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REVISTA ESPAÑOLA DE
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Sumario

REVISTA ESPAÑOLA DE
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Volumen 36
Número 4
Agosto 2023

Sumario

REVISTA ESPAÑOLA DE Quimioterapia

Volumen 36
Número 4
Agosto 2023

Cartas al Director

Contents

REVISTA ESPAÑOLA DE
Quimioterapia

Volume 36
Number 4
August 2023

Contents

REVISTA ESPAÑOLA DE Quimioterapia

Volume 36
Number 4
August 2023

Letters to the editor

Official journal of the Spanish Society of Chemotherapy

Review

Revista Española de Quimioterapia
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Eficacia, efectividad y seguridad de la vacuna antigripal adyuvada en población de 65 o más años de edad

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RESUMEN

La mayoría de las complicaciones y fallecimientos relacionados con la gripe estacional ocurren en población de 65 años o más y con enfermedades de base, y la vacuna frente a la gripe es la forma más efectiva de prevenirlas. La inmunización es menos eficaz en los adultos mayores debido a la inmunosenescencia. Las vacunas adyuvadas con MF59, diseñadas para mejorar la magnitud, persistencia y amplitud de la respuesta inmunitaria en personas de 65 años o más, se vienen utilizando en la práctica clínica desde 1997 en su formulación trivalente y, desde 2020, en formulación tetravalente. Los datos de diversos estudios muestran que estas vacunas son seguras para todos los grupos de edad, con un perfil de reactogenicidad similar al de la vacuna convencional, y que resultan especialmente efectivas para potenciar la respuesta inmunitaria en la población de 65 años o más, al aumentar los títulos de anticuerpos tras la vacunación y reducir significativamente el riesgo de ingreso hospitalario. Las vacunas adyuvadas han demostrado otorgar protección cruzada frente a cepas heterólogas y ser igual de efectivas que la vacuna de alta dosis en población de 65 años o más. En esta revisión se analiza la evidencia científica sobre la eficacia y la efectividad de la vacuna adyuvada con MF59 en la práctica clínica real en personas ≥65 años mediante una revisión narrativa y descriptiva de los datos publicados en ensayos clínicos, estudios observacionales y revisiones sistemáticas o metaanálisis.

Palabras clave: Vacuna antigripal; Vacuna adyuvada; MF59

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Efficacy, effectiveness and safety of the adjuvanted influenza vaccine in the population aged 65 or over

ABSTRACT

Most of the complications and deaths related to seasonal flu occur in the elderly population (≥65 years) with comorbidities, and the influenza vaccine is the most effective way to prevent them. Immunization is less effective in older adults due to immunosenescence. MF59-adjuvanted vaccines, designed to improve the magnitude, persistence and amplitude of the immune response in elderly people, have been used in clinical practice since 1997 in their trivalent formulation and, since 2020, in their tetravalent formulation. Data from various studies show that these vaccines are not only safe for all age groups, with a reactogenicity profile similar to that of the conventional vaccine, but also that they are especially effective in boosting the immune response in the population aged 65 or over by increasing antibody titers after vaccination and significantly reducing the risk of hospital admission. Adjuvanted vaccines have been shown to provide cross-protection against heterologous strains and to be as effective as the high-dose vaccine in the population aged 65 or over. In this review, the scientific evidence on the efficacy and effectiveness of the MF59-adjuvanted vaccine in real clinical practice in people ≥65 years of age is analyzed through a narrative and descriptive review of the literature with data from clinical trials, observational studies and systematic reviews or meta-analysis.

Keywords: Influenza Vaccine; Adjuvanted Vaccine; MF59

INTRODUCCIÓN

La gripe estacional es una infección vírica aguda que algunos años puede alcanzar incidencias del 5-10% [1]. El riesgo de complicaciones, hospitalizaciones y fallecimientos por gri-

pe es mayor en personas de 65 o más años, niños menores de 5 años, mujeres embarazadas y pacientes con comorbilidades [1]. Las epidemias de gripe anuales causan 290.000- 650.000 muertes en el mundo y 3-5 millones de casos de enfermedad grave [1]. La infección por gripe duplica la mortalidad en los pacientes coinfectados por el virus SARS-CoV-2 [2].

En los países industrializados, la mayoría de las muertes relacionadas con la gripe ocurren en población de 65 años o más [1]. Se ha descrito una mortalidad de alrededor del 12% en mayores hospitalizados por gripe [3,4]. Además, la gripe disminuye de forma notable la calidad de vida relacionada con la salud (CVRS), con una pérdida de autonomía que puede provocar gran discapacidad en hasta un 14,6% de las personas de 65 años o más [3].

La vacuna frente a la gripe es la forma más efectiva de prevenir la gripe y sus complicaciones [1]. Sin embargo, la inmunización es menos eficaz en las personas de 65 o más años debido a la inmunosenescencia [3–5]. Esto hace que los mayores muestren una respuesta menos intensa y efectiva a la vacuna en comparación con la población adulta más joven [6,7]. Con objeto de mejorar la respuesta a la vacuna antigripal en los mayores se han propuesto diversas estrategias, tales como el uso de adyuvantes (por su efecto inmunoestimulador), vías de administración alternativas, o vacunas atenuadas en lugar de inactivadas [8].

Las vacunas adyuvadas con MF59, diseñadas para mejorar la magnitud, persistencia y amplitud de la respuesta inmunitaria en población de 65 años o más, se vienen utilizando en la práctica clínica desde 1997 en su formulación trivalente y, desde 2020, también en formulación tetravalente [9–11]. Nueve estudios de evidencia con datos de práctica clínica (*real-world evidence*) publicados en 2020-2021, que analizaron varias temporadas consecutivas de gripe e incluyeron 53 millones de participantes, han demostrado que la vacuna con MF59 es más efectiva que las vacunas convencionales e igual de efectiva que la de alta dosis en población de 65 años o más [12,13]. Esto complementa la evidencia de 12 estudios de efectividad, identificados en una reciente revisión, que compararon la vacuna con MF59 frente a las vacunas convencionales no adyuvadas y que incluyeron 14 millones de participantes [12,13].

El objetivo de este trabajo es analizar la evidencia científica sobre la eficacia y la efectividad de la vacuna adyuvada con MF59 en la práctica clínica real en población ≥65 años mediante una revisión narrativa [14] de los datos publicados procedentes de ensayos clínicos, estudios observacionales y revisiones sistemáticas o metaanálisis.

METODOLOGÍA

Para elaborar este artículo, se realizó una búsqueda bibliográfica no sistemática en septiembre de 2022 en las bases de datos electrónicas Medline (PubMed) y Embase empleando los siguientes descriptores: vacuna adyuvada, gripe, vacuna antigripal, MF59 y estudios publicados desde enero de 2014 hasta septiembre de 2022 que incluyeran a población de 65 años o más. Tras revisar el contenido de las publicaciones, se seleccionaron aquellas que, a criterio de los autores, fueron más relevantes por presentar datos sobre la vacuna adyuvada con MF59 en la práctica clínica real en población de 65 años o más. Se revisaron un total de 19 estudios, incluyendo ensayos clínicos, estudios observacionales y revisiones sistemáticas/metaanálisis (Tabla 1).

EFICACIA, INMUNOGENICIDAD Y SEGURIDAD DE LAS VACUNAS ANTIGRIPALES ADYUVADAS

Ensayos clínicos. A continuación, resumimos los principales resultados de eficacia, inmunogenicidad y seguridad de las vacunas adyuvadas frente la gripe en adultos ≥65 años procedentes de 5 ensayos clínicos de fase 3 [15–19] (Tabla 2).

En el ensayo clínico con asignación aleatoria (ECA) llevado a cabo por Frey et al. [15] (2014) se evaluaron en la temporada de gripe 2010-2011 la inmunogenicidad, la seguridad y la eficacia de la vacuna trivalente adyuvada con MF59 (aTIV) en comparación con la vacuna trivalente sin adyuvar (TIV) en sujetos con o sin comorbilidad. La eficacia, la reactogenicidad y los eventos adversos (EA) graves se evaluaron hasta el día 366 tras administrar la vacuna. La vacuna aTIV indujo respuestas significativamente más elevadas de anticuerpos (por inhibición de la aglutinación) (p<0,001) que las obtenidas por la vacuna

Tabla 1 Número de estudios incluidos en la revisión en función del diseño

Tipo de estudio	Número de estudios incluidos	Número de estudios con aTIV	Número de estudios con aQIV*
Ensayos clínicos [15–19]	5	3	2
Estudios observacionales [20–31]	12	12	-
Revisiones sistemáticas/metaanálisis [13,33,34]	3	3	-

aQIV: vacuna antigripal tetravalente adyuvada y de dosis estándar; aTIV: vacuna antigripal trivalente adyuvada y de dosis estándar

***Debido a la comercialización en 2020 de la primera vacuna aQIV, todavía no se dispone de datos en vida real para esta, por lo que la mayoría de datos de efectividad de las vacunas adyuvadas proceden de estudios realizados con la vacuna aTIV. Sin embargo, debido a la formulación, composición en parte coincidente y proceso de fabricación similar entre ambos tipos de vacuna, la evidencia de la efectividad de la vacuna aTIV resulta también pertinente para la vacuna aQIV.**

Tabla 2 **Ensayos clínicos aleatorizados con la vacuna antigripal adyuvada en adultos de 65 años o más**

Autor (año) [referencia]	Diseño	n	Temporada de gripe	Resultados principales
Frey (2014) [15]	Fase 3, prospectivo, aleatorizado, controlado con placebo y enmascarado para el observador	aTIV: 3.541 TIV: 3.541	2010-11	-aTIV: respuestas significativamente más elevadas vs. TIV frente a todas las cepas homólogas y heterólogas, incluso en caso de comorbilidad -No se estableció la superioridad según los criterios predefinidos -Aunque la reactividad fue mayor en el grupo de aTIV, las reacciones fueron leves/moderadas y transitorias
Essink (2020) [16]	Fase 3, multicéntrico, aleatorizado, doble enmascaramiento, de grupos paralelos y controlado	aQIV: 889 aTIV-1: 445 aTIV-2: 444	2017-18	-aQIV: respuesta similar a aTIV frente a cepas de gripe homólogas -El beneficio inmunológico de aQIV también se demostró en los subgrupos de 65–74, 75–84 y ≥85 años y en aquellos sujetos con alto riesgo de comorbilidad -aQIV y aTIV fueron inmunogénicas y bien toleradas
Beran (2021) [18]	Fase 3, multicéntrico, aleatorizado, estratificado, doble enmascaramiento y controlado	aQIV: 3.381 Comparador: 3.380	2016-17	-aQIV: EV 19,8% frente a todas las cepas y 49,9% frente a compatibles antigénicamente -No se cumplió el criterio preespecificado para mostrar la eficacia de aQIV -85% de los aislamientos caracterizados no coincidieron con la cepa vacunal -aQIV: mayor protección contra la gripe clínicamente relevante durante las temporadas dominadas por el subtipo A(H3N2), antigénicamente divergentes -Eficacia mayor en los casos asociados a fiebre más alta (enfermedad clínicamente más significativa) -EA local más común: dolor en el sitio de inyección (16,3% aQIV y 11,2 % comparador)
Cowling (2020) [17]	Fase 3, aleatorizado, controlado, de comparación directa	QIV: 200 aTIV: 200 HD-TIV: 200 QIVr: 200	2017-18	-aTIV: mejor respuesta humoral y celular vs. QIV, especialmente para las cepas de tipo A -Efectos para las cepas de tipo B menos claros: elevados para la cepa B/linaje-Victoria, especialmente con QIV -EA leves y transitorios -Algunas reacciones locales agudas fueron más frecuentes con aTIV o con HD-TIV vs. QIV -A medio plazo, menos EA como hinchazón, dolor o sensibilidad con aTIV vs. SQIV
Schmader (2021) [19]	Prospectivo, aleatorizado, enmascaramiento simple	aTIV: 378 HD-TIV: 379	2017-18 2018-19	-Seguridad y calidad de vida de aTIV vs. HD-TIV -La proporción de pacientes que notificaron dolor moderado o intenso en el lugar de inyección que limitara o impidiera la actividad con aTIV no fue inferior vs. HD-TIV (3,2% vs. 5,8 %; diferencia –2,7 %; IC 95%: –5,8-0,4) -Cambios en las puntuaciones de CVRS: no fueron clínicamente significativos y no difirieron entre los grupos -Los resultados de seguridad indican que ambas vacunas pueden usarse en campañas de vacunación preventivas en adultos mayores

aQIV: vacuna antigripal tetravalente adyuvada y de dosis estándar, aTIV: vacuna antigripal trivalente adyuvada y de dosis estándar, EA: efecto adverso, HD-QIV: vacuna antigripal tetravalente de alta dosis, HD-TIV: vacuna antigripal trivalente de alta dosis, n: tamaño muestral, QIVr: vacuna tetravalente de hemaglutinina recombinante, TIV: vacuna antigripal trivalente sin adyuvar y de dosis estándar.

Tabla 3 **Estudios observacionales con la vacuna antigripal adyuvada en adultos ≥65 años**

Estudio (año) [referencia]	Diseño	n	Temporada de gripe	Resultados principales
Izurieta (2019) [21]	Retrospectivo de cohortes que compara 5 vacunas	>13x10^6	2017-18	-Comparación en EE.UU. de 5 vacunas (QIVc, QIVe, TIV, aTIV y HD-TIV) en la prevención de hospitalizaciones -Eficacia de QIVc: ≈ 10-11% mayor que QIVe en evitar hospitalizaciones, visitas hospitalarias y consultas -Mayor EVr en reducción de visitas hospitalarias y número de hospitalizaciones relacionadas con la gripe con QIVc y HD-TIV
Izurieta (2020) [20]	Retrospectivo de cohortes que compara 6 vacunas	>12,7x10^6	2018-19	-Comparación en EE.UU. de 6 vacunas (QIVc, QIVr, QIVe, TIV, aTIV y HD-TIV) -aTIV y HD-TIV fueron algo más efectivas que QIVe -Las vacunas QIV no mostraron diferencias significativas de eficacia entre las producidas en cultivo celular y las basadas en huevo -Las vacunas adyuvadas y la a HD-TIV a base de huevo fueron ligeramente más eficaces que las vacunas QIV basadas en huevo
Izurieta (2021) [22]	Retrospectivo de cohortes que compara 5 vacunas	>12,7x10^6	2019-20	-Comparación en EE.UU. de 5 vacunas (HD-TIV, aTIV, QIVe, QIVc y QIVr) -En la prevención de visitas hospitalarias, QIVr (EVr 13,3%: 7,4-18,9%), aTIV (8,2%: 4,2-12,0%) y HD-TIV (6,8%: 3,3-10,1%) fueron significativamente más eficaces que QIVc -La vacuna recombinante fue moderadamente más eficaz que el resto, mientras que HD-TIV y aTIV fueron más efectivas que QIVe.
Van Aalst (2020) [23]	Retrospectivo de cohortes	HD-TIV: >1,9x10^6 aTIV: 223.793	2016-17 2017-18	-Comparación de HD-TIV vs. aTIV en EE.UU. -HD-TIV se asoció a menos visitas hospitalarias por causa respiratoria que aTIV
McConeghy (2021) [24]	Por conglomerados (clusters)	aTIV: 24.926 TIV: 25.086	2016-17	-Comparación en residencias de ancianos del número de hospitalizaciones (población vacunada con aTIV vs. TIV) en EE.UU. -aTIV: más eficaz que TIV en prevenir hospitalizaciones por cualquier causa y por neumonía o gripe -Ambas mostraron una tasa de hospitalización respiratoria similar en una temporada de baja efectividad vacunal
Pelton (2020) [25]	Retrospectivo de cohortes	aTIV: 234.313 HD-TIV: 1.269.855 QIV: 212.287 TIV: 106.491	2017-18	-Comparación de aTIV, HD-TIV, QIV y TIV. -aTIV: EVr significativamente mayor en reducción de hospitalizaciones/visitas a urgencias relacionadas con la gripe vs. QIV y TIV, y similar a HD-TIV -aTIV se asoció a una EVr significativamente mayor que TIV en evitar hospitalizaciones/visitas a urgencias por causa respiratoria
Pelton (2021) [26]	Retrospectivo de cohortes	aTIV: 561.315 HD-TIV: 1.672.779	2018-19	-aTIV vs. HD-TIV en la prevención de hospitalizaciones y visitas a urgencias relacionadas con la gripe -Hospitalizaciones/visitas a urgencias relacionadas con la gripe similares entre ambas vacunas -aTIV: ligeramente más efectiva para prevenir las consultas relacionadas con la gripe y cualquier evento cardiorrespiratorio vs. HD-TIV
Levin (2021) [27]	Retrospectivo de cohortes	aTIV: 798.987 HD-TIV: 1.655.979	2019-20	-aTIV vs. HD-TIV en prevención de hospitalizaciones y visitas a urgencias por eventos cardiorrespiratorios relacionados con la gripe -aTIV: eficacia similar a HD-TIV en la prevención de hospitalizaciones/visitas a urgencias relacionadas con la gripe, hospitalizaciones totales y hospitalizaciones/visitas a urgencias por causa cardiorrespiratoria relacionadas con la gripe

Tabla 3 **Estudios observacionales con la vacuna antigripal adyuvada en adultos ≥65 años (cont.)**

Estudio (año) [referencia]	Diseño	n	Temporada de gripe	Resultados principales
Boikos (2021) [28]	Retrospectivo de cohortes	2017-2018 aTIV: 524.223 QIV: 917.609 HD-TIV: 3.377.860 2018-2019 aTIV: 1.031.145 QIV: 915.380 HD-TIV: 3.809.601	2017-18 2018-19	-Comparación de aTIV, QIV y HD-TIV en cuanto a prevención de eventos y complicaciones relacionadas con la gripe en EE.UU. -aTIV: mayor reducción de eventos médicos relacionados con la gripe vs. QIV y HD-TIV para ambas temporadas -En población anciana de alto riesgo con comorbilidades de base, EVr de aTIV superior a QIV y similar a HD-TIV
Boikos (2021) [29]	Retrospectivo de cohortes (parte de Boikos et al., 2021a)	2017-2018 aTIV: 168.125 QIV: 360.379 HD-TIV: 1.226.916 2018-2019 aTIV: 328.227 QIV: 351.260 HD-TIV: 1.375.525	2017-18 2018-19	-Comparación de aTIV, QIV y HD-TIV en cuanto a evitar consultas relacionadas con la gripe en EE.UU. -En comparación con QIV, la efectividad de aTIV fue un 7,1% (IC 95%: 3,3-10,8) y un 20,4% (16,2-24,4) mayor para prevenir consultas relacionadas con la gripe en las temporadas 2017-2018 y 2018-2019, respectivamente -Eficacia similar a HD-TIV en ambas temporadas
Imran (2022) [30]	Retrospectivo de cohortes	aTIV: 936.508 QIV: 651.034 HD-TIV: 1.813.819	2019-20	-Comparación de aTIV, QIV y HD-TIV en cuanto a prevención de eventos y complicaciones relacionadas con la gripe en EE.UU. -aTIV: mejor EVr frente eventos hospitalarios y ambulatorios vs. QIV y HD-TIV -Resultados consistentes en todos los subgrupos de edad y en ambas temporadas
Lapi (2022) [31]	Retrospectivo de casos y controles anidados	aTIV: 5.610 TIV/QIV: 41.594	2002-03 a 2018-19 (18 temporadas)	-Eficacia relativa de aTIV frente a TIV/QIV en la reducción de hospitalizaciones por cualquier causa -En comparación con la TIV/QIV, aTIV se asoció con una reducción del 12% de las probabilidades de hospitalización por cualquier causa -Los resultados para la temporada 2018-19 son consistentes para la vacuna aTIV pero no para la aQIV.

aQIV: vacuna antigripal tetravalente adyuvada y de dosis estándar; aTIV: vacuna antigripal trivalente adyuvada y de dosis estándar, c: tecnología celular, e: basada en huevo, CVRS: calidad de vida relacionada con la salud, EVr: efectividad vacunal relativa, HD-TIV: vacuna antigripal trivalente de alta dosis, n: tamaño muestral, QIV: vacuna antigripal tetravalente sin adyuvar y de dosis estándar, QIVr: vacuna tetravalente de hemaglutinina recombinante, TIV: vacuna antigripal trivalente sin adyuvar y de dosis estándar.

TIV frente a todas las cepas homólogas y heterólogas del virus de la gripe, incluso en sujetos con mayor riesgo de complicaciones por presentar comorbilidad, aunque no se estableció la superioridad según los criterios predefinidos. Respecto la seguridad, la reactogenicidad fue mayor en el grupo de aTIV; pero las reacciones fueron leves o moderadas y de corta duración.

Essink et al. [16] (2020) realizaron un ECA con doble enmascaramiento y multicéntrico en el que los pacientes fueron asignados 2:1:1 a recibir una vacuna tetravalente adyuvada con MF59 (aQIV), una vacuna aTIV-1, correspondiente a la vacuna autorizada para el hemisferio norte en la temporada de gripe 2017-2018, u otra vacuna aTIV-2 con la cepa B alternativa. El estudio tuvo por objetivos evaluar si la vacuna aQIV provocaba una respuesta inmunitaria no inferior en comparación con aTIV-1 y aTIV-2; así como examinar la superioridad de aQIV frente a la cepa B, además de analizar la reactogenicidad y seguridad. Los títulos de anticuerpos se determinaron antes de la vacunación y a los 21 días de la misma para cepas homólogas. La vacuna aQIV cumplió con los criterios de no inferioridad frente a aTIV en cuanto a diferencia en la media geométrica de los títulos de anticuerpos (MGT) y tasa de seroconversión. También cumplió con los criterios de superioridad para la cepa B. Todas las vacunas fueron inmunogénicas y bien toleradas.

En el ECA de Cowling et al. [17] (2020), adultos de 65-82 años fueron asignados a recibir una vacuna tetravalente de dosis estándar (QIV), una vacuna aTIV, una vacuna trivalente

de alta dosis (HD-TIV) o una vacuna tetravalente de hemaglutinina recombinante (QIVr) autorizadas para la temporada de gripe 2017-2018. Se analizaron los sueros de 200 receptores de cada vacuna, antes y 30 días después de la vacunación, para detectar anticuerpos frente a las cepas vacunales producidas en huevo (mediante inhibición de la aglutinación, HAI) y frente al virus A/Hong Kong/4801/2014(H3N2) de cultivo celular (mediante microneutralización, MN). Se evaluaron las respuestas de linfocitos T CD4+ y CD8+ específicos de gripe en 20 participantes por grupo. Los aumentos medios (*mean fold rises*, MFR) en los títulos de HAI para A(H1N1)pdm09 y A(H3N2), y de MN para A(H3N2) fueron significativamente superiores con las vacunas mejoradas frente a las de dosis estándar (p<0,05). De igual modo, en los receptores de la vacuna QIVr el título frente a A(H3N2) fue 2,57 veces mayor que con la vacuna de dosis estándar; la magnitud de esta diferencia fue significativamente mayor que las diferencias de 1,43 y 1,33 observadas en los receptores de vacuna de alta dosis y vacuna adyuvada con MF59, en comparación con los que recibieron una vacuna de dosis estándar. Los autores concluyeron que los sujetos que recibieron vacunas mejoradas (aTIV, HD-TIV o QIVr) mostraron una mejor respuesta inmunitaria (humoral y celular) respecto a los que recibieron la de dosis estándar.

El ECA de Beran et al. [18] (2021), con doble enmascaramiento, fue realizado en 12 países en las temporadas 2016-17 en el hemisferio norte, y en la 2017 en el hemisferio sur. Los participantes, estratificados en función de la edad (65-74 y ≥75 años) y del riesgo de complicaciones de la gripe, se asignaron al azar 1:1 a recibir aQIV o una vacuna no antigripal. Se trata del único ensayo clínico con resultados de casos de gripe confirmados por laboratorio. El resultado principal según protocolo fue la eficacia absoluta de la vacuna en prevenir casos de gripe, confirmada por RT-PCR, frente a cualquier cepa de gripe en pacientes con síntomas de gripe y fiebre ≥ 37,2ºC. Se registraron un 3,6% de casos de gripe confirmados en el grupo de aQIV y un 4,5% en el comparador, la mayoría causados por el subtipo A(H3N2). Un 85% de los aislamientos caracterizados no coincidieron con la cepa vacunal. Aun así, la vacuna aQIV mostró una eficacia según protocolo del 19,8% (IC 95% -5,3 a 38,9) frente a todas las cepas y del 49,9% (-24,0 a 79,8) frente a cepas compatibles antigénicamente. Cabe destacar que la eficacia frente a casos de gripe con pruebas de laboratorio positivas en sujetos con fiebre ≥ 38,0ºC fue del 51,1% (28,2 a 66,7). La reacción más común a la vacuna adyuvada fue el dolor en el sitio de inyección. La eficacia de la vacuna adyuvada fue mayor en los casos de fiebre más alta, que corresponden a enfermedad más relevante.

Por último, en el ECA con enmascaramiento simple de Schmader et al. [19] (2021) se compararon la seguridad, la reactogenicidad y las variaciones en la CVRS tras la vacunación con aTIV frente a HD-TIV en las temporadas 2017-2018 y 2018-2019. La proporción de pacientes que notificaron dolor moderado o intenso en el lugar de inyección con aTIV fue similar respecto a HD-TIV (3,2% frente al 5,8%; diferencia -2,7%; IC 95%: -5,8 – 0,4%). No se observaron EA de interés clínico. Ningún participante precisó atención médica por una reacción a la vacuna y no se asoció ningún EA grave a la vacunación. Los cambios en las puntuaciones de CVRS no fueron clínicamente significativos y no difirieron entre los grupos de edad con ambas vacunas.

Estudios observacionales. Resumimos seguidamente la evidencia de 12 estudios observacionales [20–31] sobre la efectividad de la vacuna antigripal adyuvada en la práctica clínica (Tabla 3).

Izurieta et al. llevaron a cabo 3 grandes estudios independientes, de cohortes y retrospectivos, en pacientes ≥65 años de la base de datos Medicare en EE.UU. [20–22]. En el primero de ellos [21], realizado en la temporada 2017-18 en más de 13 millones de sujetos que recibieron distintas vacunas frente a la gripe (QIVe basada en huevo, QIVc en cultivo celular; HD-TIV en huevo, aTIV o TIV), la efectividad vacunal relativa (EVr) de las vacunas de cultivo celular en relación con la QIVe fue del 10% (IC 95%: 7–13%). La vacuna aTIV demostró ser ligeramente más efectiva que las vacunas TIV (EVr 3,6%; IC 95%: 0,7–6,4%; p≤0,05) y QIV (EVr 3,9%; IC 95%: 1,4–6,3%; p ≤0,05) basadas en huevo sin adyuvar en la prevención de hospitalizaciones relacionadas con la gripe, pero fue menos efectiva que la vacuna QIVc (EVr 7,5%; IC 95%: 4,1–10,7%; p≤0,05) y la HD-TIV (EVr 5,3%; IC 95%: 3,3–7,3%; p≤0,05). El segundo estudio [20], realizado en la temporada 2018-19, investigó en 12 millones de personas la EVr en la prevención de consultas hospitalarias asociadas a la gripe. La efectividad fue algo superior para la vacuna basada en huevo adyuvada (EVr 7,7%; IC 95%: 3,9–11,4%; p≤0,05) y la vacuna de alta dosis (EVr 4,9%; 1,7–8,1%; p≤0,05) respecto a la QIV. En el tercero de estos estudios [22], en la temporada 2019-20, se estimó la EVr de las vacunas HD-TIV, aTIV, QIVe, QIVc y la vacuna tetravalente recombinante (QIVr) en 12,7 millones de sujetos. Se observó una superioridad significativa en la EVr de QIVr (13,3%: 7,4–18,9%), aTIV (8,2%: 4,2–12,0%) y HD-TIV (6,8%: 3,3–10,1%) respecto a la vacuna QIVe en la prevención de visitas hospitalarias, mientras que QIVc no fue significativamente más efectiva que QIVe (EVr 2,8%: -2,8–8,2%). En la temporada 2019-20 la circulación del virus de la gripe A(H3N2) fue escasa, por lo que los resultados deben interpretarse teniendo en cuenta esta circunstancia.

Un estudio de cohortes retrospectivo, llevado a cabo por Van Aalst et al. [23] (2020) en las temporadas de gripe 2016-2017 y 2017-2018, comparó la efectividad vacunal en casi 2 millones de personas ≥65 años que recibieron la vacuna HD-TIV frente a la aTIV. La EVr agrupada para ambas temporadas de HD-TIV frente a aTIV, en cuanto a hospitalizaciones relacionadas con problemas respiratorios, fue del 12% (IC 95%: 3,3–20%); 13% (-6,4–32%) para la temporada 2016-2017 y 12% (2,1–21%) para la 2017-2018.

En un estudio observacional, McConeghy et al. [24] (2021) asignaron al azar 823 residencias de ancianos de estancia prolongada para que ofrecieran a sus residentes (n=50.012) aTIV o TIV en la temporada 2016-2017. Se evaluó la efectividad de aTIV frente a TIV en evitar hospitalizaciones. Las tasas de hospitalización por neumonía o gripe y por cualquier causa fueron menores con aTIV que con TIV (HR ajustado 0,80 [IC

95%: 0,66–0,98; p=0,03] y 0,94 [0,89–0,99; p=0,02]). La tasa de hospitalización por cualquier causa respiratoria fue similar en ambos grupos de vacunados, en una temporada donde la efectividad vacunal se consideró baja [32].

Durante la temporada 2017-2018, Pelton et al. [25] (2020) evaluaron la efectividad de la vacuna aTIV respecto a otras vacunas antigripales (HD-TIV, QIV, TIV) en prevenir eventos cardiorrespiratorios relacionados con la gripe en más de 1,82 millones de personas. La vacuna aTIV fue más efectiva en reducir las consultas relacionadas con la gripe y otras hospitalizaciones/visitas a urgencias por causa respiratoria en comparación con el resto de vacunas. En cuanto a hospitalizaciones/visitas a urgencias relacionadas con la gripe, aTIV mostró una EVr significativamente mayor que QIV y TIV (aTIV vs. QIV 8,6% [IC 95%: 1,2–15,6%]; aTIV vs. TIV 11,2% [2,3–19,4%]), y fue similar a HD-TIV. También se asoció con una EVr significativamente mayor que TIV en cuanto a hospitalizaciones/visitas a urgencias por causa respiratoria (aTIV vs. HD-TIV 2,4% [IC 95%: 0,7–4%]; aTIV vs. QIV 4% [1,9–6,2%]; aTIV vs. TIV 7,2% [4,6–9,7%]). Se demostró un beneficio significativo de aTIV en los eventos relacionados con la gripe o respiratorios en comparación con el resto de vacunas. En la temporada 2018-2019, este mismo autor publicó (2021) la efectividad vacunal de aTIV en comparación con las mismas vacunas en prevenir eventos cardiorrespiratorios y relacionados con la gripe [26]. En este caso, la vacuna aTIV fue más efectiva en reducir las consultas relacionadas con gripe que la HD-TIV (6,6%; IC 95%: 2,7–10,3%; p<0,001). Además, aTIV fue similar a HD-TIV (EVr 2,0%; IC 95%: -3,7–7,3%) en prevenir hospitalizaciones/visitas a urgencias relacionadas con la gripe, pero más efectiva en reducir las hospitalizaciones/visitas a urgencias por enfermedad cardiorrespiratoria (EVr 2,6%; IC 95%: 1,9–3,2%; p<0,0001).

Otro estudio retrospectivo, llevado a cabo por Levin et al. [27], comparó la efectividad vacunal de aTIV con la de HD-TIV en la prevención de hospitalizaciones/visitas a urgencias relacionadas con la gripe y enfermedades cardiorrespiratorias. La EVr de aTIV fue similar a la de HD-TIV en evitar hospitalizaciones/visitas a urgencias relacionadas con la gripe (3,1%; IC 95%: -2,8–8,6%), hospitalizaciones totales (-0,7%; IC 95%: -1,6–0,3%) y cualquier hospitalización/visita a urgencias relacionada con enfermedad cardiorrespiratoria (0,9%; IC 95%: 0,01–1,7%).

Boikos et al. publicaron en 2021 dos estudios retrospectivos correspondientes a las temporadas 2017-2018 y 2018-2019 [28,29]. En el primero de ellos [28] se comparó, en más de 10 millones de estadounidenses ≥65 años, la efectividad de aTIV, QIV y HD-TIV en términos de prevención de consultas relacionadas con la gripe. En 2017-2018, la EVr de aTIV frente a QIV fue de 18,2% (IC 95%: 15,8–20,5%) y de 7,7% frente a HD-TIV (IC 95%: 2,3–12,8%). En 2018-2019, la EVr de aTIV frente a QIV fue de 27,8% (IC 95%: 25,7–29,9) y de 6,9% frente a HD-TIV (IC 95%: 3,1–10,6%). El segundo [29], realizado en las mismas temporadas, comparó la efectividad de aTIV, QIV y HD-TIV en evitar consultas relacionadas con la gripe en más de 3,8 millones de pacientes con al menos una comorbilidad. Respecto a QIV, aTIV fue más efectiva en evitar consultas relacionadas con la gripe en ambas temporadas (un 7,1% [IC 95%: 3,3–10,8%] y un 20,4% [IC 95%: 16,2–24,4%]). En la primera temporada, la efectividad de aTIV fue estadísticamente superior en los pacientes con diabetes; en la segunda, también fue significativamente superior en los pacientes con enfermedad pulmonar obstructiva crónica (EPOC), asma, infarto de miocardio, enfermedad cerebrovascular, enfermedad renal y cáncer. Se observó una efectividad similar de aTIV respecto HD-TIV en ambas temporadas de gripe.

En 2022, Imran et al. [30] estudiaron de forma retrospectiva la efectividad de aTIV, QIV y HD-TIV (temporada 2019-2020) en 3.553.040 sujetos ≥ 65 años. La EVr total de aTIV fue del 27,5% (IC 95%: 24,4–30,5%) frente a QIV y del 13,9% (IC 95%: 10,7–17,0%) frente a HD-TIV. La efectividad de la vacuna aTIV fue superior tanto en pacientes hospitalizados como ambulatorios. Los valores de EVr para pacientes hospitalizados (ingresos con cualquier diagnóstico) y consultas relacionadas con la gripe en pacientes ambulatorios fueron significativos en la comparación entre aTIV y QIV. La EVr de aTIV frente a HD-TIV en pacientes hospitalizados no fue estadísticamente significativa cuando la gripe fue el diagnóstico principal de ingreso, aunque sí lo fue cuando la gripe se notificó en cualquier posición de los diagnósticos asociados al ingreso. Los hallazgos se mantuvieron en los subgrupos de edad (65-74; 75-84 y ≥85 años). La vacuna aTIV se asoció significativamente a menos consultas relacionadas con la gripe que las otras dos vacunas.

En el estudio recientemente publicado de Lapi et al. [31] (2022) se ha analizado la EVr de las vacunas aTIV frente a las no adyuvadas (TIV y QIV) en la prevención de hospitalizaciones por cualquier causa en 18 temporadas de gripe en atención primaria. Este estudio realizó un análisis de casos y controles anidados empleando la base de datos Health Search e incluyó una cohorte de 58.252 pacientes vacunados con aTIV, TIV o QIV. Durante las 18 temporadas de gripe estudiadas, se identificaron 2.504 casos de hospitalización por cualquier causa y la vacuna aTIV se asoció a una reducción relativa en la probabilidad de ingreso por cualquier causa [12% (OR 0,88; IC 95%: 0,80-0,97; p<0,05)] en comparación con las vacunas no adyuvadas.

