spain as Law Projects when presented by the Government and Propositions in other cases. They are always submitted to the Congress of Deputies, except for the Propositions of the Senate which have to be considered

in the Senate, which will later submit them to Congress [113].

Non-legislative Bills, Motions and Proposals for Resolutions are acts of a similar nature that seek the adoption of a non-legislative resolution by Congress, by which Congress expresses its position on a given subject or issue, or addresses the Government urging it to act in a particular direction.

The Health and Social Services Commission of the Congress in the XII Legislature offers access on its website to the 226 initiatives processed since its constitution in September 2016 until its dissolution in March 2019, representing an average of 75 per year[114]. Of these, those referring to the field of infectious pathology as a whole do not exceed 3%. Of particular relevance in the field of infectious pathology have been those relating to the national plan for the elimination of hepatitis C and antibiotic resistance.

Governance designates the effectiveness, quality and good orientation of State intervention, which provides the State with a good part of its legitimacy in what is sometimes defined as a "new way of governing". Above all, it is used in economic, social and institutional operational terms [115]. An inherent aspect of the exercise of policy is the performance of "Authority", which is equally composed of Legitimacy (right to exercise), Personal Prestige (moral strength, leadership, honesty, knowledge, efficiency) and Power (ability to administer and lead). It is precisely in the "Personal Prestige" where their synergy with the Scientist (also covered by knowledge, honesty and leadership) should be the lever for the improvement of the Society they both serve.

Conclusion:

Initiatives on Proposals or Projects with reference to infection issues represent less than 3% of the total. Of particular relevance in recent years have been those relating to the national plan for the elimination of hepatitis C and antibiotic resistance.

What is the evolution and presence of "infection in geriatrics" in the scientific literature?

In order to respond to the scientific output on infection in geriatrics, we will proceed to describe the data sources, the search methodology and the findings, in a way deliberately guided by the recommendations of professionals in our workplace libraries.

ScienceDirect [116] is a digital platform that has provided subscription access to a large research database, hosting more than 14 million publications from 3,800 academic journals and 35,000 e-books since 1997. Clinical Key [117], owned by "Elsevier Clinical Solutions", has an intelligent search system, establishing the connection of medical terms with related content. It accesses a collection of resources of clinical guides, algorithms and patient files from Fisterra, the database of monographs of medicines marketed in Spain, the treaties of the Medical Surgical Encyclopaedia, and books and journals in Spanish from the cited publisher. Primo is the discovery/search tool used by the Castilla y León Healthcare Online Library [118] to offer a unique system to access scientific information allowing the recovery of different types of documents such as: journals, books, images, theses, and conference proceedings. Revista Española de Geriatría y Gerontología (The Spanish Journal of Geriatrics and Gerontology) is the publication channel of the Society of the same name, a publication founded in 1966 and the doyenne of the specialty in the Spanish language [119]. MEDES is an initiative of the Fundación Lilly and its database, open and free, contains bibliographical references published since 2001 in a selection of 98 Spanish journals covering 50 subjects in medicine, pharmacy and nursing, published in Spanish, with 100,000 articles [120]. Finally, PubMed is the widely implemented search engine, with free access to the MEDLINE database of citations and abstracts of biomedical research articles, offered by the United States National Library of Medicine and integrating 5,255 worldwide journals since 1966 [121].

The search was conducted with a double strategy: free text and controlled text using "Mesh". In the first strategy, a free text search was conducted in the "Science Direct" and "Clinical Key" databases with the term 'Infection in Geriatrics' resulting in 508 and 1,191 findings respectively. The Primo Search Engine (Castilla y León Online Library) returned a total of 190 results for the same term. Secondly, and also in free text, with the term 'Infection in the elderly', we proceeded to consult Revista Española de Geriatría (the Spanish Journal of Geriatrics), which generated 195 results and Medes (Medicine in Spanish) with 84 results.

The second strategy of controlled text was conducted in the PubMed database, returning the following findings: <Infection AND Geriatrics>: 997 results; <Infection AND aged> (people from 65 to 79 years old): 122.698 results and <Infection AND aged OR Aged, 80 and over>: 122.698 results (identical to the previous one). Its development over the last decade has been progressive (from figures close to 4,000 in the 2009-2010 biennium, to over 5,000 from 2014 to 2017), excluding the year 2018 from the assessment.

We have adopted their classification into thematic areas [122] and the twelve in which 95% of the results were concentrated are: sepsis and bacteraemia, pneumonia, urinary tract infections, central nervous system infections, endocarditis, prosthetic infections, skin infections, gastrointestinal infection, HIV infection, fever of unknown origin, multi-resistance and vaccinations.

Conclusion:

The scientific output on infections in the elderly, calculated by different databases, has been increasing in the last decade.

How do the problems of the elderly impact on the mainstream media? How should the media contribute to the reduction of infection in the elderly?

Presentation:

The impact of the problems of the elderly in the media is

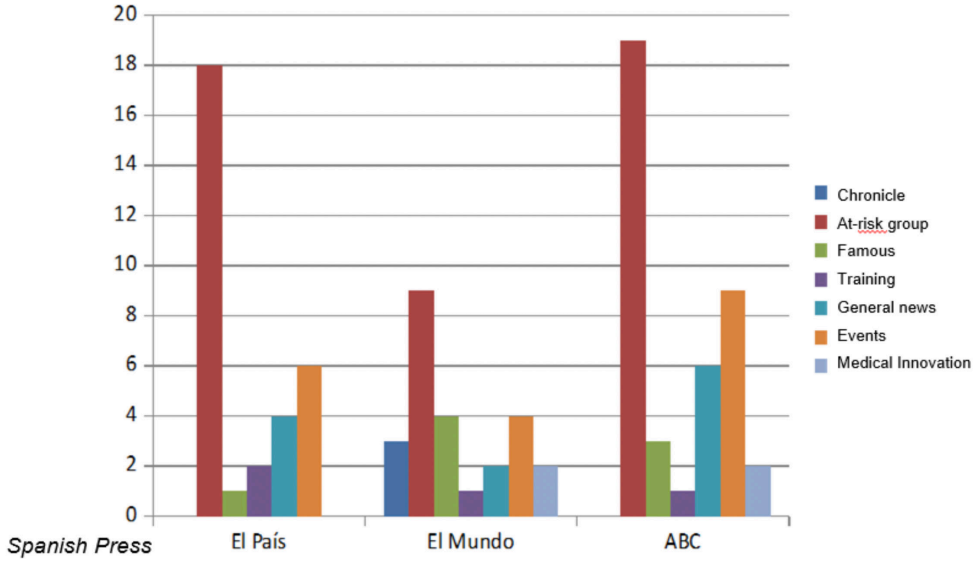

Figure 1 Citations regarding "infections" in the "elderly" in 3 major general journals of Spain

limited, deficient, incomplete, unfocused, out of context, stereotyped and with a not particularly constructive, realistic or objective bias.

The elderly are invisible in the media and when they appear, the content relating to them is characterised by simplification, victimhood, dramatization and superficiality.

The image that the media convey of old age is linked to inactivity, unproductiveness, seniority, illness, dependence and deterioration.

Old age and its problems, circumstances, needs and contributions, as a social agent and subject, are not among the priorities and themes of general media planning.

Other groups, sectors, actors or social issues such as immigration, feminism, equality, children, domestic violence, NGOs and their services, new technologies and their advantages, effects and risks, harassment in all its forms, health and sanitation, or scientific advances have much more visibility, relevance, monitoring, currency and presence in the media.

The problems related to a stage of life that we can place at around 80 years provoke a disinterest and sidelining in the information and journalism that only is unblocked in the face of news related to events, diseases, negative or sensationalist facts or anecdotes, offering a fixed, unmoving and old-fashioned image of a sector of the population that, nevertheless, is increasing due to the increase in life expectancy.

In a world where the 21st century grants youth and technology all the plaudits as to what is interesting and important, whether in the press, television, radio, websites or social networks, ageing and old age, as a concept, social and population sector, and newsworthy subject, are moved to a second or third tier on the podium of current affairs and information.

As a small demonstration of this paradox -the contrast between the rising presence of the elderly in society and their lukewarm representation in the media-, we offer a chart with a comparison of publications on the websites of three generalist newspapers, "El País", "El Mundo" and "ABC", between the years 2016-2018, with the search for "elderly" and "infection" as key words. A total of 96 news items are recorded that mention the subject studied (figure 1).

This is little news, and in most cases linked to events and to the elderly as a risk group.

This sample would require further media analysis to ratify this tendency in the treatment of the problems of the elderly and the infections they suffer, but it serves as the tip of the iceberg of relegation, insensitivity and atrophy in news treatment.

Since the onset of the economic crisis in 2008, the number of dedicated journalists specialising in social and health issues has been substantially reduced in order to divert manpower and resources mainly to political and economic content.

If, in this situation, health, science and social issues have been scaled down and cut back in the operation of the media, the elderly, as journalistic content, have been pushed to the very margins of the newsrooms with complete normality; with no agenda, no specialists, no briefings, no planning, no contextualization; to see themselves as mere circumstantial, inconsequential, occasional content, with a light, sometimes frivolous treatment, lacking depth and sensitivity; building a narrative of topics, irrelevance and disconnection from their value and presence in society.

This media portrayal of the elderly is in contrast to the ageing of the population, where reliable and accurate statistics

point to a doubling of the number of older people by 2050.

The data show that in 1960 in Spain, there were 6.7 million children under 10 years and 0.4 million people over 80 years, in 2015 the number of children under 10 had fallen to 4.6 million, and over 80 risen to 2.7 million; by 2050 the trend becomes even more acute, with under 10 years predicted at 3.8 million, and over 80, 6.2 million [123, 124].

Globally, in the century from 1950 to 2050, total population will triple; the population over 60 will grow by a factor of 10; and the population over 80 by a factor of 28, this last group going from 14 million in 1950 to 386 million in 2050.

If information concerning and affecting the elderly continues to be ignored, marginalised and simplified in the media, they will neglect and fail in their mission of gathering information, analysis, data and opinions from a sector of the population with enormous influence on the life and events of a country. Without rigorous, truthful, balanced, comprehensive and complete information on the phenomenon of old age, the view and expression of reality will be distorted, fragmented and fractured.

To help reduce infection in the elderly, the media must take several steps beforehand and activate new information strategies and actions [125, 126].

Review and reformulation of the contents for current events, relevance and interest agendas. The first step is to place general social and health issues on the same level of importance as national or international political, economic or sports information, with the consequent allocation of space, dedication and resources.

Enhancement of content for the elderly in social and health information. Within the social and health content, the news of the old and elderly must be equated in relevance, dedication, selection, monitoring and treatment to other issues related to this journalistic field, with emphasis on the quantity and quality of the information, from the rigour, planning and contextualization to gather studies and data, human stories, opinions, difficulties and needs, social influence, contributions, and challenges in this sector of the population.

The aim is to offer a complete, balanced, objective and true vision of their reality, their contributions, their heterogeneity, their variety, their complexity, their evolution and their demands and needs.

The problems arising from the increase in age, health, coexistence and economic situation, as well as cultural, sociological, family and psychological aspects, must be approached with an informational style and treatment where ageing is considered from the standpoint of normality in life, with its ups and downs, and not as a hindrance, obstacle or inappropriate or unsustainable expense.

The social and cultural role of the elderly, their knowledge and experience, their skills and abilities, should be valued as useful and enriching elements to society.

Promotion of health and sanitation information in the elderly. The next step for the media, once the general information on the elderly and very elderly has been strengthened, is to promote health and healthcare information in relation to this sector of the population.

In this context, the media would be in a position to treat and report, with much higher presence and representation criteria than at present, on the infections of the elderly within the framework of their health and well-being.

It is very difficult to reach this third step without the two previous actions, since the handling of a health problem such as infection in the elderly by the media requires a commitment and responsibility in several phases that is part of a comprehensive strategy to provide a journalistic treatment of their problems on a par with their representation and contribution to society.

It is necessary to present older people and the elderly removed from the clichés and stereotypes that link them directly and almost solely to the events, the deterioration of their health, family dependence or the hindrance or burden of their role and function in society.

It is necessary to offer complete and balanced information in which tasks such as interest in culture, modernity, the future, technology or travel; their capacity to lea in civil society, family, business or education; their initiative in domestic and community tasks; their political or social contributions; or their skills in the practice of sport are inherent. In short, to show their vitality, enthusiasm, enterprise, activity, determination, solidarity or collaboration, beyond their problems or difficulties, which must also be reflected and analysed.

It should not be forgotten that though the generation of elderly people now over 75/80 years old may have a more traditional, reserved and passive profile in certain cases -by no means in all-, the new generation of elderly people forecast for 2050, where their number will rise greatly, will experience a huge change with regard to the distorted image of the elderly today.

Conclusion:

The information that the general media dedicates to the problems of the elderly is minimal, distorted and biased. It is full of clichés and stereotypes that link them directly and almost exclusively to events, the deterioration of their health, family dependency or the hindrance or burden of their role and function in society. Information on infections in this population group is even more scarce.

Does the pharmacist, whether in the hospital or in the community, have a role controlling inappropriate antibiotic therapy in the elderly? What about vaccination?

Presentation:

The answer is YES, without a doubt [95, 127-138]. The reasons are detailed below: Studies conducted following scientific evidence criteria in recent years show that pharmaceutical care and the intervention of the pharmacist improve the overall quality of patient care, while the WHO itself states that

pharmacists "contribute decisively to the rational use of medicines". The decision on how to treat a given infection correctly with the most appropriate antimicrobial requires detailed knowledge of microbiological, clinical and pharmacological issues, but the causes of an optimal result go beyond this and extend to the so-called *non-pharmacological basis*, among which the behaviours of doctors, patients and pharmacists, as well as the relationships between them, play a fundamental role. The pharmacist is one of the apices of the so-called "human factor triangle" (made up of doctor-patient-pharmacist), a mirror image of the famous "Davis triangle" (antimicrobial-microorganism-host).

Currently, pharmaceutical care aims to obtain the maximum clinical benefit from medicines and to achieve the lowest possible risk in the use of those medicines, which entails the identification, resolution and prevention of medication-related problems (MRP): adverse drug reactions (ADR), drug-drug interactions (DDI), deficiencies in physician prescription, errors in the use of medication by the patient and breaking the *vicious circle* so frequent in the use of antimicrobials formed by **self-medication - noncompliance - storage**.

Pharmaceutical care is a process, which includes different stages: *active dispensation* (supply, delivery, dispatch >>> assistance, help, care), *educational advice* (health advice in response to a consultation/problem or instruction on the acquisition of a medicine) and *pharmacotherapeutic follow-up* (documentation and registration of the activity).

As far as the hospital pharmacist is concerned, it must be said that they not only participate actively in the rational use of antimicrobials from their role as an active member of the pharmacy commission and the antimicrobial committee, but also get involved on a daily basis in the prudent and correct application of antimicrobial therapy, in order to obtain the most *beneficial* result from the clinical point of view and the most *efficient* from the pharmaco-economic point of view. This implies that: the appropriate antimicrobial has been prescribed in accordance with a correct diagnosis and the special characteristics of the elderly patient, *it* is dispensed under the proper conditions, administered at the indicated doses, at the intervals and for the period intended, it is used with the lowest possible cost, in such a way as to prevent or minimise the development of bacterial resistance and it achieves the desired therapeutic objective.

In short, both the community and the hospital pharmacist as first-level health agents play a central role in the field of therapeutic adherence and rational use of antimicrobials, proposing their use in terms of *quality of treatment* and considering antimicrobials not only by virtue of the active ingredient contained in the corresponding pharmaceutical specialty, but also in terms of useful information ("software"). Furthermore, both must take into account that antibiotics and vaccines are the paradigm of *societal treatment* and the treatment or non-treatment of an individual can affect the community [139].

Conclusion:

The answer is YES, without a doubt. Studies conducted following scientific evidence criteria in recent years show that pharmaceutical care and the intervention of the pharmacist improve the overall quality of patient care, while the WHO itself states that pharmacists "contribute decisively to the rational use of medicines".

What is the administration doing and what can it do to reduce these problems? From an educational point of view? From the legislative-regulatory point of view?

Presentation:

In order to reduce these problems, the State Administration must, among other things, launch:

1. Prevention strategies and measures to control the transmission of the infection.

2.- Vaccination programmes in the elderly.

3.- Training and information programmes for health professionals, particularly in the area of rational use of antimicrobials and promotion of the use of appropriate definitions [140, 141].

4.- Guidelines or recommendations on recommended antimicrobial treatments for the most prevalent infections in different healthcare settings.

5.- Standards for therapeutic effort in advanced and terminal phases of illness.

From an educational point of view, it is up to the Administration:

1.- To encourage "Health Schools" that educate the population on self-care, stimulating healthy living habits and eliminating toxic habits.

2.- To promote information on predisposing risk factors for infection by multi-resistant microorganisms.

3.- To educate patients on the proper use of antimicrobials in primary care settings

4.- To educate on health and the use of antimicrobial agents from the pharmacy offices.

5.- Promote information on the disposal of surplus antimicrobials ("SIGRE Points").

From the legislative-regulatory point of view, the administration must:

1.- Promote and maintain a Reporting-Communication System for some infectious diseases (EDO, VIRAS, etc.), subdivided by age groups.

2.- Mandate the implementation of a health protection system consisting of a Pest Control Plan, an Urban, Sanitary, Bio-sanitary and Cytotoxic Waste Management Programme and a Hygiene, Food Safety and HACCP System.

3.- Legislate on Occupational Risk Prevention, obliging healthcare workers to protect themselves against certain infections to prevent them from acting as a source of contagion or a vehicle for the transmission of the infection.

4.- Regulate the implementation of measures or precau-

tions for the prevention and control of Healthcare Associated Infections (HAIs).

Some examples of the above are programmes such as: "Antibiotics: Take them seriously" (2017); the "World Antibiotic Awareness Week" (2018); the "European Antibiotic Awareness Day" (2018). A National Plan against Antimicrobial Resistance (PRAN) run by the Spanish Agency of Medicines and Health Products (AEMPS) is essential [142, 143-147].

Conclusion:

The administration has a constitutional mandate to promote health, which is of particular concern to groups as vulnerable as the elderly. Among the measures to be implemented, those of an educational nature are especially necessary, both for patients and for their caregivers and healthcare personnel. From a legislative-regulatory point of view, we cannot forget that Spain has one of the best health systems in the world.

What is the role of nursing in managing and reducing infection in the elderly? How does the training of the caregiver affect this?

Presentation:

Nurses develop preventive interventions, participate in the monitoring, control, therapeutic adherence and care plan when the infection is established. These competencies are developed inside and outside of healthcare institutions. In the home setting, the focus is on education and providing support for safe practices [148-151].

Professionals, caregivers and elderly people have to distinguish modes of transmission, identify risk factors and susceptible people who may become reservoirs or constitute a vehicle of contagion and understand basic protective and barrier measures.

The simplest, most effective and universal procedure is hand hygiene. The World Health Organization identifies five key times for washing: before and after contact with the person, before performing a clean/septic task, after the risk of exposure to body fluids, and after contact with the patient's environment [152-154].

When hygiene guidelines are given, it is worth noting other times: before, during and after handling or preparing food, before eating, before giving medication, before and after treating a wound or handling clinical devices, after using the bathroom and after handling used clothing, whether personal, bath or bedding, diapers or waste. After washing, it is important to dry the hands.

Personal hygiene and topical hydration are other prevention strategies. The skin constitutes a natural protective barrier and is particularly labile in the elderly. Its daily care guarantees its integrity and protects it from external assault. This includes body hygiene and protective measures aimed at moisture control and injury prevention. Some studies highlight the importance of oral hygiene in relation to respiratory diseases [155].

Another precaution is the sanitation of the space in which the elderly person stays so as to make it a healthy environment, including daily cleaning of surfaces, objects and utensils, ventilation, illumination preferably with natural light, and appropriate environmental temperature and humidity [156].

The tendency to unbalanced diets, malnutrition and low fluid intake increases susceptibility to infection. It is essential to promote healthy lifestyles and to provide structured plans for eating, drinking and exercise adapted to individual needs taking preferences and health problems into account [157-162].

Another strategy is the vaccination of the elderly and carers, adjusted for age, particular situation and the approved schedule in each autonomous community [163].

Although infectious diseases in the elderly do not always have obvious signs and symptoms, the caregiver detects changes in their baseline situation that may lead to a suspicion of the presence of an infectious process, so education should be provided on how to proceed in the light of this suspicion and what to do when it is confirmed.

Finally, it is necessary to emphasise the effective management of treatment (dose, administration and side effects) and periodically monitor therapeutic adherence, avoiding self-medication, in order to achieve the optimal effects of non-pharmacological and pharmacological measures, so as to enable prevention, delay deterioration, recover or maintain health [164].

Conclusion:

Nurses develop interventions for prevention, monitoring and therapeutic adherence control, participating in the care plan for infection in the elderly.

The implementation of many of the health promotion and care plans and regulations is the direct responsibility of the nursing profession.

How do senior citizens' associations deal with this problem?

Presentation:

The issue of health is a priority for the elderly and infection in particular is one of the most frequent causes of morbidity and mortality in the elderly, as has already been mentioned.

Elderly associations have traditionally focused on chronic rather than acute diseases and therefore have a huge role to play in this area.

It is the mission of the elderly associations to encourage and promote the residence of the elderly in a family and social environment that is agreeable to them. It is well known that an older person who lives comfortably at home with family members has less risk of acquiring infections than one who lives alone.

In the case of the elderly institutionalised in residences, the elderly associations have the mission to ensure the quality

of these institutions, that they are equipped with the appropriate medical, nursing and social services and that a systematic accreditation of these services is achieved. Ideally, these centres should have very significant prevention measures in place and should work closely, on the one hand, with the primary care physicians responsible for the patients, and on the other hand, with the reference hospitals to which the patients have to be transferred at some point.

Elderly associations must continue to work to improve the care of the elderly in emergency departments, not only from a technical point of view, but also by ensuring the agility of the assessment and dignified conditions for the elderly in these departments.

Finally, the elderly who are hospitalised are patients who require very rapid mobilization, avoidance of exposure to multi-resistant microorganisms and the fastest possible transfer back to where they came from. Elderly associations promote the provision of geriatric beds and services in all hospitals, where structures and organisations are set up specifically to serve the needs of elderly patients with a comprehensive idea of their care.

As we have mentioned, prevention is better than cure, and in that sense, the elderly associations can play an important role in emphasizing to the authorities, to the groups of affected people and to healthcare personnel the importance of promoting vaccination campaigns [86]

In short, associations for the elderly, whether they are focused on health or not, can play a very positive role that is often overlooked when it comes to improving health. They could work, if possible, promoting and propagating vaccination campaigns. They could also contribute more than they do to other forms of health education, from those oriented towards nutrition or physical activity, to those focused on fighting toxic habits or reporting abuse. All this is of general interest, as well as directly and indirectly affecting the field of infectious pathology.

Following the recommendations of the Expert Consensus on frailty in the elderly, active ageing and drug screening in polymedicated patients are important in preventing infections in these patients.

Conclusion:

Elderly associations must play a major role in demanding quality care policies for elderly patients, both in the fields of prevention and treatment. Target areas for intervention are the home environment, the outpatient system, nursing homes, hospital emergency departments and hospital care.

Patient associations can contribute more than they do to other forms of health education, from those oriented towards nutrition or physical activity, to those focusing on combating toxic habits or reporting abuse.

What ethical aspects would you highlight in all these problems?

Presentation:

The great social esteem that existed in ancient cultures for the elder of the group or tribe is well known. He was not only the oldest person but also the biological father, the political leader and, in many cases, the religious authority. And, as anthropologists have pointed out more than once, the "hard disk" of the community, aware of past events of which the younger generations are not, thereby bringing the social group together and giving it its own identity. Hence, the elders were not only respected but highly valued and even revered. It is enough to open the books of the Bible, for example, to find testimonies of this. Its pages over and over again reverential respect for the elder, applying such venerable terms as "Patriarch". The Bible attributes an extraordinary longevity to the first patriarchs (*Gen* 5; 11,10-26), and even to the later patriarchs, like Abraham (*Gen* 17,1.17; 18,12) and Moses (*Dt* 31,1; 34,7), and to the prophets, it is difficult to represent them as young people. Respect leads the bible authors to attribute centuries-long lives to them. Longevity is a sign of their wisdom. The so-called wisdom literature bears good witness to this veneration for the elderly. In the book of *Ecclesiasticus* we read:

In your youth you did not gather.

How will you find anything in your old age?

How appropriate is sound judgment in the grey-haired,

and good counsel in the elderly!

How appropriate is wisdom in the aged,

understanding and counsel in the venerable!

The crown of the elderly, wide experience;

their glory, the fear of the Lord. (*Sir* 25,3-6)

The theme of the wisdom and prudence of the elderly is repeated:

For the age that is honourable comes not with the passing of time,

nor can it be measured in terms of years.

Rather, understanding passes for grey hair,

and an unsullied life is the attainment of old age. (*Wis* 4:8-9)

And the book of *Proverbs*:

Grey hair is a crown of splendour;

it is attained in the way of righteousness. (*Prov* 16:31).

The contrast between the ancient civilization of Israel and the archaic Greek culture, as presented in the Homeric poems, is surprising. It is difficult to imagine Ulysses, Hector or Achilles as elders, even though in those poems there are also venerable subjects such as Menelaus, Agamemnon and Priam. The contrast between Agamemnon and Achilles is particularly significant, for the poet paints the former as an ambitious and selfish man, with an excessive ego who confronts Achilles, his best warrior, again and again. Heroes, those beings that the Greeks considered perfect and semi-divine, are by necessity young and in the fullness of their life force. In Greek statuary

it is impossible to see the decrepitude of the elderly person represented. The poet Menander coined a sentence that soon became famous and that Plautus translated into Latin: *Quem di diligunt, adulescens moritur,* "those loved by the gods die young" (*Bacchides*, 816-817). Perfection is in youth, and old age is almost embarrassing. Aristotle says that "disease is an acquired old age, old age a natural disease" (*Gen. An.* 784 b 33-4).

It was important to remember this about the attitude of our culture, the western one, towards the elderly. They've never been held in high esteem. Moreover, we can be seen that this esteem has been decreasing over time. This is demonstrated by the words we use to refer to this age group. "Viejo" (old) comes from the Latin *vetus*, the opposite of *novus*, both of which are terms that were designating things, not people. For people, the correct terms were *senex* and its opposite *iuvenis*. From *senex* comes our word "senescence", only used in a very limited sense today. Cicero wrote a dialogue *De Senectute*, using the correct term in his language. Though, in the various Spanish editions that exist, the translation is invariably *Sobre la vejez*. (On Old Age). Old age is not only an improper term, but also a derogatory one. No one sees it that way anymore, because they don't know about this process. But the transition from one term to another is an evident sign of the devaluation that the figure of the elder has undergone in Western culture, even though it was originally already much lower than that of other cultures.

If we add to this the spectacular increase in life expectancy at birth in the last century, it turns out that this devalued period, which until the beginning of the 20th century was almost anecdotal in the life of Western society (it should be remembered that life expectancy at birth in Spain had been stable at 25-30 years from the Neolithic revolution to the end of the 19th century), has become a period of no lesser and sometimes greater duration than the active life of a person. So much so that human life today can very well be divided into three 30-year periods, the first of which is devoted to vocational training, the second to production, and the third.. it is not very clear to what, among other things, because the training we were given in the first 30 years was aimed at being productive in the second phase, but we were never educated for the "third age".

The third and final phase of life, which today has an average duration of 30 years, is a continuous source of problems. It is, at least, in the economic order, as the present pension system seems difficult to maintain, and will be impossible in the near future. But, as important as this is, that's not the biggest problem. The most serious issue is that we have condemned the elderly to being a "passive class", whom INSERSO (The Institute for the Elderly and Social Services) has to ferry from one place to another in order to at least distract them. There is talk of discrimination and abuse of the elderly. In my opinion, the greatest discrimination is this, the fact that the elderly have been deprived of their own role in society; or, to put it another way, the total absence of what I have been calling the "third age culture" for some time [165]. Yes, third age culture. The third age has its own culture, distinct from the second age. Modern systems of work organisation have made "efficiency" a major objective of the culture of the second stage of life. There is no doubt that in Spain, for example, efficiency has increased three or fourfold in the last half century. And here is the origin of the problem. What do you do when you are no longer "efficient", at least in the way the economy defines efficiency?

Efficiency is a value that belongs to the category of so-called "instrumental values", "reference values" or "technical values". They are so called as they have no value in themselves, but only in reference to something else or another value. Let's think, for example, of a drug. There is no doubt that it has value, at least financially. Its most valuable asset is to relieve a symptom or cure a disease. If it wasn't good enough, we'd say "it's not good enough", and we wouldn't pay for it. This means that the value of the drug is in reference to something other than itself, such as well-being, health, life, etc. This happens to all technical instruments. If we were to find a more effective or less expensive drug, there is no doubt that we would choose it, because this is what efficiency is about: the cost/benefit ratio. Efficiency is the unit of measurement for instrumental values.

The problem is that not everything is instrumental. If they are always in the service of others, it means that these others must stand on their own, otherwise we fall into an infinite regression. These are called "intrinsic values" or "fundamental values". They are the most important in life. They are essential values, values that have worth in their own right, without reference to others. Think, for example, of dignity. Or many others, such as health, life, beauty, well-being, justice, solidarity, etc. These are all intrinsic values. Without them, life is meaningless [165]. Furthermore, they have the characteristic of not being measured in monetary units, nor is efficiency a criterion. "Health is priceless" it has always been said; "true love is neither bought nor sold"; "only the foolish confuses value and price" said Antonio Machado. And the list could go on [166].

We can now understand the importance of promoting a culture of old age. During our working life there is no doubt that the fundamental criterion must be efficiency, and therefore economy. But that is, at the same time, the least human part of life. The day is not far off when that part of our existence can be transferred to the robots. And the problem arises: What will we humans do then? Will we have anything to do?

Older people have a fundamental mission in our society, and that is to take charge of promoting intrinsic values and passing them on to younger generations. It's not all about economics. It's not all about efficiency. There are other values, which moreover are the most important, the most human.

Conclusion:

Promoting a new culture of the elderly should lead us to avoid not only the discrimination that has occurred throughout Western culture, and particularly in recent centuries, but also to give impetus to the promotion of intrinsic values, the most humane, the most important in the lives of individuals and societies. This is the very im-

portant active role that members of the third age have been entrusted with, given that in our culture the second age is obsessively consumed by the promotion of economic efficiency.

Does this matter for the control of infection in the elderly? As has already been said in previous interventions, the dynamic, active elderly, who feel that they have a mission to fulfil in society, are undoubtedly in a better position to avoid infections and to combat them when they do occur. It is not true that, as Aristotle said, old age is a "natural disease". There are many reasons to claim that it is not merely a part of life, but in many ways the most important. And it will be even more so in the future.

CONFLICTS OF INTEREST

The authors declare that they have no conflict of interest.

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Desarrollo de un modelo predictivo para mortalidad y otro para reingreso hospitalario en una cohorte de paciente con infección que requieren hospitalización

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RESUMEN

Introducción. Los objetivos del estudio fueron: identificar variables asociadas a mortalidad intrahospitalaria y reingreso hospitalario a 3 meses; identificar el impacto de la demora en el inicio de la antibioticoterapia en la mortalidad y reportar la tasa de antibioticoterapia inapropiada.

Material y métodos. Estudio observacional de cohortes retrospectivo realizado en el Hospital Universitario HM Sanchinarro en Madrid. Los criterios de inclusión fueron: edad> 18 años de edad, hospitalización desde urgencias durante el periodo 1 de septiembre 2012 al 31 de marzo del 2013 con diagnóstico de infección bacteriana. Los criterios de exclusión fueron: sospecha de infección viral y cultivos bacteriológicos negativos, expectativa de vida inferior a 6 meses, falta de información clínica, asistencia exclusivamente por el servicio de urgencias traumatológicas. Se realizaron dos modelos logísticos (mortalidad y reingreso hospitalarios).

Resultados: Se incluyeron 517 pacientes. Variables asociadas a mortalidad (30 fallecidos): frecuencia respiratoria (OR 1,12; IC95% 1,02; 1,22), saturación de oxígeno (OR 0,92; IC95% 0,87; 0,98), creatinina (OR 2,33; IC95% 1,62; 3,36), EPOC (OR 3,02; IC95% 1,06; 8,21), cáncer OR 3,34; IC95% 1,07; 9,98) y quimioterapia en los últimos 3 meses (OR 4,83; IC95% 1,54; 16,41). Variables asociadas a reingreso hospitalario (28 fallecidos): hepatopatía, GPT, antecedente de ictus e hipertensión arterial. Ambos modelos se destacan por su elevada especificidad y capacidad discriminativa pero baja sensibilidad. La demora en el inicio de la antibioticoterapia no influyo en la mortalidad ni reingreso. En 56 pacientes se identificó el microorganismo causal y el tratamiento antibiótico fue inapropiado en 11.

Conclusiones: Se registro un 5,8% de mortalidad hospitalaria y un 5,7% de reingresos. Las variables asociadas a la mortalidad intrahospitalaria difieren de las asociadas al reingreso. La demora en el inicio de la antibioticoterapia no se asoció a un efecto deletéreo. La antibioticoterapia inadecuada fue de casi el 20%.

Palabras clave: infecciones, mortalidad, reingreso, antibioticoterapia inapropiada

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Development of a predictive model for hospital mortality and re-admission in a cohort of infected patients that require hospitalization

ABSTRACT

Introduction. The aims of the study were: to develop a predictive model for hospital mortality and another for hospital re-admission, to identify the impact of antibiotic delay in the mortality rate and, to report the rate of inappropriate antibiotic therapy.

Material and methods. A cohort and retrospective study was conducted at the HM Sanchinarro University Hospital during the period September 1st, 2012 to March 31th, 2013. The inclusion criteria were: age> 18 years, hospital admission from the ED with a diagnosis of bacterial infection. The exclusion criteria were: suspected viral infection, negative bacteriological cultures, life expectancy less than 6 months, lack of clinical information, assistance exclusively by the trauma emergency department. Two logistic models were made (hospital mortality and hospital re-admission).

Results. A total of 517 patients were included. The final mortality model (30 deaths) include the following variables: respiratory rate (OR 1.12; IC95% 1.02; 1.22), oxygen saturation (OR 0.92; IC95% 0.87; 0.98), creatinine (OR 2.33; IC95% 1.62; 3.36), COPD (OR 3.02; IC95% 1.06; 8.21), cancer (OR 3.34; IC95% 1.07; 9.98) and chemotherapy in the last 3 months (OR

4.83; IC95% 1.54; 16.41). The final model for hospital re-admission (28 re-admissions) include the following variables: hepatopathy (OR 5.51; IC95% 1.57; 16.88), GPT (OR 1.005; IC95% 1.003; 1.008), history of stroke (OR 5.06; IC95% 1.04; 18.80) and arterial hypertension (OR 3.15; IC95% 1.38; 7.56). The antibiotic therapy delays not influenced the mortality or re-admission rate. In 24.3% the causative microorganism was identified and antibiotic treatment was inappropriate 19.6%.

Conclusion. Hospital mortality rate was 5.8% and re-admission rate was 5.7%. Variables associated with mortality differ from those associated with re-admission. The delay in the antibiotic initiation was not associated with a deleterious effect. Antibiotic therapy was inadequate in almost 20% of patients.

Key words: infections, mortality, re-admission, inappropriate antibiotics.

INTRODUCCIÓN

Las infecciones constituyen uno de los principales problemas sanitarios en el ámbito de las urgencias por su elevada incidencia y mortalidad. En España, el 14,3% de las consultas en urgencias son por un proceso infeccioso de las que el 23,3% requieren hospitalización [1, 2].

A pesar de los avances conseguidos en el manejo clínico, microbiológico y terapéutico en las infecciones; en urgencias la orientación diagnóstica continúa siendo clínica y el tratamiento antibiótico habitualmente empírico. Dado que el Servicio de Urgencias (SU) es una frecuente puerta de entrada de pacientes con un proceso infeccioso, disponer de datos epidemiológicos y microbiológicos locales, así como modelos predictivos para los principales eventos podría mejorar la práctica clínica.

Los objetivos principales del presente estudio son: (a) desarrollar un modelo predictivo para mortalidad intrahospitalaria; (b) desarrollar un modelo predictivo para reingreso hospitalario a 3 meses; (c) identificar el impacto de la demora en el inicio de la antibioticoterapia en la mortalidad e (d) identificar la tasa de antibioticoterapia inapropiada.

Material y métodos Estudio observacional, de cohortes retrospectiva, realizado en el Hospital Universitario HM Sanchinarro (HU-HMS) en Madrid, España. El HU-HMS es un centro privado de alta complejidad que dispone, para adultos, 14 camas de urgencias, 189 camas de hospitalización en planta y 22 camas de cuidados intensivos. Su cartera de servicios cubre todas las especialidades médicas y quirúrgicas excepto obstetricia.

Criterio de inclusión: pacientes mayores de 18 años de edad que consultaron en urgencias e ingresaron durante el periodo 1 de septiembre 2012 y el 31 marzo 2013 con diagnóstico de infección bacteriana a juicio del médico de Emergencias tratante y que requirió antibioticoterapia. Criterio de exclusión: sospecha de infección viral y cultivos bacteriológicos negativos, expectativa de vida inferior a 6 meses, falta de información clínica, asistencia exclusivamente por el servicio de urgencias traumatológicas.

El HU-HMS tiene un sistema integral de historia clínica. Mediante este sistema se seleccionaron todos los pacientes que cumplían los criterios de ingreso y ninguno de exclusión. Adicionalmente se identificó quienes reingresaron en los 3 meses posteriores al alta.

Se recogieron variables demográficas (sexo, edad), antecedentes personales (diabetes, enfermedad pulmonar obstructiva crónica (EPOC), tabaquismo, asma, accidente cerebrovascular, trombo-embolismo pulmonar, insuficiencia renal crónica, hepatopatía (esteatosis y/o cirrosis), alcoholismo, patología tiroidea (hipo y/o hipertiroidismo), tratamiento con corticoides sistémicos, coronariopatía, hipertensión arterial crónica, insuficiencia cardíaca, dislipemia, cáncer, cirugía por neoplasia, radioterapia y/o quimioterapia en los 3 meses previos), situación en urgencias (variables microbiológicas: localización del foco infeccioso, tratamiento antibiótico administrado, demora entre el registro del paciente en urgencias y la administración de la dosis inicial de antibiótico, cultivos realizados; variables clínicas: tensión arterial media, temperatura, frecuencia respiratoria, frecuencia cardíaca y saturación de oxígeno y variables analíticas: hemoglobina, leucocitosis, plaquetas, creatinina, urea, bilirrubina total, transamina glutámico oxalcético (GOT), transamina glutámico pirúvica (GPT), potasio, sodio, glicemia y proteína C reactiva (PCR) y aporte de volumen). El filtrado glomerular se estimó mediante la ecuación: $186 \times (\text{creatinina})^{-1,154} \times (\text{edad})^{-0,203} \times 0,742$ (si mujer) x 1,21 (si raza negra) [3].

Se consideró antibioticoterapia apropiada cuando la cobertura del antibiótico prescripto en urgencias incluía al microorganismo identificado [4]. Los pacientes con cultivos negativos, así como los cultivos de vigilancia (exudado nasal y rectal) no fueron considerados.

Los datos ausentes se imputaron mediante el procedimiento de imputación múltiple por ecuaciones en cadena ("multivariate imputation by chained equation" o MICE) [5]. Las variables categóricas se reportan como frecuencia absoluta y porcentaje, las continuas como mediana y rango intercuartil. Las medias se compararon mediante Mann-Whitney U test o Kruskal-Wallis y las variables categóricas con la chi-cuadrado. Se realizaron dos modelos logísticos predictivos multivariantes, uno para el evento mortalidad intrahospitalaria y otro para el evento reingreso hospitalario a 3 meses. Las variables incluidas en cada modelo logístico máximo fueron todas las que presentaron un valor de $p < 0,1$ en el análisis univariante. Los modelos se caracterizaron mediante el área bajo la curva ROC, sensibilidad, especificidad, razón de verosimilitud positiva y negativa. Adicionalmente, se compararon con el modelo "Rapid Emergency Medicine Score" (REMS) [6] modificado (no se incluyó la puntuación Glasgow). El modelo de mortalidad se validó externamente con la cohorte de pacientes del estudio publicado por Garcia-Lamberechts et al [7]. Las características de la cohorte de validación pueden apreciarse en el manuscrito original destacándose como principales diferencias que la mortalidad se registró a 30 días desde el evento índice, incluyo pacientes mayores de 75 años y que se registró inmunodepresión por lo cual a posteriori, con el propósito de evaluar el modelo de mortalidad, se equiparó

quimioterapia en los últimos 3 meses como inmunodepresión. Se consideró estadísticamente significativo un valor de p < 0,05. Todos los análisis se realizaron con librerías del programa R [8].

El Comité de Ética de la Investigación del Grupo Hospitalario HM aprobó el estudio (18.02.1181-GHM)

RESULTADOS

Durante el periodo de estudio se atendieron en el Servicio de Urgencias de adultos un total de 21.683 pacientes de los cuales 2.899 fueron ingresados. En 836 pacientes la principal causa del ingreso fue una infección. Se incluyeron en el estudio 517 pacientes, se excluyeron 319 por los siguientes motivos: infección viral (n= 23); expectativa vida inferior 6 meses (n= 57); identificación de una causa no infecciosa como responsable del ingreso durante la hospitalización (n=226); y datos incompletos (n=13).

El promedio de infecciones ingresadas fue de 73,8 pacientes por mes (setiembre n=14 [2,71%]; octubre n= 100 [19,34%]; noviembre n=84 [16,25%]; diciembre 77 [14,89%]; enero n=82 [15,86%]; febrero n=80 [15,47%] y marzo n=80 [15,47%]; p <0,01).

Los focos de las infecciones fueron: respiratorio (n=193 [37,33 %]), urinario (n=105 [20,31%]), abdominal (n=77 [14,89%]), partes blandas (n=50 [9,67%]), desconocido (n=49 [9,48%]), miscelánea (n=32 [6,19%]) y múltiples (n=11 [2,13%]). La edad y la estancia hospitalaria solo difirió en el grupo de pacientes que sobrevivieron (figura 1).

En la figura 2 se detallan los protocolos antimicrobianos específicos en función del foco infeccioso.

Fallecieron 30 pacientes (5,8%) en el hospital (tabla 1). La proporción de exitus entre los diferentes focos infecciosos fue similar (múltiples focos n=1 [9,09%]; respiratorio n=17 [8,81%], desconocido n=4 [8,16%]; abdominal n=3 [3,90%]; miscelánea n=1 [3,13%]; urinario n=3 [2,86%] y partes blandas n=1 [2,0%]; p 0,251). Las variables asociadas independientemente con la mortalidad fueron la frecuencia respiratoria (OR 1,12; IC95% 1,02; 1,22; p<0,01), saturación de oxígeno (OR 0,92; IC95% 0,87; 0,98; p<0,01), creatinina (OR 2,33; IC95% 1,62; 3,36; p<0,01), EPOC (OR 3,02; IC95% 1,06; 8,21), cáncer (OR 3,34; IC95% 1,07; 9,98; p<0,01) y quimioterapia en los últimos 3 meses (OR 4,83; IC95% 1,54; 16,41; p<0,01). El área bajo la curva ROC para el modelo logístico fue mejor que para la escala REMS (figura 3). El modelo logístico tuvo una sensibilidad de 0,10 (IC95% 0,02; 0,27), especificidad de 1,00 (IC95% 0,99; 1,00), razón de verosimilitud positiva de 48,70 (IC95% 5,22; 454,24) y negativa de 0,90 (IC95% 0,80; 1,02). El área bajo la curva ROC del modelo logístico en pacientes menores y mayores de 75 años no difirió (0.823 [IC95% 0,648-0,984] vs 0.764 [IC95% 0,622-0,901]; p 0,604). En la muestra de validación, el modelo logístico presento un área bajo la curva ROC de 0,7434 (IC95% 0,6718-0,8149). Si la creatinina es sustituida por MDRD-IMDS (Modification of Diet in Renal Disease-Isotopic Dilution Mass Spectrometry) en el modelo logístico máximo, el modelo final no incluye a la nueva variable y el área bajo la curva ROC del nuevo modelo se reduce (0,853; IC95%: 0,767-0,904).

De los 487 (94,2%) pacientes que fueron dados de alta, 28 (5,75%) reingresaron en menos de 3 meses (tabla 1). La proporción de reingresos no difirió entre los focos infecciosos (desconocido n=6 [13,3%]; partes blandas n= 4[8,1%]; miscelánea n=2 [6,4%]; respiratorio n= 9 [5,1%]; abdominal n= 3[4,1%], múltiples n= 0[0,0%]; y urinario n=4 [3,9%]; p 0,312). Las variables asociadas independientemente con el reingreso fueron la hepatopatía (OR 5,51; IC95% 1,57; 16,88; p <0,01), GPT (OR 1,005; IC95% 1,003; 1,008; p <0,01), antecedente de ictus (OR 5,06; IC95% 1,04; 18,80; p <0,01) e hipertensión arterial (OR 3,15; IC95% 1,38; 7,56; p <0,01). El modelo logístico tuvo una sensibilidad de 0,09 (IC95% 0,02; 0,26), especificidad de 1,00

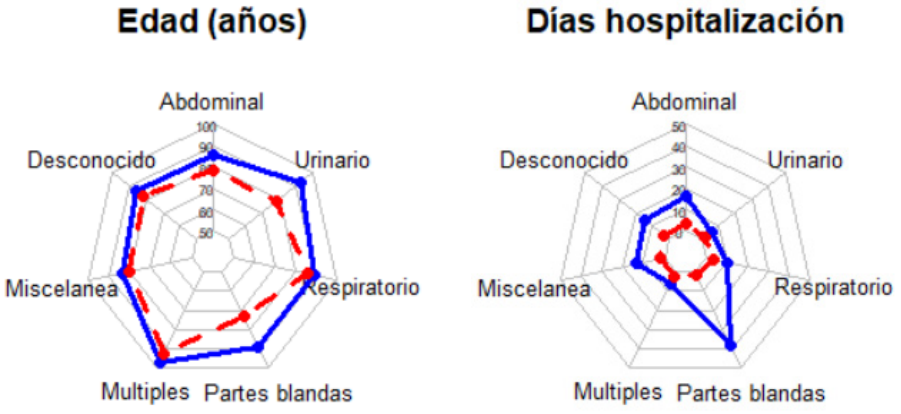

Figura 1 | **Media de edad y estadía en hospital en función del foco infeccioso (azul: muertos; rojo: sobrevivientes)**

Mediana de edad en función del foco de infeccioso (sobrevivientes p: <0.01; muertos p: 0.31).
Mediana de días de hospitalización en función del foco de infeccioso (sobreviviente p: <0.01; muertos p: 0.51).