Revisiones sistemáticas y metaanálisis. Tres revisiones sistemáticas/metaanálisis [13,33,34] recientes han estudiado la efectividad de la vacuna adyuvada con MF59 en pacientes mayores en la práctica clínica real (Tabla 4).

La primera de ellas fue publicada por Coleman et al. [33] en 2021 y su objetivo fue determinar la efectividad de la vacuna aTIV/aQIV en personas ≥65 años, comparado con la ausencia de vacunación o la vacunación con vacunas estándar o de alta dosis basadas en huevo. Este metaanálisis encontró que aTIV redujo el número de consultas debido a gripe confirmada, con estimaciones agrupadas del 40,7% (IC 95%: 21,9–54,9) y del 58,5% (IC 95%: 40,7–70,9) para visitas ambulatorias no urgentes y para pacientes hospitalizados. La estimación agrupada de EVr fue del 51,3% (39,1–61,1; I^2=0%; p=0,42) en cuanto a hospitalizaciones relacionadas con gripe o neumonía. Las estimaciones agrupadas de la EVr de aTIV en evitar consultas re-

Tabla 4 **Revisiones sistemáticas y metaanálisis de evidencia en vida real con la vacuna antigripal adyuvada en adultos ≥60 años**

Autor (año) [referencia]	Diseño	Nº estudios	Temporada de gripe	Metodología	Resultados principales
Coleman (2021) [33]	Revisión sistemática y metaanálisis	Revisión sistemática: 21 Metaanálisis: 16	2006-07 a 2019-20	-Estudios no intervencionistas publicados en revistas revisadas por pares y literatura gris desde 1997 hasta el 15 de julio de 2020, incluidos ensayos aleatorizados por grupos -Conforme a los estándares metodológicos Cochrane y las guías PRISMA-P -Dos revisores extrajeron los datos de forma independiente -El riesgo de sesgo se evaluó mediante ROBINS-I	-aTIV: EV absoluta significativa y mejor EVr vs. TIV y QIV -aTIV: EVr similar a la vacuna de alta dosis en población ≥65 años
Gärtner (2022) [13]	Revisión sistemática	11 análisis de 9 estudios	2006-07 a 2008-09 2011-12 a 2019-20	-Ensayos controlados aleatorizados, estudios observacionales y revisiones sistemáticas publicados entre el 7 de febrero de 2020 y el 6 de septiembre de 2021 -Los estudios se evaluaron con la herramienta Cochrane de riesgo de sesgo, ROBINS-I o AMSTAR 2	-9 de los 11 análisis: aTIV significativamente más eficaz vs. TIV y QIV en reducir los eventos clínicos relacionados con la gripe y los brotes de gripe -7 de los 11 análisis: aTIV eficacia similar a HD-TIV en reducir los eventos médicos relacionados con la gripe, la duración de la estancia hospitalaria y las hospitalizaciones/visitas a urgencias -3 de los 11 análisis: aTIV más eficaz que HD-TIV en reducir las consultas relacionadas con la gripe -La vacuna adyuvada y la de alta dosis son alternativas eficaces para los programas de vacunación en adultos mayores y son preferibles a las vacunas convencionales de dosis estándar
Domnich (2022) [34]	Revisión sistemática	52 estimaciones de la EVr de 10 artículos	2016-17 a 2019-20	-Ensayos controlados aleatorizados y estudios observacionales publicados hasta el 08 de abril de 2022 -Conforme a los estándares metodológicos de las guías PRISMA -Dos revisores extrajeron los datos de forma independiente -El riesgo de sesgo se evaluó mediante ROBINS-I -La herramienta GRACE (good research for comparative effectiveness) se aplicó a los estudios que cuantificaban la EVr de aTIV/aQIV frente HD-TIV/HD-QIV	-Las vacunas antigripales adyuvadas y de alta dosis están actualmente aprobadas para los adultos mayores -Las pruebas comparativas disponibles se limitan a estudios observacionales con datos del mundo real -Los resultados sobre la eficacia relativa de las dos vacunas contra la gripe son inconsistentes -Los estudios patrocinados por la industria tienden a informar de resultados más favorables -Los datos actualmente disponibles no apoyan ninguna preferencia de una vacuna sobre otra

aTIV: vacuna antigripal trivalente adyuvada y de dosis estándar, EV: efectividad vacunal, EVr: efectividad vacunal relativa, HD-TIV: vacuna antigripal trivalente de alta dosis, TIV: vacuna antigripal trivalente sin adyuvar y de dosis estándar.

lacionadas con la gripe fueron del 13,9 % (4,2–23,5; I^2=95,9%; p<0,01) comparada con TIV, del 13,7% (3,1–24,2; I^2=98,8%; p<0,01) frente a QIV, y del 2,8% (-2,9–8,5; I^2=94.5%; p<0,01) comparada con HD-TIV. Se concluyó que aTIV mostró una EV absoluta significativa, una mejor EVr en comparación con la vacuna TIV/QIV de dosis estándar, y una EVr similar a HD-TIV en población ≥65 años.

La segunda revisión sistemática, publicada por Gärtner et al. [13] en 2022, comparó la eficacia y la efectividad de las vacunas aTIV/aQIV frente a las de dosis estándar (TIV/QIV) y de alta dosis (HD-TIV/QIV) en personas de 65 años o más, para complementar la revisión sistemática de 2020 de las vacunas antigripales mejoradas llevada a cabo por el Centro Europeo para la Prevención y el Control de Enfermedades (ECDC) [12]. Se identificaron 11 análisis de 9 estudios que incluían 53 millones de participantes. En 9 de los 11 análisis la vacuna aTIV fue significativamente más efectiva que TIV y QIV en resultados relacionados con la gripe por entorno clínico y presuntos brotes de gripe [EVr de aTIV entre el 7,5% (IC 95%: 4,2–10,6%) y el 25,6% frente a TIV; y del 7,1% (IC 95%: 3,3–10,8) y el 36,3% (IC 95%: 31,0–41,2) frente a QIV]. Siete análisis encontraron una efectividad similar de aTIV frente a HD-TIV en reducir el número de consultas relacionadas con la gripe, el tiempo de estancia hospitalaria y las hospitalizaciones/visitas a urgencias. Y en dos análisis aTIV fue significativamente más eficaz que HD-TIV en reducir las consultas relacionadas con la gripe [EVr del 6,6% (IC 95%:2,7–10,3% y del 16,6% (IC 95%: 10,8–22,0), respectivamente]. En general no se encontraron diferencias significativas entre ambas vacunas para las variables analizadas. El riesgo de sesgo de los estudios identificados fue de moderado a alto.

La tercera y última revisión sistemática, publicada por Domnich et al. [34] en 2022, comparó la eficacia y la efectividad de la vacuna adyuvada (aTIV/aQIV) frente a la de alta dosis (HD-TIV/HD-QIV). Durante la búsqueda se identificaron 10 estudios que cumplían los criterios de inclusión, todos ellos observacionales, con un diseño de cohorte retrospectivo y elevado tamaño muestral. Todos fueron realizados en EE.UU. entre las temporadas de gripe 2016-2017 y 2019-2020. No se encontraron estudios que incluyeran aQIV ni HD-QIV [34]. Aunque la mayoría de las estimaciones de EVr agrupada fueron cercanas a la nulidad, algunos estudios mostraron una efectividad ligeramente superior para una vacuna u otra. En concreto, de las 52 estimaciones de la EVr de aTIV frente a HD-TIV o viceversa en población ≥ 65 años, la mayoría (31/52; 59,6%) no fueron significativas. Entre las estimaciones significativas, 13 (25,0%) favorecían a la vacuna aTIV, mientras que las 8 restantes (15,4%) eran favorables a HD-TIV. El análisis conjunto mostró que la vacuna aTIV fue superior a la HD-TIV (p < 0,05) frente a: todas las consultas médicas relacionadas con la gripe (hospitalizaciones, visitas a urgencias y consultas externas) (9,7%; IC 95%: 5,0–14,2; I^2=75,6%); consultas hospitalarias (tanto hospitalizaciones como visitas a urgencias) por neumonía (2,2%; IC 95%: 0,3–4,1; I^2=48,0%); asma/EPOC/afecciones bronquiales (1,2%; IC 95%: 0,2–2,2; I^2 = 0%), eventos cerebrovasculares (2,4%; IC 95%: 0,4–4,4; I^2=46,1%) e ictus (2,4%; IC 95%: 0,4–4,4; I^2=45,2%). Por el contrario, aTIV fue menos efectiva (p < 0,05) que HD-TIV frente a las hospitalizaciones por causa respiratoria (-13,9%; IC 95%: -25,4–3,4; I^2 = 0%) y las consultas hospitalarias (tanto estancias como visitas a urgencias) por eventos coronarios (-1,2%; IC 95%: -2,2 – -0,2; I^2 = 0%). No hubo diferencias significativas para otros parámetros. Las estimaciones de EVr se limitaron a criterios de valoración clínicos no confirmados por laboratorio (consultas médicas, hospitalizaciones, etc.) y el riesgo de sesgo de los estudios fue moderado.

DISCUSIÓN

Esta revisión de la evidencia sobre la eficacia, efectividad y seguridad de la vacuna antigripal adyuvada con MF59 en población de 65 años o más comprende diversos ensayos clínicos, estudios observacionales y revisiones sistemáticas realizados en distintas temporadas de gripe. Los resultados demuestran que las vacunas adyuvadas generan mayores títulos de anticuerpos y respuestas más sostenidas en el tiempo en comparación con las vacunas no adyuvadas de dosis estándar.

El uso de grandes bases de datos del mundo real que integran diferentes fuentes de información (incluidos datos procedentes de hospitales y farmacias) [26,28] permite evaluar la efectividad de las vacunas y complementar los resultados obtenidos a través de ECA. Entre los trabajos revisados se incluyen estudios basados en varias fuentes de datos que exploran múltiples criterios de valoración y que permiten ampliar el espectro de casos relacionados con la gripe, abarcando desde casos más graves (pacientes hospitalizados) hasta los menos graves (pacientes ambulatorios o sin hospitalización). En este sentido, los trabajos de Pelton et al. (2021) e Imran et al. (2022) indican que la vacuna aTIV parece ser más efectiva en el entorno ambulatorio al reducir las consultas relacionadas con la gripe en comparación con otras vacunas [26,30].

Cabe destacar los estudios de gran tamaño muestral realizados en pacientes procedentes de bases de datos como Medicare [20–22]. Las fuentes empleadas permitieron analizar resultados relevantes como las hospitalizaciones en los cuidados de rutina en un contexto real, difíciles de obtener en cualquier ECA. Estos estudios concluyeron que las vacunas HD-TIV y aTIV fueron más efectivas que la QIVe, y apoyan que la cantidad de antígeno y el uso de adyuvantes pueden contribuir a incrementar la efectividad vacunal.

Dado que el efecto de la gripe se extiende más allá de la enfermedad respiratoria, es importante comparar la efectividad de las vacunas en cuanto a otros resultados clínicos relevantes, como los eventos cardiovasculares [23,26,27,29]. El estudio de Pelton et al. [26] que evaluó varios aspectos relacionados con la enfermedad cardiorrespiratoria, demostró que la vacuna aTIV fue similar a la HD-TIV en prevenir hospitalizaciones/visitas a urgencias relacionadas con la gripe, pero más efectiva en reducir las hospitalizaciones/visitas a urgencias por enfermedad cardiorrespiratoria. Sin embargo, en el estudio de Van Aalst et al. [23], los datos agrupados para ambas temporadas de gripe muestran que la vacuna HD-TIV se asoció a me-

nos visitas hospitalarias por causa respiratoria que aTIV, lo cual refleja que no existe consistencia entre los distintos estudios revisados.

De igual modo, dado que el riesgo de morbilidad y mortalidad por gripe aumenta con la edad entre los adultos mayores [35,36], es importante evaluar la efectividad de las vacunas en este grupo poblacional. Los estudios analizados en esta revisión demuestran que las vacunas antigripales adyuvadas presentan resultados favorables en la población de 65 años o más, generando una respuesta inmunitaria más robusta y sostenida en el tiempo [17,18] que se traduce en una reducción de las hospitalizaciones y las visitas/consultas a urgencias [25–27]. Esta ventaja se mantiene en los distintos grupos poblacionales (65-74 años; 75-84 años y ≥85 años) [30], un aspecto crítico dada la creciente fragilidad de los pacientes con la edad.

Por otro lado, con relación a las variantes víricas, varios de los estudios revisados demuestran que la vacuna antigripal adyuvada es más eficaz frente al subtipo A(H3N2) [17,18], clínicamente importante en población de 65 años o más, e induce una mejor protección cruzada que las vacunas no adyuvadas, especialmente la formulación aQIV, ya que incluye una cepa B adicional (B/linaje Yamagata o Victoria). En el ECA de Essink et al. [16] la vacuna aQIV adyuvada con MF59 cumplió con los criterios de superioridad para la cepa B frente a una vacuna aTIV-1 y otra aTIV-2 con una cepa B alternativa. Las vacunas tetravalentes, que incluyen las cepas A y B recomendadas por las autoridades sanitarias, tienen el potencial de ofrecer una protección más amplia que las trivalentes.

Además, esta revisión muestra que, en temporadas con deriva antigénica, la vacuna adyuvada mejora los resultados de inmunogenicidad en comparación con otras vacunas estándar. El estudio de Beran et al. [18] avala el beneficio de las vacunas antigripales adyuvadas en temporadas con una discrepancia sustancial entre las cepas circulantes y vacunales. Levin et al. destacaron que la EVr fue similar entre aTIV y HD-TIV pese a que hubo poca o ninguna circulación significativa de A(H3N2) durante la temporada de 2019-2020, variante que a menudo contribuye de manera importante a las hospitalizaciones y la mortalidad relacionadas con la gripe en población de 65 o más años de edad [27]. En los 2 estudios de Boikos [28,29], la deriva antigénica de A(H3N2) fue mayor en la temporada 2018-2019 que en la 2017-2018, lo cual otorgó un mayor beneficio a la vacuna aTIV.

Desde el punto de vista de la seguridad, los resultados del estudio de Schmader et al. [19] respaldan el uso de cualquiera de las vacunas aTIV o HD-TIV para prevenir la gripe en adultos mayores. Este estudio fue el primero en determinar los efectos de la vacunación antigripal en la calidad de vida de los pacientes, sin diferencias significativas entre ambas. Se confirmó la seguridad de la vacuna adyuvada, tal y como ya demostraron Pellegrini et al. en 2009 con datos procedentes de 64 ensayos clínicos [37].

En términos económicos, el uso de la vacuna adyuvada se considera una intervención coste-efectiva [38]. Tal y como se estima en el estudio de Fochesato et al. (2022) [38] el coste incremental por año de vida ajustado por calidad que aporta la vacuna aQIV frente a la estándar es de 2.240 euros desde la perspectiva del pagador, considerando una EVr del 34,6%. El uso de vacunas adyuvadas puede suponer un ahorro para el Sistema de Nacional de Salud español, tal y como revelan de los datos de coste-efectividad disponibles [27,38–40]. El ahorro en costes sanitarios directos con la vacuna adyuvada trivalente se ha estimado en 63,6 millones de euros en comparación con la HD-TIV, debido especialmente a la diferencia de precio entre ambas vacunas [38]. Por otro lado, utilizar la vacuna adyuvada en toda la población ≥65 años podría suponer un ahorro de hasta 82 millones de euros respecto la vacuna no adyuvada [39]. La protección conferida por la vacuna antigripal es fundamental en términos económicos si se tiene en cuenta que el coste de una epidemia de gripe puede alcanzar los 56,7 millones de euros por millón de habitantes en los países industrializados [41].

Finalmente, es preciso mencionar que, entre los estudios analizados, aportan más valor aquellos realizados en varias temporadas de gripe, pues sus resultados son más fácilmente extrapolables a nuevas temporadas, así como aquellos en los que se ha realizado el diagnóstico virológico de gripe. La utilización de definiciones de gripe ligeramente distintas en los distintos trabajos y la ausencia de esta confirmación diagnóstica de laboratorio en algunos de ellos puede limitar la comparación de los datos [29–31]. Hay muchas variables cuya definición ha cambiado a lo largo del tiempo, por lo que las revisiones e investigaciones deben actualizarse de forma constante. A ello es preciso añadir otros factores ligados a la susceptibilidad de las distintas cohortes, los cambios en las vacunas y la deriva antigénica de los virus.

CONCLUSIONES

Los resultados de ensayos clínicos aleatorizados realizados con vacunas antigripales adyuvadas con MF59 en diversas temporadas de gripe demuestran que éstas generan una respuesta inmunitaria con mayores títulos de anticuerpos y respuestas más sostenidas en el tiempo respecto a vacunas no adyuvadas. También presenta mejores resultados frente al subtipo A(H3N2) e induce una mejor protección cruzada que las vacunas sin adyuvante.

Los datos post-comercialización reafirman que las vacunas adyuvadas y las de alta carga presentan una efectividad similar en cuanto a hospitalizaciones relacionadas con gripe y en pacientes de alto riesgo. Además, demuestran que la vacuna antigripal adyuvada es más inmunogénica que otras vacunas de dosis estándar en temporadas con deriva antigénica, y que presentan un buen perfil de seguridad.

Con la evidencia revisada, puede concluirse que las vacunas adyuvadas son alternativas efectivas y seguras para ser incluidas en los programas de vacunación en población de 65 o más años de edad, y que son preferibles a las vacunas convencionales de dosis estándar como estrategia de prevención frente a la gripe.

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CONFLICTOS DE INTERESES

Los autores declaran que han recibido honorarios por la participación en grupos asesores que valoraron la información aportada en este manuscrito, y se valoró la oportunidad de una revisión narrativa de la evidencia disponible. Los autores declaran que no han recibido honorarios adicionales derivados de su participación en la elaboración, escritura, revisión o valoración crítica del manuscrito.

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Review

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Infection control in long term care institutions for the elderly: A reflection document on the situation in Spain

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ABSTRACT

A progressively increasing percentage of the elderly live during the last years of their lives in nursing homes. Although these institutions are intended to mimic life at home as much as possible, they have characteristics that make them quite similar to a "nosocomiun", i.e. an establishment for the treatment of the sick. The very coexistence among the elderly, the fact of sharing caregivers and the very significant exposure to third parties, together with the frequent predisposing diseases to infection in this population, make infection frequent among residents and also easily transmissible. This leads us to ask what can be done to prevent infection in this environment and more specifically what is the state of the art of the matter in a Western European nation such as ours. The Board of Trustees of the Health Sciences Foundation has asked itself a series of questions on the subject of infection prevention in Nursing Homes, the structure of procedures, the legislation available, compliance with the measures indicated, the best indicators of the processes and therefore, the need to promote in Spain a document of recommendations to avoid infections in this pop-

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ulation whose morbidity and mortality need not be highlighted. To this end, a multidisciplinary group of experts in different aspects of this problem has been convened and asked the proposed questions. The questions were discussed by the group as a whole and led to a series of conclusions agreed upon by the participants. The results of the meeting are reported below.

Keywords: Infections in the elderly, infection prevention, nosocomial infection, urinary tract infection, respiratory infection, skin and soft tissue infection, pneumonia.

Control de la infección en residencias de ancianos: Documento de reflexión sobre la situación en España

RESUMEN

Un porcentaje progresivamente creciente de las personas mayores viven durante los últimos años de su vida en residencias de ancianos. Dichas instituciones, aunque pretenden remedar lo más posible la vida en el hogar, tienen características que las hace bastante parecidas a un nosocomio, es decir a un establecimiento destinado al tratamiento de enfermos. La propia convivencia entre los ancianos, el hecho de compartir cuidadores y la exposición muy importante a terceras personas, junto con las frecuentes enfermedades predisponentes a la infección de esta población, hacen que la infección sea frecuente entre los residentes y que además sea fácilmente transmisible. Esto nos lleva a preguntarnos qué puede hacerse para prevenir la infección en este medio y más concretamente cuál es el estado del arte de la cuestión en una nación de Europa Occidental como la nuestra. El patronato de la Fundación de Ciencias de la Salud se ha formulado una serie de preguntas sobre el tema de la prevención de la infección en las Residencias de Mayores, la estructura de la misma, la legislación vigente, el cumplimiento de las medidas indicadas, los indicadores de los procesos y por ende, la necesidad de fomentar en España un documento de recomendaciones para evitar infecciones en esta población cuya morbilidad y mortalidad no necesitan ser resaltadas. Para ello, se ha convocado a un grupo multidisciplinar de expertos en distintos aspectos de este problema a los que se les han formulado las preguntas propuestas. Las preguntas han sido discutidas por el grupo en su conjunto y han conducido a una serie de conclusiones consensuadas entre los participantes. Pasamos, a continuación a relatar los resultados de la reunión.

Palabras clave: Infecciones en el anciano, prevención de la infección, infección nosocomial, infección urinaria, infección respiratoria, infección de piel y partes blandas, neumonía

INTRODUCTION

Nursing homes logically try to reproduce living conditions for their inhabitants as close as possible to those at home. However, they are still places where people with frequent and important underlying conditions live in close proximity to each other and share caregivers in a common habitat. In this sense, nursing homes are also a nosocomium, i.e. a place where the sick are cared for and treated and where the transmission of pathogenic microorganisms is possible and frequent.

We know a lot about infection prevention measures in other nosocomial facilities, such as hospitals, but we know less about infection prevention in smaller institutions with fewer resources for this purpose, such as Long-Term Care Facilities (LTCF).

The aim of this work has been to try to compile the available information on infection control and prevention in LTCF in a Western European country such as Spain, trying to explore what room there is for improvement.

For this reason, the Board of Trustees of the Health Sciences Foundation formulated a series of questions on the existing regulations for the prevention of infection in LTCF in our country, on their degree of compliance and on the existing indicators used to monitor this process. The questions were distributed among a multidisciplinary group of experts in this field from very different points of view, including the vision of patients' associations, the media, people responsible for the administration, geriatricians, infectologists, microbiologists and other specialists.

Each question was assigned to a speaker and the conclusions were then discussed by the whole group to reach a summary of the situation accepted by all. What follows are the questions and answers that were asked. All authors have read and re-examined the complete text and gave their approval to it.

IS THERE A REGIONAL OR NATIONAL PROGRAM IN SPAIN ON INFECTION PREVENTION IN LONG-TERM CARE FACILITIES (LTCF)?

There is no common regional or national program on the prevention of nosocomial infection in LTCF, despite the fact that infectious diseases are an important cause of morbidity and mortality in the elderly, both in hospital care and in primary care consultations and, of course, in nursing homes.

In LTCF there is a high prevalence of nosocomial infection and colonization by multi-resistant microorganisms (MDR), as well as a high incidence of very often inappropriate antibiotic prescription [1].

It should also be taken into account that there is a high rate of patient transfers to referral hospitals and that there are very few diagnostic resources in nursing homes, making the management of nosocomial infection a real health problem.

The most frequent nosocomial infection is respiratory, followed by urinary tract, skin and soft tissue, gastrointestinal tract and ocular. Outbreaks can also occur relatively frequently and some centers have relatively high rates of colonization by MDR microorganisms, including colonization by methicillin-resistant *Staphylococcus aureus* (MRSA) and the presence of bacteria carrying extended-spectrum ß-lactamases (ESBL).

In order to establish an effective plan for the prevention of nosocomial infection in LTCF, it is also necessary to take into

account the atypical presentation of infections in the elderly, for which reason it would be necessary to clearly define the diagnostic standards for infection in this setting. Although there have been attempts to introduce standardized criteria for defining infection in these centers, they have not been validated in our country and are not universally used [2].

Furthermore, unlike acute care hospitals, where there are high quality epidemiological studies for the monitoring and control of nosocomial infection [3], at this level of care there are no quality data that would allow immediate establishment of adapted prevention plans.

It would be absolutely necessary to establish nosocomial infection prevention plans to protect the population living in LTCF. This population is very vulnerable and is affected by other risk factors such as immunosuppression associated with advanced age, comorbidity, the use of immunosuppressive treatments and other risk factors that are very prevalent in the institutionalized population (pressure ulcers, bladder catheters, dysphagia, incontinence, etc.). The training of professionals does not have the level achieved in our hospitals (there is a high number of geroculturists with basic training and a very small number of nurses and physicians), which makes it difficult to establish measures to contain the risk of infection both in patients/residents and between them and the professionals working in the institutions [4].

An infection prevention plan in LTCF should be mandatory in all these centers and be accompanied by an appropriate training program for the professionals working in them, the establishment of a registry of infections by MDR microorganisms, the collaboration of the microbiology services and the health authorities of the area, and effective communication between these resources and primary and hospital care.

As an initial and minimum step, it would be necessary to develop a surveillance program, with special care in applying standard precautions, with special emphasis on hand hygiene. It is also advisable to measure the infection acquired in the center, either through point prevalence or incidence studies. It is also necessary to propose active policies for the correct use of antibiotics in this population.

Conclusion

There are no common regional or national nosocomial infection prevention programs specifically devoted to Long Term Care Facilities for the elderly.

It is urgent to establish a prevention plan with minimum requirements, at least, that includes training of professionals, an infection surveillance and registry system, collaboration with reference hospital services and an adequate antibiotic use policy.

IN THE ABSENCE OF A SPECIFIC REGULATION, WHAT DOES THE LAW IN SPAIN REQUIRE?

It has already been mentioned that there is no specific legislation for LTCF that focuses on specific protection against the acquisition and transmission of infections in residents and staff. Indirectly, some of the legislation inforce in Spain that is intended to protect workers against biological hazards in the workplace could be applied, although this is not specifically the focus of our discussion.

Regarding biosafety, the Biosafety Law (Law 15/1994 of June 3, BOE, 1994) must be applied, which incorporates the Community Directives (EEC, 90/219 of April 23, 1990) into the Spanish legal system. This law was developed in a Royal Decree (RD 664/1997, May 12, 1997, BOE, 1997), on the protection of workers against risks related to exposure to biological agents at work. The EU has advanced in this protection by including a directive on the protection of workers against risks related to exposure to biological agents at work (EEC 2000/54 / EC of the European Parliament and the Council of 18 September 2000).

There is another legislative block that develops the regulations on notifiable diseases and epidemic outbreaks but of the autonomous community of Catalonia (Decree 203/2015, of September 15) which creates the Epidemiological Surveillance Network of Catalonia and regulates the notification systems of notifiable diseases and epidemic outbreaks.

Finally, there are some specific regulations such as the protection against legionellosis (RD 865/2003, of July 4, 2003), which establishes the hygienic-sanitary criteria for the prevention and control of this disease in Spain (Decree 352/2004, of July 27), which establishes the hygienic-sanitary conditions for the prevention and control of legionellosis. Undoubtedly, all the legislative aspects on risk analysis and control of critical points in the food chain (ARCPC) included in different state royal decrees (RD 3484/2000, RD 2207/1995, RD 202/2000) are also applicable to nursing homes.

Conclusion

There is no specific legislation for protection against infection in LTCF in Spain. There is general legislation on aspects such as hygiene and measures against contamination in the food chain and specific legislation on protection against diseases such as legionellosis issued by both the autonomous communities and central government authorities.

WHAT SHOULD BE THE BROAD OUTLINES OF A POTENTIAL PREVENTION PLAN FOR COMMUNICABLE INFECTIONS IN LTCF?

Three major thematic areas can be distinguished in this potential plan.

1.- General prevention measures aimed at reducing the generic risk of infections related to care or the environment where there should be sections such as the following [1]:

- Environmental and surface cleaning and disinfection

- Hand hygiene

- Proper use of gloves, gowns or aprons, masks and eye protection.

- Proper handling of personal protective equipment

- Safe handling of waste and sharps

- Cleaning system, storage and transport of bed linen and user's linen

- Proper handling of invasive devices (intravenous lines, bladder catheters, feeding tubes, etc.).

2.-Specific protocols aimed at the prevention of the most prevalent infections in residential centers.

In the context of the care of institutionalized frail elderly people, it is necessary to adequately train professionals in the detection and appropriate management of the most prevalent infections in this type of patients. Thus, every residential center should have specific protocols on, at least [5,6]:

- Immunization schedule for residents and professionals (flu, pneumococcus, hepatitis B, SARS-CoV-2, ...).

- Prevention and management of urinary tract infection associated or not with incontinence-related devices (bladder catheter, absorbents, collectors, ...).

- Prevention and management of respiratory infection (bronchoaspirative, infection in the context of COPD patients, ...).

- Prevention of wound infection, pressure ulcers, vascular ulcers, peripheral venous insufficiency, ...)

- Prevention of food-borne infections or outbreaks in residential centers.

- Prevention and management of colonization and infection by MDR microorganisms such as MRSA, BLEE-producing bacteria, *Clostridoides difficile*, ...)

3.- Protocols oriented to antimicrobial stewardship.

Improving antibiotic use in the care of the institutionalized elderly in order to protect residents and reduce the threat of antibiotic resistance is a global priority. The Centers for Disease Control (CDC) and others recommends that all nursing homes take steps to improve antibiotic prescribing practices and reduce inappropriate antibiotic use [7-10].

Studies have shown that 40-75% of antibiotics prescribed in nursing homes may be unnecessary or inappropriate. The harms caused by antibiotic overuse are significant for frail, older adults receiving nursing home care. These harms include risk of *C. difficile* infection (CDI), increased adverse events and drug-drug interactions, and MDR colonization and/or infection.

There are some experiences in Spain and outside Spain [11-13], around PROA interventions (antimicrobial use optimization programs) in nursing homes. For example, the Geriatrics Service of Granollers proposes 12 interventions and measures to improve the optimization of antimicrobial treatment in this population [14]:

1. Avoid prescribing without a face-to-face medical assessment. This is related to an increase in the use of broader spectrum antimicrobials.

2. Reconsider the treatment of respiratory infections that may not require antibiotics, such as viral bronchitis, influenza or microaspirations.

3. Avoid treatment of colonizations (especially decubitus ulcers without infection and bacteriuria).

4. Avoid unnecessary antimicrobial prophylaxis, especially for Urinary Tract Infections.

5. Avoid unnecessary use of topical antibiotics.

6. Assess the need for microbiological studies and antibiotic treatment in some end-of-life care situations.

7. Reconsider periodically the duration of antibiotic treatments.

8. Adjust treatments based on available microbiological results.

9. Promote parenteral-oral sequential therapy.

10. Use diagnostic and treatment protocols adapted to local data.

11. Monitor antimicrobial consumption.

12. Continuing education.

Conclusion

There is a need for a general plan with guidelines for the prevention and management of infections in LTCF with at least three major sections: general prevention measures, specific protocols for the prevention of the most prevalent infections, and antibiotic management plans. The plan should include hand hygiene, urinary tract infection, respiratory infection, skin and soft tissue infection, appropriate use of antimicrobials, and *C. difficile*-related infection.

IS IT NECESSARY FOR EACH LTCF TO HAVE A PHYSICIAN OR NURSE RESPONSIBLE FOR INFECTION CONTROL?

We believe so. To ensure compliance with any protocol or procedure in a nursing home, it is essential that it is led by a professional, who has the support and recognition of the center's management, and who is a reference point for the care team for the transmission of information to the rest of the professionals of both the center itself and the Public Health Service [15].

The presence of a physician in charge of each LTCF is not mandatory in different Spanish autonomous communities [16], But in order to be accredited, there must be nursing staff. Therefore, the responsible person could be, if there is one, the physician of the residence, or one of the nurses of the center.

The person assigned to be responsible for the care team of the LTCF must have sufficient knowledge and experience in the control and management of infectious diseases (clinical manifestations, mechanisms of transmission and spread, and prevention measures); have leadership and communication skills, as well as teamwork skills. He/she will be the one who must transmit all the information to the rest of the professionals

of the institution, as well as to the residents and their families, ensuring that all the necessary measures for the prevention of infections are carried out. On the other hand, he/she will inform the Public Health System of relevant events and also the Primary Care physician responsible for the care of the residence, as well as the Hospital Geriatric Specialized Services [17-19].

Their work is essential for the early detection of any case of transmissible infectious disease, as has been demonstrated in the COVID-19 pandemic, as well as for the rapid implementation of the contingency and isolation plan to prevent transmission to the rest of the residents.

Social and sanitary coordination is essential for the correct functioning of all these protocols, and should be promoted by the competent political authority, with very favorable experiences in different Communities during the present pandemic [20-23].

The SARS-COV-2 pandemic has highlighted the need for the figure of a Coordinator or person in charge in the residences for the prevention and control of the infection, being required by International Institutions (WHO) the State and the different Autonomous Communities [18,20,21,24,25].

Previously, there were numerous experiences that focused on studies of the prevalence of infectious diseases in geriatric centers (EPINGER), prevention of the transmission of MDR microorganisms during the care of colonized/infected residents in residential centers of the Junta de Andalucía. As well as with antibiotic optimization programs to promote their rational use (PROA).

The experience currently available should be used to prevent new outbreaks of this or any other infectious disease that can be transmitted in LTCF [23,26-28].

Conclusion

To ensure compliance with an infection control plan in nursing homes, a person responsible for it should be appointed within the LTCF healthcare team. This person will have the support of the institution's management and will be the center's point of reference, in charge of transmitting all the guidelines to the rest of the colleagues and to the residents and family members, as well as acting as a contact person with those responsible for health care in the Public Health Service. It must be a physician, if there is one, or a nurse.

WHAT MINIMUM ENVIRONMENTAL CONDITIONS SHOULD A LICENSED NURSING HOME HAVE?

It is necessary to emphasize that the LTCF are conceived as homes, not as health centers. In the specific case of the Community of Madrid, there is an order [29], which develops Decree 91/1990, of October 26, regarding the Authorization Regime for Services and Centers for Social Action and Social Services, which contains the criteria to be met by the centers. The following paragraphs extract those sections referring to environmental conditions that appear in the document.

A.- Material requirements

- The Centers must be located in healthy and integrated areas or close to urban centers.

- Residential area units will not be admitted in basements or crawl spaces.

- The areas must be sufficiently ventilated and illuminated, preferably with natural light.

- They shall have drinking water, with adequate pressure, from the public water supply. If it comes from water catchment or capacity, they shall have a reserve tank with capacity for at least one day.

- Hot water in sanitary appliances and kitchen with a temperature higher than 40ºC.

- Heating that guarantees a temperature equal to or higher than 20ºC.

- Evacuation of water to the municipal sewage system or to a sewage treatment plant. In any case, it is forbidden to pour into cesspools.

- Bedrooms: Usable area of 5.50 square meters per person in the case of disabled persons and 7.50 square meters per person in the case of wheelchair users.

- The maximum capacity per bedroom will be six people. The bedrooms must have natural light and ventilation.

- Toilets: When they are collective, they will be differentiated by sex. The minimum endowment will be a toilet, a sink, a shower and a bidet for every six people or fraction exceeding two people.

- Living quarters: With a minimum area of 1.80 m^2, per resident, (depending on the recording) with a minimum of 12 square meters.

- The resulting surface may be subdivided into smaller ones and, in any case, when it is larger than 60 m^2, it must be separated to allow for different environments: play area, reading area, TV, etc.

- The living rooms must be exterior.

- Dining room: It shall have a surface area of at least 1 m^2 per person, with a minimum of 10 m^2.

B.- Functional requirements

It shall be guaranteed that all users receive, by their own means or those of others, the necessary medical attention.

- There shall be a first-aid kit conveniently located and signposted, and a correct hygienic-sanitary organization shall be guaranteed.

- Personnel: They shall be adequate in number and specialization to provide the corresponding services. The full-time staff/user ratio will be 0.25 for valid users; and 0.35 for assisted users.

- Every user will have, in his or her bedroom, a suitable lockable closet with shelves and hangers; a bed equipped with

a bed base, mattress and the corresponding clothing; a bedside table; a light point with a lamp or wall lamp at the head of the bed; a power outlet; a mat.

- Each room will have shutters, blinds or curtains that can block the passage of outside light.