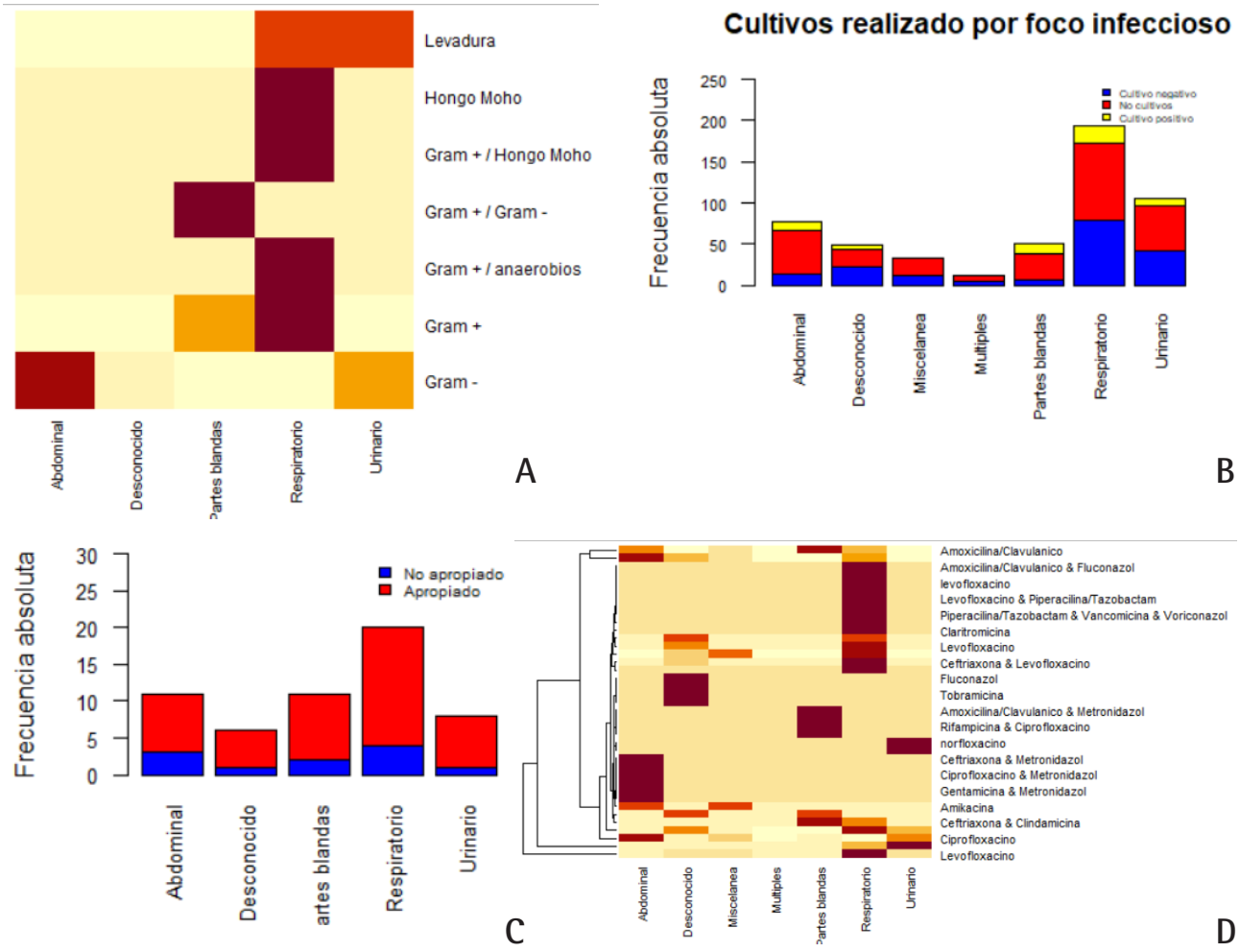

Figura 2 **Microbiología en función del foco infeccioso. (A) Tipo de microorganismo aislado en función del foco infeccioso (la intensidad del color es proporcional a frecuencia absoluta). (B) Frecuencia absoluta de cultivos realizados en función del foco infeccioso. (C) Antibioticoterapia apropiada en función del foco infecciosos. (D) Tipo de antibiotico en función del foco infeccioso (intensidad del color es proporcional a frecuencia).**

(IC95% 0,99; 1,00), razón de verosimilitud positiva de 27,32 (IC95% 3,71; 199,46) y negativa de 0,91 (IC95% 0,81; 1,03).

En 234 pacientes (45,3%) se realizaron cultivos para identificar el microorganismo causal de la infección, proporción que difirió significativamente en función del foco de la misma (desconocido n=28 [57,1%]; respiratorio n=99 [51,3%]; urinario n=49 [46,7%]; miscelánea n=12 [37,5%]; múltiple n=4 [36,4%]; partes blandas n=17 [34,0%] y abdominal n=25 [32,5%]; p 0,024).

En 56 (24,3%) pacientes se identificó el microorganismo causal de la infección siendo: grampositivos (n=25 [44,6%]), gramnegativos (n=25 [44,6%]), levaduras (n=2 [3,6%]), hongos (n=1 [1,8%]), gramnegativos + anaerobios (n=1 [1,8%]); grampositivos + anaerobios (n=1 [1,8%]) y grampositivos + gramnegativo (n=1 [1,8%]). El tratamiento antibiótico empírico fue inapropiado en 11 pacientes (19,6%) no apreciándose diferencia en función del foco infeccioso.

DISCUSIÓN

Los principales hallazgos del presente estudio son: (a) La mortalidad intrahospitalaria fue del 5,8% y la proporción de reingresos del 5,7%. (b) Es posible identificar un subgrupo de pacientes con elevado riesgo de morir en base a 6 variables clínicas medidas en urgencias (frecuencia respiratoria, saturación de oxígeno, creatinina, EPOC, cáncer y quimioterapia en los últimos 3 meses). El modelo se destaca por ser altamente específico pero muy poco sensible. (c) Es posible identificar a un subgrupo de pacientes como mayor riesgo de reingreso en base a 4 variables clínicas medidas en urgencias (hepatopatía, GPT, ictus previo e hipertensión arterial). (d) La demora en la antibioticoterapia no se asoció a un peor desenlace. (e) La proporción de antibioticoterapia inapropiada fue cercana al 20%.

El modelo de predicción de mortalidad, que de ahora en

Table 1 **Análisis univariante para el evento mortalidad y reingreso**

	Todos los pacientes (n=517)	Exitus (n=30)	Vivo (n=487)	Valor P	Todos los pacientes (n= 487)	Reingreso (n= 459)	No reingreso (n= 28)	Valor P
Generalidades								
Sexo femenino (n, %)	268 (51,8%)	13 (43,3%)	255 (52,4%)	0,440	255 (52,4%)	240 (52,3%)	15 (53,6%)	1,000
Edad (años)	63,7 [46,6;79,0]	78,9 [67,3;84,8]	63,0 [45,5;78,0]	<0,001	63,0 [45,5;78,0]	62,9 [44,5;77,6]	65,0 [58,5;84,6]	0,019
Días de hospitalización	2,51 [1,27;6,33]	10,4 [5,16;16,6]	2,44 [1,23;5,64]	<0,001	2,44 [1,23;5,64]	2,31 [1,21;5,44]	6,33 [3,20;8,75]	<0,001
Variables clínicas en urgencias								
REMS	5,00 [3,00;6,00]	7,00 [5,00;9,00]	5,00 [3,00;6,00]	<0,001	5,00 [3,00;6,00]	4,00 [3,00;6,00]	5,0 [3,75;6,00]	0,200
Aporte de volumen (ml)	0,00 [0,00;500]	0,00 [0,00;500]	0,00 [0,00;500]	0,162	0,00 [0,00;500]	0,00 [0,00;500]	0,00 [0,00;312]	0,616
Retraso inicio antibióticos (min)	318 [195;484]	346 [168;576]	317 [196;478]	0,842	316 [196;484]	308 [196;484]	362 [179;457]	0,632
Presión arterial media	89,8 [79,8;101]	86,0 [74,1;92,2]	90,2 [79,9;101]	0,037	90,3 [79,9;101]	90,2 [79,9;101]	94,5 [80,6;104]	0,517
Temperatura (ºC)	36,3 [36,0;36,9]	36,2 [36,0;37,0]	36,4 [36,0;36,9]	0,778	36,4 [36,0;36,9]	36,4 [36,0;36,9]	36,2 [36,0;36,8]	0,642
Frecuencia cardiaca (lpm)	94,0 [79,0;108]	104 [88,2;119]	93,0 [79,0;108]	0,026	93,0 [79,0;106]	92,0 [79,0;106]	98,5 [79,0;108]	0,356
Frecuencia respiratoria (rpm)	16,0 [16,0;16,0]	16,0 [16,0;26,0]	16,0 [16,0;16,0]	0,044	16,0 [16,0;16,0]	16,0 [16,0;16,0]	16,0 [16,0;16,0]	0,817
Saturación oxígeno	96,0 [93,0;98,0]	91,5 [88,0;97,0]	96,0 [94,0;98,0]	<0,001	96,0 [94,0;98,0]	96,0 [94,0;98,0]	96,0 [92,8;97,0]	0,241
Hemoglobina (g/dl)	13,0 [11,7;14,5]	11,8 [10,7;12,8]	13,0 [11,8;14,5]	<0,001	13,0 [11,8;14,5]	13,2 [11,8;14,5]	12,1 [10,4;13,0]	0,008
Leucocitosis (cel. $10^3/mm^3$)	11,1 [7,97;15,5]	10,8 [8,72;14,0]	11,1 [7,87;15,6]	0,819	11,2 [7,93;15,5]	11,2 [7,99;15,2]	11,0 [6,87;16,9]	0,692
Plaquetas (cel. $10^3/mm^3$)	229 [181;285]	220 [166;268]	231 [181;286]	0,424	231 [182;294]	231 [184;292]	226 [159;319]	0,749
Creatinina (mg/dl)	0,87 [0,70;1,08]	1,06 [0,84;2,82]	0,86 [0,70;1,06]	0,001	0,87 [0,70;1,05]	0,87 [0,70;1,05]	0,86 [0,67;1,12]	0,988
MDRD IMDS	86,0 [63,3;105]	59,7 [22,8;88,1]	87,5 [65,4;105]	<0,001	86,3 [65,4;104]	86,3 [66,1;103]	86,3 [49,3;114]	0,796
Urea (mg/dl)	35,0 [27,0;46,0]	58,5 [36,5;143]	35,0 [26,0;45,0]	<0,001	35,0 [27,0;45,5]	35,0 [27,0;45,0]	36,0 [25,0;76,2]	0,643
Bilirrubina total (mg/dl)	0,67 [0,46;0,97]	0,64 [0,50;1,38]	0,67 [0,46;0,97]	0,292	0,66 [0,45;0,94]	0,65 [0,45;0,93]	0,70 [0,55;1,29]	0,268
GOT	21,0 [16,0;32,0]	22,5 [19,0;39,8]	20,0 [16,0;32,0]	0,043	20,0 [16,0;32,0]	20,0 [16,0;29,0]	33,5 [20,8;138]	<0,001
GPT	18,0 [12,0;30,0]	18,0 [11,2;52,0]	18,0 [12,0;29,0]	0,554	18,0 [12,0;31,0]	17,0 [12,0;30,0]	37,0 [12,0;146]	0,017
Sodio (meq/l)	137 [135;139]	134 [130;137]	137 [135;139]	0,006	137 [135;139]	137 [135;139]	136 [134;139]	0,414
Potasio (meq/lg	4,23 [3,91;4,58]	4,60 [4,07;4,94]	4,23 [3,91;4,55]	0,031	4,22 [3,92;4,55]	4,22 [3,92;4,54]	4,30 [4,03;4,78]	0,208
Glicemia (mg/dl)	114 [99,0;138]	129 [107;180]	114 [99,0;135]	0,022	113 [98,0;134]	112 [97,0;133]	128 [108;156]	0,007
Proteína C reactiva	63,1 [17,1;145]	146 [88,6;219]	59,7 [16,4;134]	<0,001	58,8 [16,3;131]	58,8 [15,8;132]	63,6 [27,1;109]	0,827
Comorbilidades								
Fumador								
Exfumador	77 (14.9%)	8 (26.7%)	69 (14.2%)	0.180	69 (14.2%)	65 (14.2%)	4 (14.3%)	1.000
Fumador	61 (11.8%)	2 (6.67%)	59 (12.1%)		59 (12.1%)	56 (12.2%)	3 (10.7%)	
Nunca	379 (73.3%)	20 (66.7%)	359 (73.7%)		359 (73.7%)	338 (73.6%)	21 (75.0%)	
Insuficiencia renal crónica	23 (4.45%)	5 (16.7%)	18 (3.70%)	0.008	18 (3.70%)	16 (3.49%)	2 (7.14%)	0.277
Asma	26 (5.03%)	1 (3.33%)	25 (5.13%)	1.000	25 (5.13%)	25 (5.45%)	0 (0.00%)	0.386
EPOC	55 (10.6%)	8 (26.7%)	47 (9.65%)	0.009	47 (9.65%)	42 (9.15%)	5 (17.9%)	0.175
Ictus	17 (3.29%)	3 (10.0%)	14 (2.87%)	0.069	14 (2.87%)	11 (2.40%)	3 (10.7%)	0.040
Enfermedad trombo embolica	32 (6.19%)	3 (10.0%)	29 (5.95%)	0.420	29 (5.95%)	25 (5.45%)	4 (14.3%)	0.076
Alcoholismo	21 (4.06%)	3 (10.0%)	18 (3.70%)	0.115	18 (3.70%)	16 (3.49%)	2 (7.14%)	0.277
Hepatopatía	22 (4.26%)	0 (0.00%)	22 (4.52%)	0.630	22 (4.52%)	17 (3.70%)	5 (17.9%)	0.006
Tiroides	42 (8.12%)	3 (10.0%)	39 (8.01%)	0.726	39 (8.01%)	37 (8.06%)	2 (7.14%)	1.000
Diabetes	80 (15.5%)	9 (30.0%)	71 (14.6%)	0.035	71 (14.6%)	63 (13.7%)	8 (28.6%)	0.048
Corticoides sistémicos	16 (3.09%)	3 (10.0%)	13 (2.67%)	0.059	13 (2.67%)	12 (2.61%)	1 (3.57%)	0.541
Coronariopatía	27 (5.22%)	2 (6.67%)	25 (5.13%)	0.665	25 (5.13%)	23 (5.01%)	2 (7.14%)	0.648
Hipertensión arterial	186 (36.0%)	13 (43.3%)	173 (35.5%)	0.503	173 (35.5%)	155 (33.8%)	18 (64.3%)	0.002
Insuficiencia cardíaca	50 (9.67%)	4 (13.3%)	46 (9.45%)	0.518	46 (9.45%)	42 (9.15%)	4 (14.3%)	0.324
Dislipemia	82 (15.9%)	8 (26.7%)	74 (15.2%)	0.118	74 (15.2%)	68 (14.8%)	6 (21.4%)	0.412
Cáncer	136 (26.3%)	17 (56.7%)	119 (24.4%)	<0.001	119 (24.4%)	106 (23.1%)	13 (46.4%)	0.010
Cirugía neoplásica en los últimos 3 meses	9 (1.74%)	0 (0.00%)	9 (1.85%)	1.000	9 (1.85%)	9 (1.96%)	0 (0.00%)	1.000
Quimioterapia en los últimos 3 meses	55 (10.6%)	10 (33.3%)	45 (9.24%)	<0.001	45 (9.24%)	39 (8.50%)	6 (21.4%)	0.035
Radioterapia en los últimos 3 meses	19 (3.68%)	4 (13.3%)	15 (3.08%)	0.019	15 (3.08%)	13 (2.83%)	2 (7.14%)	0.211
Se aisló microorganismo								
No se buscó o no se identifico	461 (89.2%)	22 (73.3%)	439 (90.1%)	0.010	439 (90.1%)	416 (90.6%)	23 (82.1%)	0.180
Se identificó	56 (10.8%)	8 (26.7%)	48 (9.86%)		48 (9.86%)	43 (9.37%)	5 (17.9%)	

REMS: Rapid Emergency Medicine Score; MDRD IMDS: Modification of Diet in Renal Disease-Isotopic Dilution Mass Spectrometry.

adelante denominaremos HM-M, se caracteriza por su alta capacidad discriminativa, especificidad y aceptable sobreajuste por lo cual es una herramienta clínica apropiada para identificar pacientes en riesgo extremo de fallecer. Este grupo de pacientes podrían beneficiarse de técnicas diagnósticas más intensivas y/o de un seguimiento más estrecho. En referencia a la capacidad discriminativa, el HM-M tiende a ser superior que el modelo REMS que es considerado la referencia a nivel internacional[6]. En nuestro medio, recientemente se reportó un modelo predictivo para mortalidad denominado INFURG-OLDER y que incluye cinco variables (tumor solido con metástasis, insuficiencia respiratoria, insuficiencia renal, hipotensión arterial y disminución del nivel de consciencia) [7]. El modelo, diseñado para ser aplicado en pacientes mayores de 75 años, tiene una buena capacidad discriminativa (AUROC 0,78; IC95% 0,72-0,84). Al estratificar a los pacientes de nuestra muestra entre mayores y menores de 75 años, el modelo HM-M presentó una capacidad discriminativa similar al INFURG-OLDER en paciente mayores de 75 años pero superior en menores de esa edad. Adicionalmente, al aplicarse el modelo HM-M en la cohorte de pacientes utilizada para desarrollar el modelo INFURG-OLDER se aprecia una mínima reducción en el área bajo la curva ROC. Sin embargo, cuando se estratifica por edad, el modelo HM-M aplicado al subgrupo de mayores de 75 años tienen un área prácticamente idéntica a la reportada por el modelo INFURG-OLDER lo cual permite afirmar que la validez externa del modelo es aceptable. En ambos modelos se identifican como variables asociadas a mortalidad la presencia de cáncer, insuficiencia respiratoria y renal. Sin embargo, el HM-M no incluye el efecto de la tensión arterial y la alteración del nivel de conciencia. Esta última no pudo ser analizada en nuestro estudio dado que no fue registrada. Respecto a la edad, el modelo HM-M no la incluye, lo cual significa que esta por sí misma no es un determinante del riesgo de morir cuando hay una infección.

El retraso en la administración del antibiótico apropiado se asocia a un aumento de la mortalidad en pacientes graves [9-11], pero se desconoce el impacto en el resto de los casos [12, 13]. Nuestro estudio no encontró asociación entre el retraso en el inicio de la antibioticoterapia y la mortalidad o la tasa de reingresos. Esto puede deberse a que la mayoría de nuestros pacientes no estuvieran lo suficiente graves según se deduce de la corta estancia media y la baja tasa de mortalidad. A pesar de lo mencionado, debemos aceptar que casi 6 horas de retraso en el inicio de la antibioticoterapia podría ser excesivo y constituir un aspecto a mejorar. Nuestro estudio no fue diseñado para identificar los factores que influyen en la mencionada demora, pero Monclús et al [14] en una encuesta realizada en nuestro medio encontró que los principales factores son: claridad en las órdenes médicas, el conocimiento del efecto que tiene el tratamiento antibiótico empírico precoz en el pronóstico de las infecciones graves y el efecto de la función renal en la prescripción antimicrobiana.

El segundo modelo que se presenta en este estudio, denominado HM-R, a nuestro conocer es el primero que procura estimar el riesgo de reingresos a los 3 meses del alta. Este aspecto es trascendente dado que habitualmente se asume que, cuando se da de alta a un paciente, es porque el equipo médico considera la patología está resuelta o próximo a estarlo y por ende el nuevo reingreso no es esperable.

En referencia a la microbiología, el microorganismo causal se buscó en 1 de cada 4 pacientes lográndose identificar en el 23% de los casos; lo que supone una rentabilidad inferior a la reportada por Sainz-Rodríguez et al (46,5%) [15]. Por otro lado, es de destacar que nuestra tasa de antibioticoterapia inapropiada se aproximó al 20%, inferior al 80% reportado por Fernández-Urrusuno et al [16] y superior al 11,2% reportado por González-del Castillo et al [17]. La diferencia entre los 3 estudios realizados en nuestro medio podría radicar en la metodología aplicada; específicamente, Fernández-Urrusuno et al [16] consideraron en su análisis 668 pacientes con entidades que no requieren antibióticos o no había registro de la infección por lo cual se podría haber magnificado la proporción. Contrariamente, González del Castillo et al [17] asumieron que la antibioterapia fue apropiada en los 217 pacientes que tuvieron cultivos negativos (comunicación personal del autor) lo que podría haber infravalorado la proporción. Nuestra proporción también podría estar infravalorada dado que no consideramos la dosis, ni la duración del tratamiento, ni la sensibilidad *in vitro* del microorganismo. A pesar de las diferencias, es evidente que la antibioticoterapia inapropiada es un factor relevante que debería ser mejorado.

El presente estudio tiene varias limitaciones. Primero, su carácter retrospectivo por lo cual algunas variables [ej. escala de Glasgow o lactacidemia] no se registraron, esto determino la incapacidad de conocer algunas proporciones como la de pacientes con sepsis o shock séptico. No obstante, desde nuestro punto de vista, esta carencia no reduce el impacto de los resultados dado que los modelos predictivos tienen elevada capacidad discriminatoria. Segundo, de acuerdo a la práctica clínica habitual, el diagnóstico de infección bacteriana se basó en la opinión del facultativo del servicio de emergencias por lo cual es posible que algunas infecciones consideradas bacterianas no lo fuesen. Tercero, la tasa de reingresos podría estar infravalorada pues se consideraron solo los pacientes que reingresaron en el HU-HMS. Cuarto, la proporción de pacientes con cultivos positivos fue relativamente baja lo cual imposibilitó realizar un análisis de variables asociadas a este evento.