- Varied menus and dishes will be provided according to the needs of the users. The menus will be previously supervised by a physician, in order to ensure adequate dietary and caloric intake. In addition to the regular menu, other dietary menus will be prepared for those users who require them. Meals and cooked dishes, either with its own service or with an arranged service, will arrive at the appropriate temperature to their recipients. Likewise, there must be a cold chain to preserve and store food.

- Daily personal hygiene must be guaranteed for users who cannot look after themselves, and as often as circumstances require.

- The change of linen and underwear of the users shall be done whenever necessary, and in any case daily. Other garments shall be changed as often as necessary.

- The change of bed linen shall be made whenever required by circumstances, and in any case weekly, as well as each time there is a new admission. The same periodicity shall be required for towels, napkins, tablecloths and other linen.

- Special attention shall be paid to the maintenance, upkeep and repair, if necessary, of furniture, installations and premises, in order to prevent their deterioration, as well as to all machines, boilers, installations or instruments which, if they involve a high potential risk, shall be handled exclusively by authorized installers.

- Every Center, in addition to complying with the general legislation in force on hygiene and health, must guarantee, in a special way:

The general and permanent cleaning of the building and its dependencies, especially those of more intense use, as well as its disinfection.

The annual disinsectisation and rat extermination, or as many times as circumstances require.

The establishment of specific rules or guidelines for the personnel in matters of hygiene, of obligatory and verifiable compliance. In Centers serving risk sectors, infection and contagion prevention measures shall be adopted, as well as the necessary periodic sanitary controls.

Cleaning and disinfection of crockery and cutlery after use, as well as other instruments in common use.

In centers with a capacity of more than 50 users, there should be a suitable space for the temporary storage of waste in closed buckets.

This law is clear on the basic environmental requirements for residences for the elderly, although the "tolerance with "dormitories for up to 6 people, toilets for 6 people or very low staffing ratios" is surprising.

Conclusion

There is a specific regulation of the Consejería de Integración Social of the Community of Madrid that contains the environmental criteria to be met by the centers. In relation to the minimum conditions, the regulation is very clear about the location of the LTCF and the material and functional requirements, although it seems too tolerant in some other aspects.

WHAT ARE THE ESSENTIAL DATA IN ASSESSING THE RISK OF INFECTION OF A PERSON LIVING IN A LTCF?

It is a requirement to have an individual file for each user, which includes a complete assessment history, treatments, social and medical reports. At the time of admission to a nursing home, the resident arrives with an Individual Care Plan prepared by the Dependency Service, drawn up by whomever the regional regulations establish. These are usually social workers or multidisciplinary teams. In other countries (Germany) it is drawn up by the healthcare field. The user provides all the medical information available to him/her.

In the comprehensive geriatric assessment (CGA), for which different scales can be used, at least the following aspects should be included:

- Personal preferences and advance directives

- Quality of life

- Physical status: basic and instrumental activities of daily living, gait and balance, frailty

- Mental status: cognitive and affective

- Social status including primary caregiver overload

- Nutritional status

- Sense organs (sight, hearing)

- Complete and up-to-date pharmacological treatment

- Risk of falls and pressure ulcers

- Pain

On the specific point of the subject that concerns us, which is the assessment of the risk of infection on admission, we have not found standard recommendations, but we believe it is necessary to have at least the following data in the patient's file [5]:

Vaccination against influenza [30]

Vaccination against SARS-CoV-2 [31-33]

Vaccination against Varicella-Zoster Virus [34]

Evaluation of *S. aureus* nasal carrier status in specific circumstances [35-40]

Pneumococcal vaccination and types of vaccines received [41-44].

Verification of tetanus and pertussis vaccination status.

PPD and IGRA [45, 46]

History of past international travel

Conclusion

In addition to the Comprehensive Geriatric Assessment (CGA), an assessment of the risk of infection should be carried out on admission to nursing homes, the specific items of which are far from being agreed upon and far from constituting a standard. In our opinion, they should include, at least, the vaccination status against preventable viral diseases such as influenza, SARS-COV-2 and Varicella-Zoster, the immunity status against pneumococcal infection, the existence or not of latent tuberculosis and the colonization status against multi-resistant bacteria such as MRSA.

WHAT VACCINES SHOULD BE OFFERED TO PERSONS LIVING IN A NURSING HOME?

In the elderly, vaccination takes on greater importance because their immune system is aged and their capacity to respond to infectious processes is diminished, thus increasing the risk of developing serious complications following infections. This statement is especially relevant in people living in LTCF for the elderly, where the presence of comorbidity, functional dependence and cognitive impairment puts them at greater risk of falling ill and, if they do fall ill, more clinical complications and a higher risk of death [47].

The Spanish Society of Geriatrics and Gerontology [48] recommends systematic vaccination of the elderly against influenza, pneumococcus and tetanus. Likewise, depending on personal history and individual risk factors, vaccination against pertussis and Varicella-Zoster virus infection may also be indicated. Regarding the influenza vaccine, for this type of population and with the aim of increasing its effectiveness, it is recommended to use vaccines with increased immunogenicity.

Likewise, in residential centers for the elderly, the objective should be to achieve a minimum annual vaccination coverage against the influenza virus of over 75%, both in institutionalized persons and in the health and direct care personnel of the centers [49-55].

It should be noted that vaccination of elderly persons against SARS-CoV-2 (COVID-19) is indicated from the beginning of the year 2021. A considerable number of vaccines against SARS-CoV-2 are under study and research. In our country, institutionalized elderly people have been vaccinated with RNA-messenger (RNAm) vaccines [56-58] and they are currently receiving a booster dose.

As established in the vaccination strategy against COVID-19 of the Ministry of Health, depending on the results of future clinical trials, the data registered in the Drug Pharmacovigilance System and the distribution and availability of vaccine doses, the most appropriate vaccines for each health condition, age group, risk factors and place of residence can be selected from among the different types of vaccines.

Conclusion

Elderly people living in residential centers should be properly vaccinated against influenza, pneumococcus, tetanus and SARS-CoV-2. Likewise, in certain cases it would also be advisable to administer vaccines against diphtheria and Varicella-Zoster virus. Likewise, healthcare and direct care personnel in the centers should be vaccinated, at least, against influenza and SARS-CoV-2.

WHAT MEASURES HAVE BEEN SHOWN TO BE EFFECTIVE IN REDUCING URINARY TRACT INFECTION IN THE ELDERLY?

Urinary tract infection (UTI) is the most frequently reported infection in long-term care facilities. [59] and accounts for 30-40% of healthcare-associated infections. On the other hand, the presence of asymptomatic bacteriuria in institutionalized patients is high, with figures of 25-50% in women and 15-40% in men [4]. This bacteriuria is benign, and several studies have shown that the treatment of asymptomatic bacteriuria, whether or not accompanied by pyuria, is of no benefit and may even be harmful [60]. Therefore, screening and treatment of asymptomatic bacteriuria is not recommended. However, a frequent problem in nursing homes is that of patients with nonspecific clinical deterioration, without symptoms or localizing signs and presenting a positive urine culture. The diagnosis of symptomatic UTI requires the presence of dysuria or fever, chills or confusion plus some other genitourinary symptom (urinary frequency, flank pain, hematuria...) [61]. However, very often, those residents who present with altered mental status, falls, lack of appetite or more awkward mobility and have a positive urine culture are diagnosed with UTI, leading to overdiagnosis and inappropriate use of antibiotics, which is very common in these centers [62]. In recent years, many initiatives have been developed to improve the management of this problem and to optimize the use of antibiotics in residential centers. An important randomized study conducted in several nursing homes demonstrated how the implementation of treatment algorithms based on guidelines, i.e. treating only those UTIs (in non-catheterized patients), in which symptoms associated with the genitourinary system were observed, was safe and was associated with a clear reduction in antibiotic use [63]. Despite this, the application of these criteria in patients with advanced dementia remains a matter of debate and overuse of antibiotics is especially prevalent in this subgroup of patients. A descriptive study in patients with advanced dementia living in nursing homes showed that only 19% of probable UTIs treated with antibiotics met these criteria [64]. Another subsequent study [65,66] found that, although most suspected infections in severely demented and institutionalized patients were treated with antibiotics, this treatment was not associated with any improvement in survival.

The specific measures that have been shown to reduce urinary tract infection are well known: treating only symptomatic infections, minimizing the use of bladder catheters, catheter and perineal hygiene measures, avoiding urinary and

fecal retention, avoiding a sedentary lifestyle, improving hydration or performing antibiotic prophylaxis when changing catheters only in cases of traumatic catheterization. However, in our opinion, its implementation in the residential setting is variable and subject to improvement.

Many programs and interventions have been put in place to decrease the rate of urinary tract infection in residential facilities ranging from different models of staff education, antibiotic stewardship programs, inclusion of the role of infection preventionist or multimodal intervention programs.

Antibiotic stewardship programs have demonstrated clear benefits in hospitals and acute care settings. Some studies have also demonstrated their effectiveness in residential centers when the program includes education strategies, local guidelines and periodic review and feedback on antibiotic use [66,67]. In the case of urinary tract infection, these programs have been shown to decrease treatment rates of asymptomatic bacteriuria and improve compliance with antibiotic prophylaxis [68], although they have been insufficient to decrease the total amount of antibiotics used for suspected UTIs [69]. In 2016 the Centers for Medicare and Medicaid Services (CMS) regulations [70] included a requirement that nursing homes and long-term care facilities develop an infection prevention program that should include an antibiotic use optimization program and the inclusion of a trained agent specifically dedicated to infection prevention [71], and list the following as core actions of the program: involved leadership, pharmacy knowledge, education, action, collection and periodic reporting of infection data.

In a baseline analysis, prior to the implementation of this standard in the residencies, it was shown that the most frequent existing measures were: the existence of written guidelines on antibiotic use and the registry of antibiotics used. The more specific and time-consuming policies, such as the use of forms for each antibiotic use, the existence of approval mechanisms or the control of appropriateness of use, were used less frequently and improved when the figure of the trained preventivist was in place [70]. The lack of nursing knowledge of antibiotic policies was a major obstacle to their implementation. The involvement in the programs of the medical director of the LTCF, the nursing director and the specific preventivist is key to their implementation, for several reasons, including the high mobility of health personnel in these centers [72].

In a survey conducted in different US facilities on infection prevention and control programs in residences and the changes between 2014 and 2018 (after the CMS rule) revealed a clear increase in "antibiotic stewarsdship" programs. In the specific context of UTI the measures that had significantly increased were: the existence of reminders about decreasing catheter use, the use of external collectors, and the use of ultrasound probes to detect postvoid residual and avoid retentions. The policies that were associated with the greatest increase in these preventive measures were: 1) the existence of specific certified courses and training programs, local certified courses or courses through scientific societies, 2) the lower number of beds in the residence, but not the lower occupancy rate, and 3) the public ownership of the residence, 4) the lower number of beds in the residence, but not the lower occupancy rate, and 5) the lower number of beds in the residence [10,73]. These observed changes could not, however, demonstrate an impact on overall antibiotic utilization or a decrease in MDR infections.

Conclusion

The most effective measures to reduce UTI in elderly nursing home residents consisted of: treating only symptomatic urinary tract infections, minimizing the use of catheters, adopting perineal hygiene measures, avoiding urinary and fecal retention, avoiding a sedentary lifestyle, improving hydration, and not performing antibiotic prophylaxis when changing catheters except in cases of traumatic catheterization.

Programs to optimize the use of antibiotics, the recording of infections, the incorporation of a "preventivist" or infection consultant, staff education, the existence of accessible protocols and the involvement of the medical director of the residency are key to its success.

WHAT MEASURES TO REDUCE RESPIRATORY INFECTION HAVE BEEN SHOWN TO BE EFFECTIVE IN LTCF?

Respiratory infections are a very frequent cause of morbidity and mortality in nursing homes whose etiological diagnosis has improved with the inclusion of new diagnostic technologies [74-76]. As for viral etiology, influenza, Respiratory Syncytial Virus (RSV) infection, Coronavirus and Metapneumovirus infections stand out [49,77-81]. The most important bacterial pneumonia are pneumococcal pneumonia, [42,82,83] and polymicrobial aspiration pneumonia [84]. Legionellosis and tuberculosis are less common [45,85]. Finally, fungal infection, particularly Invasive Pulmonary Aspergillosis may occasionally occur, especially in immunocompromised patients with COPD who combine the use of corticosteroids and broad-spectrum antibiotics [86,87].

Measures to prevent respiratory infections in nursing homes for the elderly must take into account intrinsic and extrinsic risk factors for infection.

In relation to the environment, the effective measures are included in the World Health Organization (WHO) document, which brings together the guidelines and recommendations to be followed, in addition to incorporating an immunization plan for healthcare personnel [88,89]. There are recommendations for the maintenance of ambient air quality in these institutions and programs for the control of legionellosis [90].

There is literature suggesting that indoor concentrations of particulate and gaseous pollutants in nursing homes often exceed comparable outdoor environments nearby. Unlike outdoors, indoor air quality (IAQ) in nursing homes is not regulated by legislation and is rarely monitored. Therefore, an action

plan has been proposed to assess air quality in nursing homes and evaluate it periodically. This proactive approach can pave the way for the establishment of mandatory standards for indoor air quality in nursing homes that will promote the health, well-being and quality of life of LTCF residents and reduce medical costs [91].

As regards the control of legionellosis in residences for the elderly, there is no uniform legislation in the different countries and, when it exists, it is frequently not complied with. We therefore believe that this regulation and the corresponding periodic environmental control would be advisable [92].

In the individual aspects, there is no doubt that the implementation of vaccination programs for both residents and caregivers is an essential factor for the reduction and control of respiratory infection by influenza viruses and SARS-COV-2 [30,33,49,55,93-96]. There are also prospects for the use of a vaccine against RSV in the elderly population [97].

Antivirals are not recommended as chemoprophylaxis, except as part of interventions to control institutional outbreaks of influenza [98-101]. Its efficacy, for the most widely used (Oseltamivir), in a systematic review of 9 randomized clinical trials involving 4,328 patients [102], estimates a 21% reduction in symptoms versus placebo in the infected population; fewer lower respiratory tract complications requiring antibiotics for more than 48 h and fewer hospital admissions for any cause. Observational studies find association between the use of Oseltamivir and mortality reduction [103] but no randomized trial has demonstrated this. All have been conducted in healthy individuals where the mortality rate due to influenza is very low.

The efficacy of pneumococcal vaccination is linked to its antigenic composition [polysaccharide (PPV) and polyvalent conjugate (PCV)] and to the impact and application of PCV7, PCV10 and PCV13 in individuals over 65 years of age [104,105]. PPV23 efficacy data [106] are conclusive for protection from invasive disease, against all-cause pneumonia in low-income countries, and in chronically ill adults. It was not associated with a substantial reduction in all-cause mortality, possibly because of heterogeneity or lack of power of the studies.

In the CAPiTA trial (Community-Acquired Pneumonia Immunization Trial in adults) [107] PCV13 was compared in immunocompetent adults over 65 years of age versus placebo in a randomized, double-blind trial involving 84,496 adults aged 65 years or older. The protective efficacy of this vaccine for different points was estimated between 45% and 75.0%.

Conclusion

There are both environmental (air quality) and individual (vaccines) protective measures capable of reducing the incidence of respiratory infection in nursing homes, both in the case of infections caused by viruses (Influenza, SARS-COV-2) and bacterial infection (e.g. Pneumococcus). In most cases, however, legislation and its implementation are necessary.

HOW IS SKIN AND SOFT TISSUE INFECTION PREVENTED IN ELDERLY INSTITUTIONALIZED RESIDENTS?

Skin and soft tissue infections (SSTIs) acquired in residential facilities are common, with an estimated prevalence of 5% [108], the third most frequent cause of infection after urinary and respiratory infections in this group of patients. Overall, 10% of the elderly who take antibiotics in nursing homes do so because of a skin or soft tissue infection [109] which are of diverse etiology including viral, bacterial, fungal and, occasionally, parasitic. Institutionalized persons present a greater number of risk factors for SSTI due to frequent malnutrition, immunosuppression, comorbidity and higher cognitive and functional dependence, with urinary and fecal incontinence [110].

The most frequent point of entry for skin and soft tissue infections are solutions of continuity due to small wounds, trauma and surgical wounds [111]. Finally, health care centers and nursing homes have a high prevalence of skin and soft tissue infections and colonization by MDRs, among which MRSA stands out, with a carrier rate in health care centers and nursing homes that ranges between 8% and 25% [112].

For all these reasons, the prevention and control of SSTIs is an important challenge. However, the literature is scarce in well-conducted clinical trials that evaluate the efficacy of the different methods for their prevention and the recommendations are generally based on experiences obtained in other groups or on recommendations based on indirect studies or on expert opinion [113,114].

In diabetic patients, it is a fact that poor glycemic control increases the incidence of SSTI [115,116].

Another aspect of SSTI prevention is frequent skin cleansing, taking special care of the skin folds (submammary and inguinal), which should be dried with soft towel touches, avoiding the application of alcoholic lotions such as colognes or drying substances such as talcum powder, and the use of cotton garments is useful. The main problem of the skin of the elderly is skin dryness or xerosis, which affects 80 percent of people over 75 years of age, and which is combated with an adequate intake of liquids and the application of moisturizing creams all over the body surface on a daily basis.

There is data suggesting that periodic chlorhexidine showers decrease the incidence of MRSA infections but this has been done mainly in younger groups such as the military [117,118] and there is no evidence of its efficacy in institutionalized elderly populations.

There is also no evidence of the need for routine nasal decolonization to prevent MRSA infections in patients admitted to nursing homes. It is advisable to evaluate carrier status upon admission to the institution, before outbreak situations, and in patients who return or go to hospitals or change institutions.

Therefore, it is not necessary to screen for nasal carriers of *S. aureus* in general, unless there is a history of having been

colonized or infected in close contact with a colonized/infected case or if the resident has a history of having recently been in other centers with an endemic situation or active outbreak [17,18,119].

Colonization of an elderly person by MRSA should not be a reason for exclusion for admission and participation in a health care center. Patients colonized or infected by MDR microorganisms should, whenever possible, be placed in a single room, not isolated and following universal measures. If this is not possible, they should share a room with another person with the same problem. If this is also not possible, they can share a room with another person who does not have ulcers, wounds, catheters, drains or probes. They should never share a room with an immunosuppressed user. In case of ulcers or colonized skin wounds, these must be well treated and covered with a dry dressing before sharing activities in common rooms of the residence. There should be no restrictions on visitors, since in general, they have a low risk of acquiring an infection due to the protection of their saprophytic flora and can establish contact, but with the appropriate hygienic measures (hand washing, use of gloves and disposable gown if necessary). Nor are worker controls necessary, except in the case of outbreaks if it is suspected that they may be the epidemiological cause.

Conclusion

Skin and soft tissue infections (SSTI) are frequent in the elderly population living in LTCF. Their reduction requires general hygiene measures and control of predisposing factors such as skin lacerations or uncontrolled blood glucose.

There is no evidence of the need for routine screening for *S. aureus* carrier status, nor of the efficacy of systematic nasal decontamination or intermittent use of chlorhexidine showers.

WHAT INDICATORS ARE NEEDED TO MONITOR THE PREVENTION OF INFECTION CAUSED BY VIRUSES IN NURSING HOMES? HOW OFTEN SHOULD THEY BE OBTAINED?

Viral pathogens cause a significant proportion of infections in the elderly, mainly respiratory and skin infections. For example, in a recent study, 31.6% of the elderly with respiratory infections had a viral etiology (41.8% among out-of-hospital infections and 25.7% among nosocomial infections) [120] and the most frequent was influenza (14% of all patients studied). RSV is also a significant pathogen in this population [121,122].

The number of patients in a nursing home who get the flu and the number of residents and workers who are vaccinated are, in our opinion, clear indicators of the quality of care provided to the elderly in this respect [123]. These would be the most important indicators, in our opinion. But, if possible, some more could be included, as we will see below.

As we have mentioned, some of the most frequent viral infections are preventable by vaccination, so it is convenient to have a record of whether the elderly person has been vaccinated, the date of the last vaccination, whether he/she has antibodies or whether he/she needs to be vaccinated. Therefore, when the patient is admitted to the nursing home, I believe it is convenient to know his serology status against the human immunodeficiency virus (HIV), and against hepatitis A, B and C viruses. We believe that it should also be recorded when the patient was vaccinated against hepatitis A and B and make sure that he has received the previous year's influenza vaccine [124], COVID-19 and, as soon as it is available in our environment, the Varicella Zoster Virus (VZV) vaccine for adults.

In addition to the above, and whenever possible, the percentage of workers, residents, and visiting family members who have received the influenza vaccine should be recorded each year. A recent study (SHELTER study) conducted in 57 nursing homes in 7 European countries has shown that both correct vaccination against influenza and pneumococcus reduce mortality among residents, regardless of their comorbidities and functional and cognitive status [124-126]. This evidence, together with the reduction in influenza mortality in vaccinated patients, makes it an essential quality objective.

On the other hand, it is clear that the degree of influenza vaccination among nursing home employees, which ranged from 15-97% in a North American study, is clearly considered a quality criterion, since non-compliance with this obligation puts residents at unacceptable risk of suffering serious consequences [127]. It is also highly advisable to insist to family members that they should not visit their elderly with symptoms of respiratory infection or having recently been in contact with a sick person.

It is also advisable to record the number of visits to the emergency room that the elderly require and their causes [128]. Admissions due to upper respiratory infection or pneumonia and associated mortality should be recorded [129].

Finally, it also seems advisable to make sure that absolutely all new workers have received specific training on how to prevent and recognize nosocomial infections, as multicenter studies have shown that these training activities substantially improve the safety of interns and the quality of care [130]. These proposals are summarized in Table 1.

Conclusion

Indicators of the process of prevention of viral infection in nursing homes should include data on previous infection by viruses such as HIV, HBV, HCV, SARS-COV-2, Influenza and RSV on admission to the institution.

During follow-up, parameters such as vaccination rates against the different viral pathogens among residents and staff, as well as episodes of infection by these viruses and the hospital admissions they required, should be available.

Table 1 Indicators related to viral infection in nursing homes.

Indicators on admission of the elderly to the nursing home	Serology against hepatitis A, B and C, VZV, SARS-CoV-2
	Previous year's vaccination status against influenza, COVID-19 and VZV when available.
Annually in each patient	Annual flu vaccination registry
	When available, VZV vaccine registry
Annually throughout the residence	Influenza cases in the LTCF
	Cases of RSV in the residence
	Cases of Zoster in the residence
	Visits to the emergency department for upper respiratory tract infections
	Percentage of staff, interns and visiting family members who have received flu vaccine
	Percentage of newly hired staff who have received training in nosocomial infection prevention
	Consumption of alcohol-gel for hand hygiene in the nursing home

WHAT ARE THE PARAMETERS ON SARS-COV-2 INFECTION STATUS THAT SHOULD BE AVAILABLE IN NURSING HOMES?

It is not the purpose of this discussion to insist on the terrible impact that COVID has had on the elderly population and particularly among those living in nursing homes but to establish what should be the program of action for nursing home authorities to prevent diseases such as COVID-19 and its easy transmission among residents.

The challenges that the COVID-19 pandemic has posed to LTCF have been analyzed and summarized in several publications. Giri et al [131] reported a meta-analysis of publications on the subject. They retrieved 348 articles, of which 76 were included in the thematic review. Eight articles referred to asymptomatic transmission, 24 to resident-related factors (e.g., comorbidities, nutrition, cognition), 13 to facility characteristics (e.g., physical space, occupancy, facility ownership), 21 to staffing (e.g., staffing levels, staff-to-resident ratio, staff multi-employment), and 10 to external factors (e.g., availability of personal protective equipment, health and social care policies in place). The papers also examine responses to issues that arose including diagnostic testing, isolation and grouping of residents, staff protection and support, promotion of wellness, and technological innovations [131].

Proper planning and design of the built environment promotes infection control strategies in nursing home facilities. Findings can be used to guide the redesign, renovation, and modification of nursing home facilities for COVID-19 control of future public health emergencies. [132].

Among the measures that deserve special mention are:

1.- The massive use of diagnostic tests that has made it possible to identify a high proportion of asymptomatic or oligosymptomatic patients and to take the pertinent isolation measures [133].

Isolation measures

2.- The rapid classification of residents, based on their COVID history and diagnostic tests, allows these institutions to create separate areas and circuits for "positive" persons who have overcome the disease or who have evidence of disease activity [134].

3.- Adequate allocation of staff, particularly prior to vaccination, allowed, in these separate units, to assign to a particular caregiver staff, those unvaccinated and who had not passed the disease.

Prior to vaccination, in non-COVID patient areas, it was appropriate to place caregivers who had passed the disease and were considered reasonably immunized against it [135].

4.- A very severe restriction of visitation is considered to be an effective method for the prevention of COVID in these institutions [136] and written guidelines for visits should be available.

5.- Isolation periods for SARS-CoV2 infected patients classically established that residents should remain in isolation for a full 14 days after diagnosis of COVID-19 although it is possible that shorter times may be equally valid. It should be kept in mind that prolonged isolation predisposes residents to greater physical and mental deconditioning.

6.- Actions on personnel

It is very important to work with caregivers in nursing homes, given that during the COVID pandemic there have been high levels of dissatisfaction, stress and anxiety among them [137,138]. Psychological and professional support policies are needed to complement clear and consistent guidelines on the procedures for handling different situations.

The recommendations of the Japanese Geriatric Society are interesting in this regard [139].

Conclusion

The parameters that can best indicate the situation of COVID-19 and its prevention in nursing homes are, in

Table 2 Indicators of the pneumonia process in nursing homes for the elderly

Management of infection	Initial antibiotic in <8 hours in diagnosed pneumonia / Total pneumonias
	Pneumonias with hypoxemia treated with O2 /total pneumonias with hypoxemia
	Pneumonias referred to hospital /total pneumonias
	Change to oral antibiotic if clinical stability criteria are met/total pneumonias
	Pneumonia deaths/ Total pneumonias
Prevention	Influenza vaccination for residents
	Pneumococcal vaccination for residents
	Vaccination for workers

our opinion, the following:

1.- Evolution of the percentages of residents and staff vaccinated against COVID-19.

2.- Number of new cases detected each month in both residents and staff members, differentiating between those occurring in vaccinated and unvaccinated patients.

3.- Evolution and number of outbreaks of infection.

4.- Last date of revision and update of protocols for prevention and management of COVID-19.

IN NURSING HOMES, WHAT ARE THE BEST INDICATORS OF THE EVOLUTION OF BACTERIAL RESPIRATORY INFECTION?

Since viral infection and its indicators have already been discussed in other sections, we will focus on pneumonia as a quality parameter to be monitored in nursing homes.

In community-acquired pneumonia (CAP), which is the most severe expression, quality of care indicators identify and measure care that is associated either with a better prognosis of the process or with a better use of treatments. Most indicators have been described in hospitalized patients and in populations other than nursing homes. However, for the ACOVE (Assessing Care of Vulnerable Elders) expert group, pneumonia is one of the target processes for defining indicators and implementing quality of care [140,141]. In these indicators, they exclude the group of patients with advanced cognitive impairment or with a life prognosis of less than 6 months.

The indicators selected in pneumonia and/or influenza by this group are eight in total. They comprise infection management indicators and infection prevention indicators (Table 2). Although there have been reviews of pneumonia in the elderly [105], There are few studies that analyze the impact of quality indicators on pneumonia care in nursing homes. In people with advanced dementia, mortality is very high despite the use of antibiotics, and even if life is prolonged, it may be only in days, lengthening the dying process.

As a starting requirement, in nursing homes, it is essential to have an advance directives document to know the patient's desire to escalate treatment, referral to hospital, intubation or others. These data should be recorded in the clinical history to be taken into account in decision making for the diagnostic and therapeutic management of pneumonia.

Among the infection management and evolution indicators, three related to antibiotic treatment and oxygen therapy stand out. In relation to the evolution of the respiratory infection, a universal indicator in the management of pneumonia is the use of antibiotics in the first 8 hours after the diagnosis of pneumonia. This is based on several studies that demonstrate a higher survival of patients when antibiotics are started in the first 8 hours from diagnosis. For this reason, in the various SEPAR regulations [142] and in a consensus on infections in the elderly [143] is a universal recommendation and an indicator included among those recommended for nursing homes.

Simultaneously, the measurement of O_2 saturation to determine the need for oxygen therapy and its subsequent prescription and delivery is included as an indicator of quality of care. If it is indicated and not prescribed, the reason for this should be indicated in the clinical history, since it may be due to the patient's decision.

The third indicator for assessing the evolution is the need for transfer to hospital due to worsening and the need for therapeutic escalation, expressed as a percentage of the total number of pneumonias or infections. There are some programs developed specifically in nursing homes in the USA that include as an indicator the reduction of hospitalization of patients to enhance treatment in the nursing home. This program called INTERACT (Intervention to reduce acute care transfer) has also been analyzed to determine its safety, given that it could cause complications or have adverse effects if this measure is promoted and reduces necessary hospitalizations. The study conducted has shown no negative consequences on patients [144].

The last indicator of evolution and management is the change from intravenous to oral medication when clinical stability occurs, as long as there is capacity for oral intake. Clinical stability is possibly the best indicator of good therapeutic response

Table 3 Clinical stability criteria in patients with pneumonia

Heart rate < 100 bpm
Respiratory rate < 24 rpm
Axillary temperature ≤ 37.2 ºC
Systolic blood pressure > 90 mmHg
O_2 saturation > 90%
Adequate level of consciousness

and good evolution. Therefore, in daily practice, clinical stability criteria are used for decision making and include the duration of antibiotic treatment, among other things [142]. In the published guidelines on CAP, it is contemplated that if the patient has a temperature less than or equal to 37.2ºC in the last 48-72 hours and does not have more than one instability criterion, the antibiotic regimen can be terminated. In general, in the use of antibiotics, more days than necessary are prescribed with the potential problems of adverse effects such as CDI and others. The different components included in these criteria are respiratory rate (RF), heart rate (HR), axillary temperature, systolic BP, O_2 saturation and level of consciousness. The cut-off points for establishing clinical stability are detailed in Table 3. Clinical stability is usually achieved within 3-4 days of treatment in patients hospitalized for pneumonia. It should be considered that in elderly patients or those with multiple pathologies, stability can be delayed until day 5-7 without this meaning that there is a poor evolution. In fact, a publication on people living in nursing homes shows that up to 57% achieve clinical stability within 5 days of correct treatment. It is also necessary to consider each person's previous situation. If there were data on the patient's O_2 saturation at baseline, the cut-off point established to consider stability should be the return to baseline saturation and not necessarily to normal saturation. In the same way, the level of consciousness must be assessed with reference to the previous situation.

Among the infection management and evolutionary indicators, those related to early initiation of antibiotic treatment and its de-escalation, oxygen therapy and its subsequent outcome in terms of the need for hospitalization or mortality stand out.

Conclusion

Nursing homes should have figures on the evolution of the incidence density of pneumonia in the population they serve. In addition, the proportion of cases requiring oxygen therapy and hospital referral are desirable parameters. The proportion of patients with pneumonia who receive antibiotic treatment within 8 hours of diagnosis, the time to clinical stabilization, the duration of antimicrobial treatment and the time to switch to oral treatment should also be known. Undoubtedly, mortality should be included among the process indicators.

WHAT METRICS SHOULD BE USED AS INDICATORS OF GASTROINTESTINAL INFECTION IN NURSING HOMES?

Gastrointestinal infection is one of the frequent causes of infection outbreaks in nursing homes. In addition to immunosenescence, seniors frequently use medications such as proton pump inhibitors whose undesirable short- and long-term effects are well known [145-147].

Among the most frequent causes of enteric infection outbreaks in LTCF are viral pathogens such as Norovirus, Rotavirus, Calicivirus and Astrovirus [148] and bacterial such as *Clostridium perfringes* [149] and *Clostridioides difficile* [150, 151]. In a review of publications on outbreaks of enteric infections in nursing homes, the publications of 75 outbreaks are used for a meta-analysis. Sixty-nine percent of the outbreaks were associated with viral agents and 31% with bacterial agents. Transmission was mainly foodborne (52%) for those of bacterial origin and person-to-person (71%) for viral outbreaks. Norovirus infection was associated with 58% of hospitalizations but the ones with the highest mortality, however, were enteric infections caused by *Salmonella* sp. The control measures for these outbreaks are mainly general and food hygiene measures but none of the 75 published outbreak reports evaluated the effectiveness of the recommendations suggested to control each outbreak [151].

C. difficile infections (CDI) are often the consequence of untimely antibiotic use, particularly in the elderly who are on fluoroquinolones and proton pump inhibitors [152-154]. The elderly are a recognized risk group for CDI and outbreaks of CDI in institutions for the elderly are well known [155-162].

The parameters that, in our opinion, would allow a follow-up of gastrointestinal tract infection (GTI) in this population are the following:

1.- Incidence density of diarrhea in the institution (sum of patient days with diarrhea versus total daily stays).

2.- Evolution of the number of outbreaks of enteric infection and their etiology.

3.- Documented episodes of *C. difficile* infection.

4.- Days of treatment with oral antibiotics and fluoroquinolones per 1,000 stays in the institution.

Conclusion

Gastrointestinal infections can cause outbreaks in nursing homes. We believe that it is necessary to have specific protocols for their prevention and management. The most elementary indicators of these processes seem to us to be the incidence density of diarrhea, outbreaks of enteric infection and their causes, episodes of *C. difficile* infection and consumption of orally administered antimicrobials.

HOW SHOULD THE PROBLEM OF URINARY TRACT INFECTION BE FOLLOWED UP WITH FIGURES?

Urinary Tract Infection (UTI) accounts for 49% of all in-

fections in nursing homes and its incidence is estimated to be around 1 episode per 1000 stays in studies in Austria [163] and Germany [164]. ITU criteria must be strict [165] avoiding over-interpretation of simple positive urine cultures without clearly attributable symptomatology.

The frequency of indwelling urinary catheters among elderly patients in LTCF varies between 3-12%, being higher in men than in women [60,108]. Urinary catheter-associated UTI is a common cause of sepsis, hospital admission and antimicrobial use that often leads to subsequent colonization with multidrug-resistant microorganisms (MDR) [166,167].

In patients with urinary catheters, the prevalence of bacteriuria is 100% and the incidence of symptomatic UTI is estimated at 3-7 episodes per 1,000 catheterization days [166, 168]. Symptomatic UTI, defined as the presence of fever not attributable to another cause, has been estimated at 6 to 11 episodes per 1,000 catheterization days in institutionalized elderly people [169].

In this regard, it is important to correctly diagnose symptomatic UTI and differentiate it from asymptomatic bacteriuria [170]. The Infectious Diseases Society of America (IDSA) guidelines define urinary tract infection as the growth in culture of $\geq 10^3$ CFU/mL of uropathogenic bacteria in the presence of symptoms or signs consistent with urinary tract infection with no other identifiable source in a patient with indwelling urethral, indwelling suprapubic, or intermittent urethral catheterization. Compatible symptoms include fever, suprapubic or costovertebral angle tenderness, and unexplained systemic symptoms such as altered mental status, hypotension, or evidence of a systemic inflammatory response syndrome. [171].

Regarding prevention, there are few randomized controlled studies measuring the efficacy of preventive measures for UTI secondary to bladder catheterization. Among the most important measures are to perform bladder catheterization only when necessary and to remove the catheter as soon as possible. Intermittent catheterization may reduce the risk of bacteriuria, and is associated with a lower risk of complications and bacteremia [108].

For the control of UTI in nursing homes [164] surveillance of symptomatic UTI episodes (1,000 catheter-days/1,000 resident-days) and monitoring of resistant organisms in urine of catheterized patients is recommended in order to detect an increase in incidence or an infectious outbreak.

The indices we suggest to monitor this process in nursing homes could be the following:

1.- Proportion of residents with bladder catheterization or other permanent urine diversion procedures.

2.- UTI episodes per 1000 days of stay.

3.- Proportion of episodes of UTI caused by MDR.

Conclusion:

The effectiveness of surveillance and monitoring of UTI in nursing homes should be tracked by indices such as the number of patients with bladder catheterization or other urine diversion procedures, UTI incidence density, and the proportion of episodes caused by MDR microorganisms.

SHOULD THERE BE A REGISTRY TO TRACK PRESSURE ULCERS?

In a recent systematic review that included 17 valid studies, the frequency of pressure ulcers is estimated very variably in different nations. Prevalence rates ranged from 3.4 to 32.4% although the large differences in prevalence in different countries are not explained by methodological differences and data from many developed nations are missing [172].

In a study of more than 700 nursing homes in Japan, the prevalence of pressure ulcers was 9.6% and the monthly incidence was 1.9% [173] and in the United States in a sample of 2,936,146 residents in LTCF had stage 2, 3 or 4 pressure ulcers in 8.4% and deep tissue infections in 1.7% [174].

We are therefore talking about a frequent problem with multiple risk factors including peripheral vascular disease, immobility and low hemoglobin and albumin blood concentrations. It is essential to have multidisciplinary teams for prevention, specific protocols for assessment and care, and therapeutic and preventive means to address this problem [173,175]

The minimum data set needed to address pressure ulcer follow-up should include assessment of residents' risk of pressure ulcers on admission, quantification and classification of pressure ulcers, and a management manual with periodic reviews [176]. It is necessary to have the so-called "minimum data set" (MDS) to be taken into account for the assessment and scales such as the PUSH (Pressure Ulcer Scale for Healig), the PSST (Pressure Sore Status Tool), the DESING scale, the CODED scale or RESVECH 2.0 [177-182]

For all these reasons, we believe that the set of parameters aimed at monitoring the problem of pressure ulcers as a predisposing element to skin and soft tissue infection should include the evaluation of the risk of suffering from such ulcers both on admission and periodically, the prevalence of ulcers and their categorization, and the verification of the periodic review of a document for their prevention and management. In addition, episodes of skin and soft tissue infections should be recorded, as mentioned in a previous section.

Conclusion

It is necessary that follow-up records in nursing homes include the classification of residents according to the risk of pressure ulcers, the evolution of the prevalence of pressure ulcers and their classification by severity. It is also necessary to record the number of episodes of skin and soft tissue infections over time and evidence of the periodic review of written protocols for prevention and treatment of pressure ulcers.

HOW SHOULD THE PROBLEM OF COLONIZATION AND INFECTION BY MULTI-DRUG RESISTANT (MDR) BACTERIA IN A NURSING HOME BE MONITORED?

Infections and colonizations by multidrug-resistant microorganisms (MDR) are a worldwide known problem of growing importance that is no longer limited to hospitals and is also increasingly affecting other healthcare facilities such as nursing homes [73,183-187]. The subject has been reviewed in depth by Rodriguez-Villodres et al. recently [188] showing that the prevalence of colonization by different MDRs is highly variable from one continent to another.

O'Fallon et al. conducted a study with active search for MDRs in nursing home residents and found that 22.8%, 0.6% and 11.1% were colonized by MDR gram-negative bacteria, vancomycin-resistant enterococci and MRSA, respectively. MDR gram-negative bacteria were recovered in 3 (1.8%) of the 175 environmental samples cultured [189].

Elderly residents in these facilities present several risk factors for MDR colonization or infection, in particular, chronic diseases, multimorbidity, immunodeficiencies, limited mobility and frequent transfers between hospital and residence lead to an increased risk of healthcare-associated infections and, consequently, MDR carrier status [164,188,190]. A very important and modifiable risk factor is the high use of antimicrobials during the year in the institution.

In addition to the morbidity-mortality aspects, a European study has recently shown that nursing homes face costs per patient with MDR infection estimated at an average of 12,682 euros per case (ranging from 2,449 to 153,263 euros per episode). In this study, the mean duration per case of MDR infection in nursing homes was 163.3 days [191].

In general, the literature estimates that the success of decolonization measures in nursing homes is very low [192]. The reasons given are, on the one hand, poor health conditions of elderly residents combined with poor compliance and, on the other hand, lack of hygienic knowledge of nursing staff.

In 2019, the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) developed a guideline to provide recommendations on decolonization regimens targeting BGN-MDR carriers in all settings [193].

We were not able to find a firm recommendation on the parameters that should be systematically obtained to correctly monitor this problem, nor on the impact that obtaining them has on its control. Therefore, our current recommendation does not require a systematic search for MDR colonization in institutions for the care of the elderly. However, we believe it is advisable to record infections caused by MDR microorganisms and to monitor them, meaning the following: Extended Spectrum Beta-lactamase (ESBL) producing Enterobacteriaceae, Carbapenemase producing Enterobacteriaceae, MDR *Pseudomonas aeruginosa,* MDR *Acinetobacter baumanii* and MDR *Stenotrophomonas maltophilia*. Among the gram-positive microorganisms we should include MRSA, vancomycin-resistant *Enterococcus* (VRE) and *C. difficile* although in the latter case it is not genuinely an MDR.

Conclusion

We recommend the recording of episodes of infection caused by multidrug-resistant microorganisms (MDR) and not the systematic search for colonization by these microorganisms, which should only be carried out as part of actions derived from specific problems. This recommendation is due to the fact that the evidence is currently insufficient to provide recommendations for or against any intervention in patients colonized with MDR.

SHOULD THERE BE A REGISTRY ON THE USE OF ANTIMICROBIAL AGENTS IN NURSING HOMES?

Improving the use of antimicrobials in any healthcare setting (human and veterinary) is a national priority, and this applies to all settings, hospital and residential [194].

Between 40-70% of antibiotics (ATB) prescribed in a healthcare setting are unnecessary and sometimes inappropriate and, as a pharmaceutical group, they are the most prescribed in a residential facility.

The judicious use of antibiotics reduces the emergence of resistance, avoids adverse effects and lowers costs [195].

It is recommended that all facilities have a policy on antibiotic use (PROA program), for which the CDC has developed a program focused on 7 key elements [196]:

- Commitment of the center to carry out an antibiotic policy program.
- Responsible for the program: physician or pharmacist with specific training.
- Antibiotic expert pharmacist.
- Documented action plan.
- Traceability of treatments.
- Periodic reports of results to prescribers and nurses.
- Training program.

The approach to the use of ATB in institutionalized settings is not an exclusively local problem; it must be understood in territorial terms. The exchange of patients and, therefore, of the microbiota means that the resistance maps of the centers must be drawn up according to the resistance profiles of a specific territory.

For infection control in residential centers, there are a series of safe practices that should be "mandatory", such as the use of gloves, hand hygiene (with its 5 moments) and the occlusion of wounds or ulcers. In addition to these practices, there are several measures to implement infection control and prevent the spread of MDRs such as the use of closed system urine collectors, optimizing oral hygiene, and monitoring of high prevalence infections: especially urinary tract infections.

Situations in which ATB use should be avoided are viral respiratory infections, asymptomatic bacteriuria and indiscriminate use of topical ATBs.

At the present time, ATB prescribing and administration

software can allow systematic recording or analysis of prescribing profiles. But more important than having or not having such a registry is the development of a global program on infection control in the centers. This program, if coordinated on a territorial basis, is much better, since the resistance profiles are linked to a territory and to the reference hospitals of the Health Area.

In the implementation of these programs, it can be useful to take as a reference the recommendations of the 7 key points elaborated by the CDC (Centers of Disease Control) for hospitals and later adapted to the institutional environment [7,196,197].

Therefore, to the question of whether there should be a registry on the use of ATB in nursing homes, the answer is yes, but especially within the framework of a global program on the rational use of antibiotics and coordinated with the policies and resistance maps of the territory.

Conclusion

The consumption of antimicrobials in a nursing home should be a quality indicator. The denominator to be used can be the 1,000 days of stay and the numerator can be given in total Defined Daily Doses and of the large groups of antibiotics.

IS THERE A NEED FOR A "TELE-ADVISOR" WITH EXPERTISE IN INFECTION CONTROL IN THE LTCF? WHAT WOULD HIS/HER JOB BE?

As we have indicated, the optimal and more than desirable situation is to approach infection control in residential centers from a territorial perspective, which, in our country, is articulated around the territorial PROA programs. This "telecounselor" should play a key role in leading and validating the treatment and infection control programs in the residential centers in his or her area of reference.

His task would be to serve as a link between the residential centers and the reference hospital of the territory, to elaborate and validate the resistance maps of the most frequent microorganisms in the most prevalent infections (mainly urinary and cutaneous).

- Protocolization of the prescription. Analysis of action plans.

- Control of the resistance profile of the center and preparation of the resistance map of the Health Area.

- Individualized prescription support in specific cases (MultiR, nosocomial outbreaks, restricted ATB policies).

- Participation in the territorial PROA.

- Validate and collaborate in the training program of the professionals of each center.

- Monitor number of UTIs and most common microorganisms.

- Monitor bronchoaspirations.

- Establish empirical treatment protocols.

- Empower professionals. Role of nursing experts in infection control.

- Avoid movement restrictions.

- Create infection control culture.

- Implementation of safe practices.

Conclusion

We consider the figure of the "telecounselor" to be very necessary, who should be a professional with extensive training in geriatrics and infectious diseases, reporting to the territorial Health Services, who can act by stimulating and advising on valuable practices, monitoring local and area resistance patterns and leading-implementing PROA policies in his or her area of reference. Given the great variability among the different residential centers, this figure must ensure compliance with the recommended guidelines, the follow-up of MDR infections, the appearance and control of possible outbreaks of infections and the training programs for professionals.

IS FEVER A GOOD MARKER OF INFECTION IN THE ELDERLY, AND ARE DAYS WITH FEVER PER YEAR A PARAMETER TO BE MEASURED?

Fever, whether present or absent, is not a good marker of infection in the elderly if it is not accompanied by other values. Up to 30% of older adults with active bacterial or viral infections do not have fever [198,199]. Likewise, the presence of fever is not an exclusive marker of infection, as elevated body temperature may be related to other clinical entities such as: the presence of tumors, pharmacological interaction (such as neuroleptic malignant syndrome), metabolic causes (such as thyrotoxicosis) or fever that appears after excessive sun exposure, as in the case of heat stroke [198,199].

Given the unspecificity of fever as a symptom caused by multiple conditions, fever days per year is not a useful parameter in relation to the presence of infections [200]. On the other hand, the number of proven annual infections is important (those for which there is microbiological evidence as well as clinical compatibility). In this case, especially in urinary tract infections, it is possible to implement a non-pharmacological prophylaxis or, in case of lack of success of the previous one, also pharmacological prophylaxis.

Conclusion

Fever is not a good marker of infection in the older adult as it is neither sufficiently sensitive nor sufficiently specific for the presence of infection.

WHAT SHOULD A CHECKLIST INCLUDE TO PREVENT INFECTION IN ELDERLY PEOPLE LIVING IN NURSING HOMES?

Structured interventions, such as the introduction of in-

fection control packages or checklists, are very useful in increasing compliance with infection control measures and decreasing nosocomial infection rates [201,202].

A checklist is a tool to assist in the work; it generally consists of a list of tasks that when performed are verified with a check mark. It is an instrument with the following positive indicators: it improves quality standards and the use of good practices, allows critical information to be condensed, helps reduce errors of omission and facilitates reproducible evaluation. It has its limitations and should be avoided as it is time-consuming to avoid compromising work performance.

The "ckeck-list" should have the order of workflow and routine established in resident care. For its implementation, it is necessary to carry out a series of programs in the organizational culture of the institution: an educational and training plan for users of the checklist, support for professionals to clarify doubts, piloting before implementation and periodic updating of its content. It should be supported by the person or persons responsible for the infection prevention plan of the residential center [203].

The "check list" can be focused on individual patients but it can also be done periodically with the resources of the whole institution. The one dedicated to assessing the situation of individual patients could include, among others, the following items:

Checking the proper functioning of the hand hygiene device closest to the patient's bed. [114,204,205].

The presence of endovascular lines and the question of the need to maintain them.

The presence of bladder catheters or other urinary drainage devices and the question of the need to maintain them.

The existence of tachypnea or O_2 saturation by pulse oximetry less than 94%.

The existence of pressure ulcers

The existence of skin and soft tissue infections.

Administration of antimicrobials within the last 24 h.

Recent deterioration of the patient's alertness or consciousness content.

Indication of any form of isolation

Communicating the benefits of implementing a ckeck-list to the professionals who carry it out facilitates their incorporation into their daily tasks since it provides positive reinforcement for their involvement.

Conclusion

Understanding by "check-list" the systematic review of aspects of infection prevention or detection in residents of long-term care facilities, we recommend that a daily check of some items be performed on each individual. This should include checking the proper functioning and availability of hydroalcoholic gels for hand hygiene, the existence and need for maintenance of invasive procedures such as IV or urinary catheters, and the presence of signs suggestive of infection in various organs as well as the need for maintenance of antimicrobial therapy.

WHO SHOULD SIT AT A CONSENSUS TABLE TO ELABORATE A PROGRAM SUCH AS THE ONE WE ARE DISCUSSING?

Infection prevention and control should be seen as a team effort in which everyone, representatives of institutions and organizations, the scientific and medical community, residential centers and their direct and indirect care personnel, as well as the patient himself, should take part.

The public administration is key not only in its regulatory role and as guarantor of the protection and safety of citizens and, in particular, of the most vulnerable groups, but also in the monitoring of regulatory compliance. Its role in the dissemination of guidelines, health recommendations and rigorous information focused on prevention and action in the event of infection is also relevant.

On the other hand, the role of healthcare professionals is fundamental. In addition to doctors, nurses, pharmacists and other professionals linked to geriatrics and gerontology, nurses and physiotherapists are direct care staff and in addition to performing activities such as administering medication, carrying out cures, rehabilitation exercises and changing catheters, they can provide an assessment of the patient's condition and the special care that the person needs. In addition to geriatricians, specialists in infectious diseases and clinical microbiology, internists, preventive medicine and other specialists are needed for specific issues. These specialists should be delegates of their corresponding Scientific Societies.

In addition, health and social workers are knowledgeable about the patient's situation, the person's environment and the support required to prevent and control infections.

Prevention strategies should be developed in routine geriatric care and in any type of health or residential center. The management of the centers should be represented to ensure that safety and protection protocols are applied by all staff, both direct and indirect care (kitchen staff, cleaning, maintenance, etc.). In this sense, it is necessary that information is disseminated to all levels of the organization and that all personnel working in the facilities, as well as other personnel who may have access to the center, are aware of and apply measures to guarantee the protection of the resident and the rest of the personnel. Likewise, it is necessary to provide these personnel with the necessary resources for the correct development of these protocols and actions.

Promoting the co-responsibility of the patient and his/her environment in this area is essential. It is necessary to know the doubts and barriers they face in order to work on a preventive program that really meets their needs and is effective. It is essential to encourage a health-promoting attitude in its different aspects and preventive interventions in gerontological clinical practice. In addition, it is necessary to undertake awareness and communication actions to explain to residents,

their relatives and caregivers the preventive measures and, also, the corrective measures in the event of infection, in order to encourage the greatest possible collaboration. In this sense, patients' associations become a valuable ally, acting as a channel to get the information to these groups and also to convey the needs to public decision-makers and other parties involved.

Finally, the media become an important source of information and play an educational role that cannot be overlooked. The role of the media helps to shape opinion and raises awareness, as a preliminary step to a change in behavior focused, in this case, on the protection of the individual.

We would like to end with a reflection on the commitment of society in general to our elderly and also to their families and caregivers, both formal and informal. We are experiencing an aging population that is leading to a significant and progressive increase in morbidity associated with chronic and degenerative processes, which are often disabling. Therefore, there is an increasing number of elderly people with health conditions that require support. For this support to be effective, to meet existing needs and to protect the individual, it is necessary for all the agents involved to work in a coordinated and cohesive manner, with flexibility and leadership.

Conclusion

The elaboration of a document-proposal for the prevention of infection in nursing homes should include health professionals, both physicians, pharmacists and nurses of different specialties, the most involved scientific societies, administrators and managers of nursing homes, patients' associations and representatives of the administration and the media.

WHO IS RESPONSIBLE FOR SUCH AN INITIATIVE? HEALTH AUTHORITIES? SCIENTIFIC SOCIETIES? PATIENT ORGANIZATIONS/ SENIORS' ASSOCIATIONS?

The responsibility for taking the initiative to establish infection control programs in nursing homes lies with the health authorities.

It is the health authorities who should establish what type of registers should be set up, clearly indicating their content (variables to be collected), the source of the data, the periodicity, the subsequent analysis and the reports to be issued. It should also be established who is responsible for data collection and for establishing infection control programs in these centers.

The scientific content of the program should always be established in collaboration with the country's scientific societies and reference experts (research centers and universities) to ensure that the latest available knowledge is available at all times.

Patients and citizens should be informed of the record of infection in these centers, as well as the programs put in place to control it. The reporting of nosocomial infection outbreaks and the measures taken to prevent their recurrence should also be made public. Transparent information on the risks of infections in these centers should also be the responsibility of the health authorities.

As these centers are mostly privately managed and with very tight financing (in Spain the budget dedicated to long-term care is 0.7% of GDP, compared to an average of 2.5% of GDP in the EU-8), any infection control program should be accompanied by the corresponding economic report to prevent centers from failing to implement it adequately for economic reasons.

In addition to the health authorities in the establishment of plans and their monitoring and follow-up, the involvement of hospital reference services and pharmacy services is very important for the control of an adequate use of antibiotics in this population.

It is also necessary to be very strict in the monitoring of the vaccination schedule in this population, leaving its compliance to the primary health care services.

Patient organizations should be informed of the establishment and monitoring of the control plan, of the incidents in its development, of the existence of nosocomial infection outbreaks and of the measures to be adopted during visits to these centers to minimize the risk. The design of the plan should be technical.

Conclusion

The initiative for the establishment of nosocomial infection control plans in nursing homes is a responsibility of the health authorities. The results of the control parameters should be in the public domain.

WHAT CAN BE APPLIED FROM ALL THIS TO THE ELDERLY LIVING AT HOME?

The prevention of infection in the elderly living in their own homes, although not primarily the subject that concerns us, is also an aspect of the utmost interest. It has many points in common with what has been discussed for nursing homes, but also differential aspects. In addition, the place of residence of the elderly is variable and there are often changes of residence from their own home to long-stay residences and vice versa.

In view of the need to decide how to apply these measures in older adults living in the community, we will refer to those pertinent to the prevention of infection and the reduction of the risk of communicable diseases. These measures must be coordinated from the Primary Care setting and are an inseparable part of the connected fabric of our health system.

Aspects such as the vaccination program and schedule for the elderly do not merit emphasis in this section and readers are referred to other sources [47,104].

The most common home infection is respiratory infection, followed by urinary tract infection and skin and soft tissue in-

fection, and in its fundamental aspects the prevention of infections of these organs follows the same principles as in the case of patients living in nursing homes [206,207].

A particular aspect of infection prevention in the elderly living at home is the possible acquisition of infections from younger members of the family community. Good examples are Influenza, RSV and more recently and dramatically SARS-CoV-2.

Another very important aspect is the programs to improve the use of antimicrobials (PROA programs) that exist at the community level in Primary Care in some areas, led by Family Physicians [11,28,208-212]. There is evidence that the inappropriate use of antibiotics has direct consequences on the increase of infections by MDR microorganisms, taking into account that between 30-50% of antibiotic prescriptions are inappropriate.

It is therefore interesting to evolve to a system that eliminates all barriers between the patient's home and the health system and leads to the use of new technologies to promote multidirectional communication for the benefit of all types of patients who at some point in their evolution or permanently will remain in the community.

Conclusion

Infection prevention programs for the elderly living at home are also necessary. They should be coordinated by Primary Care and include vaccination programs, prevention of the most frequent infectious syndromes in the elderly, the acquisition of infection from younger people in the family environment and finally PROA programs for the rationalization of the use of antibiotics at home.

DO WE KNOW WHAT PROPORTION OF ELDERLY PEOPLE DIE IN NURSING HOMES AS A RESULT OF INFECTION?

It is difficult to know the causes of death of patients living in nursing homes, because there is no reliable registry of them. This is a problem that exists in different countries and is described in the literature, so the data are not accurate most of the time. In the cases in which the cause of death has been evaluated, it is generally taken from death certificates, with the limitations that this implies [213].

The main study on this subject, carried out years ago in the USA, evaluated the cause of death in people over 60 years of age who lived in nursing homes and during a 15-year follow-up. During this period, 75% died, 2,372 of the 3,164 people included in the study, with a mean age of 81+/-8 years. The main cause of death was cardiovascular in 63% of cases, followed by infections in 21%, most of them (15% of the total) sepsis of urinary origin, followed by respiratory infections [213].

More recently, Braggion and co-workers in the Veneto (Italy) [214] evaluated mortality rates, their determinants, and causes of death in 19,392 subjects aged ≥ 65 years admitted to nursing homes during 2015-2017. Mortality peaked in the first 4 months after admission, and thereafter, the monthly mortality rate fluctuated around 3% in men and 2% in women. Overall mortality was 34% at one year. The most represented causes of mortality were cardio-cerebrovascular diseases, neurodegenerative diseases, respiratory diseases and infections. In the table of causes provided by this work, pneumonia appears as the cause of 4% of deaths, sepsis with 3.2% and a miscellaneous of other infections with 4.2%. In Spain, according to the "Envejecimiento en red" (Ageing network) report, the mortality rate due to infections in the total population over 65 years of age is about 80 /100,000 inhabitants and year and is one of the few that did not vary between 2006 and 2017 [215].

In a study carried out in public nursing homes in Madrid in 2013, and published as a doctoral thesis, all the deaths of patients living in LTCF were studied, which numbered 713 out of a total of 5,956 places, representing 12%. The average length of stay of the deceased was 37 months. A total of 57.7% died in the nursing home and 42.2% in the hospital at a mean age of 88.9 years. The principal cause of death was not collected in 51% of cases and was due to pneumonia and other infectious processes in 8% of cases, followed by heart failure, tumors and dementia. The accompanying chronic diseases were most frequently hypertension, dementia and osteoarticular disease [216].

A study predicting mortality within one year after admission to a nursing home does not include infection among the main risk factors [217].

Conclusion:

The proportion of elderly dying in nursing homes as a direct consequence of infection is poorly known since the few studies available have been done on the basis of death certificates. The data obtained allow us to estimate that infection is a direct cause of death in at least 8 to 12% of the elderly. Pneumonia and sepsis of urinary origin are the leading causes.

ARE THERE DATA ON THE IMPACT OF IMPLEMENTING A PROGRAM SUCH AS THE ONE WE DISCUSS ON THE QUALITY OF LIFE AND SURVIVAL OF THE ELDERLY?

In the literature it is possible to find multiple initiatives dedicated to improving specific problems related to nosocomial infection in nursing homes. Examples are studies to optimize the management and prevention of urinary tract infections [218,219], hand hygiene [220] or the use of intravenous fluids and antimicrobial agents [221]. There is not as much evidence on the effectiveness of global programs such as those discussed in this paper, let alone their impact on quality of life and survival [222]. A systematic review of different interventions showed that studies with a positive impact on residents tended to change worker behavior, but that such changes in worker practices did not always lead to a better prognosis for residents [223]. The authors rec-

ommended very concrete initiatives (improving oral care, for example). The study demonstrated the most frequently encountered challenges (frequent staff turnover, work overload, attitudes, lack of resources, etc.).

Some of the elements that should be included are recording of infections and follow-up cultures, hand hygiene, isolation precautions, training programs for residents and staff, and a good antimicrobial use control program [201].

The results of a program aimed at reducing nosocomial infection in five nursing homes by improving surface cleaning and hand hygiene have been published. It included online training, recording of surface cleaning, monitoring of hand hygiene compliance, reporting of diagnosed infections, and a survey of workers. Only a non-significant reduction in total infections (6.7%) and lower respiratory tract infections (19.9%) was achieved [224]. There were no significant differences in the number of antimicrobial treatments, nor in hospitalization rates before and after the intervention. The vast majority of workers supported the intervention.

Continuing education of workers is an aspect that certainly deserves great attention. A study conducted in 184 American nursing homes with 1,626 participants showed that only 36% knew the meaning of pyuria, only 28% knew the indications for urine culture and less than 30% had learned the correct way to perform hand hygiene [130]. Another study showed that the training and qualifications of the nosocomial infection manager in each residence was related to indicators of good antimicrobial use, but was not related to patient survival [225].

Nursing homes must meet quality criteria, but voluntary inclusion in national surveillance systems, at least in the United States, did not occur until there was a financial incentive to report CDI episodes. The residences that signed up first were those that already had more quality criteria, reflected in a higher rate of pneumococcal vaccination [226]. A U.S. study examined whether voluntary accreditation of nursing homes, adopting government quality requirements and undergoing audits, had a favorable impact on patient well-being [227]. The variables considered were: vaccination rate against influenza and pneumococcus; pain; delirium; pressure ulcers and health inspection scores. A total of 246 accredited nursing homes were compared with 15,393 control nursing homes. Accredited nursing homes demonstrated better quality on all indicators analyzed.

Conclusion

It is not clear which interventions are the most effective in improving the quality of life and survival of patients in Long Term Care Facilities. The implementation of nosocomial infection prevention programs in nursing homes should pursue very specific objectives and include aspects of training of both workers and residents. It is recommended that nursing homes adhere to official control and audit programs.

HOW SHOULD THIS INFORMATION BE DISPLAYED AND USED IN THE DAILY LIFE OF A NURSING HOME?

The aspects that we consider key to the knowledge of this information in the residence are:

1. The existence of an education program on infections and on the measures that work, which is periodically given to all the technical staff, geroculturists, the residents themselves and their families. These education programs should also involve the health professionals of the health centers responsible for nursing home care.
2. The involvement of the medical and care managers in the nursing home (medical director, nursing director...) in facilitating participation in infection prevention programs.
3. The use of easily visible panels, posters with information, algorithms useful in decision making (e.g., in case of suspected urinary tract infection, or in case of fever without clear focus, or in case of a COVID +.....).
4. The existence of a registry on infections and antibiotic use in each residence, monitored sectorially like the one we are discussing.
5. The inclusion of all these data among the important data to be evaluated in the quality control of the residences:
   a) existence of preventive programs,
   b) register of infections both treated in the nursing home and referred to the hospital,
   c) record of vaccinations
   d) existence of a consultant
   e) contingency plans for epidemics such as COVID.
6. Preparation of an annual report on infection in residences by Public Health / General Directorate of Social and Health Centers.

Conclusion

Information on quality control indicators in nursing homes should be discussed periodically among all levels of nursing home workers. They should be transmitted to the health authorities who will anonymously distribute them widely, not only to professionals but also to family members.

SHOULD THE HEALTH AUTHORITY REQUIRE A SET OF DATA LIKE THE ONES WE ARE TALKING ABOUT INTO A CENTRAL DATABASE FOR PROFESSIONAL AND PUBLIC KNOWLEDGE?

Management to prevent healthcare-associated infections is a typical example of the use of one of the general principles of quality management in healthcare institutions: each institution should compare its own infection rates for defined risk groups of patients with reference data and identify problems relating to specific types of infection in particular clinical care

units. This comparison should stimulate a careful analysis of the process of care and options for improvement [228].

In order to achieve good infection control management within health care institutions, surveillance strategies should be designed according to the specific needs of the institutions. [229].

The implementation of a registration system and the reporting of infections to a central database is a measure that has proven to be effective in increasing knowledge of infections and establishing health policies for the control and prescription of antibiotics [230]. Experience in nursing homes is limited, even at the international level.

Since 2012 the enrollment of residences for infection reporting to the National Health Safety Network (NHSN) in the United States has been a national priority since the Centers for Disease Control and Prevention (CDC) put the spotlight on LTCF [231].

The assessment made by the nursing homes that have registered in the NHSN is positive: they consider that reporting provides greater awareness of infection prevention, provides motivation to develop a prevention program and improves the quality of care in the centers.

Other advantages that the recording and reporting of infections can provide are to reinforce the detection of infections, to establish a correlation between the infection rate of a nursing home or nursing homes in a care area with triggering factors, to facilitate the tracking of an outbreak, to compare nursing homes by encouraging best practices, to promote studies to evaluate the impact of prevention measures carried out, and to promote patient safety [232].

In the United States, it was found that the benefits were perceived in centers that participated on a voluntary basis but also in centers that participated on a mandatory basis. The main reason for not wanting to participate was the workload involved or the absence of a professional to take responsibility for this task [233].

Therefore, the answer to the question posed is affirmative. From our point of view, reporting a process makes one responsible for that process. However, in order for the implementation to be successful, an adequate knowledge of the most prevalent infections in nursing homes must be obtained beforehand [234], carry out training programs for center professionals and provide them with a double support, internal and external, to clarify doubts, consolidate learning and maintain motivation.

In the hospital setting there is more tradition and knowledge of the importance of submitting information with a "feed-back". It is very important for motivation that the residencies obtain information from the data they provide to the registry system, which should be accompanied by an analysis of the data collected and a proposal for intervention [234]. The subsequent evaluation should assess the quality of the data submitted and the suggested intervention. This is a positive stimulus for whoever generates the information.

Conclusion

Recording and reporting infections to a central database is an effective measure to increase knowledge, develop prevention programs, analyze health care and improve the quality of services provided.

The data collected should be publicly available so that their analysis can benefit the center itself, but also other residential centers by promoting best care practices.

The participation of a nursing home in an infection registry system and the quality of the data provided, as well as the impact of the prevention measures carried out, should be considered as care indicators in the evaluation of a nursing home.

IS THE PRESS AWARE OF THIS ISSUE AND WHAT ROLE SHOULD IT PLAY?

It is difficult to say whether journalists working in the media are sufficiently aware of the situation in nursing homes and the control of infections that can occur in them. In our opinion, the answer is no, and there are several reasons for this. The first, and fundamental, is the lack of specialization prevailing in the written press, radios, televisions and web pages. The previous economic and financial crisis had its consequent impact on the media. The former newsrooms, divided into areas with specialists in different subjects (economics, politics, events, religion, environment, education, health, etc.) were adapting to an environment marked by lower sales of copies and/or a drop in advertising revenues. This led to staff reductions and the emergence of the figure of the generalist journalist, a professional who knows everything, but, in reality, hardly knows anything. Thus, it is not uncommon that journalists who used to report on religion or science have had to start reporting in recent years on television, culture, entertainment, or political parties, to cite just a few examples. The result has been a worsening of the quality of reporting that has become more acute over time. Not only are the news stories on a variety of subjects worse, but also less information of their own is being produced, which pushes all the media to deal with the same subjects, reducing the information spectrum. The second reason for the media's neglect of information on nursing homes is purely journalistic. Information on senior centers competes for space in the society and local sections with others on religion, education, environment, health, science and, sometimes, even events. We know from experience that it is very difficult to get a space with these competitors when, on top of that, it has been reduced as a consequence of the economic crisis. If there are ten news items on different topics and there are only three pages to publish them, information on residences has all the chances of being left out. And a third factor is the intrinsic nature of the information on this type of care for the elderly. What is newsworthy in the information on LTCF? There is usually little and, moreover, it is a field in which the principle of "good news is not news" applies: in the end, only negative

news ends up being published or disseminated. Positive news has no place.

The outbreak of the pandemic in March 2020 brought information about nursing homes and the elderly out of ostracism and suddenly became front page news, especially during the first wave. In our opinion, the information disseminated about what happened in them was biased by political confrontation and conditioned by the three evils I mentioned above, producing a sort of "perfect storm". The image that was finally transmitted to the public by the media was that the facilities were a perfect breeding ground for the spread of the virus, governed by satrap and exploitative businessmen, and left to their own devices by the health authorities. This image does not coincide with reality despite the avalanche of deaths allegedly due to Covid-19 that occurred inside them, especially during the first wave of the pandemic. The residences have been in the news again since the third wave, coinciding with the vaccination process against the SARS-CoV-2 virus that has been carried out in them since December 27th. The authorities judiciously decided to start inoculating the doses in this group because it is the one with the highest case fatality rate. Specifically, from June 22 to the present day, 22% of those over 90 years of age who were infected have died from Covid, a percentage which stands at 14.2% among those aged 80 to 89 years and 5.3% among those aged 70 to 79 years, according to data compiled by the Carlos III Health Institute and the National Epidemiological Surveillance Network.

Conclusion

The mass media has little and deficient information on the problems of infection transmission in nursing homes and on the possibilities of reducing these risks. The reasons for this are to be found in the decrease of specialized health sections in many media since more than a decade ago.

WHAT ETHICAL ISSUES ARE RAISED BY THE TOPICS AND POSITIONS THAT HAVE BEEN DISCUSSED THROUGHOUT THIS MEETING?

Our era is peculiar for several reasons. One of them is that people's average life expectancy has more than doubled compared to earlier times, such as the beginning of the 20th century. This phenomenon has been accompanied by others no less significant: the secondary and tertiary sectors of the economy have come to occupy most of the population, so that as the countryside was depopulated, urban concentrations became megacities. Another phenomenon of no lesser importance has been the access of women to productive work. All this has created a new situation, unprecedented in the annals of human history, which no one could have foreseen and for which no one was prepared.

Let us briefly recall the previous situation, which, with no great variations, had been maintained over several millennia, at least from the Neolithic revolutions until the arrival of the industrial revolution. The first took place at different dates in different places, but the average figure is around 5,000-3,000 BC. The second, the so-called industrial revolution, began in England in the mid-19th century, but did not become global until well into the 20th century. Between these two dates, the human species remained in a type of society that is often referred to as "agricultural culture". The basic occupation was the cultivation of the land, a task assigned to men. These were the so-called "productive" activities. The other major sector was that of "reproductive" activities, reserved for women, who were responsible, among other things, for raising children and caring for the elderly. This was carried out in dwellings that today are called "patriarchal" (think of the Catalan farmhouses, the Galician pazos or the Castilian manor houses), in which three or even four generations coexisted, and in which there was a permanent system of care for children, the elderly and the sick. The elder, on the other hand, was the most revered member of the community, if only because he was the origin, not only biologically but also economically, of the whole group.

This is what sociologists usually call the "patriarchal family". In it there were several very significant facts. One, that there were always elders in it. Another, that they were respected and revered for their own condition. And a final one, that they all considered it natural that they should be cared for in their own home. To throw them out or send them elsewhere would have been considered socially and morally execrable.

Things began to change with the industrial revolution. Industrial warehouses appeared in the suburbs of the cities, if only because cheap labor was plentiful there. The large patriarchal dwellings gave way to apartments or city apartments, in which only one generation, or at most two, can live. This is the so-called "nuclear family". Since both members of the family need to work, caring for children, the elderly and the sick is almost impossible. Exceptionally, acute situations can be taken care of, but certainly not chronic ones. In such cases, the support of other institutions is necessary. In the case of illnesses, these are hospitals, which are now taking on a new role, taking on a special role. And in the case of the elderly, the solution has been found in the establishment of an extensive network of assisted living facilities. The very organization of life in modern society has made them indispensable.

The old man usually looks at these institutions with a sidelong glance and with caution. He is well aware that in the traditional society, the one in which he was born, the old people's home was judged as morally and humanly negative. The old man had dedicated his life to his family, and it seemed logical that the family should not abandon him when he was no longer useful. In fact, the impossibility of caring for the elderly in the family has generated an enormous guilt complex in many families, who continue to consider themselves obliged not to abandon their elders, despite the near impossibility of doing so in the situation of nuclear families.