Sin embargo, el presente estudio también tiene varias fortalezas. Primero, se realizó un robusto análisis estadístico incluyendo la utilización de uno de los modelos más aceptados para la imputación de los valores desconocidos. Este análisis permitió incrementar la potencia del estudio sin modificar el error. Segundo, se definió infección bacteriana de acuerdo al criterio del emergencista sin requerirse cultivos positivos lo cual refleja la práctica clínica habitual. Tercero, la validez externa del modelo HM-M se verifico al aplicarse el modelo a una cohorte independiente y reproducirse el resultado. Cuarto, los modelos descritos se basan en variables habitualmente registradas en el servicio de urgencias por lo cual podrían fácilmente incluirse en el protocolo de asistencia al paciente infectado sin generar costes o carga de trabajo extra. Debemos aceptar

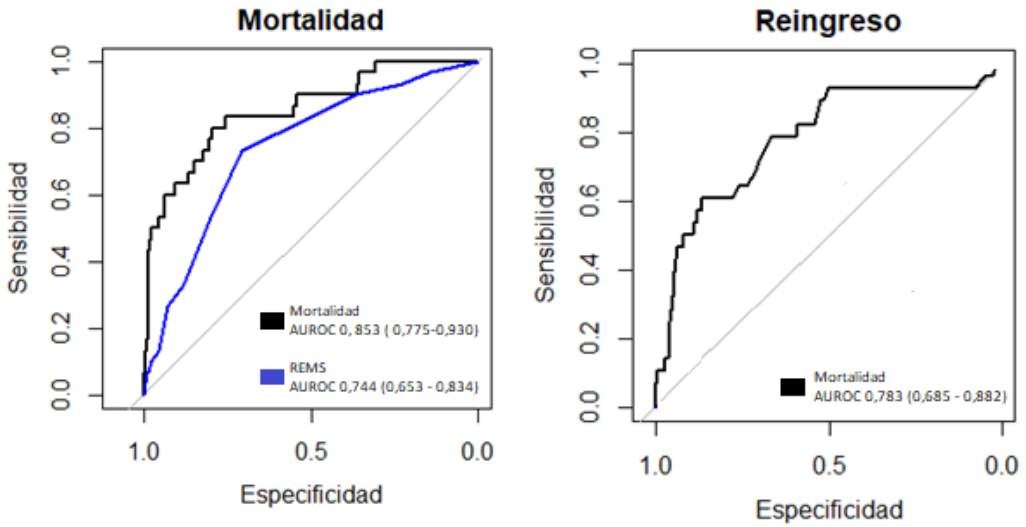

Figura 3 | **Capacidad discriminativa del modelo logístico para mortalidad y reingreso en comparación con la puntuación REMS.**

Comparación de AUROC para mortalidad entre cohorte de derivación y validación p=0.004
REMS: "Rapid Emergency Medicine Score"

que ambos modelos se caracterizan por su baja sensibilidad, por lo cual de cara al futuro podrían beneficiarse de la incorporación de nuevas variables, en especial de biomarcadores moleculares [18-20]. Quinto, la inclusión de todos los pacientes en un periodo de tiempo específico reduce sustancialmente el sesgo de selección.

En suma, el presente estudio muestra que el 28,8% de los ingresos desde urgencias son por infecciones, con una mortalidad hospitalaria del 5,8% y una tasa de reingreso del 5,7%. Se presentan dos modelos denominados HM-M y HM-R con excelente capacidad discriminativa, especificidad pero baja sensibilidad. El modelo HM-M fue validado en una cohorte independiente manteniendo sus características. La demora en el inicio de la antibioticoterapia no se asoció a un efecto deletéreo en la evolución de los pacientes y casi el 20% de los pacientes recibió una antibioticoterapia inapropiada. La incorporación de nuevas tecnologías moleculares para la rápida identificación del microorganismo causal podría colaborar en la mejoría de este problema.

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CONFLICTOS DE INTERÉS

Los autores declaran no tener ningún conflicto de intereses.

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Healthcare-associated pneumonia: a prospective study in Spain

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ABSTRACT

Objective. The aim of the study was to describe the epidemiological characteristics and factors related to outcome in *Streptococcus pneumoniae* and methicillin-resistant *Staphylococcus aureus* (MRSA) healthcare-associated pneumonia (HCAP).

Patients and method.: A 3-year prospective observational epidemiological case study of HCAP was conducted in seven Spanish hospitals. Microbiological and patient characteristics and outcomes were collected and classified by causative pathogen into 4 categories: "*S. pneumoniae*", "MRSA", "Others" and "Unknown". Patients were followed up 30 days after discharge.

Results. A total of 258 (84.6%) patients were enrolled (170 were men [65.9%]). Mean age was 72.4 years ± 15 years (95% CI [70.54-74.25]). The etiology of pneumonia was identified in 73 cases (28.3%): *S. pneumoniae* in 35 patients (13.6%), MRSA in 8 (3.1%), and other microorganisms in 30 patients (11.6%). Significant differences in rates of chronic obstructive pulmonary disease ($p < 0.05$), previous antibiotic treatment ($p < 0.05$), other chronic respiratory diseases, inhaled corticosteroids ($p < 0.01$), and lymphoma ($p < 0.05$) were observed among the four groups. Patients with MRSA pneumonia had received more previous antibiotic treatment (87.5%). Thirty-three (12.8%) patients died during hospitalisation; death in 27 (81.2%) was related to pneumonia.

Conclusions. The etiology of HCAP was identified in only one quarter of patients, with *S. pneumoniae* being the most prevalent microorganism. Patients with chronic respiratory diseases more frequently presented HCAP due to MRSA than to *S. pneumoniae*. Death at hospital discharge was related in most cases to pneumonia.

Keywords: Healthcare-associated pneumonia; *S. pneumoniae*; methicillin resistant- *Staphylococcus aureus*.

Neumonía asociada a cuidados sanitarios: un estudio prospectivo en España

RESUMEN

Objetivo. Describir las características epidemiológicas y factores relacionados con la neumonía asociada a cuidados sanitarios (NACS) causada por *Streptococcus pneumoniae* y *Staphylococcus aureus* resistente a meticilina (SARM).

Pacientes y métodos. Estudio epidemiológico observacional prospectivo de casos a 3 años en siete hospitales españoles. Se recogieron las características microbiológicas y de los pacientes y sus resultados y se clasificaron en función del patógeno causante en 4 categorías: "*S. pneumoniae*", "SARM", "Otros" y "Desconocido". Al alta, se realizó un seguimiento de 30 días.

Resultados. Se incluyeron 258 (84,6%) pacientes (170 hombres [65.9%]; edad media 72,4 años ± 15 años (95% IC [70,54-74,25]). La etiología de la neumonía se identificó en 73 casos (28,3%): *S. pneumoniae* en 35 pacientes (13,6%), SARM en 8 (3,1%) y otros microorganismos en 30 pacientes (11,6%). Hubo diferencias significativas en tasas de enfermedad pul-

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monar obstructiva crónica ($p < 0,05$), tratamiento antibiótico previo ($p < 0,05$), otras enfermedades respiratorias crónicas, corticoides inhalados ($p < 0,01$) y linfoma ($p < 0,05$) entre los cuatro grupos. Los pacientes con NACS causada por SARM recibieron tratamiento antibiótico previo en mayor medida (87,5%). Treinta y tres (12,8%) pacientes murieron durante la hospitalización; en 27 (81,2%) debido a la neumonía.

Conclusiones. Se identificó la etiología de la NACS en solo un cuarto de los pacientes, siendo *S. pneumoniae* el patógeno más frecuente. En los pacientes con enfermedades respiratorias crónicas fue más frecuente la NACS causada por SARM. La muerte tras el alta hospitalaria se relacionó con la neumonía en la mayoría de los casos.

Palabras clave: neumonía asociada a cuidados sanitarios; *S. pneumoniae*; *Staphylococcus aureus* resistente a meticilina.

INTRODUCTION

Pneumonia has traditionally been classified as either community-acquired (CAP) or hospital-acquired pneumonia (HAP), with both entities being characterised by different microbiological profiles [1]. However, over the years, this classification has become less clear, leading in 2005 to the appearance of a new category called healthcare-associated pneumonia (HCAP). HCAP is used to define pneumonia that develops in non-hospitalised patients who are in frequent contact with the healthcare environment and who appear to be at increased risk of infection with multi-drug resistant (MDR) pathogens [2, 3] and a poorer outcome than patients with CAP [2, 4-6]. As a result, a different approach is required when selecting empiric antibiotic therapy in these cases [2, 3, 7-10]. However, it is important to bear in mind that the concept of HCAP has been the subject of debate in recent years, and that several studies have recently questioned our capacity to identify resistant pathogens [11-14].

One of the challenges in the correct management of patients with pneumonia is achieving an accurate microbiological diagnosis. Despite the availability of several tests, the etiologic agent remains unidentified in at least 50% of CAP cases [15, 16]. Globally, *Streptococcus pneumoniae* is the most frequently identified etiologic agent in both CAP and HCAP patients [17, 18], including in Spain [6, 19]. Importantly, methicillin-resistant *Staphylococcus aureus* (MRSA) has also been identified as an important causative agent in pneumonia, especially HCAP. Although its incidence is variable in America and Europe, recent studies conducted in Italy and Spain have identified MRSA as a causative agent in 7%-12.3% of cases [7, 20].

Since an accurate diagnosis is not always possible, we conducted a prospective observational epidemiological study in seven hospitals from different locations across Spain to describe the epidemiological characteristics and factors related to outcome in *S. pneumoniae* and MRSA HCAP.

PATIENTS AND METHODS

Study design. A multicentre prospective study was conducted between October 2013 and August 2016 in seven hospitals in Spain.

The study was performed in accordance with the Declaration of Helsinki, the protocol was reviewed and approved by the Institutional Ethics Committee of Cantabria (Spain) (reference 24/2013) and at all participating hospitals, according to local standards, and informed consent was obtained from each patient. The study was non-interventional, and patients were managed according to the criteria of their treating physicians.

Patients and definitions. Patients ≥ 18 years of age admitted with HCAP with new infiltrates on a chest X-ray and hospitalised at least for 24h in any of the participating hospitals were evaluated. Criteria for bloodstream infection described elsewhere were followed for patient classification [9]. Inclusion criteria were: hospitalisation in an acute care facility for ≥ 2 days within 90 days before the infection; residence in a nursing home or long-term-care facility; intravenous antibiotic therapy, chemotherapy, or wound care, within 30 days before the infection; or regular hospital visits or haemodialysis [3].

In addition, for inclusion in the study, a sample of blood or normally sterile fluid (pleural fluid, cerebrospinal fluid or peritoneal fluid) with or without a corresponding respiratory sample was required (obtained before antibiotic treatment or in the first 24h after starting antibiotic treatment).

Pneumonia was classified into two categories, complicated or non-complicated, depending on clinical presentation. Complicated pneumonia was defined by the presence of lung parenchymal infiltrates and pleural effusions of any size or character on chest X-ray or computed tomography, and body temperature > 38°C [21].

Treatment failure was defined as persistence or progression of clinical symptoms/signs of pneumonia after two days of treatment, or progression of chest X-ray anomalies, or the development of new pulmonary or extra-pulmonary clinical symptoms/signs of pneumonia consistent with an active infection.

Microbiological evaluation. Normally sterile fluids (pleural fluid, cerebrospinal fluid or peritoneal fluid), nasopharyngeal swabs and blood were cultured. *S. pneumoniae* and MRSA isolates were tested for antibiotic susceptibility by microdilution according to Clinical and Laboratory Standards Institute (CLSI) recommendations [22]. Furthermore, all nasopharyngeal swabs were subjected to real time PCR, targeting *lytA* for the detection of *S. pneumoniae* [23]. Pneumococcal urinary antigen was detected using the BinaxNOW kit without concentration (Binax Inc., Portland, ME, USA).

Data collection and follow-up. The following patient data were collected: sex, age, place of residence, admission and discharge date if applicable, epidemiological and medical conditions, microbiological study results, history of vaccination, and outcomes. The Charlson Comorbidity Index (CCI) score was calculated to assess comorbidity [24] and CURB-65 and PORT Severity Index (PSI) scores were calculated to stratify patients according to risk of mortality [25, 26].

Follow-up was performed in outpatient clinics or by telephone thirty days after discharge, and included requirement of a new hospitalisation, whether related or not to the HCAP episode, and mortality, whether related or not to pneumonia.

Data were analysed in two different ways. An initial analysis was conducted according to the presence or absence of *S. pneumoniae* or MRSA, since *S. pneumoniae* colonisation is considered a pre-requisite for pneumococcal infections [27] and several studies have confirmed that MRSA nasal colonisation is a risk factor for subsequent infection [28]. To maximise results, all samples that were positive for either colonisation or infection were included. A second analysis according to the causative agent identified in each of the participating centres' laboratories was performed, and results were classified into four different categories: "*S. pneumoniae*", "MRSA", "Others" and "Unknown".

Statistical analysis. The results were analysed using a commercially available statistical software package (SPSS, version 17.0; SPSS Inc., Chicago, Illinois, USA). Data were expressed as mean value ± standard deviation (SD) or median value and interquartile range (IQR). Chi-squared (χ^2) and Fisher exact test or likelihood ratio were used for categorical variables, and the 2-tailed t test or Mann-Whitney test for continuous variables, as appropriate. Statistical significance was set at $\alpha = 0.05$.

RESULTS

Between October 2013 and September 2016, 305 patients in seven Spanish hospitals were considered for inclusion in the study (Figure 1). Of these, 47 (15.4%) were ineligible because they did not meet any of the inclusion criteria. A total of 258 (84.6%) subjects were finally enrolled and subsequently analysed; 170 were men (65.9%). Patient distribution according to hospital of origin was as follows: 74 (23.7%) from hospital 1; 78 (30.2%) from hospital 2; 24 (9.3%) from hospital 3; 18 (7%) from hospital 4; 36 (14%) from hospital 5; 19 (7.4%) from hospital 6, and 9 (3.5%) from hospital 7. Mean age overall was 72.4 years (SD: 15 years) (95% CI [70.54-74.25]) and there were no age differences between HCAP patients colonised or infected with *S. pneumoniae* (72.6 years; SD = 11.6) or MRSA (70.6 years; SD = 17.0).

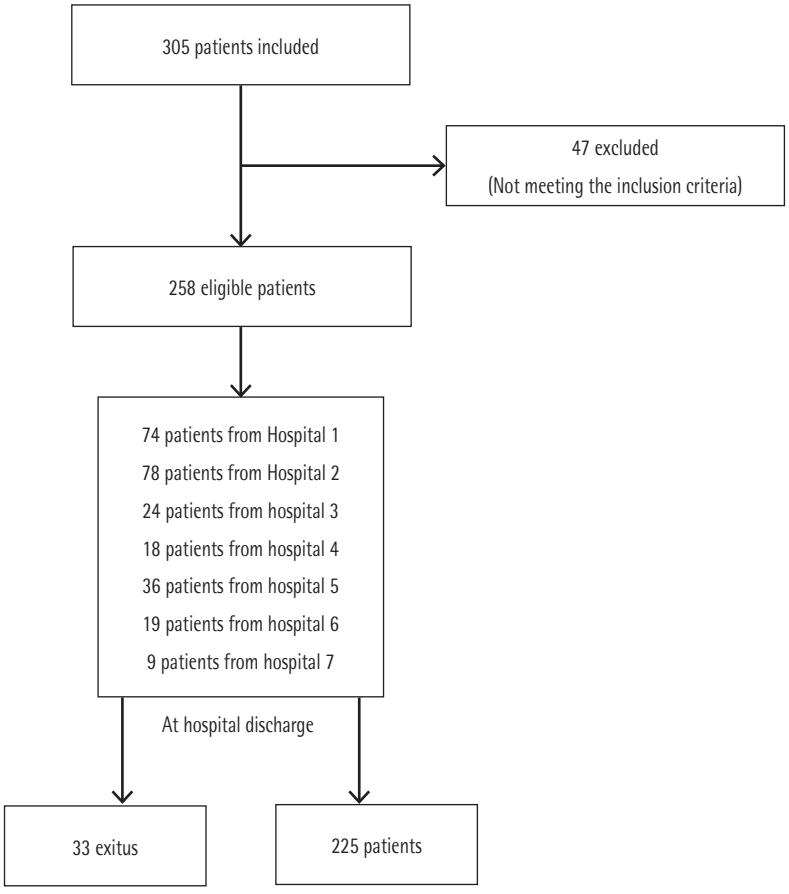

Figura 1 | **Flow chart representing study methodology.**

Table 1 **Patient's clinical characteristics according to the presence or absence of either *Streptococcus pneumoniae* or methicillin-resistant *Staphylococcus aureus*.**

	S. pneumoniae		p-value	MRSA		p-value
	Presence n = 64	Absence n = 194		Presence n = 30	Absence n = 228	
Age, mean ± SD	71.22 ± 13.99	72.78 ± 15.52	0.218	75.3 ± 15.92	72.01 ± 15.04	0.276
Sex, n (%)						
Male	42 (65.6)	128 (66)	0.959	20 (66.7)	150 (65.8)	0.924
Female	22 (34.4)	66 (34)		10 (33.3)	78 (34.2)	
Relevant history, n (%)						
Hospitalisation (previous 2 months)	29 (45.3)	96 (45.9)	0.563	16 (53.3)	109 (47.8)	0.569
Malignancy	25 (39.1)	68 (35.1)	0.562	5 (16.7)	88 (38.6)	0.019
COPD	19 (29.7)	60 (30.9)	0.852	16 (53.3)	63 (27.6)	0.004
Previous pneumonia	21 (32.8)	55 (28.4)	0.497	13 (43.3)	63 (27.6)	0.076
Diabetes	17 (26.6)	54 (27.8)	0.843	7 (23.3)	64 (28.1)	0.585
Institutionalised patients	22 (34.4)	48 (24.7)	0.133	15 (50)	55 (24.1)	0.003
Heart failure	13 (23.3)	52 (26.8)	0.300	11 (36.7)	54 (23.7)	0.124
Previous antibiotic treatment	38 (59.4)	106 (54.6)	0.508	21 (70)	123 (53.9)	0.096
Previous chemotherapy (in the last 30 days)	14 (21.9)	32 (16.5)	0.330	1 (3.3)	45 (19.7)	0.027
Antibiotic treatment (7 days prior to hospital admission):						
Yes	17 (44.7)	52 (49.1)	0.647	9 (42.9)	60 (48.8)	0.616
No	21 (55.3)	54 (50.9)		12 (57.1)	63 (51.2)	
With penicillin	6 (35.3)	9 (17.3)	0.119	2 (22.2)	13 (21.7)	0.970
With cephalosporins	1 (5.88)	6 (11.5)	0.503	3 (33.3)	4 (6.7)	0.013
With macrolides	0 (0)	5 (9.6)	0.184	0 (0)	5 (8.3)	0.369
With quinolones	5 (29.41)	20 (38.5)	0.500	3 (33.3)	22 (36.7)	0.846
Antibiotic treatment (8 days-2 months prior to hospitalisation):						
Yes	30 (78.9)	86 (81.1)	0.770	5 (23.8)	23 (18.7)	0.584
No	8 (21.1)	20 (19.9)				
With penicillin + β-lactamase inhibitor	10 (33.3)	19 (22.1)	0.221	2 (12.5)	27 (27)	0.214
With cephalosporin	3 (10)	14 (16.3)	0.402	4 (25)	13 (13)	0.208
With macrolides	0 (0)	3 (3.5)	0.300	0 (0)	3 (3)	0.483
With quinolones	11 (36.7)	25 (29.1)	0.439	5 (31.3)	31 (31)	0.984
Previous pneumococcal vaccinations						
Yes	23 (35.9)	80 (41.2)		13 (43.3)	90 (39.5)	
No	25 (39.1)	67 (34.5)	0.289	11 (36.7)	81 (35.5)	0.827
Unknown	16 (25)	47 (24.2)		6 (20)	57 (25)	
Comorbidities, n (%)						
CCI, median (range):	2 (2.56-3.63)	3 (2.99-3.65)	0.490	3 (2.33-3.81)	3 (2.99-3.59)	0.603
Absence of comorbidity	13 (20.3)	46 (23.7)		7 (23.3)	52 (22.8)	
Low comorbidity	20 (31.3)	41 (21.1)	0.255	6 (20)	55 (24.1)	0.875
High comorbidity	31 (48.4)	107 (55.2)		17 (56.7)	121 (53.1)	
Heart failure	3 (4.7)	21 (10.8)	0.481	12 (40)	53 (23.2)	0.047
Chronic respiratory disease	27 (42.2)	76 (39.2)	0.670	20 (66.7)	83 (36.4)	0.001
Moderate/severe chronic liver disease	2 (3.1)	0 (0)	0.013	0 (0)	19 (8.3)	0.607
CURB-65 score, n (%)						
0-1 (1.5% mortality)	24 (39.3)	58 (31)		9 (32.1)	73 (33.2)	
2 (9.2% mortality)	16 (26.2)	65 (34.8)	0.370	6 (21.4)	75 (34.1)	0.270
≥3 (22% mortality)	21 (34.4)	64 (34.2)		13 (46.4)	72 (32.7)	
PSI class, n (%)						
I-II	5 (8.8)	16 (8.8)		4 (15.3)	17 (8)	
III	11 (19.3)	25 (13.8)	0.427	4 (15.4)	32 (15.1)	0.519
IV-V	41 (72)	140 (77.3)		18 (69.3)	163 (76.9)	

CCI, Charlson comorbidity index; MRSA, Methicillin-resistant *Staphylococcus aureus*; PSI, *Pneumonia* Severity Index; SD, standard deviation; *S. pneumoniae*, *Streptococcus pneumoniae*

Table 2 **Hospitalisation-related events and follow-up according to the presence or absence of either *Streptococcus pneumoniae* or methicillin-resistant *Staphylococcus aureus*.**

	S. pneumoniae		p-value	MRSA		p-value
	Presence	Absence		Presence	Absence	
	n = 64	n = 194		n = 30	n = 228	
Treatment failure, n (%)	4 (6.3)	34 (17.5)	0.027	6 (20)	32 (14)	0.386
Length of stay, mean ± SD	9.5 ± 6.34	11.31 ± 8.92	0.291	11.03 ± 5.95	10.84 ± 8.66	0.285
Antibiogram-guided treatment, n (%)						
Yes	25 (39.1)	28 (14.4)	0.000	13 (43.3)	40 (17.5)	0.001
No	39 (60.9)	166 (85.6)				
With penicillin + β-lactamase inhibitor	3 (12)	10 (35.7)	0.045	4 (30.8)	9 (22.5)	0.547
With cephalosporins	10 (40)	5 (17.9)	0.074	2 (15.4)	13 (32.5)	0.234
With quinolones	1 (4)	2 (7.1)	0.201	0 (0)	0 (0)	0.398
Patient status at hospital discharge, n (%)						
Cure without sequelae	54 (84.4)	151 (77.8)		20 (66.7)	185 (81.1)	
Cure with sequelae	4 (6.3)	16 (8.2)	0.526	4 (13.3)	16 (7)	0.179
Death	6 (9.4)	27 (13.9)		6 (20)	27 (11.8)	
Death related to pneumonia						
Yes	5 (83.3)	22 (81.5)	0.915	4 (66.7)	23 (85.2)	0.287
No	1 (16.7)	5 (18.5)		2 (33.3)	4 (14.8)	
Follow-up within 30 ± 7 days of discharge, n (%)						
Yes	49 (76.6)	150 (77.3)	0.900	19 (63.3)	180 (78.9)	0.056
No	15 (23.4)	44 (22.7)		11 (36.7)	48 (21.1)	
Radiographic resolution						
Complete	17 (35.4)	57 (41)		2 (12.5)	72 (42.1)	
Partial	7 (14.6)	41 (29.5)	0.021	4 (25)	44 (25.7)	0.023
Unknown	24 (50)	41 (29.5)		10 (62.5)	55 (32.2)	
Resistant sequelae						
Yes	47 (97.9)	126 (90.6)		14 (87.5)	159 (93)	
No	1 (2.1)	12 (8.6)	0.253	2 (12.5)	11 (6.4)	0.648
Unknown	0 (0)	1 (0.7)		0 (0)	1 (0.6)	

MRSA, Methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; *S. pneumoniae*, *Streptococcus pneumoniae*

Previous pneumococcal vaccination was reported in 103 of the 258 patients (39.9%), 93 (90.3%) of whom had received the polysaccharide vaccine (PPSV), three patients (2.9%) had received the conjugated vaccine (PCV), one patient (1%) had received both PCV + PPSV, and the type of vaccine was unknown in six cases (5.8%).