It is clear that families cannot be blamed. But the problem does not end there. We have organized modern society around the basic principle of the economy, efficiency. This became the

Table 4 **Mortality in nursing homes. Adapted from Glette et al [15].**

Country	Date	Approach to measuring COVID-19 linked deaths in care homes	Total number deaths linked to COVID-19*	Number of deaths of care home residents linked to COVID-19	Number of deaths in care homes linked to COVID-19	Number of care home resident deaths as % of all COVID-19 deaths	Number of deaths in care homes as % of all COVID-19 deaths
Australia	22/01/2021	C	909	685		75%	
Austria	24/01/2021	C	7,328	3,243		44%	
Belgium	19/01/2021	C + P	20,457	11,722	8,854	57%	43%
Canada	23/01/2021	C + P	18,974	11,114		59%	
Denmark	19/01/2021	C	1,837	719		39%	
Finland	22/01/2021	C	644		243		33%
France	20/01/2021	C + P	71,342	30,395	21,646	43%	30%
Germany	22/01/2021	C	50,642	14,066		28%	
Hong Kong	25/01/2021	C	169	32	0	19%	0%
Hungary	27/08/2020	C	612	142		23%	
Ireland	13/12/2020	C + P	2,110		1,084		51%
Israel	25/10/2020	C	2,404	861		36%	
Netherlands	15/01/2021	C	12,774	6,529		51%	
New Zealand	12/01/2021	C + P	25		16		64%
Norway	20/01/2021	C	533		318		60%
Portugal	10/01/2021	Unclear	7,803	2,254**		29%**	
Singapore	24/01/2021	C	29	4	0	14%	0%
Slovenia	17/01/2021	C	3,371	1,875		56%	
South Korea	07/09/2020	C	336	27	0	8%	0%
Spain	22/01/2021	C + P	66,557	26,328		40%	
Sweden	18/01/2021	C + P	9,949	4,656	4,249	47%	43%
England (UK)	15/01/2021	C + P	88,674	29,381	21,615	33%	24%
Wales (UK)	15/01/2021	C + P	5,884	1,470	1,267	25%	22%
N. Ireland (UK)	15/01/2021	C + P	2,124	862	642	41%	30%
Scotland (UK)	17/01/2021	C + P	7,448	3,266	2,867	44%	38%
United Kingdom	As above	C + P	104,130	34,979	26,391	34%	25%
United States	07/01/2021	C + P	357,124	139,699		39%	

C: confirmed; P: probable

guiding category of human activity from the 18th century onwards, when, with Adam Smith and his disciples, economics became a scientific discipline. And this is the criterion that governs industrial work, which revolutionized human life from that same century onwards. In industrial society, in contrast to agricultural society, the culture of efficiency dominates. Thus, inefficient people become part of the debit side, not the credit side, together with the sick, the lazy, the thugs, etc.

The old, by definition, is inefficient. In modern culture, this has a very negative social and even moral connotation. It is not that citizens consciously and intentionally undervalue the elderly. It is an unconscious process, and therefore much more subtle and difficult to control. In the age of efficiency, the elderly are seen as a hindrance, a burden or a burden. This leads, also unconsciously, to their discrimination. To the point that one does not know what to call an elderly person, because the terms all end up having negative connotations. The Latin term for old is senex, whose opposite is iuvenis. One is either iuvenis or senex. These are terms that in classical Latin were applied only to living beings, and especially to people. For things other terms were used, vetus and novus. A book is new or old, etc.

Well, in the modern world, unlike what happened in all previous centuries, the old man will be called "old" (derived from vetus), so that "senecto" (derived from senex) will be relegated to the category of cultism. And since old is a clearly derogatory term when applied to human beings, others have been sought to replace it. One is "elder", which comes directly from the French, and the other from the Latin antiquus. Despite appearances, it is no less discriminatory than vetus, because it is also a term referring to things, not people.

So what to call them? From this point on, the proliferation of euphemistic terms began. There has been talk of "passive classes", of "third age", of "senior citizens", of "elderly people", etc. Basically, we do not know what to call them properly, because the terms, although at first they may seem correct, soon take on a negative meaning, which brings back the specter of discrimination.

It is also a problem to properly name discrimination against the elderly. In English, the term "ageism" has taken hold and was soon imported into our language as "ageism". Some, more purist, proposed as an alternative "etaísmo" or "edaísmo". The Fundéu of the Real Academia Española says that the correct term is "edadismo", which, however, has not yet been incorporated into the official dictionary.

From all that has been said so far, it would seem natural that the mistreatment of the elderly would take place in family homes, given their precarious conditions. But the Covid-19 pandemic has shown that discrimination is so subtle and so widespread that it also affects those institutionalized in assisted living facilities, and that those who are trained to care for and assist this type of person are not exempt from it. In this regard, the data that have just become known are very revealing. Of every 100 institutionalized in nursing homes, 17 have died during the pandemic in the Community of Madrid, 14 in those of Castilla la Mancha and 11 in those of Castilla-León and Extremadura. The number of deaths in homes for the elderly is close to 30,000, according to provisional data from the Ministries of Social Rights, Health and Science and Innovation.

According to IMSERSO data, during the first wave it is possible to "estimate as plausible a range between 47% and 50% of deaths in residences with respect to the total number of deaths due to COVID-19 disease in the first wave. If this estimate is valid, and according to some preliminary international studies, the Spanish case would be situated in terms of percentage of deaths of users of residential centers with respect to the total number of COVID-19 deaths in intermediate parameters for the first wave, similar to those of the United Kingdom (45%), France (46%), Sweden (46%), Scotland (47%) or Northern Ireland (49%); significantly below Belgium (61%), Australia (75%), Canada (80%) or Slovenia (81%) and above Denmark (35%), Austria (36%), Israel (39%) or Germany (39%) [18] (Table 4).

The total number of deaths in nursing homes has not yet been calculated, but according to IMSERSO data, as of May 31, 2021, "there is a very high impact on excess mortality in people with care in nursing homes, with an excess of deaths of 26,299 people (10.56% of the total number of dependent people cared for in nursing homes). While highlighting that such excess was concentrated in the months of March-May, while in June 2020-January 2021 excess mortality was similar regardless of the place of provision, except in October 2020 and from February 2021 where there was lower excess mortality in people with residential care than in home support" [235].

(The total number of deaths due to COVID-19 includes only those confirmed, so the figures may be lower than the real ones, particularly in the first part of the pandemic).

A certain percentage of deaths in nursing homes, not easy to quantify, is due to the biological condition of the elderly, with a clear decrease in biological reserves and immune response. But another percentage, not negligible, has to do with the lack of specialized care, sometimes with overcrowding and, finally, with the fact that in certain places they have been discriminated against, denying them transfer to health centers. In the case of Spain, this has even been stated in guidelines issued by some autonomous communities.

Conclusion.

The great moral problem in the elderly population is discrimination, which ends up being mistreatment, and which is sometimes overt, but other times it is subtle and, on certain occasions, is even unknown even to the people who practice it. Hence the need to educate the population in general, and particularly those who are directly involved in nursing home care.

TRANSPARENCY DISCLOSURE

For transparency purposes, please note that GSK has contributed to the funding of this publication. Its contents reflect the authors' own opinions, criteria, conclusions and/or findings, which may not necessarily coincide with those of GSK. GSK always recommends the use of its products in accordance with the data sheet approved by the health authorities.

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Review

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Reduction in the risk of progression of solid organ transplant recipients infected by SARS-CoV-2 treated with monoclonal antibodies

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ABSTRACT

Recipients of solid organ transplants (SOT) are at higher risk of infection by SARS-CoV-2 virus especially due to chronic immunosuppression therapy and frequent multiple comorbid conditions. COVID-19 is a potentially life-threatening disease in SOT recipients, with an increased likelihood of progressing to severe disease, with the need of hospitalization, admission to the intensive care unit (ICU) and mechanical ventilatory support. This article presents an updated review of different aspects related to the outcome of COVID-19 in SOT recipients. In unvaccinated SOT recipients, COVID-19 is associated with a high mortality rate, in-patient care and ICU admission, and impaired graft function or rejection in severe disease. In vaccinated SOT recipients even after full vaccination, there is a reduction of the risk of mortality, but the course of COVID-19 may continue to be severe, influenced by the time from transplant, the net state of immunosuppression and having suffered graft rejection or dysfunction. SOT recipients develop lower immunity from mRNA vaccines with suboptimal response. Treatment with mAbs provides favorable outcomes in non-hospitalized SOT recipients at high risk for severe disease, with lower rates of hospitalization, emergency department visits, ICU care, progression to severe disease, and death. However, broad vaccination and therapeutic options are required, particularly in light of the tendency of the SARS-CoV-2 virus to adapt and evade both natural and vaccine-induced immunity.

Keywords: solid organ transplant, COVID-19, SARS-CoV-2, vaccines, immunosuppression, monoclonal antibodies, sotrovimab.

Reducción del riesgo de progresión en receptores de trasplantes infectados por SARS-CoV-2 tratados con anticuerpos monoclonales.

RESUMEN

Los receptores de trasplantes de órganos sólidos (TOS) presentan un alto riesgo de infección por el virus SARS-CoV-2 debido al tratamiento inmunosupresor y múltiples comorbilidades. La COVID-19 puede ser potencialmente mortal en receptores de TOS, con un aumento de la probabilidad de progresión a enfermedad grave. Este trabajo presenta una revisión actualizada del impacto de la COVID-19 en receptores de TOS. En los receptores de TOS no vacunados, la COVID-19 se asocia con una alta tasa de mortalidad, hospitalización, ingreso en la UCI y deterioro del injerto o rechazo. En los pacientes vacunados, incluso con pauta de vacunación completa, se reduce el riesgo de mortalidad, pero el curso de la COVID-19 puede continuar siendo grave en función del tiempo desde el trasplante, el estado neto de inmunosupresión y haber sufrido rechazo o disfunción del injerto. Los receptores de TOS presentan una baja inmunogenicidad a las vacunas de ARNm y respuesta subóptima. El tratamiento con anticuerpos monoclonales (AMC) en receptores de TOS no hospitalizados con alto riesgo de enfermedad grave, se asocia con menores tasas de hospitalización, visitas a urgencias, ingreso en UCI, progresión a enfermedad grave y muerte. Sin embargo, se requieren nuevas vacunas y opciones terapéuticas, teniendo en cuenta la tendencia del virus SARS-CoV-2 a adaptarse y a evadir tanto la inmunidad natural como la inducida por la vacuna.

Palabras clave: trasplante de órgano sólido, COVID-19, SARS-CoV-2, inmunosupresión, vacunas, anticuerpos monoclonales, sotrovimab.

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INTRODUCTION

The current pandemic of SARS-CoV-2 infection posed unprecedented threats to global healthy populations, sick patients with any disease, healthcare systems, economic burden, and governments' responsibilities to ensure the health and safety of their communities. The coronavirus disease 2019 (COVID-19) had also had a major impact on solid organ transplantation (SOT), specially on the mortality of these patients, since they are more likely to develop severe forms of the disease as compared to the general population. This may be because they are unable to mount a robust immunity against SARS-CoV-2.

Although effective treatment options and vaccines have been a game changer, the ongoing pandemic continues to pose unique challenges to fully resume disrupted transplantation activities. A population-based study of nationwide cohorts of consecutive kidney, liver, lung, and heart transplants from 22 countries estimated an overall 16% reduction in transplant activity comparing rates in 2020 and 2019 [1]. An analysis of the impact of COVID-19 pandemic on the size of US transplant waiting lists showed an increase in waiting list mortality and decreased transplant and candidate listings [2]. A review of data provided by the US United Network of Organ Sharing (UNOS) [3] comparing monthly transplants in January and February 2020 with those performed during the entire month of April 2020 demonstrated a 35.9% decrease in organs transplanted, with the largest reduction seen in kidney and lung transplants; moreover, increases in waitlist deaths. The impact on organ transplantation also varied with respect to organ type with preferential deferral of kidney transplant candidates who were stable on renal replacement therapy and/or had lower immunologic barriers to transplantation [4]. However, the majority of reports noted a decline in SOT in all organ types, with living donor programs generally suspended or curtailed in many sites [5-7], recent evidence has also shown that there is low risk for a transplant recipient to get infected from an already infected donor, especially in non-pulmonary organs (kidney, liver, and heart) being transplantation a safe practice, with a low risk of transmission, regardless of the presence of symptoms at the time of procurement [8].

From another perspective, transplant recipients may be at a higher risk of infection by SARS-CoV-2 due to the use of immunosuppression, underlying comorbidities, and frequent contact with the healthcare system. However, they are also more likely to be diagnosed early because of a more overt symptomatology than immunocompetent subjects or due to closer follow-up at the hospital or the transplant center. In Spain, in SOT (n = 665) and hematopoietic stem cell transplant (HSCT) (n = 113) recipients diagnosed with COVID-19 until 13 July 2020, the incidence of COVID-19 was twofold higher compared to the Spanish general population [9]. The mortality rate was 27%, with age > 60 years, lung transplantation, and hospital-acquired COVID-19 as risk factors for death. However, during the ongoing pandemic, from 2020 to 2021 mortality in SOT recipients has decreased from 20-25% to 8-10% as a result of increased and early availability of SARS-CoV-2 testing, adherence to non-pharmaceutical interventions (face covering, hand hygiene, physical distancing) to control spread of infection, development of novel treatments, and vaccination [10]. Nevertheless, transplant patients have less post-vaccination protection than the general population, this condition of lower protection should have implications for treatment [8].

Although the COVID-19 pandemic is likely to move to an endemic phase, with vaccination and novel therapeutic options potentially reducing infection rates in SOT recipients [11-13], there are still limited data on the risk of poor outcomes and progression of SARS-CoV-2 infection, response to vaccination, or efficacy of monoclonal antibody therapy in SOT. Therefore, an updated review of recently published relevant studies addressing these aspects is here presented. The aim of the review is to provide clinicians involved in organ donation and transplantation with some updated evidence for an optimal approach to the care of SOT patients in daily practice, in particular in reference to how COVID-19 impacts on

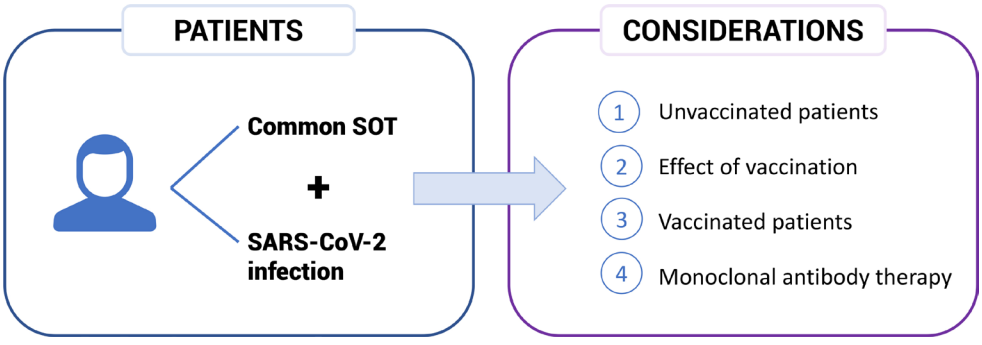

Figure 1 Different aspects of SARS-CoV-2 infection in solid organ transplantation (SOT) recipients include the severity of the disease in unvaccinated in comparison to vaccinated patients, the immune response to vaccines, and the effect of treatment with monoclonal antibodies on the course of the disease.

the overall management of SOT recipients and the use of mAbs as an available treatment to reduce the risk of progression of these patients (Figure 1). It should be noted that even though this review focuses on monoclonal antibodies, there are other treatments available against COVID-19, such as antivirals.

METHODS

A narrative review was carried out to cover all the points of interest to be reflected, being these both the risk of COVID-19 disease progression of SOT patients when infected by SARS-CoV-2 and the use of mAbs as early treatment to avoid COVID-19 progression. The information of interest was divided into four blocks, including: 1) outcomes in unvaccinated SOT recipients, 2) response to SARS-CoV-2 vaccine of SOT recipients, 3) outcomes in vaccinated SOT recipients, and 4) effect of treatment with monoclonal antibodies on the course of COVID-19 in SOT recipients.

The literature search was conducted in MEDLINE/PubMed database in May 2022 using MeSH terms and the following strategy: ((covid[Title/Abstract]) OR (sars-cov-2[Title/Abstract])) AND ((solid organ transp*[Title/Abstract]) OR (transpl*[Title/Abstract]) OR (SOT[Title/Abstract])) AND ((risk[Title/Abstract]) OR (bad outcome*[Title/Abstract]) OR (progno*[Title/Abstract]) OR (hospit*[Title/Abstract]) OR (death[Title/Abstract]) OR (mortal*[Title/Abstract])). Also, (vaccin*[Title/Abstract]) was added in the search of the second and third blocks, and ((monoclonal antibody [Title/Abstract]) OR (mab [Title/Abstract]) OR (treatment [Title/Abstract])) in the search of the fourth block. The search period ranged from June 2021 to May 2022 and was limited to articles published in English. In September 2022, the fourth block search was actualized, extending the search date to that moment. Also, due to updated vaccination programs leading to booster doses, especially in immunocompromised patients, relevant publications that provide key information for the aim of this review, were also allowed to be included. Hematopoietic cell transplant recipients were excluded. Regarding 'article type', no limits were established, although reviews, systematic reviews, and meta-analysis with the largest number of patients and participating centers were prioritized. Reference lists of retrieved articles were checked for additional potentially eligible studies. Full texts were obtained from all articles included in the present review. After excluding publications with the other formats, such as editorials, comments on articles, or opinion studies, the authors met via teleconference for discussion and agreement of the selected bibliography. The authors were not blinded to the authors, institutions, or journals while selecting studies or extracting data.

1. OUTCOMES IN UNVACCINATED SOT RECIPIENTS

In this block, three studies, a systematic review and meta-analysis [14], a structured review [15], and a cohort study [16] were focused on the outcomes of SARS-CoV-2 infection in SOT, whereas another three studies each assessed COVID-19 in specific lung [17], liver [18], and kidney [19] transplant recipients.

The systematic review and meta-analysis [14] included 14 retrospective and 1 prospective studies which had been published in 2020 that provided clinical outcomes of COVID-19 transplant recipients (n = 1485) vs. non-transplant controls. The overall quality of the evidence, according to Newcastle-Ottawa Scale (NOS) ranging from 7 to 9, was moderate. SOT recipients were predominantly male and more likely to present with higher proportions of comorbidities. Transplant recipients with COVID-19 showed as compared with non-transplanted patients a higher risk of admission to the intensive care unit (ICU) (odds ratio [OR] 1.57, 95 % confidence interval [CI] 1.07-2.31, $p = 0.02$) and mortality (hazard ratio [HR] 1.54, 95 % CI 1.03-2.32, $p = 0.037$) (1.40-fold increase odds of mortality than non-SOT recipients). In addition, in three studies that matched SOT recipients with the general population by age, sex, and comorbidities, SOT recipients also showed an increased risk of mortality (HR 1.42, 95% CI 1.01-2.0, $p = 0.046$).

In a structured review of cohort studies, case series, case-control studies, and case reports published in 2020, 164 publications were identified with 3,451 cases of SARS-CoV-2-infected SOT recipients, in which data on outcome were available for 3,353 patients (97.2%) [15]. Main outcomes included hospitalization in 84 % of patients (with SARS-CoV-2 infection recovery in 53.6%), mortality rate of 21.1%, changes in immunosuppressive medication in 57.9%, and disease progression involving an impaired allograft function in 22.6%.

In a study of the largest database on COVID-19 in the United States (National COVID Cohort Collaborative) [16] based on SOT patients who were tested for COVID-19 between January and November 2020, 18,121 SOT patients were identified, 1,925 (10.6%) of whom had a positive test for SARS-CoV-2. The outcome in the 90 days after COVID-19 positivity was analyzed. The presence of COVID-19, compared to SOT patients without COVID-19 positivity, significantly increased the risk of a composite variable (myocardial infarction, stent occlusion/thrombosis, angina, stroke, transient ischemic attack, chronic heart failure or death of any cause) (OR 1.92), as well as the risk of graft loss (OR 79.7), rejection (OR 31.8), death (OR 8.43), acute kidney injury (AKI) (OR 2.35), and graft failure (OR 1.23). Compared with all other organ types, kidney transplant recipients had the highest risk of AKI and graft loss.

COVID-19 is a life-threatening disease for unvaccinated lung transplant recipients. In a single German high-volume lung transplantation center [17], clinical outcomes of 31 recipients with SARS-CoV-2 infection among 1,046 patients followed between March 2020 and May 2021 showed a mortality rate of 39%, and 84% of patients required in-patient care. Pulmonary function parameters worsened significantly, and in patients with pre-existing chronic lung allograft dysfunction, there was a substantial deterioration in graft function, with a mortality rate of 43%. The Charlson Comorbidity Index was a predictor of mortality (4/5.5) (HR 1.5, 95% CI 1.5-2.2, $p = 0.023$).

In a review of eight studies published from January 2020 to January 2021, that evaluated COVID-19 infection in 494 liv-

er transplant recipients, 80% required hospital admission and 17% ICU care (of which 21% required mechanical ventilation) [18]. The overall mortality rate was 17%. Finally, in a systematic review and meta-analysis of 48 observational studies comprising 3,137 kidney transplant recipients with COVID-19 [19], the mortality rate for hospitalized patients was 21%, increasing to 53% among patients admitted to the ICU ($p < 0.0001$) and up to 68% in those who required mechanical ventilation support. In addition, the pooled prevalence of acute respiratory distress syndrome (ARDS) and AKI was 58% and 48%, respectively. There was a higher mortality risk associated with ARDS (OR 19.59), need of ICU care (OR 13.39), mechanical ventilation (OR 3.80), and age ≥ 60 years (OR 3.90).

Take home message

- **Unvaccinated SOT recipients with COVID-19 have a significant high risk of progression to severe COVID-19 disease and mortality.**
- **Impaired allograft function, graft rejection or graft loss are consequences of the severity of SARS-CoV-2 infection.**
- **Intensive surveillance is necessary in unvaccinated SOT patients for severe clinical outcomes.**

2. RESPONSE TO SARS-COV-2 VACCINE OF SOT RECIPIENTS

Vaccines against SARS-CoV-2 have been shown to constitute an important preventive option against COVID-19, especially in fragile patients, such as transplant patients. However, available data indicate that COVID-19 vaccines may be less effective in immunocompromised populations such as SOT recipients, although vaccines are safe and not related to rejection or other major adverse events. For this section of the review, selected reports included two systematic reviews (one with meta-analysis) [20,21], a descriptive review [22], a comparison of antibody titers between SOT recipients and healthy controls [23], three reviews in kidney transplant patients [24-26], one review and meta-analysis in the subgroup of patients receiving anti-CD20 therapies [27], and a retrospective study in liver transplant recipients [28]. Additionally, two prospective cohort study in renal patients [29,32], and two studies in SOT recipients [30,31] were also included to give information about the effect of a third or fourth dose.

A systematic review that assessed the immunogenicity of COVID-19 vaccine after primary complete vaccination in immunocompromised populations, based on 157 studies in 25,209 patients, including 47 studies in 5,974 SOT recipients (23.7%) until August 2021 [20]. Non-response rates, defined as no presence of anti-SARS-CoV-2 spike protein antibodies or absence of neutralizing antibodies, ranged from 19% to 100%, with 35-98% in recipients of kidney transplantation, 19-63% in liver transplantation, 25-88% in heart transplantation, and 59-100% in lung transplantation. Also, most studies found lower non-response rates in cellular than in antibody response. The use of calcineurin inhibitors, antimetabolites, and corticosteroids were associated with higher non-response rates or lower antibody titers. Non-responder status was also associated with older age and lower estimated glomerular filtration rate. The authors found inconsistency in the results with regards to the impact of time since transplantation on vaccine response.

The seroconversion after second dose of COVID-19 mRNA vaccines was evaluated in a systematic review and meta-analysis of 26 studies conducted in 2021 in 3,207 immunocompromised patients and 1,726 healthy controls [21]. Thirteen studies were focused on immunocompromised patients due to SOT, showing that transplant recipients were less likely to develop seroconversion than controls (relative risk reduction [RRR] 0.67, 95% CI 0.53-0.76, $p < 0.01$). No significant differences ($p = 0.55$) were observed in the subgroup analysis based on the type of transplantation (kidney vs. others [heart, lung, and liver]).

A descriptive review based on 24 studies in SOT recipients [22], suboptimal humoral immune responses following two doses of mRNA SARS-CoV-2 vaccine was reported, particularly in kidney and lung transplant recipients (seropositivity rates from 8.2% to 66% and from 10% to 47.4% for kidney and lung transplant recipients, respectively). However, seropositivity rates were higher for liver (37.5 % to 80%) and heart (18.2% to 62%) transplant patients. Among 148 kidney transplant recipients, 35% developed neither humoral nor cellular immune responses. Advanced age and magnitude of immunosuppression correlated to the immune response.

In a single-center prospective observational cohort study of 200 SOT recipients (liver, kidney and lung) and 200 age- and sex-matched controls [23], in which anti-receptor-binding domain (RBD) immunoglobulin IgG was measured after two doses of BNT162b2 vaccine, humoral (36% SOT vs 97.5% controls with positive response, p<0.001) and cellular responses (13.1% SOT vs 59.4% controls with positive response, p<0.001) 6 months after vaccination were inferior in SOT recipients than in healthy controls. Antibody levels increased from first vaccine dose to 2 months but declined from 2 months to 6 months. Statistically significant risk factors ($p < 0.001$) for humoral non-response 6 months after the first vaccine dose were increasing age (risk ratio [RR] 1.23 per decade increase), being less than 1 year from transplantation (RR 1.55), lung (RR 1.63), and kidney (RR 1.70) as type of organ transplantation with liver as reference, the use of mycophenolate (RR 1.54) or corticosteroids (RR 1.45) as immunosuppressive therapy, and *de novo* non-skin cancer as comorbidity (RR 1.52).

Other studies have evaluated the immune response in kidney transplant patients [24-27]. In a systematic review of 18 prospective cohort studies with 2,453 patients, 693 of which were kidney transplant recipients, the antibody response was evaluated 1-6 weeks after receiving the second dose of a mRNA vaccine [24]. The seroconversion rate ranged between 2.5% and 37.5% (overall 27.2%), with advanced age, high-dose corticosteroids in the last 12 months, and maintenance im-

munosuppression regiments including mycophenolate mofetil (MMF) as variables associated with low or absent antibody response. In another review [25], immune response after two doses of anti-SARS-CoV-2 vaccine ranged between 11% and 48%, with longer time from transplantation, first kidney transplant, better kidney function, and less immunosuppression related to more likely to seroconvert. In a meta-analysis of 27 cohort and case-control studies with 1,452 kidney transplant patients and 477 healthy controls, humoral and cellular immune responses ranged from 2.6% to 29.87% and from 5.13% to 59.84%, respectively, for up to 4 weeks post-vaccination completion with mRNA vaccines, whereas all healthy controls maintained ≥ 93% of both responses [26]. Moreover, another meta-analysis of immune responses in patients treated with anti-CD20 antibodies showed a low humoral response rate of 14% for the subset of kidney transplant recipients, which was a lower level of response than other conditions also treated with anti-CD20 such as hematological malignancies or autoimmune diseases. [27]. In patients receiving a liver transplant, alcohol-induced cirrhosis as underlying disease and MMF for immunosuppression have been identify as risk factors for seronegativity [28].

SENCOVAC is a prospective, multicentric study of four cohorts of vaccinated patients with different status of chronic kidney disease (CKD). In an analysis of vaccine response (by measurement of antibody titers), 6 months after the primary vaccination, the authors included 175 kidney transplant recipients who have received, at least, two doses of mRNA vaccine. 118 patients received a third dose. At 6 months, 80% of kidney transplant patients among those who had received a third dose of vaccine (median 125 days after second dose) were categorized as responders vs only 53% of responders among those with only two doses (p=0.002). However, 20% of patients did not respond after a third those [29]. After third dose, patients had higher anti spike antibody titers than those without the third dose (p< 0.001). In addition, 62% of kidney transplant patients that did not respond after two doses, seroconverted after third those. Thus, a third antigenic event seems relevant in this population although still a meaningful size keeps not well protected, not responding to vaccine [29].

Similar results were reported by Kamar et al. after studying, retrospectively, 101 SOT patients (78 kidney, 12 liver, 8 lung-heart, 3 pancreas). There were 40% of SOT patients with detectable anti SARS-CoV-2 IgG before the third dose. After the third those, this percentage increased up to 68%. Among patients that remained seronegative after second dose (n=59), 44% seroconverted 4 weeks after third dose [30].

In a prospective study in Denmark, SOT patients (kidney 73.2%, liver 16.2%, heart 4.7%, lung 3.7%) were included for study of humoral response after BNT162b2 vaccination. 395 and 335 patients were studied after second and third dose respectively. SARS-CoV-2 spike IgG antibodies were detected in 49.4% of patients after two doses and 77.9% after the third dose. The rate of seroconversion was 47.5% after the third dose for those who remained seronegative after second dose (n=200). In terms of quantification, an overall increased in antibody titer was observed after third dose (overall mean increase 831.0 BAU/mL). Factors associated with poor response were increased age, shorter time since transplantation and treatment with prednisolone and proliferation inhibitors [31].

In a further publication, the SENCOVAC study group, analyzed the impact of a fourth dose of vaccine, 12 months after primary vaccination. They included 396 kidney transplant patients (278 with three doses and 118 with four doses). The fourth dose increased the antibody titers in patients with hemodialysis and non-dialyzed patients with chronic kidney disease, but not in kidney transplant patients. Additionally, being a kidney transplant patient was shown to be an independent predictor factor of negative humoral response at 12 months (OR 7.8; p<0.001) [32].

Steroids and mycophenolate mofetil were found to be associated with lower anti-Spike antibody titers (p=0.030 and p=0.004, respectively) [32].

Take home message

- **SOT recipients develop poor response to two doses of COVID-19 mRNA vaccines, with a lower seroconversion rate as compared to healthy population.**
- **Older age, burden of immunosuppressive regimen, maintenance with mycophenolic acid and corticosteroids, less than 1 year after transplantation, and impaired renal function are risk factors for humoral non-response.**
- **Kidney transplant patients increased antibody titers and seroconversion after third dose. However, 20 % of patients did not respond at all and those that did respond had lower antibody titers than other populations.**
- **Fourth dose of vaccine does not seem to meaningful improve the response in kidney transplant patients.**
- **Given the suboptimal immune response to two doses of vaccine, vaccination by at least three doses would be desirable.**

3. OUTCOMES IN VACCINATED SOT RECIPIENTS

The evidence of whether effective anti-SARS-CoV-2 vaccines may significantly reduce the risk of morbidity and mortality-associated with COVID-19 in SOT recipients is unclear [33]. Relevant studies assessed in this block included a retrospective registry-based analysis [34], a cohort study [35], a retrospective multicenter study [36], an observational data linkage cohort analysis [37], and a population-based cohort study [38].

A study that linked four national registries in the United Kingdom was conducted to identify outcomes within 28 days of a laboratory confirmed SARS-CoV-2 infection in unvaccinated SOT recipients and those who had received 2 doses of Pfizer-BioNTech BNT162b2 or Oxford-AstraZeneca ChAdOx1-S vaccine [34]. Vaccination was not associated with reduction

of the risk of testing positive (incidence risk ratio [IRR] 1.29, 95% CI 1.03-1.61), the incidence rate of SARS-CoV-2 infection was 34.4 and 39.2 per 100,000 person-days for unvaccinated and vaccinated SOT recipients respectively. However, vaccinated patients showed a higher chance of survival at 28 days as compared with unvaccinated patients (91.8% vs. 88.8%, $p = 0.002$); after risk adjustment (for type of organ received, time since transplant, sex, age, ethnicity, NHS region, calendar month and, in some analyses, vaccine type), vaccinated patients showed a 20% reduction in the risk of death (HR 0.80, 95% CI 0.63-1.00, $p = 0.05$). Older age, Black ethnicity, lung transplantation, and care location were associated with a higher risk of death.

A cohort study of 449 SOT patients vaccinated with one of the two approved mRNA vaccines at the moment of study (BNT162b2 and mRNA-1273), observed severe course of COVID-19 was common in a small number of SOT recipients (n=15) who tested positive for COVID-19 even after their full vaccination (two doses of mRNA vaccine at the moment of the study) [35]. Fifteen patients (3.3%) tested positive using SARS-CoV-2 PCR, with negative antibody titers in 9 (60%) of them. Seven patients had mild COVID-19, but the remaining 8 (53.3%) required hospitalization, 7 of which had severe disease and 2 of them died. These findings were confirmed in a review of 18,215 fully vaccinated SOT recipients at 17 transplant centers [36], in which there were 151 breakthrough infections (0.83%) defined per Centers of Disease Control and Prevention criteria ≥ 14 days after completing all recommended vaccine doses. Of these 151 cases of breakthrough infections, 87 (57.6%) required hospitalization and 14 patients died, with a mortality rate of 9.3%. Compared with the general population of 101 million fully vaccinated adults in the United States through April 30, 2021, SOT recipients in this study had 82-fold higher risk of breakthrough SARS-CoV-2 infection and 485-fold higher risks of breakthrough infection with associated hospitalization and death.

In kidney transplant recipients, an observational cohort study linking national datasets in Scotland reported that as of September 19, 2021, 5,281 had received two doses of approved SARS-CoV-2 vaccine [37]. There were 814 (15.4%) cases of SARS-CoV-2 infection. Vaccine effectiveness rates were 39% (95% CI 2-58) against infection and 40% (95% CI 0-59) against hospitalization. Within 28 days of a SARS-CoV-2 positive PCR test, the mortality rate among kidney transplant recipients was 10% (compares to < 0.1% of the vaccinated general Scottish population admitted to the hospital or dying due to COVID-19 during the same period). In the multivariate analysis, predictors of breakthrough infection following two doses of SARS-CoV-2 vaccine were kidney transplant (vs. dialysis) and socioeconomic deprivation.

Naylor et al. conducted a population-based cohort study, including 12,842 SOT patients in Canada (kidney, liver, lung, heart and pancreas). Patients were included as for December 2020 and were followed-up until November 2021, as the vaccine program were developed in this population. 54.1% received three doses, with 12.7% who remain unvaccinated. Vaccine effectiveness against severe outcomes (hospitalization or mortality) was shown, again, to be lower in this population vs general population, for both two (54%) and three (67%) doses. However, it was notably improved with the third administration [38].

Take home message

- **The level of protection provided by vaccination from symptomatic SARS-CoV-2 disease in SOT recipients is lower than in the general population.**
- **A primary vaccine course of two doses appears to have a limited effect on COVID-19 and its complications, including hospitalization and fatal outcome.**
- **A third dose notably improves vaccine effectiveness in SOT patients.**
- **Alternative immunization schemes (booster dose, higher doses) and modulation of immunosuppression during vaccination need to be more extensively assessed in SOT recipients.**

4. EFFECT OF TREATMENT WITH MONOCLONAL ANTIBODIES ON THE COURSE OF COVID-19 IN SOT RECIPIENTS

SOT recipients are candidates for the use of anti-spike SARS-CoV-2 monoclonal antibodies (mAbs) for early treatment or prevention of COVID-19 because of special characteristics of this population, particularly chronic use of immunosuppression treatment, multiple underlying medical comorbidities, suboptimal immunogenic response to complete vaccination scheme, and, occasionally, the age of the transplant patient. For all these main reasons, SOT recipients are at higher risk of developing severe COVID-19 with the potential need of care in the hospital including ICU admission, and ultimately to die from the disease. Neutralizing antibodies targeting the spike protein of SARS-CoV-2, such as bamlanivimab-etesevimab, casirivimab-imdevimab, tixagevimab-cilgavimab or sotrovimab have been approved for the treatment of mild-to-moderate COVID-19 in non-hospitalized patients with laboratory-confirmed SARS-CoV-2 infection, who are at high risk of progression or severe disease and/or hospitalization. It is recommended that treatment should be started as soon as possible after a positive test and within 10 days of symptom onset. Also, some mAbs can be used for post-exposure prophylaxis (PEP) (casirivimab-imdevimab) or pre-exposure prophylaxis (PreP) (casirivimab-imdevimab and tixagevimab-cilgavimab).