Patient characteristics according to presence or absence of either *S. pneumoniae* or MRSA. Of the 258 samples tested by PCR for *S. pneumoniae* identification, 53 were positive. The remaining 205 negative specimens were further tested, yielding one culture-positive sample and 10 BINAX-positive samples. As a result, 64 cases (24.9%) of *S. pneumoniae* were identified. Furthermore, the serotype was identified in 14 of these samples; the identified serotypes included ST11A, *n* = 3, 21.4%; ST8, *n* = 2, 14.3%; and one case each of the following: ST1, ST7F, ST6C, ST9N, ST10A, ST16F, ST22, ST31, ST35B (*n* = 1, 7.1% for each).

MRSA was identified in 30 patients (11.6%), six of which were isolated from normally sterile fluid samples such as blood or pleural fluid, or from the corresponding respiratory sample and nasopharyngeal exudates in the remaining 24.

Clinical data according to the presence or absence of either *S. pneumoniae* or MRSA are shown in Table 1. As observed among the patients with significant medical histories, malignancy and previous chemotherapy (in the last 30 days) were more frequent in patients in whom MRSA was not isolated,

Table 3 | **Patient's clinical characteristics according to causative pathogen**

	S. pneumoniae (n = 35)	MRSA (n = 8)	Other microorganisms (n = 30)	Unknown (n = 185)	Total (n = 258)	p-value
Age, mean ± SD	72.57 ± 11.60	70.63 ± 13.15	73.93 ± 17.03	72.19 ± 15.58	72.40 ± 15.15	0.780
Sex, n (%)						
Male	24 (68.6)	7 (87.5)	19 (63.3)	19 (63.3)	170 (65.9)	0.522
Female	11 (31.4)	1 (12.5)	11 (36.7)	11 (36.7)	88 (34.1)	
Patient-related factors, n (%)						
Hospitalisation (previous 2 months)	17 (48.6)	5 (62.5)	19 (63.3)	84 (45.4)	125 (48.4)	0.266
Malignancy	17 (48.6)	4 (50)	9 (30)	63 (34.1)	93 (36)	0.290
COPD	12 (34.3)	3 (37.5)	16 (53.3)	48 (25.9)	79 (30.6)	<0.05
Previous pneumonia	8 (22.9)	2 (25.0)	10 (33.3)	56 (30.3)	76 (29.5)	0.772
Diabetes	7 (20)	1 (12.5)	8 (26.7)	55 (29.7)	71 (27.5)	0.462
Institutionalised patients	9 (25.7)	2 (25)	11 (36.7)	48 (25.9)	70 (27.1)	0.686
Heart failure	7 (20)	1 (12.5)	10 (33.3)	47 (25.4)	65 (25.2)	0.510
Previous antibiotic treatment	21 (60)	7 (87.5)	21 (70)	95 (51.4)	144 (55.8)	<0.05
Antibiotic treatment (7 days prior to hospital admission):						
Yes	9 (42.9)	2 (28.6)	8 (38.1)	50 (52.6)	69 (47.9)	0.396
With penicillins	3 (33.3)	1 (50)	0 (0)	5 (10)	15 (21.7)	0.149
With cephalosporins	0 (0)	1 (50)	0 (0)	6 (12)	7 (10.1)	0.120
With macrolides	0 (0)	0 (0)	1 (12.5)	4 (8)	5 (7.2)	0.579
With quinolones	2 (22.2)	1 (50)	5 (62.5)	17 (34)	25 (36.2)	0.340
Antibiotic treatment (8 days-2 months prior to hospitalisation):						
Yes	16 (76.2)	6 (85.7)	18 (85.7)	76 (80)	116 (80.6)	0.055
With aminopenicillins	7 (43.8)	1 (16.7)	3 (16.7)	18 (23.7)	29 (25)	0.296
With cephalosporins	1 (6.3)	1 (16.7)	4 (22.2)	11 (14.5)	17 (14.7)	0.745
With macrolides	0 (0)	0 (0)	1 (5.6)	2 (2.6)	3 (2.6)	0.467
With quinolones	6 (37.5)	3 (50)	7 (38.9)	20 (26.3)	36 (31)	0.267
Previous pneumococcal vaccinations						
Yes	14 (40)	2 (25)	12 (40)	75 (40.5)	103 (39.9)	0.951
No	13 (37.1)	4 (50)	12 (40)	63 (34.1)	92 (35.7)	
Unknown	8 (22.9)	2 (25)	6 (20)	47 (25.4)	63 (24.4)	
Current inhaled corticosteroid treatment, n (%)						
Yes	12 (34.3)	2 (25)	13 (43.3)	32 (17.3)	59 (22.9)	<0.01
No	23 (65.7)	6 (75)	17 (56.7)	153 (82.7)	199 (77.1)	
Comorbidities, n (%)						
CCI, median (range):	2 (2.44-4.01)	3.5 (1.48-5.77)	3 (2.91-3.59)	3 (2.91-3.59)	3 (2.99-3.54)	0.973
Absence of comorbidity	6 (17.1)	2 (25)	5 (16.7)	46 (24.9)	59 (22.9)	
Low comorbidity	13 (37.1)	0 (0)	6 (20)	42 (22.7)	61 (23.6)	0.955
High comorbidity	16 (45.7)	6 (75)	19 (63.3)	97 (52.4)	138 (53.5)	
Chronic respiratory disease	17 (48.6)	4 (50)	18 (60)	64 (34.6)	103 (39.9)	<0.05
Lymphoma	6 (17.1)	0 (0)	0 (0)	13 (7)	19 (7.4)	<0.05
CURB-65 score, n (%)						
0-1	14 (41.2)	3 (50)	9 (31)	56 (31.3)	82 (33.1)	
2	10 (29.4)	3 (50)	9 (31)	59 (33)	81 (32.7)	0.371
≥3	10 (29.4)	0 (0)	11 (37.9)	64 (35.8)	85 (34.3)	
PSI class, n (%)						
I-II	2 (6.3)	0 (0)	3 (10.3)	16 (9.5)	21 (8.8)	
III	6 (18.8)	3 (37.5)	3 (10.3)	24 (4.2)	36 (15.1)	0.691
IV-V	24 (75)	5 (62.5)	23 (79.3)	129 (76.3)	181 (76.1)	
Presentation of pneumonia at hospital admission						
Non-complicated pneumonia	14 (40)	3 (37.5)	6 (20)	86 (46.5)	109 (42.2)	0.043
Complicated pneumonia	21 (60)	5 (62.5)	24 (80)	99 (53.5)	149 (57.8)	
Presentation of pneumonia at hospital admission (patients with COPD)						
Non-complicated pneumonia	5 (41.7)	1 (33.3)	2 (12.5)	24 (50)	32 (40.5)	0.043
Complicated pneumonia	7 (58.3)	2 (66.7)	14 (87.5)	24 (50)	47 (59.5)	

CCI, Charlson Comorbidity Index; COPD, Chronic Obstructive Pulmonary Disease; MRSA, Methicillin-resistant *Staphylococcus aureus*; PSI, Pneumonia Severity Index; *S. pneumoniae*, *Streptococcus pneumoniae*;

Table 4 Hospitalisation-related events and follow-up according to pneumonia-causing pathogen

	S. pneumoniae (n = 35)	MRSA (n = 8)	Others microorganisms (n = 30)	Unknown (n = 185)	Total (n = 258)	p-value
Treatment failure, n (%)	3 (8.6)	2 (25)	4 (13.3)	29 (15.7)	38 (14.7)	0.576
Length of stay (days), mean ± SD	9.57 ± 6.77	22.13 ± 16.31	13.17 ± 10.61	10.24 ± 7.39	10.86 ± 8.38	0.005
Patient status at hospital discharge, n (%)						
Cure without sequelae	30 (85.7)	3 (37.5)	26 (86.7)	146 (78.9)	205 (79.5)	
Cure with sequelae	2 (5.7)	3 (37.5)	3 (10)	12 (6.5)	20 (7.8)	0.047
Death	3 (8.6)	2 (25)	1 (3.3)	27 (14.6)	33 (12.8)	
Death related to pneumonia						
Yes	3 (100)	0 (0)	1 (100)	23 (85.2)	27 (81.2)	0.034
No	0 (0)	2 (100)	0 (0)	4 (14.8)	6 (18.2)	
Follow-up within 30 ± 7 days of discharge, n (%)						
Yes	29 (82.9)	4 (50)	28 (93.3)	138 (74.6)	199 (77.1)	0.020
No	6 (17.1)	4 (50)	2 (6.7)	47 (25.4)	59 (22.9)	
Radiographic resolution						
Complete	15 (51.7)	1 (25)	9 (36)	49 (38)	74 (39.6)	
Partial	4 (13.8)	1 (25)	4 (16)	39 (30.2)	48 (25.7)	0.315
Unknown	10 (34.5)	2 (50)	12 (48)	41 (31.8)	65 (34.8)	
Resistant sequelae						
Yes	1 (3.4)	1 (25)	3 (12)	173 (92.5)	13 (7)	
No	28 (96.6)	3 (75)	22 (88)	120 (93)	48 (25.7)	0.731
Unknown	10 (34.5)	2 (50)	12 (48)	41 (31.8)	65 (34.8)	

MRSA, Methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; *S. pneumoniae*, *Streptococcus pneumoniae*

while institutionalisation and COPD were more common in the MRSA-positive patient group. No differences in any comorbidities were detected according to the presence or absence of *S. pneumoniae*. No differences were observed in previous antibiotic treatment, regardless of the presence or absence of either *S. pneumoniae* or MRSA. However, treatment with cephalosporins seven days prior to hospital admission was significantly more frequent in patients with MRSA (n = 3; 33.3% *vs.* n = 4; 6.7%, $p < 0.05$). Previous pneumococcal vaccination was reported in 23 patients (35.9%) in the *S. pneumoniae* group; of these, 22 (95.7%) had received the polysaccharide vaccine (PPSV). In the MRSA group, 13 patients (43.3%) had previously received pneumococcal vaccination; of these, 12 (92.3%) had received PPSV and only one patient had received the conjugated vaccine (7.7%).

CCI score was also calculated, and no differences were found between the groups colonised or infected with either *S. pneumoniae* or MRSA and their respective control groups. Interestingly, specific comorbidities were significantly more frequent in groups that were positive for any of the pathogens, including the incidence of heart failure and chronic respiratory disease in the MRSA-positive group (n = 12; 40% *vs.* n = 53; 23.2% , $p < 0.05$; n = 20; 66.7% *vs.* n = 83; 36.4% , $p = 0.001$ respectively), and the incidence of moderate/severe chronic liver disease in the *S. pneumoniae*-positive group (n = 2; 3.1% *vs.* n = 0; 0% , $p < 0.05$).

No significant differences in CURB-65 and PSI scores were reported between the groups.

Outcomes according to the presence or absence of either *S. pneumoniae* or MRSA. Relevant data are presented in Table 2. Treatment failure rates were higher in patients not infected or colonised by *S. pneumoniae* (n = 34; 17.5% *vs.* n = 4; 6.3%, $p < 0.05$). There were no differences in the mean length of stay (LOS) among the groups. Treatment was guided by antibiogram significantly more often in groups in which either *S. pneumoniae* or MRSA were identified ($p < 0.001$ and $p = 0.001$, respectively). Treatment with a penicillin plus a β-lactamase inhibitor was more common in the group in which *S. pneumoniae* was not identified (n = 10; 35.7% *vs.* n = 3; 12%, $p < 0.05$).

Although death was more frequently reported in the absence of either *S. pneumoniae* (n = 27; 13.9% *vs.* n = 6; 9.4%) or MRSA (n = 27; 11.8% *vs.* n = 6; 20%), the differences were not statistically significant.

Patient characteristics according to causative agent. The etiology of pneumonia was identified in 73 of the 258 patients (28.3%). *S. pneumoniae* was identified in 35 cases (13.6%), MRSA in 8 (3.1%), and other microorganisms were identified in 30 cases (11.6%). In the latter group, the most common microorganisms were *Escherichia coli* (n = 5, 16.7%), followed by *Klebsiella pneumoniae* (n = 4, 13.3%) and *Haemophilus influenzae* (n = 3, 10%).

Clinical data are shown in Table 3. Among patient-related factors, the incidence of chronic obstructive pulmonary disease (COPD) (n = 79; 30.6%) differed significantly depending on the HCAP causative agent ($p < 0.05$) and was higher in the group of microorganisms other than *S. pneumoniae* and MRSA ("Others" group). A total of 144 patients (55.8%) had received previous antibiotic treatment, with a higher prevalence in the MRSA group (n = 7; 87.5%) compared to the other categories ($p < 0.05$). Regarding comorbidity, there was no difference in the CCI score among the analysed groups, with more than half of the patients showing high comorbidity (n = 138; 53.5%). However, the incidence of chronic respiratory disease and lymphoma was significantly higher in the "Others" and "*S. pneumoniae*" groups, respectively ($p < 0.05$ in both cases).

No significant differences among groups were reported in comorbidity measured with the CURB-65 and PSI scores. The most frequent comorbidity was complicated pneumonia (n = 149; 57.8%), that also showed differences among the groups (*S. pneumoniae*: n = 21; 60%; MRSA: n = 5; 62.5%; Others: n = 24; 80%; Unknown: n = 99; 53.5%. $p < 0.05$). Complicated pneumonia was also more common than non-complicated pneumonia in the 79 patients with COPD (n = 47; 59.5% and n = 32; 40.5% respectively), and the incidence of complicated pneumonia was also significantly related to the etiology of the episode (*S. pneumoniae*: n = 7; 58.3%; MRSA: n = 2; 66.7%; Others: n = 14; 87.5%; Unknown: n = 24; 50%. $p < 0.05$).

Outcomes according to HCAP causative agent. Relevant data are presented in Table 4. Thirty-eight patients (14.7%) were treatment failures. Mean LOS was 10.86 days ± 8.38 days [95% CI (9.83-11.89)] and differed according to the etiology of pneumonia ($p < 0.01$), with the longest stays recorded in the MRSA group [22.13 days ± 16.31 days; 95% CI (8.49-35.76)] compared to the other categories.

Overall, 33 (12.8%) patients died during hospitalisation, 27 (81.2%) of which were considered related to pneumonia. Of these cases, 3 were caused by *S. pneumoniae*, one by other microorganisms, and in 23 cases the etiology was unknown. These differences were statistically significant ($p < 0.05$).

A follow-up visit within 30 ± 7 days of discharge was successfully performed in 199 patients (77.1%).

DISCUSSION

Our data provides an updated overview of the epidemiological status of HCAP in Spain. To our knowledge, this is the first study in which these patients were evaluated according to the etiology of pneumonia and according to the presence or absence of two of the most relevant pathogens implicated in the disease, *S. pneumoniae* and MRSA.

Our results show that *S. pneumoniae* is the most frequent causative agent of pneumonia identified in our population, confirming the results of previous studies conducted in Spain [6, 19, 29], United Kingdom [30] and Japan [4]. However, it is interesting to observe that the etiology of pneumonia could not be determined in most patients, something that underlines two diagnostic-related issues widely discussed in the literature: the lack of sensitivity of conventional cultured-based methods and the difficulty of obtaining good quality specimens from the lower respiratory tract [31, 32]. Taking into account these problems, we performed an analysis based on the causative agent, and also included patients in whom etiology could not be determined.

In our series, a previous history of COPD was the third most frequent clinical characteristic reported. COPD also showed significant differences when pneumonia was classified according to etiology, being most common in the "Others" group. Interestingly, chronic respiratory diseases identified at presentation was the comorbidity that was also most frequent in patients with pneumonia due to causative agents other than MRSA or *S. pneumoniae*. Our results confirmed that, on the one hand, COPD is common in HCAP patients. Indeed, previous studies have demonstrated that its incidence as a comorbid condition is comparable to [19] or even higher than in CAP patients [29], in whom COPD can also be considered as the most frequent comorbidity associated with the development of pneumonia [33]. In view of the available data, it is tempting to think that this might also be the case in HCAP patients. On the other hand, although *S. pneumoniae* is one of the most frequently identified pathogens both in stable periods and in exacerbations in COPD, our results suggest that HCAP patients with this pathology may be exposed to a greater potential risk of presenting colonisation or infections by other microorganisms.

Another important factor was prior use of antibiotics, and indeed, this is one of the criteria that may define an HCAP patient [3]. Interestingly, we found significant differences among the analysed groups, with the MRSA group accounting for a higher proportion of patients who had received previous antibiotic treatment. These results are not surprising considering that prior antibiotic use (particularly cephalosporins and quinolones) is considered one of the major risks for healthcare-associated MRSA infections [34].

Besides these cases of prior antibiotic use, common causative agents such as *S. pneumoniae* and known risk factors for pneumococcal disease, which include many of the comorbidities already mentioned [35], must be taken into account, and the importance of a preventive approach by vaccination for patients with these conditions must be emphasised. In fact, our data also show that, in the *S. pneumoniae group*, only around one-third of patients had received previous pneumococcal vaccinations despite their baseline risk conditions. This highlights the need for including pneumococcal vaccination

as part of routine recommendations for the management of these patients. Although serotype information is limited in this study due to the low numbers, it is interesting to note the presence in HCAP of some of the serotypes most frequently found in CAP cases (1 or 7F, and in the last few years also 8), and the absence of others usually very common in CAP in adults such as serotype 3, as observed in previous studies in Spain [36].

In terms of the risk of mortality, neither CURB-65 nor PSI scores were significantly different according to the etiology of pneumonia, in line with the results suggested in the study by Polverino et al [19]. In this Spanish study, no differences were reported between the agents causing pneumonia when HCAP and CAP patients were compared. However, increased mortality was reported in the former group, which led the authors to conclude that the microbiological etiology could not be the principal cause of the difference.

Clinical outcomes in HCAP patients seem to be worse than in CAP patients [6, 19, 29]. As such, they require longer hospital stays [6] and, as our results suggest, this time depends on the microorganism identified as causative agent. Specifically, patients with MRSA pneumonia showed the longest LOS, underlining the problems that this pathology represents in terms of management and costs, as discussed by other authors [37]. Although it was not possible to evaluate the influence of treatment on outcomes, the etiology of pneumonia appears to be an important factor when evaluating the outcomes and treatment required by these patients. On the other hand, patients' status at hospital discharge also differed according to the causative agent and, although death related to pneumonia was not frequent, it was identified as the cause of death in the two patients with MRSA pneumonia who died. This stresses the need for a special focus on resistant pathogens, that, specifically in the case of MRSA, are the cause of increased mortality and morbidity rates [38, 39]. In line with this, an overall mortality rate of 17.8% was reported at the end of the study, which is within the range of previous estimates for HCAP patients in Spain [19, 29].

From our analysis of cases according to the presence or absence of *S. pneumoniae* or MRSA, our results were particularly relevant in the case of MRSA. First, despite *S. pneumoniae* being the most frequent pathogen reported, we were still able to detect 11.6% cases positive for MRSA, which not only confirms the results obtained by Polverino et al. [19], but also highlights the growing problem of antibiotic resistance. Our data allows us to envisage a MRSA-positive patient profile in which COPD and previous institutionalisation are frequent underlying factors. Indeed, both have been previously recognised as risk factors for MRSA infection [40-43]. Furthermore, heart failure and chronic respiratory diseases were especially frequent in these patients. This illustrates a common problem in clinical practice in the form of delayed resolution of pneumonia, which is often affected by underlying COPD [44], a comorbidity or underlying factor that we also detected in our population.

The concept of HCAP was firstly introduced to define patients at higher risk of antibiotic-resistant pathogens, who would thus require broad-spectrum therapy [2, 3]. However, over the course of this study, an intense debate on the usefulness of that definition in identifying these patients has sprung up. Thus, in recent years, several studies have concluded that the definition of HCAP may be sensitive but lacking in specificity and, as a consequence, it does not accurately identify resistant pathogens [11-14]. Indeed, three recent studies have proposed new methods to define patients with an increased risk of developing pneumonia due to multidrug-resistant bacteria [45-47].

This study has some limitations. Firstly, our sample size was limited, preventing us from making predictions and association analysis. Secondly, microbiological and serotype data on *S. pneumoniae* were also limited, and the impact of certain serotypes on HCAP could not be evaluated. Nevertheless, this multicentre prospective study is the first to evaluate HCAP patients according to the etiology of their pneumonia, thus helping identify risks and prognostic factors that might help to guide treatment in these patients, with enough statistical power.

Therefore, despite the limitations, the results show that the etiology of patients with HCAP is still unknown in most cases, although *S. pneumoniae* appears as the most prevalent microorganism. In patients with COPD, however, a major proportion of HCAP caused by other microorganisms other than *S. pneumoniae* and MRSA was observed. Importantly, death in the overall population within the first month after discharge was related in most of the cases to pneumonia. Our study offers an updated view of the characteristics and outcomes of these patients in the Spanish population, but further research is needed to provide data to help identifying predictive factors for HCAP to improve prevention and management strategies.

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The first 100 cases of COVID-19 in a Hospital in Madrid with a 2-month follow-up

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ABSTRACT

Background. There are few descriptions of the clinical presentation and evolution of consecutive SARS-CoV-2 infections with a long-enough follow up.

Methods. Description of the first consecutive 100 patients with microbiologically-proven COVID-19 in a large hospital in Madrid, Spain including a minimum of two-month follow up.

Results. The median age of the patients (52% males) was 61.5 years (IQR=39.5-82.0) and the median BMI was 28.8 kg/m^2 (IQR=24.7-33.7). Overall 72% of the patients had one or more co-morbid conditions with a median age-adjusted Charlson index of 2 (IQR=0-5.7). Five patients (5%) were immunosuppressed. The most common symptoms at the time of diagnosis were fever (80.0%), cough (53.0%) and dyspnea (23.0%). The median O_2 saturation at the time of first examination was 94% (IQR=90-97). Chest X-ray on admission was compatible with pneumonia in 63% of the cases (bilateral in 42% and unilateral in 21%). Overall, 30% were managed at home and 70% were admitted to the hospital. Thirteen patients were admitted to the ICU with a median of 11 days of stay in the Unit (IQR=6.0-28.0). CALL score of our population ranged from 4 to 13. Overall, 60.0% of patients received antibiotic treatment and 66.0%, empirical antiviral treatment, mainly with lopinavir/ritonavir (65%) or hydroxychloroquine (42%). Mortality, with a minimum of 60 days of follow up, was 23%. The median age of the deceased patients was 85 years (IQR=79-93).

Conclusions. We found a high mortality in the first 100 patients diagnosed with COVID-19 at our institution, associated with advanced age and the presence of serious underlying diseases.

Keywords: SARS-CoV-2, COVID-19, Coronavirus

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Los primeros 100 casos de COVID-19 en un Hospital de Madrid con seguimiento de 2 meses

RESUMEN

Antecedentes. Existen pocas descripciones de la presentación clínica y evolución de infecciones consecutivas por SARS-CoV-2 con un seguimiento lo suficientemente largo.

Métodos. Descripción de los primeros 100 pacientes consecutivos con COVID-19 probada microbiológicamente en un gran hospital de Madrid, incluyendo un seguimiento mínimo de dos meses.

Resultados. La mediana de edad de los pacientes (52% hombres) fue de 61,5 años (RIC=39,5-82,0) y la mediana de IMC fue de 28,8 kg/m^2 (RIC=24,7-33,7). El 72% de los pacientes tuvieron una o más comorbilidades con un índice de Charlson ajustado a la edad de 2 (RIC=0-5,7). Cinco pacientes (5%) estaban inmunodeprimidos. Los síntomas más comunes al momento del diagnóstico fueron fiebre (80,0%), tos (53,0%) y disnea (23,0%). La mediana de saturación de O_2 en el momento del primer examen fue del 94% (RIC=90-97). La radiografía de tórax al ingreso fue compatible con neumonía en el 63% de los casos (bilateral en el 42% y unilateral en el 21%). El 30% fueron manejados en su domicilio y el 70% ingresados en el hospital. Trece pacientes ingresaron en la UCI con una mediana de 11 días de estancia en la Unidad (RIC=6,0-28,0).

El score CALL de nuestra población varió de 4 a 13. En general, el 60,0% de los pacientes recibió tratamiento antibiótico y el 66,0%, tratamiento antiviral empírico, principalmente con lopinavir/ritonavir (65%) o hidroxicloroquina (42%). La mortalidad, con un mínimo de 60 días de seguimiento, fue del 23%. La mediana de edad de los pacientes fallecidos fue de 85 años (RIC=79-93).

Conclusiones. Encontramos una alta mortalidad en los primeros 100 pacientes diagnosticados con COVID-19 en nuestra institución, asociada con edad avanzada y presencia de enfermedades subyacentes graves.

Palabras clave: SARS-CoV-2, COVID-19, Coronavirus

INTRODUCTION

The COVID-19 epidemic is yielding highly variable data on incidence, evolution and mortality from one report to another, largely because the populations described are not comparable. On the other hand, the rush to provide valid scientific information on the epidemic means that many reports are preliminary and do not offer a sufficiently comprehensive perspective on the evolution of patients [1-10].

The first case of COVID-19 was confirmed in the Community of Madrid on February 27th, 2020 in a 24-year-old patient who had recently travelled to northern Italy. On March 1st, 2020, our institution (Hospital General Universitario Gregorio Marañón - HGUGM) admitted the first confirmed case to the Center and within 10 days another 99 patients were diagnosed consecutively. During this period, the diagnosis of SARS-CoV-2 infection was offered exclusively to symptomatic patients.

The criteria for hospital admission was initially systematic but soon those who did not have severity criteria began to be treated at home.

Having these first 100 patients a follow-up of 60, or more days in all cases, our objective is to evaluate this first series, with a special perspective on its presentation, treatment, evolution, and mortality.

MATERIAL AND METHODS

Location of the study. The Hospital General Universitario Gregorio Marañón is a general and reference hospital, linked to the Universidad Complutense, with 1,350 beds, serving a population of approximately 350,000 inhabitants in the southeast area of Madrid. The Centre performs highly complex surgery, attends to patients with malignant diseases of both solid and haematological organs, has a very active transplant programme and is a reference center for many diseases. The Clinical Microbiology and Infectious Diseases Service is a multidisciplinary unit with a long history of care, teaching and research.

Type of study and population. This is a single-centre retrospective observational study that includes the first 100 consecutive patients with a proven diagnosis of COVID-19 in the HGUGM since the beginning of the epidemic, with a minimum follow-up of 60 days after etiological confirmation.

Procedures. The diagnosis of COVID-19 was performed in all cases from nasopharyngeal samples by reverse transcriptase polymerase chain reaction (Roche/Thermo Fisher RT-PCR) with prior extraction of viral RNA by NucliSENS® easyMag® (bioMérieux). A cycle threshold value (Ct-value) of less than 37 was considered positive. PCR (Roche/Thermo Fisher RT-PCR) from nasopharyngeal exudate was performed from the virus medium in which the samples are transported. The rest of the analytical determinations in blood followed the conventional methods established in our hospital.

Data collected. The following data were collected for each patient: demographic characteristics, underlying conditions, previous contact with suspected cases, days with symptoms prior to diagnosis by PCR, hospital stay, ICU stay, presence of pneumonia (unilateral/bilateral), oxygen saturation, laboratory analysis, severity of infection, antibiotic, antifungal and antiviral therapy, clinical evolution and mortality.

Definitions. Immunosuppressed patients were considered to be those with active solid organ tumor, malignant/hematological neoplasms under chemotherapy, HIV patients (<200 CD4), neutropenic individuals (<500 mm^3), solid organ transplant recipients or those under corticosteroid therapy at doses equivalent to ≥15 mg of prednisone (or equivalent)/day in the 30 days prior to admission.

Proven infection by SARS-CoV-2 was considered when a patient had signs and symptoms compatible with COVID-19 and a positive PCR in nasopharyngeal exudate.

The severity of the patients' disease was classified by the "CALL (comorbidity, age, lymphocyte and LDH) score" [11], which ranks 3 levels of risk according to their probability of progression. Those patients with 4-6 points have less than 10% chance of progression and are considered low risk (Class A). Patients with 7-9 points had a 10-40% chance of progression and are at intermediate risk (Class B) and patients with 10-13 points with more than 50% chance of progression are considered at high risk (Class C).

Statistical analysis. The median and interquartile range, were used for descriptive analysis of continuous variables. A value of $p<0.05$ was considered significant. Categorical variables were compared with the chi-square test and continuous variables using the Mann-Whitney test. A multivariate forward analysis including variables with $p<0.01$ in the univariate analysis was carried out to identify mortality risk factors. Statistical analysis was performed using IBM SPSS Statistics v.21 (IBM Corp., Armonk, NY).

Ethical aspects. This study was approved by the HGUGM Ethics Committee with the code MICRO.HGUGM.2020-020.

RESULTS

Of the first 100 proven patients with COVID-19 at the HGUGM, 52% were male. The age of the patients ranged from

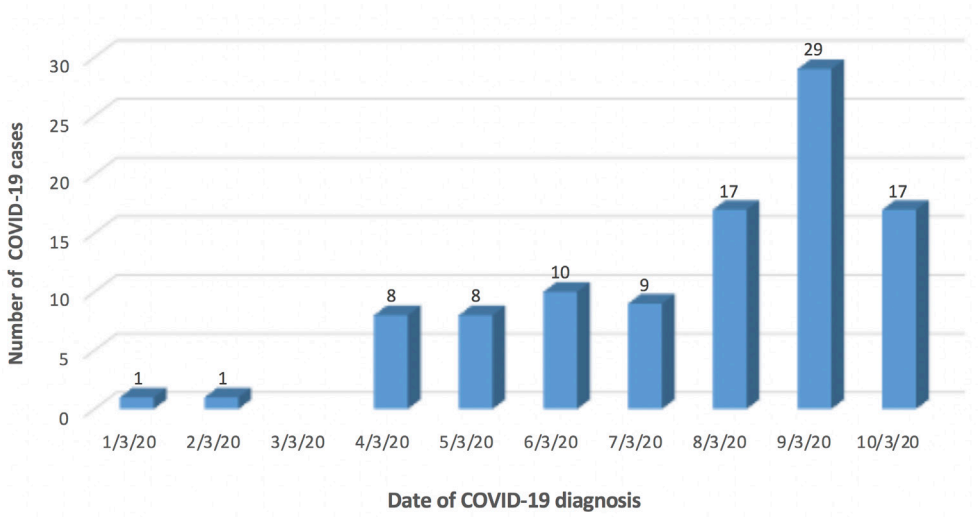

Figure 1 Evolution of admissions of the first 100 cases with confirmed COVID-19 at Hospital General Universitario Gregorio Marañón.

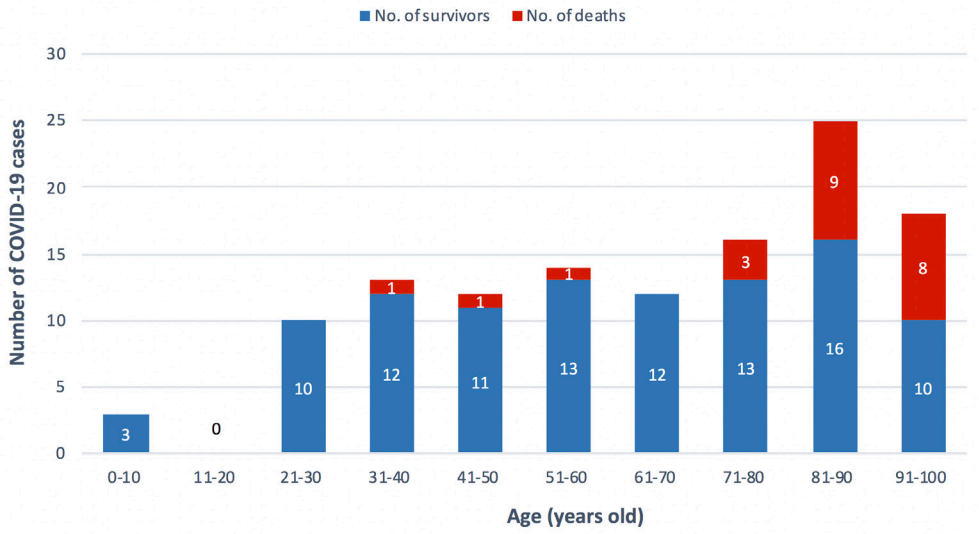

Figure 2 Distribution of the first 100 COVID-19 cases (survivors/deaths) in the Hospital General Universitario Gregorio Marañón by decades of life.

3 months to 99 years with a median of 61.5 years (IQR=39.5-82.0). Figure 1 shows the speed at which the first 100 cases of COVID-19 were diagnosed in our institution and Figure 2 shows their distribution by decades of life and mortality rate.

The median patient weight was 75.8 kg (IQR=64.7-85.0) and the median Body Mass Index (BMI) was 28.8 kg/m^2 (IQR=24.7-33.7 kg/m^2). The characteristics of the patients and the main underlying diseases are shown in Table 1.

The most common comorbidities were hypertension (31%), heart disease (22%) and diabetes mellitus (19%). The age-adjusted Charlson index [12] ranged from a minimum of 0 to a maximum of 10 (median 2, IQR=0-5.7). Five patients (5%) were immunosuppressed. Twenty-eight percent of the patients had no underlying disease.

The most common symptoms presented by patients at the time of diagnosis were fever (80.0%), cough (53.0%) and dyspnea (23.0%), followed by myalgia (7.0%), chest discomfort (5.0%) and asthenia (4.0%) (Table 1). The median number of days patients referred symptoms prior to performing the diagnostic PCR of COVID-19 was 4.0 (IQR= 2.0-7.0) with a mini-

Table 1 Demographic, clinical characteristics and evolution of patients.

	Cases (n=100)
Age, median, IQR	61.5 (39.5–82.0)
Sex, male, n (%)	52 (52.0)
BMI, kg/m2	28.8 (24.7-33.7)
Underlying diseases, n (%)	
Cardiopathy	22 (22.0)
Diabetes mellitus	19 (19.0)
Malignant/Hematological neoplasia	11 (11.0)
Chronic obstructive pulmonary disease	10 (10.0)
Chronic renal disease	8 (8.0)
Chronic hepatic disease	7 (7.0)
Neurologic disease	6 (6.0)
Solid tumor	6 (6.0)
Psychiatric disease	1 (1.0)
Hemodialysis	0
HIV	0
Solid organ trasplantation	0
Other	
Hypertension	31 (31.0)
Hypothyroidism	8 (8.0)
Asthma	4 (4.0)
Cushing illness	1 (1.0)
Celiac disease	1 (1.0)
Lupus	1 (1.0)
Sarcoidosis	1 (1.0)
Myopathy	1 (1.0)
Crohn disease	1 (1.0)
Peptic esophagitis	1 (1.0)
Osteoporosis	1 (1.0)
Thyroiditis de Hashimoto	1 (1.0)
Colon angiodysplasia	1 (1.0)
Latent tuberculosis	1 (1.0)
None, n (%)	28 (28.0)
Inmunodepressed, n (%)	5 (5.0)
Charlson Index adjusted to age, median, IQR	2 (0-5.7)
Previous contact, n (%)	47 (47.0)
Days with symptoms previous to PCR, median, IQR	4.0 (2.0-7.0)
Symptoms, n, %	
Fever	80 (80.0)
Cough	53 (53.0)
Dyspnoea	23 (23.0)
Myalgia	7 (7.0)
Thoracic pain	5 (5.0)
Asthenia	4 (4.0)

Table 1 Demographic, clinical characteristics and evolution of patients (cont.)

	Cases (n=100)
Headache	3 (3.0)
Confusional syndrome	3 (3.0)
Vomiting	3 (3.0)
Diarrhea	3 (3.0)
Dizziness	2 (2.0)
Odinofagia	2 (2.0)
Rhinorrea	1 (1.0)
Conjunctivitis	1 (1.0)
Pleuritic pain	1 (1.0)
Syncope	1 (1.0)
Need of hospitalization, n (%)	70 (70.0)
Days of hospital stay, median, IQR	9.0 (7.0-15.2)
Need of ICU hospitalization, n (%)	13 (13.0)
Days of ICU stay, median, IQR	11.0 (6.0-28.0)
Pneumonia, n (%)	63 (63.0)
Unilateral pneumonia	21 (21.0)
Bilateral pneumonia	42 (42.0)
Oxygen saturation at hospital admission, median, IQR	94.0 (90.0-97.0)
Lower level of **oxygen saturation** during hospitalization, median, IQR	92.0 (88.0-94.0)
Antiviral treatment, n (%)	66 (66.0)
Antibiotic treatment, n (%)	60 (60.0)
Antifungal treatment, n (%)	5 (5.0)
Clinical outcome at 30 days, alive, n (%)	77 (77.0)
Recovered at home	72 (72.0)
Hospitalized	2 (2.0)
At ICU	3 (3.0)
Clinical outcome at 60 days, alive, n (%)	77 (77.0)
Recovered at home	75 (75.0)
Hospitalized	1 1.0)
At ICU	2 (2.0)
Mortality	23 (23.0)
Related to COVID	22 (22.0)
Not related to COVID	1 (1.0)
Complications	
Cardiopathy	18 (18.0)
Acute respiratory distress syndrome	30 (30.0)
Sepsis syndrome	17 (17.0)
Proven bacterial sepsis	9 (9.0)
Acute kidney injury	27 (27.0)
Acute liver injury	25 (25.0)
Pulmonary embolism	1 (1.0)

Table 2 **Prognostic factors and clinical response to different treatments**

	Total	Univariate analysis			Multivariate analysis	
	(n=100)	Survivor (n=77)	Non-survivor (n=23)	p	OR (95% CI)	p
Age, years, median (IQR)	61.5 (39.5-82.0)	54 (35.5-70.5)	85.0 (79.0-93.0)	<0.01		
0-18	3 (3.0)	3 (3.9)	0 (0)	0.584		
19-44	29 (29.0)	28 (36.4)	1 (4.3)	<0.01		
45-54	11 (11.0)	9 (11.7)	2 (8.7)	0.737		
55-64	11 (11.0)	11 (14.3)	0 (0)	0.064		
65-74	11 (11.0)	11 (14.3)	0 (0)	0.064		
≥75	35 (35.0)	15 (19.5)	20 (87.0)	<0.01		
Sex, male, n (%)	52 (52.0)	41 (53.2)	11 (47.8)	0.812		
BMI, kg/m^2	28.8 (24.7-33.7)	27.9 (24.4-30.5)	30.8 (26.7-33.5)	0.05		
BMI<30	42/69 (60.9)	34/50 (68.0)	8/19 (42.1)	0.049		
BMI 30-40	24/69 (34.8)	14/50 (28.0)	10/19 (52.6)	0.055		
BMI >40	3 /69 (4.3)	2/50 (4.0)	1/19 (5.3)	0.818		
Smoker, n (%)	20 (20.0)	14 (18.2)	6 (26.1)	0.391		
Underlying diseases						
Diabetes, n (%)	19 (19.0)	10 (13.0)	9 (39.1)	<0.01		
Malignant/Hematological neoplasia, n (%)	11 (11.0)	5 (6.5)	6 (26.1)	0.017		
Solid tumor, n (%)	6 (6.0)	1 (1.3)	5 (21.7)	<0.01		
COPD, n (%)	10 (10.0)	4 (5.2)	6 (26.1)	<0.01		
Cardiopathy, n (%)	22 (22.0)	13 (16.9)	9 (39.1)	0.042		
Neurologic disease, n (%)	6 (6.0)	3 (3.9)	3 (13.0)	0.053		
Hypertension, n (%)	31 (31.0)	16 (20.8)	15 (65.2)	<0.01	4.47 (1.36-14.66)	0.013
Symptoms						
Disnea, n (%)	23 (23.0)	12 (15.6)	11 (47.8)	<0.01		
Cough, n (%)	53 (53.0)	47 (61.0)	6 (26.1)	<0.01		
Antibiotic treatment, n (%)	60 (60.0)	39 (50.6)	21 (91.3)	<0.01		
Antiviral treatment, n (%)	66 (66.0)	48 (62.3)	18 (78.3)	0.212		
Lopinavir/ritonavir	65 (65.0)	47 (61.0)	18 (78.3)	1.0		
Hydroxycloroquine	42 (42.0)	33 (42.9)	9 (39.1)	0.250		
Interferon-beta	27 (27.0)	19 (24.7)	8 (34.8)	0.783		
Remdisivir	7 (7.0)	6 (7.8)	1 (4.3)	0.664		
Darunavir	1 (1.0)	1 (1.3)	0	1.0		
Ritonavir	1 (1.0)	1 (1.3)	0	1.0		
Oseltamivir	2 (2.0)	1 (1.3)	1 (4.3)	1.0		
Tocilizumab, n (%)	11 (11.0)	8 (10.4)	3 (13.0)	1.0		
Oxygen saturation on admission, median (IQR)	94 (90-97)	95 (93-97.2)	90 (87-92)	<0.01		
Lower oxygen saturation during the hospitalization, median (IQR)	92 (88-94)	93 (90-95)	83.5 (80.2-89)	<0.01		
Bilateral pneumonia, n (%)	42 (42.0)	23 (29.9)	19 (82.6)	<0.01		
Age-adjusted Charlson Index, n (%)	1.5 (0-5.7)	0 (0-3)	6 (5-8)	<0.01	1.55 (1.26-1.91)	<0.01
CALL Score, median (IQR)	10 (8-11)	9 (7-11)	11 (10-12)	<0.01		
Length of hospitalization, days, median (IQR)	9.0 (7.0-15.2)	9 (7-22)	8 (5-14)	0.109		
Days at ICU, median (IQR)	11.0 (6.0-28.0)	27 (8.7-28)	9 (3-14.5)	0.07		
Days of hospital stay previous to ICU admission, median (IQR)	2 (0-3)	2 (1.2-3.7)	0 (0-2)	0.05		
Complications						
Cardiopathy	18 (18.0)	6 (7.8)	12 (52.2)	<0.01		
ARDS	30 (30.0)	9 (11.7)	21 (91.3)	<0.01		
Sepsis	17 (17.0)	8 (10.4)	9 (39.1)	<0.01		
Kidney injury	27 (27.0)	12 (15.6)	15 (65.2)	<0.01		
Liver injury	25 (25.0)	22 (28.6)	3 (13.0)	0.174		
Pulmonary embolism	1 (1.0)	0	1 (4.3)	0.230		

COPD: chronic obstructive pulmonary disease, ARDS: acute respiratory distress syndrome

Table 3 **Summary of main laboratory results.**

	Total (n=100)	Survivor (n=77)	Non-survivor (n=23)	p
Lymphocyte count (10E3/µL), median, IQR	0.9 (0.7-1.3)	1 (0.7-1.4)	0.7 (0.5-1.1)	<0.01
<1.3	55/77 (71.4%)	36/55 (65.5)	19/22 (86.4)	0.094
<0.8	31/77 (40.3%)	18/55 (32.7)	13/22 (59.1)	0.042
Platelets (10E3/µL), median, IQR	155 (136-205.2)	159 (136-239.5)	155 (100-188)	0.189
<140	24/78 (30.8%)	15/56 (26.8)	9/22 (40.9)	0.278
≥140	54/78 (69.2%)	41/56 (73.2)	13/22 (59.1)	
C-reactive protein (mg/dL), median, IQR	4 (2-9.6)	2.7 (1.5-6.5)	6.3 (3.3-17.6)	<0.01
Procalcitonin (µg/L), median, IQR	0.05 (0.03-0.13)	0.04 (0.03-0.08)	0.12 (0.1-0.5)	<0.01
<0.1	53/79 (67.1%)	44/56 (78.6)	9/23 (39.1)	<0.01
≥0.1 a <0.25	12/79 (15.2%)	5/56 (8.9)	7/23 (30.4)	0.022
≥0.25 a <0.5	6/79 (7.6%)	4/56 (7.1)	2/23 (8.7)	1.0
≥0.5	8/79 (10.1%)	3/56 (5.4)	5/23 (21.7)	0.042
D-dimer (ng/mL), median, IQR	284 (219-794)	274 (208-680.5)	2010 (565-)	0.154
ALT (U/L), median, IQR	24 (15-37)	24.5 (15-38.7)	24 (17-34)	0.754
≤41	64/79 (81.0%)	44/56 (78.6)	20/23 (87.0)	0.533
>41	15/79 (19.0%)	12/56 (21.4)	3/23 (13.0)	
LDH (U/L), median, IQR	256 (192.5-345.7)	226 (191-297)	316 (224-434)	0.047
≤250	32/66 (48.5%)	28/49 (57.1)	4/17 (23.5)	0.024
250-500	28/66 (42.4%)	17/49 (34.7)	11/17 (64.7)	0.046
>500	6/66 (9.1%)	4/49 (8.2)	2/17 (11.8)	1.0
IL-6 (pg/mL), median, IQR	166.3 (61.4-)	166.3 (61.4-)	-	-
Blood urea nitrogen, (mg/dL), median, IQR	31 (19-79)	21 (17-31)	106 (61.7-205.7)	<0.01
Ferritin (µg/L), median, IQR	598 (267-1048.5)	494 (153-681)	2922 (676-)	0.222
NTproBNP (ng/L), median, IQR	1036 (274-3981)	465 (74-2500.5)	1520.5 (588.2-5900)	0.012

mum of 1 day and a maximum of 14 days. Forty-seven percent of the patients stated that they had had previous contact with a person diagnosed with COVID-19, either proven or probable.