A number of clinical reviews of the general implications of mAbs against SARS-CoV-2 have been recently published (figure 2) [47-58]. In the particular group of SOT recipients, the use of mAbs, recommended in the outpatient management of mild-moderate COVID-19, has been associated with a lower risk of hospitalizations, emergency department (ED) visits, need for ICU care, mechanical ventilation, and fatal outcomes. Similar benefits have been reported for PEP, treatment of SOT patients with recurrent episodes of COVID-19 and possible

vaccine-breakthrough infection [46]. Studies of mAbs in SOT recipients collected from the literature were divided according to the type of mAbs used: bamlanivimab and casirivimab-imdevimab [47-51], patients were include from March 2020 to September 2021, when the prevalent VOCs and VOIs were those before Omicron (mainly Alpha, Beta Gamma, Epsilon and Delta), and sotrovimab, including patients from September 2021 to August 2022, when the prevalent VOCs were Delta and Omicron BA.1 and BA.2 [52-58]. Most data referred to retrospective case series reports of relatively small study populations.

4.1. Bamlanivimab and casirivimab-imdevimab

Several studies have evaluated bamlanivimab and casirivimab-imdevimab as emergency use in SOT recipients. In a retrospective review from the Mayo Clinic of 73 SOT patients treated with mAbs, between November 2020 and January 2021, most commonly with bamlanivimab monotherapy (75.3%) and completing the full 28-day follow-up period, the rates of ED consultation and hospitalization were 15.1% (63.6% for respiratory symptoms) and 12.3%, respectively [47]. There was one ICU admission not related to COVID-19, no deaths, or advanced respiratory support, and minimal adverse events were reported. Notably, in patients who were hospitalized, mAb administration was later than in those who did not require hospitalization (median 6 days from symptom onset vs 4 days, p=0.03), reinforcing the importance of early intervention with these treatments. The same group of authors also reported data of 28 SOT recipients who presented mild-to-moderate COVID-19 after full vaccination (defined as two doses of mRNA vaccine; except one patient who underwent vaccination with Johnson & Johnson and 4 patients who received a third dose), all patients received casirivimab-imdevimab, with a median time of infusion of 3 days after symptoms onset. ED visits were reported by 4 patients (14.3%) and only 1 patient (3.6%) required hospital admission. No ICU admission or deaths were reported [48].

These results are similar to those obtained in another single-center retrospective analysis of 165 SOT recipients with no records of covid vaccination, 93 of which received mAbs (76.3% bamlanivimab and 22% casirivimab-imdevimab) and 72 did not (comparator cohort) [49]. The 30-day hospitalization rate was 8.7% in the study cohort vs. 15.3% in the comparator cohort, but differences after adjusting for age did not reach statistical significance (OR 0.49, 95% CI 0.18-1.32, $p = 0.16$). None of the patients that received casirivimab-imdevimab were hospitalized but all patients hospitalized in the mAbs group had received bamlanivimab monotherapy. Two episodes of biopsy-proven acute rejection were observed in the mAbs group, but it was unknown whether they could be attributed to mAbs therapy, COVID-19, or immunosuppression adjustments. There were 2 deaths in the comparator cohort and none in the mAbs-treated cohort.

In a single center retrospective review of abdominal transplant patients between February 2020 and February 2021, anti-SARS-CoV-2 mAbs therapy (33/34 received bamlanivimab) was provided to 17 kidney transplant recipients and 17 liver transplant recipients. Only 5 patients required hospitalization, none required ICU admission, and all 34 patients survived [50]. In a comparison of outcomes of abdominal transplant recipients who would have been qualified for mAbs therapy but did not receive the treatment, mAbs reduced the rates of hospitalization from 32% to 15% ($p = 0.045$) and death from 13% to 0% ($p < 0.04$). There were no major adverse reactions [50].

In a single-center analysis of 95 kidney transplant recipients diagnosed with COVID-19 from March 2020 to April 2021, 20 (21%) of which were treated with mAbs (15 bamlanivimab, 1 bamlanivimab-etesevimab, 3 casirivimab-imdevimab and 1 mAb treatment not known). The primary endpoints were hospitalization or ED visits [51]. Antiviral treatment with mAbs was associated with a marked decrease in hospitalization or ED visits (15% vs. 76%, $p < 0.001$; HR 0.216, $p = 0.04$ after adjustment for potential confounders and time-dependent symptom variable). In the multivariate analysis, age, chronic kidney disease, and Hispanic ethnicity were independent factors for hospitalization or ED visits. There were no deaths in the 20 patients treated with mAb whereas there were 8 (10.7%) in the 75 not treated with mAbs.

4.2 Sotrovimab

Several groups have reported their experiences regarding the use of sotrovimab in SOT recipients. In a report of 51 SOT patients who received sotrovimab (during both the Delta- and Omicron-predominant periods), 1 patient experienced progression of COVID-19 symptoms and required 5-days hospitalization. None of the patients required ICU care or died [52]. In this study, patients received sotrovimab on an average of 3.5 days after the onset of symptoms and 2 days after laboratory confirmation of SARS-CoV-2 positivity. 35% of patients in this study were vaccinated with 3 doses, and 45% had an incomplete vaccination regimen (less than 3 doses) with the remained 10% unvaccinated. In another single-center study [53] based on 15 SOT recipients diagnosed with SARS-CoV-2 infection between December 2021 and January 2022 and with a mild to moderate disease, 13 (86.7%) of which had received two or three doses of mRNA COVID-19 vaccines, 2 patients (13.3%) required hospitalization because of rapidly progressive respiratory distress symptoms requiring oxygen therapy. There were no deaths. Sotrovimab infusion was well-tolerated with no reported adverse events. In another single-center prospective cohort study of 300 SOT patients infected with SARS-CoV-2 (51 treated with sotrovimab, of which 80% were vaccinated), it was observed that vaccination ≥3 doses and treatment with sotrovimab are independently protective factors in the progression to severe COVID-19 disease. Regarding sotrovimab treatment, the number needed to treat (NNT) to prevent a patient from requiring supplemental oxygen was 6.64 (95% CI, 4.56 to 13.66), and to prevent one hospitalization was 8.5 (95% CI, 4.83 to 59.1). Once again, there were no deaths in the group of patients treated with sotrovimab [54].

In kidney transplant recipients, a comparison of the clinical outcome of 25 patients with mild-to-moderate Omicron

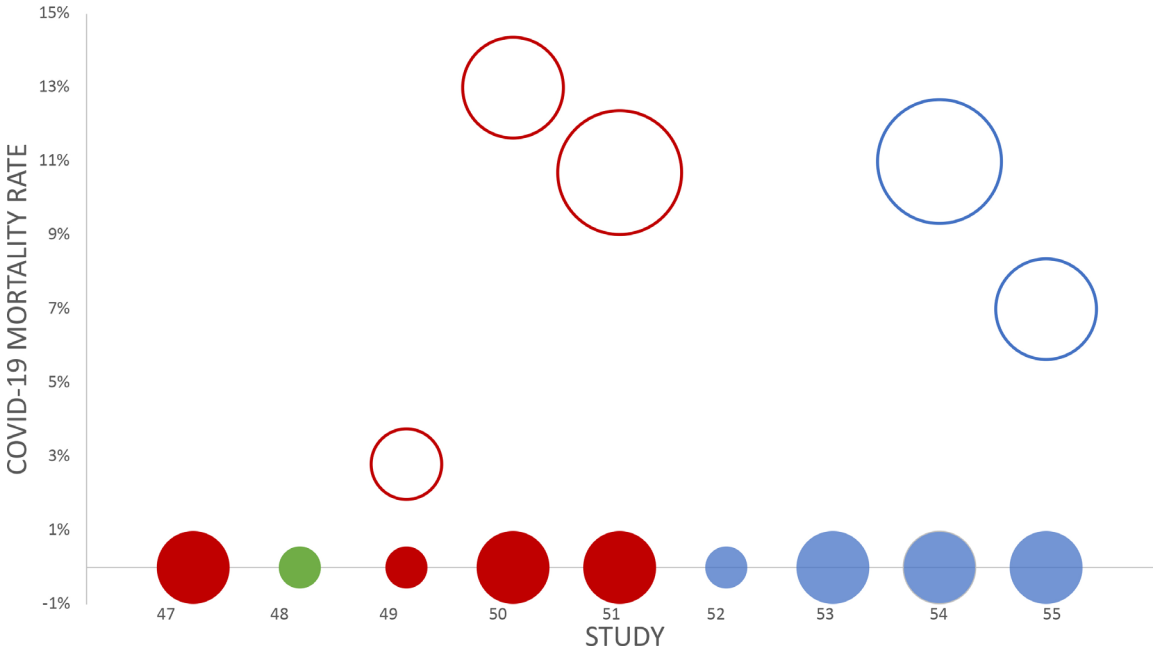

Figure 2 | **COVID-19 progression rates in each study based on treatment or not with mAb**

Colors indicate mAb used for treatment, red: bamlanivimab or casirivimab+imdevimab; green: casirivimab + imdevimab; blue: sotrovimab. Solid fill: mAb treatment (treated group); not solid fill: not mAb treatment (control group). Circles size: hospitalization rate, bigger the circle, higher hospitalization rate:

The numbers of the studies correspond to the reference included in the bibliography section. The patients included in the different studies present different vaccination status. In addition, the outcomes were collected at different dates from the treatment administration, the majority at one-month post-treatment, however, in some studies it is not specified. Three of the publications included in the sotrovimab treatment block have not been included in this graph, one of them is Villanego F, et al. Clin Kidney J. 2022;15(10):1847-55 [56], which at the beginning of the study, 81.7% of the patients were hospitalized, so progression is measured as COVID-19 mortality, being 8.5%. Furthermore, 42% had an oxygen saturation < 95% at admission, and 43,9% of patients were administered >5 days from symptom onset, representing a more severe population and suboptimal administration. Differences were observed between patients treated ≤5 days from the onset of symptoms and those treated >5 days (2.2% vs 16.7%; p=0.020 mortality). The second one, Vathsala A, et al. Transpl Infect Dis. 2022:e13930 [57], where hospitalization is not determined; COVID-19 progression is determined by the need for supplemental oxygen (21.6%; <4 days 14.3% vs ≥4 days 55.6%; p=0.015) and mortality (9.8%). The third publication not included is Negin Farhadian, et al. Immunopharmacol Immunotoxicol. 2022;1-7 [58], since it is a meta-analysis where several publications are included, indicating that sotrovimab treatment reduces the risk of hospitalization (OR 0.29, p<0.001), ICU admission (OR 0.17, p = 0.009) and death (OR 0.15, p=0.010) compared to the control group without mAb treatment.

COVID-19 who received sotrovimab with 100 patients who did not receive sotrovimab showed a reduced rate of hospitalization (4 patients, 16% vs. 35 patients, 35%) and ICU admission (1 patients, 4% vs. 17 patients, 17%), and no patient died as compared to 11% in non-sotrovimab-treated patients. The Kaplan-Meier analysis showed significant differences in mortality (p = 0.044) and severity (measured as mortality and/or ICU admission) of Omicron COVID-19 disease (p = 0.045) between kidney transplant recipients treated or not treated with sotrovimab [55]. Notably, median time from symptoms onset and sotrovimab administration were 5 days, however the 1 patient who suffered COVID-19 progression was administered after 11 days. Overall, 92% of patients had received at least one dose of mRNA vaccine, with 76% and 86% vaccinated with three or four doses in the sotrovimab and control group respectively.

In a Spanish multicenter retrospective cohort study [56], a total of 82 kidney transplant recipients with SARS-CoV-2 Omicron BA.1 infection were treated with sotrovimab, of which was administered early (≤ 5 days from the onset of symptoms) in 46 patients (56.1%). Overall, more than 86.8% of patients had received three doses of vaccine before their COVID-19 diagnosis and 42.6% had an oxygen saturation < 95% at admission. Early treatment was associated with a reduced risk of progression to severe disease with need of mechanical ventilation (2.2% vs. 36.1%, p < 0.001), ICU admission (2.2% vs. 25%,

p = 0.002), and mortality due to COVID-19 (2.2% vs. 16.7%, p = 0.02). In the multivariate analysis, early use of sotrovimab was the only protective risk factor (OR 0.026) for a composite outcome defined as the need for ventilatory support or ICU care or COVID-19-related mortality. There was a good safety profile, even in patients with multiple comorbidities or advanced chronic kidney disease stage.

In another retrospective study of 51 SARS-CoV-2-infected (49% Delta and 51% Omicron BA.1 variants) kidney transplant recipients treated with sotrovimab, 11 (21.6%) progressed to severe COVID-19 disease and 5 (9.8%) patients died. Those who had earlier administration of sotrovimab were less likely to have more severe disease (14.3% of patients administered sotrovimab at < 4 days after symptom onset needed supplemental oxygen therapy vs. 55.6% among those treated at ≥ 4 days [p = 0.015]) [57].

Finally, in a meta-analysis of 6 cohort studies which reports the clinical outcomes of SOT patients treated with sotrovimab vs a control group between January 2021 and August 2022, it was shown that treated patients had a lower frequency of COVID-19 disease progression (Figure 2). Sotrovimab treatment was shown to reduce the risk of hospitalization (OR 0.29, p < 0.001), ICU admission (OR 0.17, p = 0.009) and death (OR 0.15, p = 0.010) compared to the control group without mAb treatment [58].

Take home message:

- **Treatment with the anti-spike available mAbs formulations provides favorable outcomes in SOT recipients at high risk for severe COVID-19 disease.**
- **SOT recipients with SARS-CoV-2 infection treated with mAbs as compared with untreated comparator groups had lower rates of hospitalization, ICU admissions, progression to severe disease, and death.**
- **Early administration (≤ 4-5 days of symptom onset) seems to improve benefits of mAbs treatment.**
- **Treatment with mAbs is safe with a few adverse events generally mild, and no effect on graft losses or rejection.**

CONCLUDING REMARKS

The available evidence based on relevant studies published in the literature reinforces the importance of an early diagnosis of COVID-19 in SOT recipients and completion of a fully anti-SARS-CoV-2 vaccination schedule. Despite a lower rate of humoral and cellular immune response, compared to general population. All studies reviewed, find that repeated doses of vaccination increase the humoral response up to 70 - 80% of transplant patients with detectable antibodies after 3 doses. The third dose seems to be key for this population, with remarkable rates of seroconversion after its administration. However, despite vaccination, a considerable percentage of this group remains at high risk and should be treated soon after COVID-19 diagnosis. Among current available therapeutic options, mAbs have been shown to be both effective and safe in this population. Treatment of COVID-19 with mAbs in SOT recipients, in particular early treatment after diagnosis, is associated with a reduced likelihood of progression to severe COVID-19. Reduction of the risk of severe disease entails decreases in hospitalization, ICU care, ventilatory support, ED visits, mortality, and, very especially to take into account in this immunosuppressed population, the reduction or avoidance of the risk of opportunistic infections by multiresistant hospital bacteria and by fungi that cause invasive fungal infection (CAPA, CAM) with high intrinsic mortality promoted by SARS-CoV-2.

Although neutralizing capacity of some mAbs have been reported to be reduced against new circulating variants, it is not known, how in vitro neutralization data correlates with clinical efficacy. This is specially noting in the case of sotrovimab, a mAb that has a double mechanism of action, not only neutralizing but also with effector function that is mediated by the Fc region of the mAb [59]. This effector function has been shown, in animal models, to be an additional protection mechanism beyond virus neutralization, being critical for the maintenance of its activity against SARS-CoV-2 variants that reduced its neutralizing activity such us BA.2 [60-66]. Several recent studies in real practice, have shown the same effectiveness data of the antibody against Omicron BA.2 vs BA.1, being BA.1 a variant against which sotrovimab neutralization capacity is not impacted [60, 61]. In addition, some preprints have been published showing maintained clinical efficacy for BA.5 also [62]. Same kind of not peer reviewed works, have reported that effector function is maintained for other variants with higher fold changes such us BQ.1.1 [63], and that sotrovimab is able to reduce viral load in animal models for this variant [63,64]. Although more evidence and continuous surveillance is needed, to monitor a potential impact in the effectiveness of these therapeutic mAbs, they are an important therapeutic option, especially in SOT patients, who can be excluded from other therapeutic options because of interactions with concomitant medications.

Findings of the present review are timely and informative to the transplant community. The ability to draw firm conclusions is limited by the retrospective nature of data collection, the absence of a control group and the limited number of participants in most studies. It is difficult to use this data to estimate comparative effectiveness of mAbs therapies in SOT recipients exposed to or infected with SARS-CoV-2 and at high risk of developing severe COVID-19, however the weight of evidence is in favor of a benefit of mAb treatment. It is necessary to continue to explore the best approach in preventing severe COVID-19 in this vulnerable SOT patient population in the context of limited immunogenicity of vaccines and possible surge of COVID-19 infections.

Successful utilization of anti-SARS-CoV-2 mAbs requires a multidisciplinary team approach, close monitoring for efficacy and tolerability, and awareness of circulating variants.

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CONFLICTS OF INTEREST

F.J. Candel has presented conferences in meetings sponsored by GSK, MSD, Pfizer, Correvio, Astellas, Gilead, Meiji and Shionogi; M. Salavert has presented conferences in meetings sponsored by Angelini, Gilead, GSK, MSD, Menarini, Pfizer, Tedec-Meiji and Shionogi; D. Lorite Mingot, M. Manzano Crespo, P. Pérez Portero and R. Cuervo Pinto are employees of GSK, and hold shares in the company.

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Manejo de la pandemia de COVID-19 en hospitalización domiciliaria en dos hospitales comarcales españoles: qué significó, quiénes atendimos, quién falleció y como evolucionó la asistencia a lo largo del tiempo

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RESUMEN

Introducción. La Hospitalización a Domicilio (HAD) es una modalidad de ingreso alternativa que puede resultar de gran utilidad en momentos de estrés sanitario como la pandemia de COVID-19. En el presente trabajo se recoge el manejo de los pacientes ingresados con COVID-19 en HAD en dos hospitales comarcales españoles durante dos años.

Métodos. Se realizó un estudio descriptivo, observacional y retrospectivo de los pacientes ingresados en HAD con COVID-19. Posteriormente se realizó un análisis para caracterizar a los pacientes que fallecieron en HAD o a 30 días del alta y otro para comparar el manejo entre la primera fase del estudio (2020) y la segunda (2021 y parte de 2022).

Resultados. Se reclutaron 167 pacientes. Un 52,1% se trasladaron para vigilar que continuaban mejorando frente a un 40,7% en los que se hizo para vigilar que no empeoraran. Los pacientes que fallecieron en HAD resultaron más ancianos (87,5 años de media), más comórbidos y con mayor probabilidad de ser no reanimables en caso de paro cardiaco (No RCP) (85%). En la segunda fase del estudio se ingresaron pacientes más ancianos, más comórbidos y en mayor grado No RCP que los ingresados en 2020.

Conclusiones. La HAD es un recurso útil para aumentar la resiliencia de los sistemas sanitarios en casos de estrés como supuso la enfermedad por COVID-19. El desarrollo y crecimiento de las unidades ya existentes, así como la creación de otras nuevas allá donde no existan, puede ser una herramienta básica para la medicina del futuro.

Palabras clave: Hospitalización a Domicilio; COVID-19; Coronavirus; Mortalidad; Epidemia; Pandemia.

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Management of COVID-19 pandemic in hospital at home in two regional Spanish hospitals. what it meant, who we cared for, who died and how assistance has evolved over time

ABSTRACT

Introduction. Home Hospitalization (HH) is an alternative hospitalization modality that can be very useful in times of health stress such as the COVID-19 pandemic. This paper includes the management of patients admitted with COVID-19 in HH in two county spanish hospitals for two years.

Methods. A descriptive, observational and retrospective study of all patients admitted at HH with a diagnosis of COVID-19 disease was carried out. Subsequently, further analysis was carried out to characterize the patients who died in HH or 30 days after discharge and another to compare the management between the first phase of the study (2020) and the second one (2021 and part of 2022).

Results. A total of 167 patients were recruited. A 52.1% moved to watch that the recovery continued compared to 40.7% in which it was done to watch that they did not worsen. The patients who died in HAD were older (mean 87.5 years), more comorbid and more likely to have do-not resucitate orders (DNR) in case of cardiac arrest (85%). In the second phase of the study, older patients, more comorbid patients and with a greater degree of DNR orders were admitted than those admitted throughout 2020.

Conclusions. HAD is a useful resource to increase the resilience of health systems in cases of stress such as the disease caused by COVID-19. The development and growth of existing units, as well as the creation of new ones where they do not exist, could be a basic tool for the medicine of the future.

Keywords: Home Care Services, Hospital-Based; COVID-19; Coronavirus; Mortality; Epidemics; Pandemics.

INTRODUCCIÓN

La Hospitalización a Domicilio (HAD) se ha definido como una modalidad de ingreso alternativa a la hospitalización convencional que puede producir similares o mejores resultados en cuanto a mortalidad, reingreso o estancia [1]. Su utilidad para reducir el consumo de los recursos del hospital ha sido demostrada también en episodios de epidemia de gripe [2]. En 2020, la pandemia de COVID-19 fue un «cisne negro» que puso a prueba los sistemas sanitarios mundiales, haciéndose necesario conocer si la HAD pudo ser o será en el futuro un elemento decisivo a la hora de afrontar tales retos.

Hasta la fecha, y pese a la enorme bibliografía existente sobre la COVID-19, son pocos los trabajos que analizaron su manejo en régimen de HAD. Al inicio de la pandemia ya se vio que la HAD también podía tener utilidad y ser segura a la hora de tratar la COVID-19 [3,4]. Aunque fueron series pequeñas y preliminares se pudo elaborar el primer documento de consenso [5]. Otros estudios posteriores intentaron dirimir los factores de riesgo asociados a reingreso y la verdadera magnitud de la descarga hospitalaria que produjo [6-8].

Sin embargo, la mayoría de los trabajos analizaron solo el manejo de la HAD en etapas incipientes de la pandemia y, sobre todo, como factor de reducción de ingresos. Pese a la enorme potencialidad de la HAD para hacer más resilientes los sistemas sanitarios durante momentos de estrés como la pandemia de COVID-19 [9], todavía se hace necesario aumentar el conocimiento de lo que supuso la HAD durante la pandemia.

En el presente trabajo exponemos los datos del manejo real de la HAD en dos hospitales comarcales que dan cobertura a la zona sur de Navarra durante un periodo que comprende tanto épocas de estrés como otras de menor presión asistencial (desde marzo de 2020 hasta marzo de 2022). Se registraron todos los pacientes atendidos en HAD con diagnóstico de COVID-19. Los objetivos del mismo son detallar qué tipo de pacientes se atendieron, cuáles fueron los resultados y qué modelos mentales de toma de decisiones llevaron a cabo los facultativos en dicho contexto.

PACIENTES Y MÉTODOS

Incluímos todos los casos mayores de 18 años con diagnóstico de presunción de COVID-19, infección por coronavirus o SARS-COV-2 ingresados en régimen de HAD entre marzo de 2020 y marzo de 2022. Excluimos aquellos pacientes en los que, finalmente, e independientemente de las pruebas, el médico clínico decidió que no tenían infección por coronavirus. Los criterios de ingreso en HAD fueron los mismos que se empleaban en la práctica clínica habitual para otras enfermedades. Los casos se reclutaron del Hospital Reina Sofía de Tudela (HRS) y del Hospital García Orcoyen de Estella (HGO), ambas poblaciones sitas en Navarra.

Registramos variables demográficas, clínicas, de comorbilidades, de procedencia de ingreso (desde urgencias, desde planta de hospitalización o directamente en el domicilio), motivo de ingreso en el hospital, motivo de traslado a HAD y estado en ese momento, de uso de oxigenoterapia, de indicación de No Reanimación cardiopulmonar en caso de paro cardíaco (No RCP) o Limitación del Esfuerzo Terapéutico (LET) y de resultados (estancia, mortalidad durante el ingreso, reingreso en el hospital desde HAD y mortalidad o reingreso a los 30 días del alta; todo ello para causa relacionada o no con la COVID-19). Las variables de mejoría antes del traslado se dieron como afirmativas si quedaba reflejado o implícito en la historia clínica o los registros informáticos que durante la estancia en planta se dio mejoría clínica, gasométrica (pO2 o SaO2), radiológica (radiografías sucesivas) o de laboratorio (descenso de reactantes); y negativa si hubo empeoramiento o, simplemente, no pudo objetivarse mejoría (el paciente se trasladó en un estado similar al ingreso, el paciente fue directamente a domiciliaria sin pasar un solo día en el hospital o no se pidieron pruebas de control antes de trasladarlo a HAD). Rellenamos las variables de No RCP o LET gracias a la interpretación de la lectura comprensiva de la historia y curso evolutivo de cada paciente, dejando como datos perdidos aquellos en los que no fue sencillo determinarlo. Para las variables de motivo de traslado a HAD en cada paciente pudo darse más de una. La recopilación de datos se realizó por varios investigadores médicos a través de la lectura de historias clínicas y registros informáticos.

Realizamos un estudio descriptivo, observacional y retrospectivo. Posteriormente llevamos a cabo dos análisis adicionales de interés científico. En primer lugar, comparamos las características de los casos que habían fallecido durante el ingreso en HAD o a los 30 días del alta de HAD frente a los que no, en aras de intentar objetivar qué tipo de paciente de HAD ha fallecido en este periodo de estudio. En segundo lugar, realizamos un estudio comparativo entre la primera fase de la pandemia respecto a la segunda, tomando como punto de corte el 1/1/2021. Se decidió esta fecha en particular por ser considerada por los autores como un punto de inflexión en la pandemia por tres motivos: la superación de la primera y segunda olas, el inicio de la vacunación en diciembre de 2020 y la posibilidad de asumir que la información clínica y la experiencia de los facultativos a la hora de tratar la COVID-19 resultaron significativamente superiores a lo largo de 2021. Para este último análisis excluimos al HGO por existir datos perdidos.

Para el análisis descriptivo usamos porcentajes, medias y cuartiles. Para el contraste de hipótesis se utilizamos Chi cuadrado para las variables cualitativas y T de student para las variables normales cuantitativas. Empleamos el programa estadístico SPSS© versión 15. Se obtuvo autorización del Comité Ético de Navarra.

RESULTADOS

Características de los pacientes y del curso en hospitalización convencional. Se reclutaron 167 pacientes. El HRS aportó el 85,6% de la muestra. Ambos hospitales se consideran comarcales y atienden un área rural de similares características. La comorbilidad más frecuente fue la demencia (35,9%) y

Tabla 1 **Características generales de los pacientes.**

Variable	Valor
Hospital; HRS n (%)	143 (85,6)
Sexo mujer; n (%)	80 (47,9)
Edad; media (p25/p50/p75)	75,5 (63/81/88)
HAD fuera de su domicilio habitual; n (%)	8 (4,8)
Índice de Charlson; media (p25/p50/p75) (n=165)	4,5 (0/5/7)
Demencia; n (%)	60 (35,9)
Insuficiencia cardíaca; n (%)	46 (27,5)
Diabetes; n (%)	40 (24)
Institucionalizados; n (%)	57 (34,1)
Ingresa en el hospital por NAC COVID; n (%)	100 (59,9)
Ingresa en el hospital por causa respiratoria asociada a COVID; n (%)	135 (80,8)
Otras causas de ingreso hospitalario	
NAC bacteriana; n (%)	24 (14,4)
Otras infecciones; n (%)	21 (12,6)
Fiebre; n (%)	15 (9)
Cardiológica; n (%)	14 (8,4)
Fracaso renal agudo; n (%)	12 (7,2)
Digestivas; n (%)	11 (6,6)
ETEV; n (%)	5 (3)
COVID nosocomial; n (%)	10 (6)
COVID fue un hallazgo casual; n (%)	22 (13,2)
Ingreso en UCI; n (%)	1 (0,6)
Desaislado durante la estancia; n (%)	5 (3)
Estancia en el hospital; media (p25/p50/p75) (n=109)	5,4 (2/5/8)
Estancia en HAD; media (p25/p50/p75) (n=137) *	7,1 (4,5/6/8)
Pacientes no RCP e indicación de LET**	
Paciente claramente no RCP desde el principio; n (%) (n=159)	74 (46,5)
Paciente en el que se indica LET desde el principio; n (%) (n=166)	24 (14,5)
Paciente en el que se indica LET en algún momento del curso evolutivo; n (%)	17 (10,2)
Paciente en el que se indica LET desde el principio o en algún momento del curso evolutivo; n (%)	39 (23,4)

Salvo que se especifique con contrario la n será de 167 pacientes. Siglas: HRS, Hospital Reina Sofía; p25/p50/p75, percentiles 25, 50 y 75; HAD, Hospitalización a Domicilio; NAC, Neumonía Adquirida en la Comunidad; ETEV, Enfermedad Tromboembólica Venosa; UCI, Unidad de Cuidados Intensivos; RCP, Reanimación Cardiopulmonar; LET, Limitación del Esfuerzo Terapéutico. *Para el cálculo se excluyen exitus durante su estancia en el hospital. ** Se excluyen los casos en los que fue difícil precisar o responder a dicha pregunta.

un 46,5% de los pacientes fueron claramente No RCP desde el principio del ingreso. La estancia media en el hospital fue de 5,4 días, siendo de 7,1 en HAD. Respecto al uso de oxígeno, un 65,9% de los pacientes precisaron oxigenoterapia en HAD, la mayoría de ellos con flujos bajos. En las Tablas 1 y 2 se recoge información más detallada.

Manejo en HAD. La mayoría de traslados se hicieron por patología respiratoria por COVID-19 (77,2%) con un tiempo medio de 10 días desde el inicio de los síntomas. Objetivar algún tipo de mejoría no fue necesario para los clínicos en un 41,3% de los casos. Un 52,1% de los pacientes se trasladaron para vigilar que continuaba la recuperación frente a un 40,7%

Tabla 2 **Uso de oxigenoterapia**

Variable						
OCD previa; n (%)				Valor		
Precisó oxígeno en HAD; n (%)				16 (9,6)		
Precisó prescripción de oxígeno al alta; n (%) (n=137)*				110 (65,9)		
Días con oxigenoterapia durante el ingreso (hospital y HAD); media (p25/p50/p75) (n=117)				38 (27,7)		
				10,4 (6/10/14)		
Necesidad de oxigenoterapia (litros por minuto)	Basal	<2	2 a 5	5 a 10	10 a 15	OAF
Flujo máximo de oxígeno administrado en el hospital; n (%)(n=128)	36 (28,1)	40 (31,3)	33 (25,8)	10 (7,8)	8 (3,3)	1 (0,8)
Flujo de oxígeno necesario al traslado a HAD; n (%)	86 (51,5)	44 (26,3)	29 (17,4)	6 (3,6)	1 (0,6)	0
Flujo máximo de oxígeno administrado en HAD; n (%) (n=156)	47 (29,9)	67 (43)	34 (21,8)	5 (3,2)	3 (1,9)	0

Salvo que se especifique con contrario la n será de 167 pacientes. OCD, Oxigenoterapia Crónica Domiciliaria; HAD, Hospitalización a Domicilio; p25/p50/p75, percentiles 25, 50 y 75. OAF, Oxígeno a Alto Flujo.

***Se excluyeron pacientes fallecidos o reingreso al hospital.**

en los que se hizo para vigilar que no empeoraran. El 10,2% de los casos tuvieron que reingresar en el hospital. La mayoría de reingresos y exitus hospitalarios fueron producidos por la COVID-19 (Tabla 3).

Características del paciente diagnosticado de COVID-19 que falleció en HAD. El paciente fallecido en HAD tuvo más edad, comorbilidades, demencia y probabilidad de estar institucionalizado que el que sobrevivió. Asimismo, tuvo más estancia en el hospital, sin existir diferencias en cuanto a la estancia en HAD; y fue menos probable objetivar en él algún tipo de mejoría antes del traslado. La probabilidad de ser No RCP o iniciar LET desde el principio o durante el curso fue mucho mayor en los pacientes fallecidos (Tabla 4).

Comparativa entre fases de la epidemia. Para el análisis solo se incluyeron los casos de HRS. Los pacientes diagnosticados de COVID-19 e ingresados en régimen de HAD durante 2020 fueron más jóvenes, menos comórbidos, llevaban más días desde el inicio de los síntomas y fue más probable encontrar mejoría en ellos antes de trasladarlos a HAD respecto a los pacientes ingresados en 2021 y principios de 2022. Fue también mucho menos probable que se consideraran No RCP o se iniciaran medidas de LET al principio o durante el ingreso, sin que se encontraran diferencias en cuanto a la estancia hospitalaria o en HAD. Aunque hubo cierta tendencia a encontrar un mayor grado de mortalidad en los pacientes de 2021 y principios de 2022, esta no alcanzó significación estadística (Tabla 5).

DISCUSIÓN

En el presente trabajo encontramos datos muy reseñables sobre la práctica real de asistencia a los pacientes con COVID-19 en régimen de HAD durante un largo periodo de tiempo, objetivando que el prototipo de paciente fallecido fue de muy avanzada edad, muy comórbido y en la mayoría de los casos considerado No RCP o LET. La inercia de manejo en la segunda parte del periodo respecto a la primera, lo que traduciría un cambio de comportamiento a la hora de usar la HAD, sugiere que con el paso del tiempo la HAD se ha empleado más para pacientes de mayor edad, más comórbidos y en fases más tempranas de la enfermedad, muchas veces sin haber comprobado mejoría antes de cursar el ingreso en la misma. Esto implicaría que se ha optimizado su uso para los pacientes que realmente lo necesitaban, a diferencia del principio de la pandemia, cuando todavía no se tenía tanta experiencia sobre el manejo de la enfermedad.

En comparación con otros artículos similares, nuestro trabajo comprende un periodo mucho más largo que los demás. Los datos recogidos en dichos trabajos son muy heterogéneos aunque en algunos supuestos coinciden con los nuestros. En el trabajo de Lwin et al [3], muy precoz al inicio de la pandemia, con una edad media similar a la de nuestra muestra, 7 de los 23 los pacientes ingresados en HAD requirieron reingreso en el hospital y solo uno falleció. El uso de oxígeno fue exclusivamente hospitalario. En la serie de Pericàs et al [4], ya con 63 pacientes, solo uno recibió oxígeno en HAD. La edad media de la muestra fue 51 años, un 4,8% de los pacientes reingresaron y ninguno falleció, lo que contrasta con nuestros datos (edad media de 75,5 años, 10,2% de reingresos y 24% de mortalidad). En otra serie española de gran tamaño [8] se objetivó la gran capacidad de HAD para aumentar la resiliencia de los sistemas sanitarios. La muestra fue de 917 casos, los reingresos fueron un 6,2% y solo falleció una paciente, aunque, nuevamente, los criterios de admisión de ingresos seleccionaron pacientes más jóvenes y menos graves que los recogidos en nuestro trabajo. En otros estudios internacionales [10] se vio asimismo pacientes más jóvenes y con mejores resultados. Cabe reseñar también en este punto la utilidad de los hoteles y otros edificios que se medicalizaron durante la pandemia y que resultaron de utilidad para aliviar la presión hospitalaria.