O_2 saturation at the time of first examination ranged from a minimum of 80% to a maximum of 99%, with a median of 94% (IQR=90-97). A total of 19.8% of patients had saturation <90% on admission.

Sixty-three percent of the patients presented alterations in the chest X-Ray on admission, compatible with the diagnosis of pneumonia (Table 1). Radiological images were classified as bilateral pneumonia in 42% of patients and as unilateral in 21%. The infiltrates generally had a ground glass pattern but on some occasions they were clear alveolar infiltrates (Figure 3).

Overall, 70% of COVID-19 cases were admitted to hospital. The length of hospital stay for those patients who remained hospitalized ranged from a minimum of 1 day to a maximum of 32 days, with a median of 9 days (IQR=7.0-15.2). Thirteen patients required admission to the ICU during the course of their hospitalization, with a minimum of 2 days and a maximum of 28 days of stay and a median of 11 days (IQR=6.0-28.0). The mortality rate of these patients admitted to ICU was 38.5% (5/13). The median time from the onset of symptoms associated with COVID-19 in these patients until they were admitted to the ICU was 5 days (IQR=1.5-9.5) with a minimum of 1 day and a maximum of 13 days. Patients admitted to the ICU were previously hospitalized on the ward for a median of 2 days (IQR=0-3) with a minimum of 0 days and a maximum of 6 days.

Fourteen patients of our study cohort also showed other type of infections (n=17). Three of them were coinfections present at the same time as the diagnosis of SARS-CoV-2 and 14 were nosocomially acquired. The origin of all of them was

Table 4 Comparative study in terms of severity scale (CALL score)

	Class A and B (low and intermediate risk) n=29	Class C (high risk) n=37	p
Age, median, IQR	51 (34.5-71)	76 (64-86)	<0.01
Charlson Index, median, IQR	0 (0-5)	4 (2-6.5)	<0.01
Oxygen saturation on admission, median, IQR	95 (94-97)	92 (88-95)	<0.01
Dyspnoea, n, %	4/29 (13.8%)	15/37 (40.5%)	0.027
Antibiotic treatment, n, %	19/29 (65.5%)	33/37 (89.2%)	0.032
Complications			
Cardiopathy, n, %	2/29 (6.9%)	3/37 (35.1%)	<0.01
ARDS, n, %	6/29 (20.7%)	18/37 (48.6%)	0.023
Kidney injury, n, %	5/29 (17.2%)	28/37 (48.6%)	0.01
Survivor at 30-day follow-up (at home), n, %	26/29 (89.7%)	18/37 (48.6%)	<0.01
Laboratory			
Lymphocyte count, median, IQR	1.3 (1.1-1.5)	0.7 (0.4-0.9)	<0.01
C-reactive protein, median, IQR	2.3 (1.3-4.7)	5.3 (2.8-11.8)	<0.01
Procalcitonin, median, IQR	0.04 (0.03-0.06)	0.09 (0.04-0.3)	<0.01
LDH, median, IQR	212 (190.5-267.5)	283 (211.5-399.5)	<0.01

ARDS: acute respiratory distress syndrome

urinary (n=6), respiratory (n=5), bloodstream (n=4, 2 primary bacteremia and 2 catheter-related bacteremia), gastrointestinal (n=1) and catheter-related (n=1) infections. The most frequently isolated microorganisms were *Escherichia coli* (n=5), *Staphylococcus epidermidis* (n=2), *Staphylococcus aureus* (n=1), *Enterobacter cloacae* (n=1), *Klebsiella pneumoniae* (n=1), *Micrococcus luteus* (n=1), *Enterococcus faecalis* (n=1), *Staphylococcus haemolyticus* (n=1), *Aspergillus fumigatus complex* (n=1), Respiratory Syncytial Virus (n=1) and *Clostridium difficile* (n=1). Nine cases of proven bacterial sepsis were detected among 17 patients with sepsis syndrome.

Overall, 60.0% of patients received antibiotic treatment and 66.0% of patients received antiviral treatment, with lopinavir/ritonavir (65%) or hydroxychloroquine (42%) in an empirical basis. The main treatments are shown in Table 2. A greater use of antibiotics was observed in patients who died compared to survivors (91.3% vs 50.6%, p<0.01) but no significant differences were detected between both groups in terms of any type of antiviral or monoclonal antibody administered as treatment to the COVID-19.

Laboratory findings showed lymphopenia in 71% of patients diagnosed with COVID-19 with analytical determination on admission. Fourteen of the 23 patients with D-dimer determination (60.9%), had values greater than 250 ng/mL. IL-6 was only measured in 3 patients of our cohort but values were elevated in all the cases. Lymphocyte levels were lower in patients who died (p<0.01) compared to those who survived. C-reactive protein, procalcitonin, LDH, blood nitrogen-urea and NTproB-NP values were significantly higher in non-survivors compared to survivors at 30-60 days after diagnosis of COVID-19 (Table 3).

The median CALL score of the total patient cohort was 10, corresponding to Class C severity with a probability of more than 50% high risk of disease progression. The minimum CALL score was 4 (Class A) and the maximum was 13 (Class C) (Table 2). A significantly higher CALL score (p<0.01) was observed in patients who died compared to those who did not die (11 vs 9). When comparing patients with low-intermediate severity (Class A and B CALL score) with patients with high severity (Class C, CALL score), it was observed that those with greater probability of disease progression (Class C) presented greater age (p<0. 01), higher Charlson index (p<0.01), more dyspnea (40.5% vs 13.8%, p<0.01), higher percentage of antibiotic use (89.2% vs 65.5%, p<0.05) and a greater presence of complications such as heart disease (p<0.04), respiratory distress (p<0.05) and kidney damage (p=0.01) (Table 4). The percentage of survivors was lower in this group (48.6% goes 89.7%, p<0.01). Regarding laboratory findings, lymphocyte, C-reactive protein, procalcitonin and LDH levels were significantly higher in these high severity patients (p<0.01).

At 30 days of follow-up after positive PCR test for SARS-CoV-2, 23 patients (23%) had died, 72 (72%) were recovering

at home, 2 (2%) remained hospitalized and 3 (3%) were in the ICU. After 60 days of follow-up, no more deaths were detected in our cohort, one of the 2 patients who had been hospitalized at 30 days remained hospitalized and the other was at home. As for the ICU patients, 2 remained hospitalized at 60 days and the third was discharged after 49 days of admission. Figure 2 shows the distribution of patients who survived and died by age groups (decades).

A comparative study between live and dead patients 30-60 days after diagnosis of COVID-19 showed that dead patients were significantly older ($p<0.01$), had a higher Charlson index ($p<0.01$) and had a higher percentage of bilateral pneumonias ($p<0.01$). The frequency of complications was higher in non-survivors than in survivors. Table 2 shows this comparison and the profile of the deceased patients in detail. By performing a multivariate analysis including variables with statistical significance in the univariate analysis less than 0.01, the presence of hypertension and age-adjusted Charlson Index were identified as risk factors associated with death.

The age of the deceased patients ranged from 39 to 99 years with a median of 85 years (IQR=79-93). Only 3 of the 23 deceased patients (13%) were under 75 years of age. One of them (51 years old) had diabetes mellitus, Cushing's disease, high blood pressure, hepatitis C and SARS-CoV-2 coinfection with RSV. Another (45 years old) had diabetes mellitus, high blood pressure, morbid obesity, chronic renal disease, *Clostridium difficile* colitis and was a carrier of a biological mitral prosthesis. The third, was a 39 years old patient with epidermoid carcinoma of the cervix treated with surgery in 2014 and currently with stage IV anal canal carcinoma in progression, with peritoneal carcinomatosis in treatment with palliative chemotherapy. The 23 patients who died had a median Charlson Index of 6 (IQR=5-8). Eleven patients (47.8%) had a BMI greater than 30 and 3 were immunosuppressed. Nineteen patients (82.6%) had bilateral pneumonia and 4 (17.4%) had unilateral pneumonia.

DISCUSSION

Our study shows a high mortality of the first hundred patients treated with COVID-19 in our institution, associated with advanced age and the presence of serious underlying diseases in our population. Twenty of the 23 (23%) deceased patients were over 75 years of age and all had serious comorbidities.

The mortality in our series is similar to that reflected by Western countries such as Italy, UK, USA and others (19% to 39%) [3, 13-15] and differs significantly from that reported from China or Korea (0.9% to 7.5%) [4, 16-20]. It is clear that when calculating mortality the denominators matter [17, 21, 22].

The basic reason for these differences are to be found in the median age of the respective populations which was between 62 and 65.5 years in Western publications [3, 13, 15] and between 41 and 47 in the case of Chinese publications [4, 18]. In addition, comorbidity appears as a clear factor of poor prognosis as well as the level of care [23, 24].

Mortality in the case of China is even more surprising, since the initially reported cases considered pneumonia as a constant in clinical presentation [2, 25-28], to the extent that the presence of certain lesions in the thoracic CT was considered a diagnostic criterion in the early stages [29-31]. However, as demonstrated by our first 100 microbiologically confirmed patients, pneumonia was absent in a high proportion of cases and is even less frequent in subsequent series where diagnostic suspicion is spread to less severe or asymptomatic patients [4, 19, 32].

An interesting aspect of our series is the evaluation of the ability to predict and anticipate patients with poor clinical evolution. Our study has used the CALL score [11] and validated its usefulness. For example, all the patients sent home, evolved well during the follow-up and did not require admission in the two months of follow-up.

No antiviral treatment has been shown to be effective to date. Most patients in our cohort were treated with lopinavir/ritonavir but none of the different types of antivirals administered during this first period have shown significant differences between patients who survived and those who died [33-39].

Our results and previous studies show that lymphopenia is common in COVID-19 cases, suggesting that SARS-CoV-2 infection causes an inhibition of the cellular immune response and a significant number of complications as seen in our patient cohort. We have also observed that elevation of markers such as C-reactive protein and procalcitonin is common in severe COVID-19 cases [4, 40].

Our study aims to contribute to a better understanding of the clinical evolution and mortality among the cases of COVID-19 in different continents, with a follow-up perspective of more than two months. The real mortality will not be known until the true dimension of the epidemic can be analyzed through population studies and the number of deceased cases can be related to the underlying diseases and the situation of the hospitals at different times of the epidemic.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest

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¿Es útil la estratificación de la sensibilidad antibiótica de los patógenos urinarios en el Servicio de Urgencias?

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RESUMEN

Objetivo. Determinar la sensibilidad antibiótica de los patógenos causantes de infección del tracto urinario (ITU) estratificándola en función de datos clínicos y demográficos de los pacientes.

Material y métodos. Se analizó sensibilidad antibiótica de las bacterias aisladas en orina de 144 pacientes con ITU escogidos al azar y se estratificó en función del sexo, la edad, el tipo de ITU, el haber padecido o no ITU previa y del tratamiento antibiótico previo.

Resultados. Se analizó la sensibilidad global de todas las cepas y de las cepas de *E. coli* observándose diferencias significativas en función del sexo (fluoroquinolonas), la edad (cefuroxima, ertapenem, gentamicina), el tipo de ITU (cefuroxima, cefotaxima, ertapenem, fluoroquinolonas), el haber tenido ITU previa y antibioterapia previa (cefotaxima, fluoroquinolonas, fosfomicina).

Conclusiones. El empleo de datos clínicos y demográficos adaptados a la población y a la epidemiología local de resistencia de los uropatógenos, podría ayudar a la elección del tratamiento empírico de la ITU.

Palabras clave: Infección urinaria, Sensibilidad antibiótica, Servicio de Urgencias, tratamiento empírico

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Is stratification of antibiotic susceptibility of urinary pathogens useful in the Emergency Department?

ABSTRACT

Objective. The aim of the study wat to analyze the antibiotic susceptibility of the pathogens causing urinary tract infection (UTI) and to stratify the results in function of patient´s clinical and demographic dates.

Material and methods. The susceptibility of the pathogens isolated in the urine of 144 patients with UTI randomly chosen was analyzed. The results were stratified in function of sex, age, type of UTI, previous UTI and previous antibiotic treatment.

Results. The susceptibility of the all isolates and of the *Escherichia coli* isolates was analyzed. There were significant differences between groups in function of sex (fluoroquinolones), age (cefuroxime, ertapenem and gentamicin), type of UTI (cefuroxime, cefotaxime, ertapenem and fluoroquinolones), previous UTI and previous antibiotic treatment (cefotaxime, fluoroquinolones and fosfomycin)

Conclusions. The use of clinical and demographic data according to population and local resistance epidemiology of the pathogen causing UTI may help to select an adequate empirical treatment for UTI

Key words: urinary tract infection, antibiotic susceptibility, emergency department, empirical treatment

INTRODUCCIÓN

La infección del tracto urinario (ITU) es una de las patologías infecciosas más prevalentes en los servicios de Urgencias y conlleva un elevado uso de antibióticos. El progresivo aumento global de las resistencias antibióticas y la heterogeneidad de los pacientes tratados en Urgencias implica una gran comple-

jidad a la hora de establecer tratamientos antibióticos empíricos. Por otro lado, se han producido cambios epidemiológicos en los pacientes que presentan ITU en Urgencias como son el aumento de la prevalencia (actualmente un 3,2%), el aumento de la edad, la presencia de más comorbilidades y de mayor gravedad clínica, tanto en España [1] como en los Estados Unidos [2]. Esto implica uso de antibióticos de más amplio espectro y mayor probabilidad de fracaso del tratamiento empírico.

La correcta selección de tratamientos empíricos es importante para la curación del paciente, la reducción de costes hospitalarios y la menor selección de resistencias; para ello es necesario conocer los patrones locales de sensibilidad antibiótica, suministrados por los servicios de Microbiología, que además influyen en la elección de dichos tratamientos [3, 4].

Planteamos la hipótesis de que los datos de sensibilidad antibiótica de los uropatógenos son distintos en función de las características clínicas y demográficas de la población, y que su conocimiento permitiría escoger tratamientos empíricos más adecuados.

El objetivo es determinar la sensibilidad antibiótica de los patógenos aislados de pacientes con infección urinaria atendidos en el servicio de Urgencias del Hospital Universitario de Getafe, estratificar los resultados en función de los datos clínicos y demográficos y analizar si existen diferencias entre los grupos.

MATERIAL Y MÉTODOS

Estudio transversal en el que se analizó de manera prospectiva, entre enero y junio de 2018, la sensibilidad antibiótica de las bacterias aisladas en las muestras de orina de 144 pacientes adultos (≥18 años) con ITU atendidos en el servicio de Urgencias del Hospital Universitario de Getafe, Madrid, que fueron escogidos al azar entre aquellos que presentaron un cultivo positivo de orina (>10^4 ufc/mL). La sensibilidad antibiótica se determinó mediante microdilución en caldo (paneles Beckman, USA) para ampicilina, amoxicilina-clavulánico, piperacilina-tazobactam, cefuroxima, cefotaxima, ertapenem, gentamicina, nitrofurantoína, fluoroquinolonas (ciproflaxacino y levofloxacino), cotrimoxazol y fosfomicina. Los resultados se interpretaron de acuerdo a las guías EUCAST de 2018 [5].

Los episodios se clasificaron en ITU complicada y no complicada según los datos clínicos y demográficos. Los resultados de sensibilidad se estratificaron, para el global de patógenos aislados así como para *Escherichia* coli, en función del sexo, la edad, el tipo de ITU (complicada, no complicada), el haber padecido o no ITU previa y del tratamiento antibiótico previo.

Los grupos se compararon mediante la determinación de la Chi al cuadrado o la prueba exacta de Fisher.

RESULTADOS

De los 144 pacientes estudiados 56 fueron hombres (38,9%) y 88 mujeres (61,1%), con una edad media ± desviación estándar de 67,7 ± 22,15 años. Del total, 87 tuvieron ITU complicada (edad media ± desviación estándar de 72,9 ± 17,8 años) de los que 56 fueron hombres (64,4%), y 57 tuvieron ITU no complicada, todo mujeres, con una edad media ± desviación estándar de 59,8 ± 25,66 años. Las diferencias de edad entre los grupos de ITU complicada y no complicada fueron estadísticamente significativas (*p=0,003*)

El principal microorganismo aislado fue *E. coli* seguido de *Klebsiella pneumoniae*, *Enterococcus faecalis* y *Proteus mirabilis* (figura 1).

La sensibilidad global de todas las cepas y de las de *E. coli* puede observarse en la tabla 1.

Al estratificar los resultados de sensibilidad global (n=141) en función del sexo, se observó que: los de mujeres presentaban una mayor sensibilidad a fluoroquinolonas (81,8% mu-

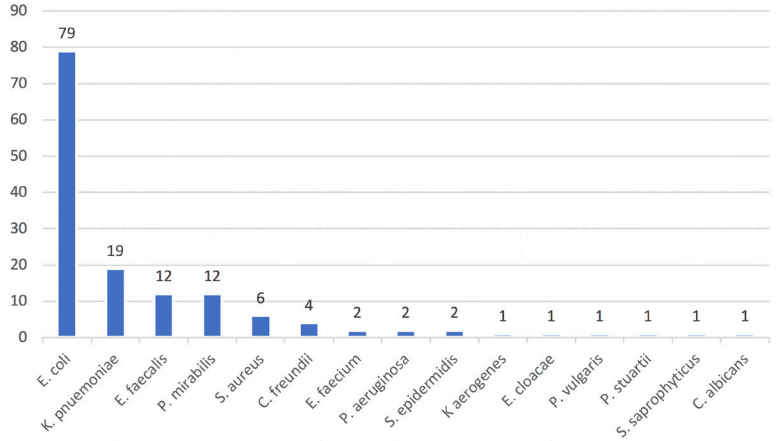

Figura 1 Microorganismos aislados en los 144 casos de ITU.

Tabla 1 **Porcentaje de sensibilidad de los 141 uropatógenos y de las 79 cepas de *E. coli*.**

Antibiótico (% de sensibilidad)	Uropatógenos* n=141	*E. coli* n=79
Ampicilina	36,2	40,5
Amoxicilina-clavulánico	75,9	81
Piparacilina-Tazobactam	95	98,7
Cefuroxima	70,9	87,3
Cefotaxima	77,3	89,9
Ertapenem	87,2	100
Gentamicina	80,9	94,9
Nitrofurantoína	87,9	100
Ciprofloxacino	73,8	77,2
Levofloxacino	73,8	77,2
Cotrimoxazol	59,6	64,6
Fosfomicina	85,8	96,2

Se excluyeron 1 cepa de *C. albicans* y 2 aislados de *S. epidermidis*.

jeres *vs.* 60,4% hombres; *p= 0,005*); Los del grupo con edad ≤65 años, una mayor sensibilidad a cefuroxima (82,6% ≤ 65 *vs.* 65,3% >65; *p= 0,033*), ertapenem (95,7% ≤65 *vs.* 83,2% >65; *p= 0,037*) y gentamicina (91,3% ≤ 65 *vs.* 75,8% > 65; *p= 0,028*); Los del grupo que presentaron ITU no complicada una mayor sensibilidad a cefuroxima (80,7% ITU no complicada *vs.* 64,3% ITU complicada; *p= 0,035*), cefotaxima (89,5% ITU no complicada *vs.* 69% ITU complicada; *p= 0,004*), ertapenem (94,7% *vs.* 82,1%; *p= 0,028*) y fluoroquinolonas (84,2% *vs.* 66,7%; *p= 0,020*); Los del grupo que no presentaron ITU previa tuvieron mayor sensibilidad a cefotaxima (81,6% *vs.* 65,8%; *p= 0,047*), fluoroquinolonas (81,6% *vs.* 52,6%; *p= 0,001*) y fosfomicina (90,3% *vs.* 73,7%; *p= 0,012*); Por último, los de pacientes que no recibieron tratamiento antibiótico previo presentaron mayor sensibilidad que aquellos que sí lo recibieron respecto a cefotaxima (83% *vs.* 62,5%; *p= 0,015*), fluoroquinolonas (83% *vs.* 50%; *p= 0,0002*) y fosfomicina (91% *vs.* 68,8%; *p= 0,004*). En el resto de los antibióticos estudiados no se observaron diferencias estadísticamente significativas al comparar los distintos grupos.

Al estratificar los resultados de sensibilidad de *E. coli* (n=79) en función del sexo se observó en cepas de mujeres una mayor sensibilidad a fluoroquinolonas (87% mujeres *vs.* 56% hombres; *p= 0,002*). La sensibilidad de las cepas responsables de ITU no complicada fue mayor respecto a ampicilina (52,8% en ITU no complicada *vs.* 30,2% en ITU complicada; *p=0,042*) y cefotaxima (100% en ITU no complicada *vs.* 81,4% en ITU complicada; *p=0,007*). Las cepas aisladas en pacientes que no tuvieron ITU previa presentaron una mayor sensibilidad a fluoroquinolonas (83,9% sin ITU previa *vs.* 52,9% con ITU previa; *p=0,018*). No se apreciaron diferencias estadísticamente significativas en el resto de antibióticos en los otros grupos analizados.

DISCUSIÓN

El conocimiento de la sensibilidad de los patógenos implicados en la infección urinaria, a nivel local [6], es importante para que los clínicos puedan establecer un tratamiento antibiótico adecuado; dicha información epidemiológica influye en sus decisiones de tratamiento empírico [3].

Sin embargo, los datos de sensibilidad global aportados por los servicios de Microbiología pueden estar sesgados. Por ejemplo, sobreestiman las resistencias de los uropatógenos que producen ITU no complicada ya que en muchos casos no se suele enviar urocultivo mientras que se aconseja enviarlo en todas las ITU complicadas y en fracasos de ITU no complicada, ambos causados por bacterias más resistentes [7, 8]. Se necesitan otros métodos más eficaces para informar la sensibilidad.

En este estudio se han observado diferencias significativas de sensibilidad entre grupos, lo que corrobora nuestra hipótesis y habla de la necesidad de antibiogramas adaptados a grupos específicos de pacientes, más que de antibiogramas generales. Lo mismo ocurre en algún trabajo reciente en otros países [8 ,9, 10].

La sensibilidad global de los uropatógenos aislados muestra una alta tasa de resistencia a fluoroquinolonas (>25%) y cotrimoxazol (>40%), por lo que no serían una buena opción. Sin embargo, la sensibilidad a fosfomicina y nitrofurantoína es muy elevada por lo que serían adecuados para el tratamiento empírico de las ITU no complicadas, como recomiendan guías recientes [7, 11]. Las fluoroquinolonas no se consideran tratamiento de elección de ITU no complicada [7, 11], pero serían una alternativa ya que la sensibilidad de los agentes causales es superior al 80%.