Tabla 3 **Manejo en Hospitalización a Domicilio**

Variable	Valor
Ingreso directo desde urgencias; n (%)	7 (4,2)
Ingreso directo en el domicilio sin pasar por el hospital; n (%)	58 (34,7)
Ingreso desde planta de hospitalización; n (%)	102 (61,1)
Motivo de traslado asociado a problemas por COVID respiratorios; n (%)	129 (77,2)
Motivo de traslado asociado a problemas por COVID no respiratorios; n (%)	32 (19,2)
Ingreso para vigilar si hay empeoramiento en fases muy incipientes de la enfermedad o cuando no hay suficiente información del curso; n (%)	74 (44,3)
Antes del traslado se objetivó algún tipo de mejoría; n (%)	98 (58,7)
Clínica; n (%)	95 (56,9)
De laboratorio; n (%)	70 (41,9)
Gasométrica; n (%) (n=144)	36 (25)
Radiológica; n (%) (n=144)	36 (25)
Días desde síntomas hasta ingreso en HAD; media (p25/p50/p75) (n=148)	10 (5/10/13,7)
Días desde la positivización de la PCR hasta el ingreso en HAD; media (p25/p50/p75) (n=165)	8,3 (3/7/12)
Motivo de traslado a HAD (un paciente puede tener varios)	
Vigilancia por parte de un especialista de que continúa la recuperación; n (%)	87 (52,1)
Vigilancia estrecha por si hay empeoramiento relacionado con la NAC o SDRA estrictamente relacionados con el COVID; n (%)	68 (40,7)
Continuar tratamientos con posología o uso hospitalario no relacionados con el COVID, incluyendo TADE; n (%)	46 (27,6)
Continuar tratamientos con posología o uso hospitalario relacionados con el COVID; n (%)	38 (22,8)
Descompensación de comorbilidades; n (%)	21 (12,6)
Cuidados paliativos; n (%)	13 (7,8)
Sobreinfección o aparición de nuevas enfermedades infecciosas; n (%)	13 (7,8)
Necesidad de oxigenoterapia a altos flujos; n (%)	8 (4,8)
Tratamiento y control de la ETEV; n (%)	6 (3,6)
Otros; n (%)	5 (3)
Reingreso en el hospital desde HAD; n (%)	17 (10,2)
Relacionado con el COVID; n (%)	9 (52,9)
No relacionado con el COVID; n (%)	7 (41,2)
Petición del paciente o familiares; n (%)	1 (5,9)
Días hasta reingreso; media (P25/50/75)	4,4 (2/3/5,5)
Exitus en el hospital o en HAD; n (%)	31 (18,6)
Producido por COVID; n (%)	25 (80,6)
Días desde ingreso en HAD hasta exitus en el hospital o en HAD; media (p25/p50/p75)	9,3 (3/8/15)
Exitus a 30 días del alta; n (%) (n=135)	9 (6,7)
Producido por COVID; n (%)	5 (55,6)
Días desde alta hasta exitus a 30 días; media (P25/50/75)	13,25 (7,25/11,5/20,5)
Reingreso a 30 días del alta; n (%) (n=132)	10 (7,6)
Producido por COVID; n (%)	5 (50)
Días desde alta hasta reingreso; media (P25/50/75)	10,3 (2/10,5/14)

Salvo que se especifique con contrario, la n será de 167 pacientes. Siglas: HAD, Hospitalización a Domicilio; PCR, Reacción en Cadena de la Polimerasa; NAC, Neumonía Adquirida en la Comunidad; SDRS, Síndrome de Distrés Respiratorio del Adulto; TADE, Tratamiento Antibiótico Domiciliario Endovenoso; ETEV, Enfermedad Tromboembólica Venosa; p25/p50/p75, percentiles 25, 50 y 75.

Tabla 4 **Análisis de la mortalidad: Exitus durante el ingreso o a los 30 días del alta de HAD.**

	Fallecidos (n=40)	No fallecidos (n=127)	p
Edad; media (p25/p50/p75)	87,5 (83,8/88,5/92,0)	71,7 (61/76/86)	<0,001
Índice de Charlson; media (p25/p50/p75)	7,1 (6/7/8)	3,6 (0/4/6)	<0,001
Demencia; n (%)	29 (72,5)	31 (24,4)	<0,001
Institucionalizados; n (%)	28 (70)	29 (22,8)	<0,001
Días desde síntomas hasta ingreso en HAD; media (n=148) (p25/p50/p75)	6,9 (1/7/12)	11 (6/11/14)	0,007
Estancia en el hospital; media	8,3 (3/8/10,5)	5 (2/4/7)	0,017
Ingresa en el hospital por NAC COVID; n (%)	18 (45)	82 (64,6)	<0,028
Antes del traslado se objetivó mejoría; n (%)*	11 (27,5)	87 (68,5)	<0,001
Paciente claramente no RCP desde el principio; n (%) (n=159)	34 (85)	40 (31,5)	<0,001
Paciente en el que se indica LET desde el principio; n (%) (n=166)	14 (35)	10 (7,9)	<0,001
Paciente en el que se indica LET en algún momento del curso evolutivo; n (%)	16 (40)	1 (0,8)	<0,001
Paciente en el que se indica LET desde el principio o en algún momento del curso evolutivo; n (%)	28 (70)	11 (8,1)	<0,001

Ejemplo de lectura de tabla: la demencia se dio en 29 (72,5%) de los fallecidos respecto a 31 (24,4%) en los no fallecidos con una p <0,001. Salvo que se especifique con contrario la n será de 167 pacientes. p25/p50/p75, percentiles 25, 50 y 75; HAD, Hospitalización a Domicilio; NAC, Neumonía Adquirida en la Comunidad; RCP, Reanimación Cardiopulmonar; LET, Limitación del Esfuerzo Terapéutico; No hubo diferencias en cuanto a sexo, a si el COVID fue un hallazgo casual, si el COVID fue nosocomial, a la estancia en régimen de HAD o a los días desde positividad de la PCR hasta ingreso en HAD.

*** La significación estadística se dio para las cuatro variables de mejoría clínica (clínica, de laboratorio, gasométrica o radiológica).**

Nosotros tuvimos un 4,8% de la muestra en dicha situación (teniendo en cuenta que solo un pequeño porcentaje de nuestros pacientes derivados a los hoteles estaban cubiertos por un ingreso de HAD), pero existe también una serie española con 516 pacientes con dicho régimen de ingreso de los cuales solo un 5,4% reingresaron [11].

Sobre el manejo de la oxigenoterapia, con un 65,9% de prescripción durante el ingreso en HAD en nuestro trabajo destacamos haber hecho un amplio uso de la misma, muy superior al de las otras series publicadas [3,4,6,8].

Respecto al análisis de las características asociadas a los traslados a HAD, creemos haber aportado datos no recogidos en la bibliografía consultada y que son de gran utilidad para comprender lo que ha significado dicha modalidad de ingreso durante este periodo en nuestro medio. Resulta reseñable que solo se objetivó mejoría en un 58,7% de los casos antes del traslado, y que la mejoría gasométrica o radiológica solo fue necesaria un 25% de las ocasiones para los facultativos. No en vano, respecto a los dos principales motivos de traslado a HAD, frente a un 52,1% de los casos en los que se hizo para vigilar que continuaba la recuperación, en un 44,3% pareció hacerse sabiendo que el paciente podía empeorar pero prefiriendo tenerlo en HAD pese a ello respecto a la hospitalización convencional o al manejo ambulatorio (alta), lo que pudo tener gran importancia a la hora de aliviar la presión asistencial. En relación con las variables de reingreso y exitus durante la estancia o a 30 días, aunque son superiores a los de otras series, creemos que son unos resultados esperables asumiendo las características de la población atendida (edad avanzada, comorbilidad...). En el caso de la mortalidad, y enlazando con la Tabla 4, encontramos que los pacientes que fallecieron en HAD fueron aquellos de los que cabría esperar un exitus en caso de contraer la COVID-19, ya no solo por tener una media de edad y de Índice de Charlson de 87,5 años y 7,1 puntos, respectivamente, sino por el hecho también de que un 85% fueron claramente No RCP desde el inicio y en un 70% de los casos se indicó LET durante algún momento del curso evolutivo. Estos datos son, a nuestro parecer, novedosos y de gran relevancia, ya que este tipo de variables no suelen recogerse en los trabajos observacionales de cualquier enfermedad que estudian la mortalidad y, sin ellas, sería imposible evaluar adecuadamente «quién se está muriendo realmente» en cada supuesto. En este caso, por ejemplo, los datos parecen orientar a que los resultados adversos del ingreso en HAD (reingreso o mortalidad), estuvieron controlados o asumidos por las decisiones clínicas que se tomaron al respecto, primando, quizá, el confort personal y familiar o la salvaguarda del índice de ocupación hospitalario sobre otra serie de medidas que, según se interpreten, podrían considerarse desde fútiles hasta obstinación terapéutica.

Por último, en lo tocante a las diferencias entre ambos periodos (2020 o 2021 en adelante), creemos haber detectado las diferencias de manejo de la COVID-19 en régimen de HAD secundarias a los factores que fueron diferentes entre un momento y otro, a saber, el conocimiento recabado, la inmu-

Tabla 5 **Comparativa entre periodos, 2020 (1/3/20 – 31/12/20) frente 2021 y 2022 (1/1/21 – 31/3/22).**

Periodos de estudio	2020	2021 y 2022	p
Número de pacientes, n (%)	74 (51,7)	69 (48,3)	-
Edad; media (p25/p50/p75)	68,5 (53/67,5/86)	81 (75,5/86/90)	<0,001
Índice de Charlson; media (p25/p50/p75)	2,85 (0/0/6)	5,6 (4/6/8)	<0,001
Demencia; n (%)	11 (14,9)	31 (44,9)	<0,001
Institucionalizados; n (%)	11 (14,9)	25 (36,2)	0,003
Días desde síntomas hasta ingreso en HAD; media (n=148) (p25/p50/p75)	11,8 (9/12/14)	8,4 (1,5/6/12)	0,003
Ingresa en el hospital por NAC COVID; n (%)	58 (78,4)	37 (53,6)	0,002
Antes del traslado se objetivó mejoría; n (%)	55 (74,3)	37 (53,6)	0,01
Clínica; n (%)	55 (74,3)	34 (49,3)	0,002
De laboratorio; n (%)	40 (54,1)	24 (34,8)	0,021
Gasométrica; n (%) (n=122)*	30 (44,1)	2 (3,7)	<0,001
Radiológica; n (%) (n=122) *	25 (36,8)	8 (14,8)	0,007
Paciente claramente no RCP desde el principio; n (%) (n=143)	20 (27)	35 (50,7)	<0,001
Paciente en el que se indica LET en algún momento del curso evolutivo; n (%)	2 (2,7)	14 (20,7)	0,001
Paciente en el que se indica LET desde el principio o en algún momento del curso evolutivo; n (%)	5 (6,8)	14 (20,3)	0,017
Exitus en el hospital o en HAD; n (%)	8 (10,8)	14 (20,3)	0,116
Exitus a los 30 días del alta; n (%)	2 (3)	6 (10,9)	0,082

Salvo que se especifique con contrario la n será de 167 pacientes. p25/p50/p75, percentiles 25, 50 y 75; HAD, Hospitalización a Domicilio; NAC, Neumonía Adquirida en la Comunidad; RCP, Reanimación Cardiopulmonar; LET, Limitación del Esfuerzo Terapéutico. No hubo diferencias en cuanto a sexo, que el COVID fuera un hallazgo casual, COVID nosocomial, inicio de LET desde el principio, traslado a HAD con oxigenoterapia, reingreso al hospital desde HAD, reingreso a 30 días del alta, estancia hospitalaria o en HAD, días de oxigenoterapia o días hasta exitus extrahospitalario y reingreso.

***Se excluyeron los casos en los que las pruebas gasométricas o radiológicas no fueron relevantes para evaluar el curso de la enfermedad.**

nidad adquirida por la población (natural o tras la vacunación), la presión asistencial o la posible atenuación de la virulencia del virus. A este respecto, es necesario destacar que pese a que hubo una tendencia no significativa a encontrar mayor mortalidad en la segunda fase del periodo de estudio, también estos pacientes fueron más mayores, más comórbidos o tuvieron mayor indicación de No RCP o LET, todo esto último siendo estadísticamente significativo. La interpretación que hacemos de estos datos sería que durante 2020 la HAD se empleó para pacientes con menores probabilidades basales de fallecer, que estaban menos graves, llevaban más días de evolución o en los que se había constatado con mayor frecuencia mejoría clínica durante el periodo de hospitalización. Por el contrario, en el periodo de 2021 y principios de 2022 la HAD tuvo mayor utilidad para atender a pacientes más frágiles en los que poder indicar LET o asistencia al final de la vida. Al tratarse de un estudio observacional de todos los casos atendidos en el hospital HRS, creemos que en esta tabla se recoge con fidelidad cómo se adaptó la HAD a las necesidades del hospital en cada fase de la pandemia.

Nuestro trabajo tiene algunas limitaciones. Además de todas las asumibles a la naturaleza de los estudios observacionales, el hecho de haber incluido solo los datos de dos hospitales comarcales, perdiendo incluso los pacientes de uno de ellos para el análisis de la Tabla 5, no recoge los usos que se hayan podido hacer en otros lugares de España. Sin embargo, el trabajo tiene algunas fortalezas como el disponer de un tamaño muestral importante, el haber recogido todos los casos durante un largo periodo de tiempo, el examen del prototipo de paciente que falleció a través de la lupa de las órdenes de No RCP o LET, elemento que se echa en falta en la mayoría de estudios observacionales, especialmente en relación con esta pandemia, o la gran cantidad de datos aportados, pese a que algunos sean interpretativos, sobre lo que ha supuesto este manejo holístico de la COVID-19 en régimen de HAD.

A modo de conclusión, la HAD supuso en nuestro medio un elemento crucial a la hora de luchar contra la pandemia de COVID-19, tanto en sus momentos más crudos como en las fases posteriores, en las que la enfermedad ha sido integrada como «una más» dentro de nuestra práctica clínica habitual. Compartimos los pensamientos de otros autores que han definido la HAD como un recurso indispensable de cara al futuro por su capacidad de aumentar la resiliencia de los sistemas sanitarios, su seguridad, su versatilidad, su rápida escalabilidad y

su mayor coste-efectividad [9,12]. Integrar los enormes adelantos tecnológicos en cuanto a telemedicina podría potenciar todavía más la mejora los resultados de la atención de pacientes en HAD [13]. Consideramos que el desarrollo y crecimiento tanto de las unidades ya existentes de HAD como la creación de otras nuevas en las áreas de salud donde no existen puede resultar de vital importancia a la hora de hacer a nuestro sistema sanitario más robusto, especialmente en los tiempos venideros en lo referente tanto a la aparición de nuevos retos de salud como a la probable necesidad de practicar la medicina en un contexto económico y social de menor flujo de recursos.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses

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Influence of epidemiological and clinical factors in the reactogenicity to Comirnaty® vaccine in health care workers of a Spanish university teaching hospital (COVIVAC study)

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ABSTRACT

Introduction. Comirnaty® is an mRNA vaccine against COVID-19 which has been administered to millions of people since the end of 2020. Our aim was to study epidemiological and clinical factors influencing reactogenicity and functional limitation after the first two doses of the vaccine in health care workers (HCWs).

Material and methods. Prospective post-authorization cohort study to monitor safety and effectiveness of the vaccine.

Results. Local side effects were mild and presented both with first and second dose of Comirnaty. Systemic side effects were more frequent after 2nd dose. Nevertheless, previous SARS-CoV-2 infection was associated with systemic effects after the first dose of the vaccine (OR ranging from 2 to 6). No severe adverse effects were reported. According to multivariate analysis, the degree of self-reported functional limitation after the first dose increased with age, female sex, previous COVID-19 contact, previous SARS-CoV-2 infection, and Charlson Comorbidity Index (CCI). After the second dose, the degree of functional limitation observed was lower in those with previous SARS-CoV-2 infection, and it was positively associated to the degree of functional limitation after the first dose.

Conclusion. Systemic adverse effects were more frequent after the second dose of Comirnaty. Previous SARS-CoV-2 infection was associated with systemic effects after the first dose. Age, female sex, previous COVID-19, previous isolation due to COVID-19 contact, and CCI showed to be independent predictors of the degree of functional limitation after the 1st dose of Comirnaty®. After the 2nd dose, the degree of functional limitation was lower in those who previously had SARS-CoV-2 infection.

Keywords: COVID-19, Vaccines, Comirnaty, reactogenicity

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Influencia de factores epidemiológicos y clínicos en la reactogenicidad a la vacuna Comirnaty® en trabajadores sanitarios de un hospital universitario español (estudio COVIVAC)

RESUMEN

Introducción. Comirnaty® es una vacuna de ARNm contra el COVID-19 que se ha administrado a millones de personas desde finales de 2020. Nuestro objetivo fue estudiar los factores epidemiológicos y clínicos que influyen en la reactogenicidad y la limitación funcional asociadas tras las dos primeras dosis de la vacuna en trabajadores de la salud.

Metodología. Estudio de cohorte prospectivo post-autorización para evaluar la seguridad y eficacia de la vacuna.

Resultados. Los efectos secundarios locales fueron leves y se presentaron tanto con la primera como con la segunda dosis de Comirnaty. Los efectos secundarios sistémicos fueron más frecuentes después de la segunda dosis. No obstante, la infección previa por SARS-CoV-2 se asoció con efectos sistémicos tras la primera dosis de la vacuna (OR de 2 a 6). No se informaron efectos adversos graves. El análisis multivariante demostró que el grado de limitación funcional tras la primera dosis aumentó con la edad, el sexo femenino, contacto previo con COVID-19, la infección previa por SARS CoV-2 y el índice de comorbilidad de Charlson (ICC). Tras la segunda dosis, el grado de limitación funcional observado fue menor en aquellos con infección previa por SARS-CoV-2, y se asoció positivamente al grado de limitación funcional tras la primera dosis.

Conclusión. Los efectos adversos sistémicos fueron más frecuentes después de la segunda dosis de Comirnaty. La infección previa por SARS-CoV-2 se asoció con efectos sistémicos después de la primera dosis. La edad, el sexo femenino, infección por COVID-19 previa, el aislamiento previo por contacto de COVID-19 y el ICC se mostraron como predictores inde-

pendientes del grado de limitación funcional tras la 1ª dosis de Comirnaty®. Después de la 2.ª dosis, el grado de limitación funcional fue menor en los que previamente tenían infección por SARS-CoV-2.

Palabras clave: COVID-19, Vacunas, Comirnaty, reactogenicidad

INTRODUCTION

Since December 2019 more than 295 million COVID-19 cases and almost 5.5 million deaths have been reported worldwide [1]. The magnitude of the health problem has driven the focus of public health efforts to the development of effective and safe vaccines with an unprecedented celerity [2]. Comirnaty®, an mRNA BNT162b2 vaccine, developed by Pfizer-BIONTech, has been one of the first vaccines in being approved by EMA (European Medicines Agency) and FDA (USA Food and Drug Administration) [3,4]. This vaccine showed to be reasonable safe, and evidenced a high efficacy in preventing symptomatic (over 90%) and severe COVID-19 (over 95 %) in clinical trials conducted in adults, younger people (from 12-15 years old) and lately, in children (from 5 to 11 years) [5-8]. In different post-authorization studies conducted in Israel, the vaccine showed an effectiveness over 95% in preventing symptomatic COVID-19, and even higher in preventing severe illness or death [9,10]

In the different clinical trials conducted (adult people, adolescents, children), the safety profile of the vaccine showed to be acceptable, reporting mild to moderate side effects, such as injection site pain, fatigue, and headache, though some serious allergic reactions were observed [5,7,8]. In other post-authorization studies, less frequent side effects, (with around 1 per 10,000 incidence rate) such as myocarditis, and pericarditis, more common in young male people, have been reported [11,12]. Other possible less frequent side effects are under study. Further observational post-emergency use authorization studies are needed in order to more precisely define the safety profile of these new vaccines [13].

The COVIVAC-1 is a prospective cohort investigation on the safety and effectiveness of Comirnaty® vaccine in health care workers of a university teaching Spanish hospital who received two doses of the vaccine, taking into account epidemiological and clinical variables such as age, sex, ethnicity, blood group, comorbidities, previous COVID-19 infection, or previous exposure to COVID-19.

MATERIAL AND METHODS

COVIVAC-1 is a prospective cohort study about safety and effectiveness of mRNA BNT162b2 vaccine (Comirnaty®). This investigation was conducted in health care workers (HCW) of the HM Sanchinarro, a university teaching hospital in Madrid (Spain), who had received two doses of the vaccine. The first phase of the study, concerning safety, was carried out after reception of both doses of the vaccine. In this phase, which was focused on safety issues of the vaccine, the health care workers answered an online questionnaire about previous health conditions (including comorbidities, previous exposure to COVID-19 at home or at work, previous COVID-19 infection, or previous isolation due to COVID-19 contact), age, sex, ethnicity, blood group, date of administration of each dose, and possible adverse effects, from mild to severe. All participants agreed to enter the study (informed consent) at the time of receiving the second dose of vaccine. The study was approved by the Ethics Advisory Board of HM hospitals.

Quantitative data were presented with mean and standard deviation, or median and interquartile range in case of non-parametric data. Qualitative data were presented with proportions and percentages. Association was studied with Pearson coefficient for normal quantitative data, and chi square test in case of parametric qualitative data. In non-parametric data, Spearman coefficient and Fisher's exact test were applied, respectively. Logistic regression was applied to study the association of the different secondary effects to previous COVID-19 infection or exposure, and linear regression (multivariate) was used to study the association of clinical and epidemiological factors to the degree of functional limitation with each dose of the vaccine. Data analysis was performed with STATA software version 16.1.

RESULTS

Up to 278 HCW answered the questionnaire (85 male, 193 female). The mean age was 39.34 years in men, and 36.31 years in women ($p<0.05$). The complete description of the characteristics of participants is presented in Table 1.

Regarding previous exposure to SARS-CoV-2, more than 60% of HCW reported previous exposure to COVID-19 patients without adequate protection in the laboral environment, around 15% at home, and around 15% had been isolated before the vaccination due to COVID-19 contact. 19 per cent of them reported previous SARS-CoV-2 infection The list of symptoms in those with previous COVID-19, as well as other more concrete data about previous exposure to COVID-19 might be consulted in Table 2.

The most frequent adverse effect was local pain, significantly slightly more common after first dose (83 vs 78%, $p<0.05$). On the other hand, systemic symptoms including fever (from mild to severe), dysthermia, use of antipyretic, headache, cough, vomiting, diarrhoea, adenopathy, myalgia, arthralgia, and work absenteeism, were significantly more frequent after the second dose of the vaccine ($p<0.05$). More concrete details might be consulted in Table 3. The degree of post-vaccine limitation was significatively higher after the second dose of the vaccine (Figure 1).

Previous COVID-19 was significantly associated with higher incidence of low-grade fever (OR 2.96), asthenia (OR 2.48), headache (OR 2.8), dysthermia (OR 4.36), myalgia (OR 5.69), use of antipyretic (OR 3.46), and post-vaccine functional limitation, after the first dose of Comirnaty®. On the other hand, after the second dose of Comirnaty®, previous COVID-19 was

Table 1 Descriptive summary of Health Care Workers fully vaccinated with Comirnaty

Sex n (%)	Men 85 (30.58)	Women 193 (69.42)		
Age mean (IC 95%)	39.34 (36.58-42.10)	36.31 (34.93-37.70)		p = 0.031
BMI mean (IC 95%)	25.37 (24.69-26.09)	22.63 (22.10-23.17)		p < 0.0001
Ethnicity n (%)	Caucasian 76 (89.41)	Caucasian 166 (86.01)		
	Asian 0 (0)	Asian 2 (1.04)		
	Latin 9 (10.59)	Latin 23 (11.92)		
	Black 0 (0)	Black 1 (0.52)		
	Other 0 (0)	Other 1 (0.52)		p=0.749
Blood Group n (%)	0- 8 (12.12)	0- 12 (7.55)		
	0+ 23 (34.85)	0+ 53 (33.33)		
	A+ 31 (46.97)	A+ 76 (47.80)		
	B+ 4 (6.06)	B+ 18 (11.32)		p=0.483
Comorbidities n (%)				
COPD- Asthma	3 (3.53)	14 (7.25)		p=0.234
Acute Myocardial Infarction	0 (0)	0 (0)		p=0.606
Cardiac Failure	0 (0)	0 (0)		p=0.182
Vascular Peripheric Disease	4 (2.07)	2 (1.18)		p=0.0325
Stroke	0 (0)	0 (0)		p=0.0325
Dementia	0 (0)	0 (0)		p=0.883
Rheumatologic Disease	4 (2.07)	0 (0)		p=0.808
Ulcus	0 (0)	2 (2.35)		
Hepatic steatosis	0 (0)	2 (2.35)		
Hepatic Cirrhosis	0 (0)	0 (0)		
DM with target organ damage	0 (0)	0 (0)		
DM without target organ damage	4 (2.07)	2 (2.35)		
Hemiplegia	0 (0)	0 (0)		
Kidney Chronic Disease	0 (0)	0 (0)		
Tumour	3 (1.55)	1 (1.18)		
Leukaemia	0 (0)	0 (0)		
Lymphoma	0 (0)	0 (0)		
Metastasis	0 (0)	0 (0)		
AIDS	0 (0)	0 (0)		
Charlson Index n (%)	0	75 (88.24)	167 (86.53)	p=0.896
	1	8 (9.41)	21 (10.08)	
	2	2 (2.35)	4 (2.07)	
	3	0 (0)	1 (0.52)	

associated with lower incidence of moderate fever (OR 0.13) and cough (OR 0.16), and, as with the first dose, with greater incidence of asthenia (OR 2.48). The rest of adverse effects studied did not show significative association with previous COVID-19 (Table 4).

Finally, we employed linear regression analysis to study the predictive capacity of different factors and covariables in the degree of self-reported (from 0 to 5) functional limitation after each dose of the vaccine. Neither ethnicity, blood group, or body mass index revealed themselves as significant predic-

Table 2 Previous exposure to SARS-CoV2 in HCWs receptors of COVID-19 mRNA BNT162b2 (n =278)

COVID-19 Laboral contact n (%)	167 (60.07)
COVID-19 Cohabiting Contact n (%)	40 (14.39)
Isolation due to COVID-19 contact n (%)	42 (15.11)
N. isolations due to COVID-19 contact	
1 isolation n (%)	29 (70.73)
2 isolations n (%)	9 (21.95)
3 isolations n (%)	3 (7.32)
Previous COVID-19 diagnose n (%)	53 (19.06)
PCR n (%)	31 (11.15)
Ag test n (%)	3 (1.08)
Serology n (%)	19 (6.83)
Hospitalization due to COVID-19	1 (0.36)
ICU admission due to COVID-19	1 (0.36)
Symptoms in previous COVID-19 cases in vaccinated health care workers n (%)	
Fever	24 (45.28)
Cough	21 (39.62)
Dyspnoea	9 (16.98)
Diarrhoea	10 (18.87)
Headache	33 (62.26)
Dysgeusia	28 (52.83)
Anosmia	33 (62.26)
Asthenia	44 (83.02)
Myalgia	26 (49.06)
Odynophagia	8 (15.09)
Chest tightness	9 (16.98)
Extreme weakness	1 (1.89)
Rash	2 (3.77)

tors of functional limitation after the first or second dose of Comirnaty®. After the first dose of Comirnaty®, in the multivariate model, we found a positive independent association between degree of functional limitation and age (years), female sex, previous SARS-CoV-2 infection, previous isolation due to COVID-19 contact, and Charlson Comorbidity Index Punctuation. By contrast, after the second dose of the vaccine, in the multivariate model, the degree of functional limitation was positively associated with the degree of functional limitation (0 to 5) after the first dose of vaccine ($p<0.001$), and it was significatively lower in people with previous COVID-19 (Table 5)

DISCUSSION

In our group of health care workers fully vaccinated with Comirnaty®, around 90% did experience at least one side effect. Most of the self-reported side effects were mild to moderate. The main adverse effect observed after the first and second dose of Comirnaty® was local pain. In general, systemic side effects were significatively more intense after the second dose of the vaccine. The degree of self-reported functional limitation (from 0 to 5) after vaccination was also significantly higher after the second dose of the vaccine ($p<0.05$).

This echoes the results of the clinical trial conducted by Polack [5], and the cohort study by Chapin-Bardales [14], with over three and half million participants, using the V-safe Active Surveillance System, in USA.

On the contrary, another evidence from our study was that in those with previous SARS-CoV-2 infection, systemic side effects were more intense after first dose of Comirnaty®. These findings were in congruence with those reported by Me-

Table 3 Adverse effects after 1st and 2nd dose of COVID-19 mRNA BNT162b2 vaccine (n =278)

Adverse effect	1st Dose n (%)	2nd Dose n (%)	P
None	31 (11.15)	27(9.71)	0.48
Local erythema	35 (12.59)	30 (10.79)	0.25
Local swelling	51 (18.35)	51 (18.35)	1
Local pain	232 (83.45)	217 (78.06)	0.025
Low grade fever (under 38ºC)	18 (6.47)	62 (22.30)	<0.0001
Fever >38ºC & < 39ºC	6 (2.16)	31 (11.15)	<0.0001
Fever >39ºC	0 (0)	7 (2.52)	<0.01
Asthenia	72(25.90)	72 (25.90)	1
Headache	60 (21.58)	104 (37.41)	<0.0001
Dysthermia	39 (14.03)	97 (34.89)	<0.0001
Cough	13 (4.68)	46 (16.55)	<0.0001
Vomiting	1 (0.36)	16 (5.76)	<0.001
Diarrhoea	6 (2.16)	20 (7.19)	0.002
Adenopathy	11 (3.96)	27 (9.71)	0.002
Myalgia	23 (8.27)	80 (28.78)	<0.0001
Arthralgia	16 (5.76)	46 (16.55)	<0.0001
Antipyretic use	44 (15.83)	95 (34.17)	<0.0001
Urgent care need	0 (0)	0 (0)	
Work absenteeism	4 (1.44)	16 (5.76)	0.003
Post-vaccine limitation			
None (0)	182 (65.70)	122 (43.88)	< 0.001
Very Mild (1)	45 (16.25)	38 (13.67)	
Mild (2)	22 (7.94)	34 (12.23)	
Moderate (3)	12 (4.33)	38 (13.67)	
Severe (4)	13 (4.69)	34 (12.23)	
Very Severe (5)	3 (1.08)	12 (4.32)	

ni [15] in the British COVID Symptom Study and D'Arminio [16] on HCW in Italy.

A very rare adverse effect attributed to mRNA vaccines (Pfizer and Moderna) has been the development of myocarditis and/or pericarditis, mainly in the first week after the second dose, as reported by Kim [17], Montgomery [18], Marshall [19] or Boehmer [20]. No events of pericarditis or myocarditis post-vaccination with Comirnaty® were reported in our series of 278 HCW. No deaths or other serious adverse events were reported in our study.

A strength of our study is the attention paid to different epidemiological and clinical factors and their influence in the reactogenicity to Comirnaty®. In this way, in the multivariate linear regression analysis we found that age, female sex, Charlson Comorbidity Index Punctuation, previous SARS CoV-2 infection, and previous isolation due to COVID-19 contact

Table 4 OR of previous COVID-19 and adverse effects after mRNA BNT162b2 vaccine (n =278)

Adverse effect*	Dose 1 OR (IC 95%)	p	Dose 2 OR (IC 95%)	p
Low grade fever (<38ºC)	**2.96 (1.08-8.04)**	**0.033**	0.66 (0.30-1.45)	0.303
Fever >38ºC & < 39ºC	0.85 (0.10-7.40)	0.880	**0.13 (0.02-0.94)**	**0.043**
Asthenia	**2.48 (1.32-4.67)**	**0.005**	**2.48 (1.32-4.67)**	**0.005**
Headache	**2.80 (1.46-5.38)**	**0.002**	0.83 (0.44-1.56)	0.565
Dysthermia	**4.36 (2.11-9.00)**	**<0.0001**	0.77 (0.40-1.47)	0.425
Cough	1.29 (0.34-4.86)	0.71	**0.16 (0.04-0.69)**	**0.014**
Myalgia	**5.69 (2.35-13.78)**	**<0.0001**	0.97 (0.50-1.88)	0.932
Arthralgia	**4.82 (1.72-13.52)**	**0.003**	1.04 (0.47-2.31)	0.925
Antipyretic use	3.46 (1.71-6.99)	**0.001**	0.89 (0.47-1.69)	0.721
Post-vaccine limitation				
None (0)	1		1	
Very Mild (1)	**2.28 (1.04-5.01)**	**0.039**	0.63 (0.24-1.66)	0.349
Mild (2)	2.35 (0.84-6.59)	0.103	0.45 (0.15-1.38)	0.162
Moderate (3)	**6.28 (1.88-21.01)**	**0.003**	1.20 (0.52-2.77)	0.671
Severe (4)	2.80 (0.80-9.75)	0.108	0.32 (0.09-1.14)	0.080
Very Severe (5)			0.67 (0.14-3.24)	0.620

*The rest of adverse effects did not show significant association (OR) with previous COVID-19, nor with 1st dose, neither with 2nd dose.

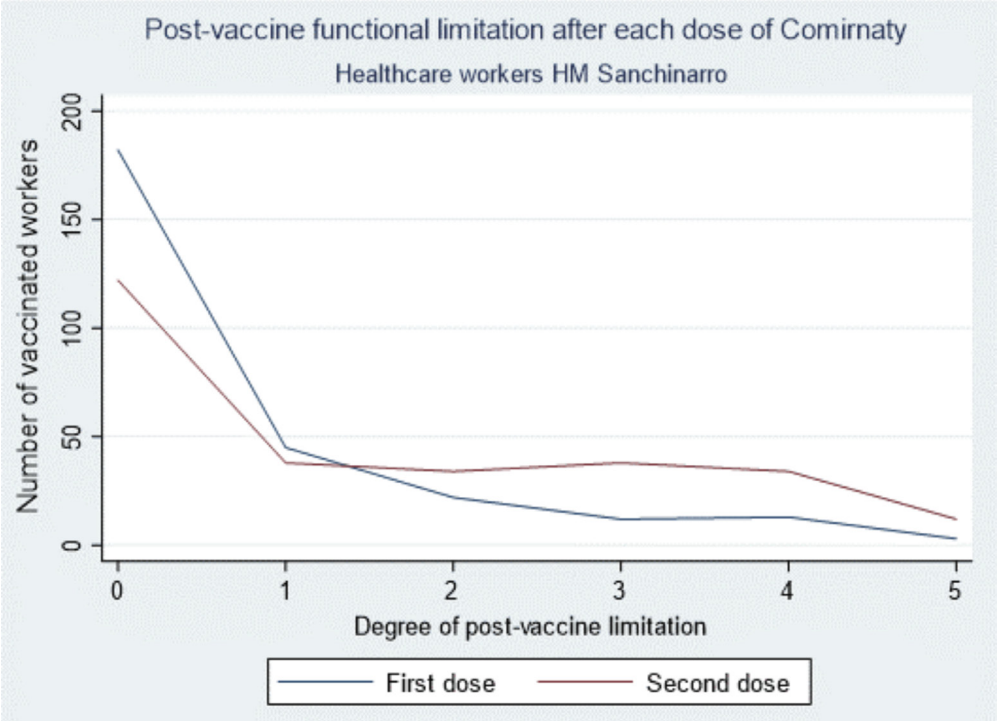

Figure 1 Degree of functional limitation (0 to 5) in HCWs after 1st & 2nd dose of Comirnaty

Table 5 Multivariate Linear regression model of post-vaccine limitation after 1st & 2nd dose of Comirnaty®

	Model after 1st dose		
	Coef.	CI 95%	P Wald
Age (each year)	0.0016	0.001 to 0.002	<0.001
Male Sex	-0.34	-0.62 to - 0.05	0.021
Charlson Index	0.35	0.05 to 0.65	0.020
Previous COVID-19	0.61	0.27 to 0.95	<0.001
Isolation due to COVID-19 contact	0.47	0.09 - 0.84	0.015
	Model after 2nd dose		
	Coef.	CI 95%	P Wald
Age (each year)	0.00003	-0.001 to 0.001	0.963
Male Sex	-0.20	-0.60 to 0.20	0.332
Charlson Index	-0.04	-0.45 to 0.38	0.859
Previous COVID-19	-0.55	-1.03 to -0.06	0.027
Isolation due to COVID-19 contact	-0.11	-0.64 to 0.42	0.687
Functional limitation after 1st dose (0 to 5)	0.48	0.31 to 0.64	<0.001

were independent predictors of a higher degree of functional limitation after the first dose of Comirnaty®. After the second dose, previous COVID-19 was associated with a lower functional limitation, and only the degree of functional limitation after the first dose revealed itself as an independent predictor of greater impairment. Other evidences from our analyses not published in previous works include that no differences in functional limitation post-vaccination were observed according to body mass index, ethnicity, or blood group.