En un estudio retrospectivo reciente [14] se obtienen en *E. coli* diferentes porcentajes de sensibilidad de los nuestros (cotrimoxazol, amoxicilina/clavulánico y ciprofloxacino) en ITU no complicada, lo que de nuevo resalta la importancia de la epidemiología local [6]. La hospitalización previa era un predictor de mayor resistencia a cotrimoxazol y ciprofloxacino [15], algo que no hemos estudiado.

Según los resultados obtenidos, como ejemplo, en nuestro medio en pacientes graves con ITU complicada sería recomendable no emplear como tratamiento empírico amoxicilina/clavulánico, fluoroquinolonas, o cefalosporinas de 3ª generación solas, y sí piperacilina-tazobactam o ertapenem, y posteriormente desescalar en función del antibiograma.

Las bacterias productoras de beta-lactamasas espectro extendido (BLEE) (n=11) y los enterococos (n=12) procedían principalmente de pacientes ancianos, varones, con tratamientos previos y con ITU complicada (datos no mostrados), lo que condiciona más resistencia en esos grupos. El conocimiento de los factores de riesgo de infección por bacterias productoras de BLEE [14] o por enterococos puede también ayudar a escoger un tratamiento empírico adecuado.

Una fortaleza de este estudio es la inclusión de la sensibilidad de otros uropatógenos además de *E. coli*, lo que permite

obtener una visión más ajustada a la realidad. Otra es que es prospectivo y que se han estudiado muchos antibióticos útiles para el tratamiento de la ITU, a diferencia de otros estudios.

La principal limitación es el hecho de que los patógenos se aislaron de pacientes de un único hospital (que atiende a una población de 219.000 personas), por lo que se trata de un estudio local. Sin embargo, pensamos que teniendo en cuenta la epidemiología local y los datos demográficos y clínicos de los pacientes, sería útil para muchos otros ámbitos. Un mayor tamaño muestral podría aumentar en algunos subgrupos el número de antibióticos con diferencias estadísticamente significativas.

En conclusión, el empleo de los datos clínicos y demográficos de los pacientes es de gran importancia en los resultados de sensibilidad de las bacterias causantes de ITU en Urgencias. Su conocimiento, actualizado y adaptado a la población atendida y a la epidemiología local de las resistencias, podría ayudar a los clínicos a una mejor elección del tratamiento empírico de las ITU. En el futuro sería interesante un seguimiento temporal ya que la resistencia a antibióticos es un proceso dinámico.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflictos de intereses.

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Carta al Director

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Debut pediátrico de fascitis necrotizante

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Sr. Editor: La fascitis necrotizante (FN) es un cuadro muy grave, causado por una infección bacteriana de la piel y tejidos blandos subcutáneos, cuya evolución es hacia la destrucción y necrosis de los tejidos en un corto espacio de tiempo. Hasta en un tercio de los casos llega a ocasionar un shock séptico con fallo multiorgánico, que eleva la mortalidad de este cuadro hasta el 25%. Dependiendo del agente causante la FN se clasifica en polimicrobiana (tipo I) y estreptocócica (tipo II). Los principales microorganismos implicados son *Streptococcus* beta-hemolítico del grupo A, y con menor frecuencia *Staphylococcus aureus* [1].

Presentamos el caso de un paciente de 12 años de edad, con antecedentes de intervención quirúrgica del tendón de Aquiles para corrección de pie cavo-varo izquierdo a los 10 años de edad y un episodio de dolor en miembro inferior izquierdo (MII) con impotencia funcional y edema, tras una otitis media aguda tratada con amoxicilina clavulánico, que mejoró con reposo domiciliario y antiinflamatorios en los 5 meses previos.

Es atendido en urgencias por presentar un cuadro de fiebre, vómitos y deposiciones líquidas, que sugiere una gastroenteritis aguda. En la anamnesis refiere dolor de carácter intermitente en el gemelo izquierdo desde la intervención quirúrgica. Cuarenta y ocho horas mas tarde presenta un cuadro de sudoración profusa, con dolor intenso, edema e impotencia funcional en MII, acompañado de coluria. Se realiza extracción sanguínea urgente, destacando entre los datos analíticos una hiperbilirrubinemia total (6 mg/dL) a expensa de la fracción directa (5,20 mg/dL), elevación de GOT (152 U/L), GPT (144 U/L), CK total (2.530 U/L, que alcanzó valores de 40.100 U/L), LDH (410 U/L), creatinina (2,02 mg/dL), Proteína C reactiva (358 mg/dL), procalcitonina (28 ng/mL) y Dímero D (6.600 ng/mL), con hiponatremia (126 mmol/L) e hipopotasemia (2,80 mmol/L). La Ecografía Doppler de MII muestra una obstrucción al flujo a nivel de la arteria poplítea con hipoperfusión arterial distal, sin objetivar signos directos de trombosis, y un edema importante que plantea la posibilidad diagnóstica de un síndrome compartimental. La imagen del Angio-TC sugiere que la hipoperfusión arterial distal impresiona de ser secundaria a la intensa edematización. El Angio-TC de tórax no muestra signos de tromboembolismo pulmonar agudo.

El paciente es trasladado al servicio de cuidados intensivos por presentar inestabilidad hemodinámica, con hipotensión, taquicardia, polipnea y acidosis metabólica (niveles ácido láctico > 10 mmol/L), precisando tratamiento con aminas vasoactivas, soporte ventilatorio invasivo y antibioterapia de amplio espectro (vancomicina y meropenem). Previamente se había realizado extracción sanguínea para hemocultivo.

Tras valoración por Traumatología se decide cirugía urgente por sospecha de FN, que se confirma durante la intervención, siendo necesaria la amputación proximal del MII. Se enviaron muestras quirúrgicas, de exudado de herida y hemocultivos al laboratorio de microbiología clínica para estudio. El laboratorio de urgencias informa, en el frotis del exudado de la herida, la presencia de flora mixta, con predominio de cocos grampositivos, a la espera de los resultados del cultivo microbiológico (figura 1). Finalmente, en el cultivo de exudado de herida, fascia muscular y hemocultivo se aísla *S. pyogenes* (Grupo A), cuyo estudio de sensibilidad a antimicrobianos se realiza en disco placa observando el halo de inhibición de crecimiento, resultando sensible a cefotaxima, vancomicina, clindamicina, eritromicina y penicilinas.

Durante la estancia en la unidad de cuidados intensivos, el paciente sufre un shock séptico con fallo multiorgánico secundario a fascitis necrotizante por *S. pyogenes*, de causa no aclarada, presentando varias paradas cardiorespiratorias y siendo reintervenido en varias ocasiones para ampliar la amputación.

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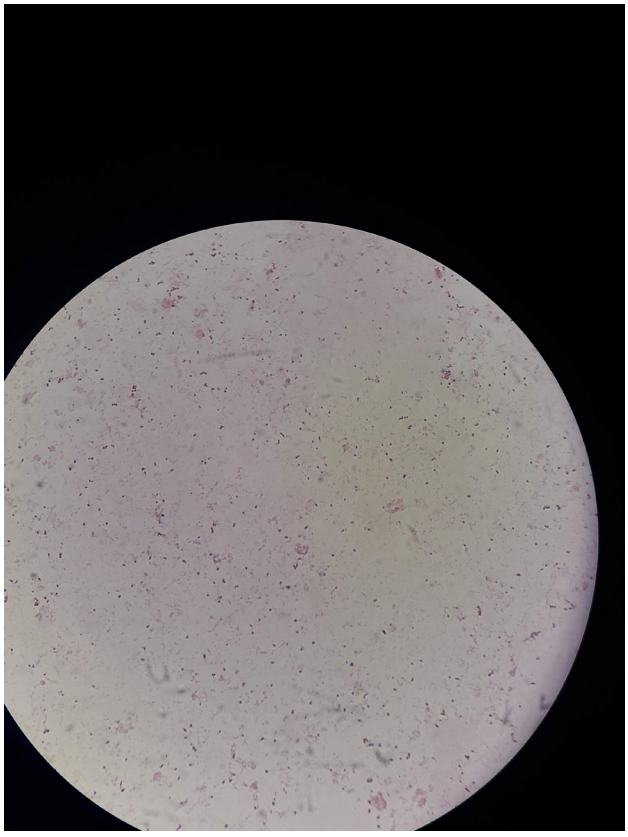

Figura 1 | **Extensión en porta de muestra de frotis de exudado herida quirúrgica con tinción de Gram. Obsérvese el predominio de cocos grampositivos.**

La FN por *S. pyogenes* es una infección infrecuente, considerada una urgencia médica debido a su alta tasa de mortalidad por el compromiso sistémico y la rápida progresión que presenta. Su pronóstico está determinado por un diagnóstico precoz e instauración de un inmediato y agresivo tratamiento [2, 3].

Se desarrolla generalmente en las extremidades tras un traumatismo o una lesión previa. Consiste en una severa inflamación a nivel de la vaina del musculo, que provoca trombosis y necrosis del tejido subcutáneo y de la fascia adyacente. Debido a la rareza de esta enfermedad, presenta una prevalencia de 0,02% en la población pediátrica [4, 5]. A diferencia de los adultos, que suelen estar condicionados por una situación de inmunodepresión, la FN ocurre con mayor frecuencia en niños sanos. Los eventos predisponentes comúnmente reconocidos incluyen cirugía, traumatismo, ampollas de varicela rotas e inyección intramuscular [6].

El diagnóstico erróneo más frecuente es la celulitis, que a su vez es el diagnóstico diferencial más frecuente [5], sin embargo en nuestro caso inicialmente se pensó en un diagnostico compatible con trombosis venosa profunda.

En el caso que describimos, el paciente no era inmunodeprimido y como condición predisponente, solo se señaló una cirugía en MMII 2 años antes y un episodio de otitis media tratada con antibioterapia de amplio espectro que podría haber generado un embolismo séptico con asiento en MMII. Por la exploración sabemos no se encontró puerta de entrada para explicar la infección a dicho nivel. Por lo tanto tenemos dos probables orígenes del cuadro de FN en este paciente.

La relevancia de este caso radica en la presentación infrecuente de FN en un paciente pediátrico sin condición predisponente a priori de inmunodepresión y la dilatación en el tiempo del debut del cuadro clínico en relación a los dos antecedentes epidemiológicos descritos.

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CONFLICTOS DE INTERÉS

Los autores declaran no tener ningún conflicto de intereses.

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Letter to the Editor

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Emerging infectious diseases: *Streptococcus suis* meningitis

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Sir,

Community-acquired bacterial meningitis is a serious infection with a high mortality rate. This disease is defined as a neurological emergency. Thus, early diagnosis and targeted treatment are of vital importance. *Streptococcus suis* is an important infectious agent of zoonotic origin bacterial meningitis, with a high incidence of auditory complications secondary to the development of labyrinthitis, and occasionally septic shock, with pig cattle being the main source of infection [1].

The number of human infections caused by this microorganism has increased substantially. Traditionally, it has been considered a sporadic disease. However, it can be the cause of outbreaks and epidemics, such as those detected in some Asian countries [2]. In contrast, the number of cases reported in Spain is limited [3-5].

We present the case report of meningitis with associated secondary bacteremia due to *S. suis* in a 56-year-old man, obese, smoker and occasional alcohol drinker, treated at our Hospital Emergency Department.

At the Primary Care center, the patient presented oppressive holocranial headache of strong intensity, fever of five days' duration (38ºC), hearing loss, vomiting, and dysthermic sensation. The onset of the disease was after the preparation, handling, and intake of roast pork. The following treatment was administered by medical personnel: an anxiolytic (diazepam), analgesics (metamizole, tramadol) and an antiemetic (metoclopramide). Subsequently, he was referred to our Hospital Emergency Department for persistent headache despite the medication dispensed. On initial physical examination, the patient displayed 85% oxygen saturation, diaphoresis, signs of meningeal irritation, and a progressive state of agitation. A cranial computed tomography scan without pathological findings of interest and a lumbar puncture showing an outflow of cerebrospinal fluid (CSF) with a cloudy-whitish appearance were performed. The CSF sample was sent to the laboratory for bacteriological culture and cytochemical study. In addition, samples were collected for blood culture.

In the initial analytical tests, the following results were obtained: white blood cell count 18.7 x 10^3/µL (4.0-10.5 x 10^3/µL), hemoglobin 15.2 g/dL (13.5- 18.0 g/dL), platelet count 115 x 10^3/µL (130-450 x 10^3/µL), glucose 141 mg/dL (60-110 mg/dL), creatinine 0.8 mg/dL (<1.25 mg/dL), lactate 15.7 mg/dL (5.7-22 mg/dL), C-reactive protein 7 mg/dL (<0.5 mg/dL), procalcitonin 0.45 ng/mL (<0.5 ng/mL).

CSF cytochemical characteristics showed the following results: glucose <10 mg/dL (50-80 mg/dL), total protein 950 mg/dL (15-45 mg/dL) and 13,720 leukocytes/µL (98% polymorphonuclear neutrophils). Gram-positive diplococci were observed on the Gram stain.

Due to his clinical situation, the patient was admitted to the Intensive Care Unit (ICU). The initial differential diagnosis suggested purulent meningitis with septic encephalopathy, immediately initiating administration of dexamethasone (8 mg / iv / 6 h) and broad-spectrum antimicrobial therapy with ampicillin, ceftriaxone, vancomycin, and acyclovir.

After 24 hours, the Microbiology Laboratory reported alpha-hemolytic streptococci isolation in CSF and blood cultures, identified as *S. suis* using the commercial Vitek-2 system (Biomerieux®). In addition, the antibiotic resistance profile was determined using epsilon-test strips (Biomerieux®). The bacterial isolate presented antibiotic susceptibility to penicillin [Minimal Inhibitory Concentration (MIC) = 0.064 mg/L], cefotaxime (MIC = 0.064 mg/L), levofloxacin (MIC = 0.5 mg/L) and vancomycin (MIC = 0.15 mg/L). The results were interpreted using the clinical breakpoints established by European Committee on Antimicrobial Susceptibility Testing (EUCAST). According to antibiogram results, antimicrobial targeted treatment with cefotaxime was initiated.

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After six days of ICU admission and favorable clinical evolution, he was referred to the Internal Medicine Service and stayed for three weeks.

The patient referred hearing loss at admission. Hence, an inter-consultation with otorhinolaryngology was performed to complete the study with audiometry and complementary tests. Although all these tests appeared normal, he manifested an exacerbation of hearing loss and appearance of tinnitus.

Due to favorable clinical evolution, the patient was discharged after four weeks in treatment with amoxicillin / clavulanic acid and scheduled follow-up with the specialists involved.

Human *S. suis* infections are mainly due to recent contact with sick or asymptomatic pigs, and the consumption of its contaminated meat derivatives. Consequently, the infection appears mainly among pig cattle workers, being considered in many countries as an occupational disease [6, 7].

The development of different strategies to prevent this disease through animal control implies the use of metaphylactic agents or vaccination [8]. Furthermore, the improvement in the hygienic conditions of pig cattle also affects the decrease of *S. suis* pork infections and its transmission to humans. [1].

Likewise, the instruction and training of personnel working with pigs or their derivatives is essential. Measures aimed at reducing this disease include the use of barrier methods during animal handling, hand washing, and proper cooking of meat before ingestion [1].

The relative inexperience in this zoonosis and the difficulty of the microbiological diagnosis [9], emphasize the importance of a complete anamnesis to obtain crucial information and guide clinical suspicion towards this infection. As an example, the early use of dexamethasone seems to reduce the incidence of hearing loss and patient neurological sequelae in these cases [10].

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

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Diagnóstico diferencial de la neumonía en los tiempos del COVID-19

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Sr. Editor: La abrupta aparición de casos provocados por la pandemia de COVID-19 ha condicionado la atención de los pacientes en los servicios de urgencias (SU) [1]. El cuadro clínico se caracteriza por fiebre y síntomas respiratorios, asociados a infiltrados pulmonares intersticiales en los casos más graves [2]. Durante estos meses, ante cualquier paciente con síntomas respiratorios ha sido obligado descartar infección por SARS-CoV-2 [3]. No obstante, existen otras etiologías de origen infeccioso que pueden presentarse con características clínicas, radiológicas e incluso analíticas similares, y que deben tenerse en cuenta en el diagnóstico diferencial [4, 5]. Más aún cuando el diagnóstico alternativo puede dar lugar a un manejo terapéutico diferente.

Se presenta el caso de una mujer de 32 años, sin antecedentes de interés, que acudió al SU por cuadro asteniforme con fiebre y disnea de dos semanas de evolución. En urgencias destacaban saturaciones basales en torno al 80%, frecuencia respiratoria de 22 rpm y crepitantes gruesos bilaterales en la auscultación pulmonar. Se realizó un análisis sanguíneo donde se objetivó linfopenia y elevación de proteína C reactiva, D-dímero y LDH. La radiografía de tórax (figura 1) mostró infiltrados intersticiales bilaterales. Dada la situación epidemiológica se solicitó una PCR de SARS-CoV-2 que resultó negativa. Aún así, considerando la alta sospecha clínica de infección por SARS-CoV-2, se inició tratamiento con hidroxicloroquina y lopinavir/ritonavir. Durante el ingreso hospitalario presentó al octavo día un empeoramiento clínico y radiológico (figura 2), por lo que se optó por iniciar tratamiento con esteroides a altas dosis (metilprednisolona 250 mg durante 3 días). No hubo mejoría clínica, requiriendo aumento de oxigenoterapia (reservorio a 15 lpm). Se solicitó la determinación de IL-6 que resultó mayor de 40 pg/ml, por lo que se decidió iniciar tratamiento con tocilizumab. En los días sucesivos persistió el empeoramiento clínico. El D-dímero en ese momento era de 2.500 ng/mL, por lo que se realizó una tomografía computarizada de tórax con contraste donde no se objetivó tromboembolismo pulmonar y se constataron los infiltrados bilaterales. Ante este resultado y debido a la persistencia de reactantes inflamatorios elevados, se instauró tratamiento con anakinra.

Ante la ausencia de mejoría clínica, se reinterrogó a la paciente que refirió un síndrome constitucional de varios meses de evolución relacionado con deposiciones diarreicas durante el último año, bicitopenia en estudio por hematología y múltiples parejas sexuales en la última década. Se comenzó en ese momento tratamiento con cotrimoxazol y prednisona, ante la sospecha de neumonía por *Pneumocystis jirovecii*, y se solicitó serología de VIH que resultó positiva. Se realizó broncoscopia con lavado broncoalveolar con IFI positivo para *P. jirovecii* y PCR de SARS-CoV2 negativo. Se mantuvo el tratamiento médico instaurado y se inició tratamiento antirretroviral de gran actividad (TARGA). La paciente presentó finalmente buena evolución clínica, siendo dada de alta tras 35 días de ingreso.

Con este caso queremos ejemplificar la importancia de realizar un adecuado diagnóstico diferencial, incluso durante una época de pandemia como la vivida, evitando errores diagnósticos iniciales que conducen a un error en la estrategia terapéutica inicial.

El TARGA ha supuesto un cambio en la historia natural de la infección por el VIH, siendo excepcionales en este momento que los pacientes tratados padezcan una infección oportunista [6]. Sin embargo, el diagnóstico tardío, cuando presentan menos de 350 linfocitos CD4/µL, ocurre en España en el 50% de los nuevos diagnósticos [7]. Las infecciones oportunistas continúan siendo, en estos pacientes con infección oculta, causa importante de morbilidad y mortalidad. Los SU debemos estar

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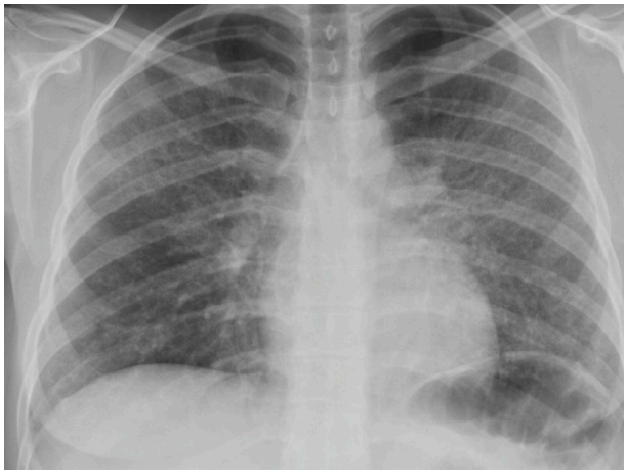

Figura 1 | **Radiografía de tórax al ingreso del paciente**

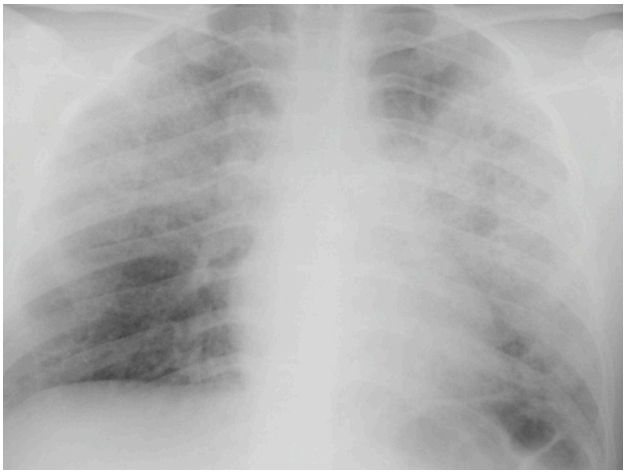

Figura 2 | **Radiografía de tórax al octavo día de ingreso hospitalario**

atentos a ello cuando establecemos el diagnóstico diferencial de los pacientes [8].

Las características típicas de la neumonía por *P. jirovecii* son la presencia de fiebre, tos, disnea, hipoxemia e infiltrados bilaterales que se inician en las regiones parahiliares y progresan a las zonas apicales y periféricas. Pueden existir elevación de la LDH y linfopenia [9]. Constituye, por tanto, un cuadro difícilmente distinguible de la neumonía provocada por SARS-CoV-2. En este sentido, una anamnesis epidemiológica dirigida puede ser clave para establecer una sospecha clínica inicial. Además, no debemos olvidar que la mortalidad global de la neumonía por *P. jirovecii* en pacientes hospitalizados puede alcanzar del 15 al 20% [9].

Por otra parte, la prevalencia de neumonía como condición indicadora de infección por VIH es del 4-9%, y es aún más común (16%) en presentadores tardíos [10]. Estos datos aconsejan incluso la determinación serológica para el VIH de manera sistemática a todos los pacientes con neumonía.

En conclusión, la alta prevalencia de una enfermedad en momentos o entornos determinados puede condicionar el diagnóstico, pero no debemos olvidar que una buena historia clínica con atención a los detalles epidemiológicos son claves para establecer el diagnóstico certero, más allá de las determinaciones analíticas o las pruebas de imagen.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflictos de intereses.

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