A limitation of our study was the limited number of participants, though this could be counterbalanced with the higher degree of precision in the answer to the questionnaire due to the fact that all of them were HCW. Although this limitation, we obtained results in congruence with much greater studies, such as the ones conducted by Chapin Bardales or Menni [14,15].

CONCLUSION

In conclusion, in the same way as other studies, globally we found a higher incidence of systemic side effects with the second dose of Comirnaty® than with the first dose, while in those previously infected by SARS-CoV-2 systemic adverse effects were more intense after the first dose. No events of myocarditis neither pericarditis were reported in our HCW population. No deaths or major severe adverse events were reported. The degree of functional limitation after the first dose was independently associated with age, female sex, previous COVID-19 isolation, previous SARS-CoV-2 infection, and punctuation in the Charlson Comorbidity Index. The degree of functional limitation after the first dose showed to be an independent predictor of a higher degree of functional limitation after the second dose, while previous SARS-CoV-2 infection was associated with a lower functional limitation after the second dose. Further post-emergency use authorization studies are still needed in order to define more precisely the safety profile of these new vaccines against COVID-19.

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None to declare.

CONFLICT OF INTEREST

Authors declare no have conflict of interest

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Capacidad del qSOFA1-lactato para predecir mortalidad a 30 días en los pacientes atendidos por infección en urgencias

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RESUMEN

Objetivo. Evaluar y comparar la capacidad del lactato y del *quick Sepsis-related Organ Failure Assessment* (qSOFA) para predecir mortalidad a 30 días en los pacientes que acuden al servicio de urgencias (SU) por un episodio de sospecha de infección.

Método. Estudio observacional de cohortes, multicéntrico, prospectivo. Se incluyó por oportunidad a pacientes ≥18 años atendidos por sospecha de infección en 71 SU españoles del 01/10/2019 al 31/03/2020. Se analizó la capacidad predictiva con el área bajo la curva (ABC) de la característica operativa del receptor (COR) y los valores de sensibilidad (Se), especificidad (Es), valor predictivo positivo (VPP) y negativo (VPN).

Resultados. Se incluyeron 4.439 pacientes con edad media de 67 (DE:18) años, 2.648 (59,7%) fueron hombres y fallecieron a los 30 días 459 (10,3%). Para la mortalidad a 30 días el ABC-COR obtenida con el modelo qSOFA=1 más lactato 2 mmol/l fue de 0,66 (IC 95%: 0,63-0,69) con una Se:68%, Es:70% y VPN:92%, mientras que qSOFA=1 obtuvo ABC-COR de 0,52 (IC 9%: 0,49-0,55) con una Se:42%, Es:64% y VPN:90%.

Conclusiones. Para predecir mortalidad a los 30 días en los pacientes que acuden al SU por un episodio de infección, el modelo qSOFA=1 + lactato≥2 mmol/L mejora significativamente el poder predictivo conseguido de forma individual por qSOFA1 y llega a ser muy similiar al de qSOFA≥2.

Palabras clave: Sepsis, Lactato, Pronóstico, Mortalidad, qSOFA, Servicio de Urgencias,

Ability of qSOFA1-lactate to predict 30-day mortality in patients seen for infection in the Emergency Department

ABSTRACT

Objectives. To evaluate lactate and the Quick Sepsis-Related Organ Failure Assessment (qSOFA) and compare their ability to predict 30-day mortality in patients treated for infection in emergency departments (ED).

Methods. Prospective multicenter observational cohort study. We enrolled a convenience sample of patients aged 18 years or older attended in 71 Spanish ED from October 1, 2019, to March 31, 2020. Each model's predictive power was analyzed with the area under the receiver operating characteristic curve (AUC), and its values of sensitivity (Se), specificity (Sp), positive predictive value (PPV) and negative (NPV).

Results. A total of 4439 patients with a mean (SD) age of 18 years were studied; 2648 (59.7%) were men and 459 (10.3%) died within 30 days. For 30-day mortality, the AUC-COR obtained with the qSOFA = 1 model plus 2 mmol/l lactate was 0.66 (95% CI, 0.63-0.69) with Se: 68%, Es: 70% and NPV:92%, while qSOFA = 1 obtained AUC-COR of 0.52 (95% CI, 0.49-0.55) with a Se:42%, Es:64% and NPV:90%.

Conclusions. To predict 30-day mortality in patients presenting to the ED due to an episode of infection, the qSOFA =1 + lactate≥2 mmol/L model significantly improves the predictive power achieved individually by qSOFA1 and becomes very similar to qSOFA≥2.

Keywords: Sepsis, Lactic acid, Prognosis, Mortality, Quick Sepsis-Related Organ Failure Assessment (qSOFA), Emergency Department,

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INTRODUCCIÓN

La atención a pacientes con sospecha de infección en los servicios de urgencias (SU) se incrementó significativamente antes de la pandemia COVID-19 hasta un 15-20% de las atenciones diarias en 2019 [1]. Además, en 2020-2021 por el impacto del SARS-CoV-2, estas cifras han podido elevarse hasta el 50-80% [2]. Asimismo, la gravedad clínica (pacientes con sepsis, comorbilidad, neutropénicos, ancianos, sospecha de bacteriemia, etc.) y la mortalidad a corto plazo (30 días) también han sufrido un incremento en la última década [2,3]. En este contexto, la sepsis representa uno de los mayores problemas de salud pública en todo el mundo, por su incidencia y mortalidad a 30 días (24,4% para la sepsis y 34,7% para el *shock* séptico) [2,3]. Hoy en día, el SU representa un eslabón clave ya que es donde se realiza la sospecha de sepsis, su reconocimiento, la toma de muestras microbiológicas y se debe comenzar un tratamiento precoz y adecuado, lo que determinará la evolución clínica del enfermo [2,4-6].

En 2016, los criterios de Sepsis-3 recomendaron el empleo del *quick Sepsis-related Organ Failure Assessment* (qSOFA) en pacientes no ingresados en medicina intensiva [7]. Inmediatamente se suscitó una gran controversia ya que q-SOFA mostraba una pobre sensibilidad para detectar pacientes con posible mala evolución, lo que impulsó que múltiples estudios compararan el rendimiento del qSOFA con otras escalas y algunos biomarcadores [8-12]. Por este motivo, se ha recomendado la utilización conjunta de escalas y biomarcadores para determinar el diagnóstico de infección bacteriana, sepsis y el pronóstico de mortalidad [9,10-13]. Se considera al lactato como el mejor marcador de hipoperfusión e hipoxia tisular y valores ≥2 mmol/L constituyen un factor independiente de mortalidad, incluso sin hipotensión [11-13]. Sin embargo, durante el desarrollo de los estudios de cara a establecer los criterios de Sepsis-3, el lactato no cumplió con los umbrales estadísticos para su inclusión en la construcción del modelo de qSOFA, lo que podría justificarse por la gran cantidad de valores ausentes en el registro [7,14]. Fruto de estas consideraciones, la última actualización de la Campaña Sobrevivir a la Sepsis no recomendó como *screening* de sepsis el empleo de q-SOFA de manera aislada, comparado con otras escalas [5]. Algunos autores han propuesto añadir el lactato a q-SOFA (qSOFA-lactato), ya que se consigue un mayor rendimiento diagnóstico, sobre todo para los pacientes de teórico bajo riesgo inicial (qSOFA1) [9,14,18].

El objetivo de este estudio fue evaluar la capacidad del lactato para mejorar el rendimiento predictivo de mortalidad a corto plazo en pacientes de riesgo bajo (qSOFA=1) del SU con sospecha de infección.

MÉTODOS

Análisis secundario del registro MPB-INFURG-SEMES [9,19], que es un estudio observacional, multicéntrico, prospectivo, descriptivo y analítico de pacientes atendidos por sospecha de infección en 71 SU de la Red del Grupo INFURG-SEMES(Grupo de Infecciones de la Sociedad Española de Medicina de Urgencias y Emergencias)(ver adenda) a los que se realizó un seguimiento durante 30 días. Del 01/10/2019 al 31/03/2020 se incluyeron con un muestreo por oportunidad a pacientes ≥18 años diagnosticados de un proceso infeccioso y en los que, por sus características epidemiológicas y presentación clínica, los médicos responsables indicaron la obtención de muestras analíticas con determinación de biomarcadores (lactato) y cultivos microbiológicos. Se excluyeron las pacientes de obstetricia-ginecología (ver criterio inclusión y exclusión completos en publicaciones previas) [9,19].

Como variable dependiente se consideró la mortalidad cruda a los 30 días. Como variables independientes aquellas que se consideraron clínicamente relevantes, las que pudieran influir en el pronóstico y evolución, sociodemográficas, de comorbilidad y analíticas (se asumieron y adoptaron las definiciones, técnicas, métodos establecidos para la recogida de muestras, valores de referencia y variables estudiadas del estudio primigenio) [9,19].

Se aplicaron los criterios de selección de pronóstico de pacientes en las definiciones del qSOFA y las variables que la constituyen según la tercera conferencia de consenso de sepsis (Sepsis-3) [7].

Para el análisis estadístico se utilizaron medias y sus desviaciones estándar (DE) para variables cuantitativas y números absolutos y porcentajes para las cualitativas. Las comparaciones se realizaron con la pruebas de ji cuadrado o exacta de Fisher, la t de Student y la U de Mann-Whitney, según el tipo de variable. Se consideró significativo un valor de $p<0,05$. Los contrastes fueron bilaterales. La eficacia para la predicción de mortalidad a los 30 días se estudió mediante el análisis del área bajo la curva (ABC) de la característica operativa del receptor (COR) con el intervalo de confianza al 95(IC 95%) y se comparó frente al valor neutro (0,5). Se calculó el rendimiento pronóstico de estas y de los nuevos modelos elegidos con los cálculos de sensibilidad (Se), la especificidad (Es), el valor predictivo positivo (VPP) y el valor predictivo negativo (VPN), así como sus IC 95% por métodos binomiales exactos. Los errores estándar de las ABC se calcularon por métodos no paramétricos. La comparativa entre ABC-COR de las variables y nuevos modelos combinados predictivos se realizó por la prueba de ji cuadrado para comparar ABC-COR respecto a ABC-COR de referencia elegidas. Por su parte, las proporciones se compararon con el test de McNemar para muestras independientes (accesible en la calculadora: http://home.ubalt.edu/ntsbarsh/business-stat/otherapplets/pairedprop.htm). El análisis estadístico se realizó con los programas IBM-SPSS Statistics 22 para Windows y STATA/MP 16.0.

El estudio ha seguido la Declaración de Helsinki y fue aprobado por el Comité Ético de Investigación Clínica (CEIC) del Complejo Hospitalario Universitario de Toledo (398/2109), así como por los CEIC/CEIm de referencia de los centros participantes.

Tabla 1 **Características clínico-epidemiológicas, de evolución, analíticas y de destino la muestra global y estudio univariable en función de la existencia o no de fallecimiento del paciente a 30 días**

DATOS DEMOGRÁFICOS-EPIDEMIOLÓGICOS	Total n=4.439	Valores perdidos	Supervivientes a 30 días n=3.980 (89,7%)	Fallecidos a 30 días n= 459 (10,3%)	Valor p
Edad (años), media (DE)	67 (18)	0 (0,0)	66 (19)	77 (14)	<0,001
Edad >65 años n (%)	2.661 (59,9)	0 (0,0)	2.293 (57,6)	368 (80,2)	<0,001
Género masculino n (%)	2.648 (59,7)	0 (0,0)	2.370 (59,5)	278 (60,6)	0,356
Institucionalizado n (%)	382 (8,6)	0 (0,0)	274 (6,9)	108 (23,5)	<0,001
COMORBILIDADES					
Neoplasia sólida, n (%)	523 (11,8)	0 (0,0)	459 (11,5)	64 (13,9)	0,077
Leucemia/Linfoma, n (%)	199 (4,5)	104 (2,3)	174 (4,4)	25 (5,4)	0,183
Enfermedad hepática, n (%)	119 (2,7)	0 (0,0)	111 (2,8)	8 (1,7)	0,119
Enfermedad cardiaca crónica, n (%)	502 (11,3)	0 (0,0)	384 (9,6)	118 (25,7)	<0,001
HTA	2.001 (45,1)	0 (0,0)	1753 (44,0)	248 (54,0)	<0,010
Enfermedad renal crónica, n (%)	431 (9,7)	0 (0,0)	358 (9,0)	73 (15,9)	<0,001
Enfermedad cerebrovascular, n (%)	447 (10,1)	0 (0,0)	371 (9,3)	76 (16,6)	<0,001
Demencia, n (%)	490 (11,0)	0 (0,0)	368 (9,2)	122 (26,6)	<0,001
EPOC, n (%)	724 (16,3)	0 (0,0)	634 (15,9)	90 (19,6)	0,027
Diabetes Mellitus, n (%)	867 (19,5)	0 (0,0)	720 (18,1)	147 (32,0)	<0,001
Índice de Charlson [media (DE)]	2,8 (2,6)	0 (0,0)	2,6 (2,5)	4,2 (2,8)	<0,001
Índice de Charlson ≥3	2.039 (45,9)	0 (0,0)	1.722 (43,3)	317 (69,1)	<0,001
Índice de Barthel [media (DE)]	83 (30)	148 (3,3)	86 (28)	58 (40)	<0,001
Índice de Barthel ≤60, n (%)	813 (18,9)	148 (3,3)	601 (15,1)	212 (46,2)	<0,001
DATOS CLÍNICOS Y DE GRAVEDAD					
Temperatura en grados centígrados [media (DE)]	37,4 (7,9)	14 (0,3)	37,4 (7,9)	37,3 (6,5)	0,704
Temperatura > 38,3°C, n (%)	1.505 (34,0)	14 (0,3)	1.361 (34,2)	144 (31,4)	0,120
FC en lpm [media (DE)]	99,9 (20,6)	67 (1,5)	99,4 (20,1)	104,1 (24,0)	<0,001
FC > 90 lpm	3.014 (68,9)	67 (1,5)	2.673 (67,2)	341 (74,3)	0,001
FR en rpm [media (DE)]	21,2 (13,1)	306 (6,9)	21,01 (11,81)	23,28 (16,62)	<0,001
FR ≥ 22 rpm	1.640 (39,7)	306 (6,9)	1.355 (34,0)	285 (62,1)	<0,001
Alteración de la consciencia ECG ≤14, n (%)	832 (19,1)	91 (2,1)	589 (14,8)	243 (52,9)	<0,001
PAS en mmHg [media (DE)]	122,3 (27,4)	30 (0,7)	123,7 (26,8)	110,6 (30,1)	<0,001
PAS ≤ 100 mmHg, n (%)	1.005 (22,8)	30 (0,7)	805 (20,2)	200 (43,6)	<0,001
Criterios de sepsis-2 (SRIS ≥2), n (%)	2.928 (71,06)	319 (7,2)	2.579 (64,8)	349 (76,0)	<0,001
qSOFA = 0, n (%)	1.623 (40,07)	386 (8,7)	1.594 (40,1)	29 (6,3)	<0,001
qSOFA = 1, n (%)	1.606 (39,65)	386 (8,7)	1.410 (35,4)	196 (42,7)	<0,001
qSOFA = 2, n (%)	646 (15,95)	386 (8,7)	504 (12,7)	142 (30,9)	<0,001
qSOFA = 3, n (%)	178 (4,39)	386 (8,7)	86 (2,2)	92 (20,0)	<0,001
Criterios de sepsis-3: qSOFA ≥2, n (%)	824 (20,34)	386 (8,7)	590 (14,8)	234 (51,0)	<0,001
Criterios Shock séptico (Sepsis-3), n (%)	405 (10,0)	389 (8,8)	282 (7,1)	123 (26,8)	<0,001

Tabla 1 **Características clínico-epidemiológicas, de evolución, analíticas y de destino la muestra global y estudio univariable en función de la existencia o no de fallecimiento del paciente a 30 días (cont.)**

DATOS DE EVOLUCIÓN Y DESTINO	Total n=4.439	Valores perdidos	Supervivientes a 30 días n=3.980 (89,7%)	Fallecidos a 30 días n= 459 (10,3%)	Valor p
Destino inicial de los pacientes, n (%)		0 (0,0)			<0,001
Alta	748 (16,9)	0 (0,0)	730 (18,3)	18 (3,9)	
Observación y unidad corta estancia	335 (7,6)	0 (0,0)	327 (8,2)	8 (1,7)	
Planta de hospitalización convencional	2.722 (61,3)	0 (0,0)	2404 (60,4)	318 (69,3)	
Unidad de Cuidados Intensivos	284 (6,4)	0 (0,0)	226 (5,7)	58 (12,6)	
Fallecimiento en urgencias	38 (0,9)	0 (0,0)	0 (0,0)	38 (8,3)	
Mortalidad a los 30 días	459 (10,3)	0 (0,0)	0 (0,0)	459 (100,0)	
HALLAZGOS ANALÍTICOS Y MICROBIOLÓGICOS					
Bacteriemia verdadera n (%)	899 (20,5)	0 (0,0)	753 (18,9)	146 (31,8)	<0,001
Creatinina ≥ 2 mg/dl n (%)	588 (13,3)	26 (0,6)	444 (11,2)	144 (31,4)	<0,001
Leucocitos por mm^3 [media (DE)]	14.144 (11.639)	0 (0,0)	14.024 (11.435)	15.191 (13.255)	0,043
Leucocitosis > 12.000/ mm^3	2.681 (60,4)	0 (0,0)	2.370 (59,5)	311 (67,8)	<0,001
Cayados (bandas) > 10%, n(%)	238 (7,4)	1.225 (27,6)	199 (5,0)	39 (8,5)	0,001
Plaquetas por mm^3 [media (DE)]	219.800 (106.892)	26 (0,6)	218.092 (102.998)	227.500 (136.116)	0,105
Trombopenia < 150.000/mm^3, n(%)	999 (22,6)	26 (0,6)	881 (22,1)	118 (25,7)	0,042
Lactato sérico en mmol/l ([media (DE)]	2,75 (2,96)	747 (16,8)	2,64 (2,93)	3,65 (3,09)	<0,001
Lactato ≥ 2 mmol/L, n (%)	1.562 (42,3)	747 (16,8)	1.292 (32,5)	270 (58,8)	<0,001
Procalcitonina en ng/ml [media (DE)]	3,41 (10,17)	139 (3,1)	3,06 (9,38)	6,24 (15,05)	<0,001
Proteína C reactiva en mg/l [media (DE)]	15,01 (12,08)	362 (8,15)	14,67 (11,86)	18,16 (13,57)	<0,001

DE: desviación estándar; n: número casos; AB: antibióticos; EPOC: Enfermedad pulmonar obstructiva crónica; C: centígrados; FC: frecuencia cardiaca; lpm: latidos por minuto; FR: frecuencia respiratoria; rpm: respiraciones por minuto. ECG: escala del coma de Glasgow; PAS: presión arterial sistólica; SRIS: síndrome de respuesta inflamatoria sistémica; qSOFA: quick Sepsis-related; Criterios de sepsis (SRIS^3 2) según conferencia de Consenso de 2001 (Sepsis-2) (Descritos en referencia 1); Criterios de sepsis (qSOFA ^{3} 2) según la tercera conferencia de consenso (Sepsis-3) (Descritos en referencia 7)

RESULTADOS

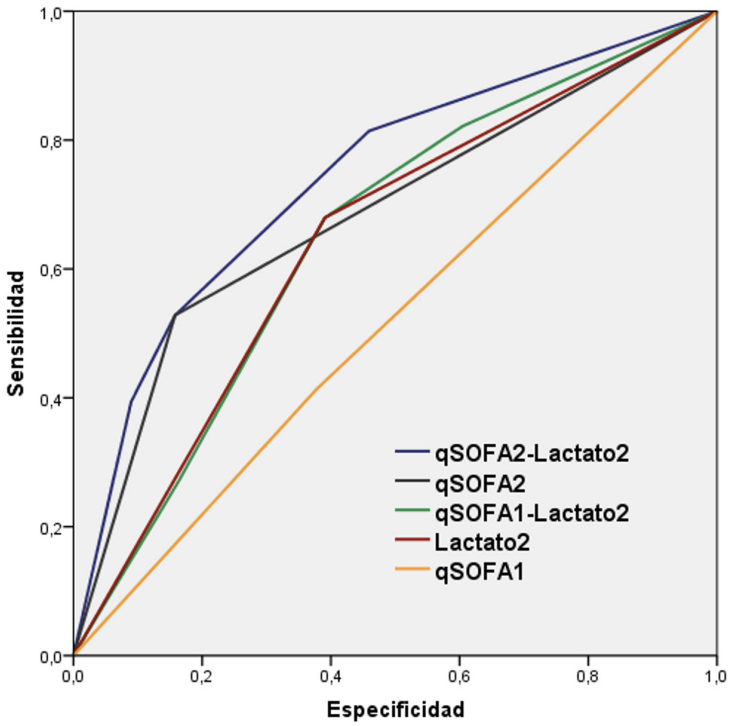
De los 4.923 pacientes seleccionados, finalmente se incluyeron 4.439 (se excluyeron 484 por perder su seguimiento o cambiar a otro diagnóstico en los 30 días tras visitar urgencias), con una edad media de 67 (DE 18) años, rango 18-103 años. El 59,9% (2.661) tenían más de 65 años y 2.648 (59,6%) eran varones.

En la primera evaluación, según la puntuación de la escala qSOFA, se clasificaron 1.623 pacientes (40,07%) como qSOFA=0, 1.606 (39,65%) con qSOFA=1 y 824 pacientes (20,34%) en el grupo qSOFA ≥2 [646 (15,95%) qSOFA=2 y 178 (4,39%) qSOFA=3], considerándose 386 (8,7%) como valores perdidos al no estar registrado uno de sus tres criterios.

En el seguimiento de los 4.439 pacientes durante 30 días fallecieron 459 (10,3%), de estos 38 (0,9%) durante su estancia en urgencias y según puntuación de la qSOFA: 29 (1,8%) con puntuación qSOFA=0; 196 (12,2%) con qSOFA=1; 142 (21,98%) con qSOFA=2 y 234 (28,4%) con un qSOFA≥2.

En la tabla 1 se muestran las características sociodemográficas, epidemiológicas, comorbilidades, funcionales, clínicas, de gravedad, de evolución y destino de los pacientes, así como los resultados de las determinaciones analíticas y de microbiología de la muestra global del estudio con los datos del estudio comparativo de los casos de los pacientes que fallecieron o no a los 30 días.

En la figura 1 se muestra la capacidad predictiva de mortalidad a los 30 días en pacientes atendidos en el servicio de urgencias por sospecha de infección, así como los parámetros de rendimiento pronóstico (Se, Es, VPP y VPN) de qSOFA=1,



Mortalidad a corto plazo (30 días)	ABC-COR (IC 95%) Valor p	Se % (IC 95%)	Es % (IC 95%)	VPP % (IC 95%)	VPN % (IC 95%)	Comparativa de proporciones*
qSOFA ≥ 2 + lactato ≥ 2 mmol/L	0,74 (0,71-0,77) p<0,001	60 (35-45)	91 (90-92)	35 (31-40)	93 (92-94)	p < 0,01
qSOFA ≥ 2	0,69 (0,66-0,72) p<0,001	51 (46-56)	85 (84-86)	28 (25-32)	94 (93-95)	
qSOFA=1 + lactato ≥ 2 mmol/L	0,66 (0,63-0,69) p<0,001	68 (61-75)	70 (67-73)	20 (17-22)	92 (90-94)	p < 0,01
qSOFA=1	0,52 (0,49-0,55) p = 0,386	42 (38-47)	64 (62-65)	12 (10-13)	90 (89-92)	
Lactato ≥ 2 mmol/L	0,63 (0,61-0,66) p<0,001	68 (63-72)	61 (59-63)	18 (16-20)	94 (93-95)	

Figura 1 **Rendimiento para la predicción de mortalidad de los criterios definitorios de sepsis 2 (SRIS ≥ 2) y qSOFA=1 y su comparativa con los nuevos modelos combinados al añadir el lactato**

Rendimiento para la predicción de mortalidad de los criterios definitorios de sepsis 2 (SRIS ≥ 2) y qSOFA=1 y su comparativa con los nuevos modelos combinados al añadir el lactato

ABC-COR: área bajo la curva de la característica operativa del receptor; IC 95%: intervalo de confianza al 95%; IC: intervalo de confianza; Se: sensibilidad; Es: especificidad; VPP: valor predictivo positivo; VPN: valor predictivo negativo; qSOFA ≥2: Criterios de sepsis 3 (quick Sepsis Related Organ Failure Assessment) según la tercera conferencia de consenso (Sepsis-3) (referencia 7).

Nota: la comparativa de proporciones se realizó con el test de McNemar. Los valores p reflejados en la columna "comparativa de proporciones" se refiere a las diferencias encontradas entre los modelos combinados y los valores de qSOFA: (qSOFA ≥ 2 + lactato ≥ 2 mmol/L con qSOFA ≥2 y por otro lado qSOFA=1 + lactato ≥ 2 mmol/L con qSOFA =1)

qSOFA ≥2 y los nuevos modelos combinados con lactacidemia ≥2 mmol/L.

DISCUSIÓN

Los resultados del presente estudio nos permiten confirmar la mejora del rendimiento predictivo de riesgo de mortalidad a 30 días que ofrece el lactato en pacientes con qSOFA=1, para los pacientes atendidos en los SU con sospecha de un proceso infeccioso. Este hecho ya había sido señalado por otros autores, así como para los mayores de 75 años [9,11-15,17,18], aunque, en la mayoría de las ocasiones en pacientes con qSOFA ≥2, es decir, los clasificados como de alto riesgo de mala evolución y en los que se activa el "código sepsis" y se indica su ingreso [1,9,12-14]. Todo ello, en la nueva línea recomendada de no utilizar como *screening* de sepsis el q-SOFA de manera aislada, comparado con otras escalas, por su baja Se [5,16]. En nuestro estudio, qSOFA muestra una insuficiente Se (51% y 42% para qSOFA≥2 y qSOFA=1, respectivamente) y mejor Es (85% y 64%), similar a los resultados en distintos metanálisis (Se: 45-55% y Es 85-88%) [8,20]. Asimismo, el nuevo modelo (qSOFA ≥2 + lactato≥2 mmol/L) consigue un mayor rendimiento predictivo de mortalidad a 30 días (ABC de 0,74 y Es de 91%) que qSOFA≥ 2 aislado (0,69 y 85%). Y, por su parte, (qSOFA =1 + lactato≥2 mmol/L) consigue también un mejor resultado (ABC de 0,66 y Es de 70%) que qSOFA=1 aislado (0,52 y 64%), pero también mejora significativamente la Se (68% *vs.* 42%) y el VPN (92% *vs.* 90%), siendo el responsable de ello la incorporación del lactato. En este sentido, Seymour *et al* [14], en el mismo artículo que validó el qSOFA, publicaron que la mortalidad hospitalaria de los pacientes q-SOFA=1 con niveles de lactato sérico ≥2 mmol/L era similar a los pacientes con q-SOFA ≥2. El estudio de Churpek et *al* [15], propuso bajar el umbral de positividad a q-SOFA ≥1 (q-SOFA1), ya que estos pacientes tenían un comportamiento similar a los SIRS ≥2. Y De Santos Castro PA, *et al* [17] encuentran que la baja Se del qSOFA1 de 42% aumentaba al 78% con una Es de 70% al añadir el lactato (qSOFA-lactato). Por lo tanto, el qSOFA-lactato puede representar una útil herramienta de ayuda a la hora de reclasificar aquellos pacientes con qSOFA=1, para así optimizar las decisiones inmediatas que se deben tomar en los SU: indicación de extracción de hemocultivos, administrar una terapia antimicrobiana adecuada y precoz y el ingreso hospitalario o el alta domiciliaria, entre otras [1,4,5,16].

Nuestro estudio tiene distintas limitaciones. En primer lugar, el reclutamiento de casos fue por oportunidad (cuando los investigadores estaban de guardia), con el componente de sesgo de inclusión introducido. En segundo lugar hubo datos perdidos (lactato en el 16,8% y alguno de los criterios de qSOFA en el 8,7%). Además, el 9,8% de los pacientes incluidos inicialmente fueron excluidos en los 30 días de seguimiento. En tercer lugar, el momento y el tipo de tratamiento no se evaluaron, y estos aspectos pueden condicionar el desenlace de la enfermedad.

A pesar de estas limitaciones, creemos que el estudio es un reflejo de la realidad clínica de nuestros SU.

Como conclusión de este estudio podemos señalar que para predecir mortalidad a los 30 días en los pacientes que acuden al SU por un episodio de infección, el modelo qSOFA=1 + lactato≥2 mmol/L mejora significativamente el poder predictivo conseguido de forma individual por qSOFA1 y llega a ser muy similiar al de qSOFA≥2. Aunque, futuros estudios multicéntricos de validación externa del modelo son necesarios.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses

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Elevada tasa de resistencia a macrólidos y fluoroquinolonas en *Mycoplasma genitalium* en el área sur de Tenerife

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RESUMEN

Introducción. *Mycoplasma genitalium* (MG) es un reconocido patógeno de transmisión sexual. El aumento de las resistencias asociadas a las principales líneas de tratamiento (macrólidos y quinolonas) justifican un estudio genético de mutaciones para mejorar las tasas de curación.

Material y métodos. Un total de 8.508 muestras fueron analizadas entre abril de 2018 y julio de 2022 para la detección de MG mediante la técnica de PCR multiplex Allplex™ STI Essential Assay.En los casos positivos para MG se estudió el dominio V del gen *23S rRNA* y los genes *gyrA* y *parC*. Se evaluó la importancia clínica de las mutaciones y se revisaron las historias clínicas para obtener información demográfica y de tratamiento.

Resultados. Se realizó estudio de resistencias a 92 muestras (65 hombres y 27 mujeres). En lo relativo al estudio genotípico, 28 pacientes presentaban mutaciones a macrólidos (30,43%). La más habitual fue A2059G (18.48%). Para las quinolonas, 5 pacientes (5,43%) presentaron mutaciones clínicamente relevantes en el gen *parC*. Destaca un paciente con la mutación G295 en *gyrA* asociada a G248T en *parC*. Treinta individuos se sometieron al test de cura (TOC). La azitromicina fue el régimen empírico más común y el moxifloxacino la principal alternativa.

Conclusiones. La elevada tasa de resistencias en nuestro entorno evidencia la necesidad de realizar una terapia dirigida por el estudio genotípico de resistencias a macrólidos, apoyándonos en la detección de mutaciones en *parC* y *gyrA* para predecir la susceptibilidad a quinolonas y en el uso del TOC para evaluar la respuesta al tratamiento.

Palabras clave: *Mycoplasma genitalium*, macrólidos, fluoroquinolonas.

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High macrolides and fluoroquinolones resistance rate in *Mycoplasma genitalium* in southern Tenerife

ABSTRACT

Introduction. *Mycoplasma genitalium* (MG) is a recognized sexually transmitted pathogen. Increasing resistance to main lines of treatment (macrolides and quinolones) justifies a genetic study of mutations to improve cure rates.

Material and methods. A total of 8,508 samples from April 2018 to July 2022 were processed using Allplex™ STI Essential Assay. In MG positive cases *23S rRNA V domain*, *gyrA* and *parC* genes were studied. Mutations detected were checked to assess their clinical significance and medical records were reviewed to obtain demographic and treatment information.

Results. Resistance study was performed on 92 samples (65 men and 27 women). In relation to the genotypic study, 28 patients presented mutations to macrolides (30.43%).Most common was A2059G (18.48%). For quinolones, 5 patients (5.43%) had clinically relevant mutations in *parC* gene.Of note was a patient with G295 mutation in *gyrA* associated with G248T in *parC*. Thirty subjects underwent a test of cure (TOC). Azithromycin was the most common empirical regimen and moxifloxacin the main alternative.

Conclusions. High rate of resistance in our environment evidences the need for targeted therapy by genotypic study of macrolide resistance, supported by the detection of mutations in *parC* and *gyrA* to predict quinolones susceptibility and the use of TOC to evaluate treatment response.

Keywords: *Mycoplasma genitalium*, macrolides, fluoroquinolones.

INTRODUCCIÓN

Mycoplasma genitalium (MG) es un microorganismo de transmisión sexual reconocido como un grave problema de salud a nivel global debido a su alta tasa de resistencia a antimicrobianos. Se asocia a cervicitis, enfermedad pélvica inflamatoria e infertilidad en mujeres, aunque destaca como causante de uretritis no gonocócica en varones, en porcentajes que oscilan entre el 10-30% [1].

Históricamente, la presencia de requerimientos especiales en el cultivo y su lento crecimiento dificultan su identificación y la realización del antibiograma. En la actualidad, las técnicas de amplificación de ácidos nucleicos han supuesto una revolución en el diagnóstico de este patógeno [2].

En relación al tratamiento, la ausencia de pared celular limita las opciones terapéuticas. Las últimas recomendaciones de The International Union against Sexually Transmitted Infections (IUSTI) proponen como tratamiento de elección azitromicina 500 mg/día 1 día, seguido de 250 mg/ día durante 4 días. No obstante, en los últimos años, diferentes metaanálisis han notificado un importante incremento de las resistencias asociadas a macrólidos; del 10 % en estudios anteriores a 2010, a alrededor del 50 % en estudios publicados en 2016 y 2017 [3].

La principal alternativa terapéutica son las fluoroquinolonas, con un porcentaje de resistencias mucho menor (7-10%) [4], siendo la pauta más aceptada moxifloxacino 400 mg/día durante 7 días.

En este contexto, el tratamiento dirigido basado en la detección por reacción en cadena de la polimerasa (PCR) de las principales mutaciones que confieren resistencias a macrólidos, permite comenzar de forma precoz con el tratamiento de segunda línea, mejorando el porcentaje de curación inicial de un 60 a un 90 % aproximadamente [5].

Para evaluar la eficacia del tratamiento, la IUSTI recomienda la realización de un test de cura (TOC) a partir de la tercera semana de la finalización del tratamiento [6].

El objetivo de este estudio se centra en conocer la epidemiología y las resistencias asociadas a MG en el área sur de Tenerife, haciendo hincapié en el impacto que estas mutaciones tienen en el tratamiento.

MATERIAL Y MÉTODOS

Un total de 8.508 muestras fueron analizadas en el período de abril de 2018 a julio de 2022 para la detección de MG mediante la técnica de PCR multiplex en tiempo real Allplex™ STI Essential Assay (Seegene).

Se excluyeron las muestras positivas de pacientes a los que se le realizó estudio de resistencias dentro de los 3 meses anteriores. Además, una carga bacteriana baja (Ct>30) supuso un importante hándicap para la amplificación y posterior detección de resistencias.

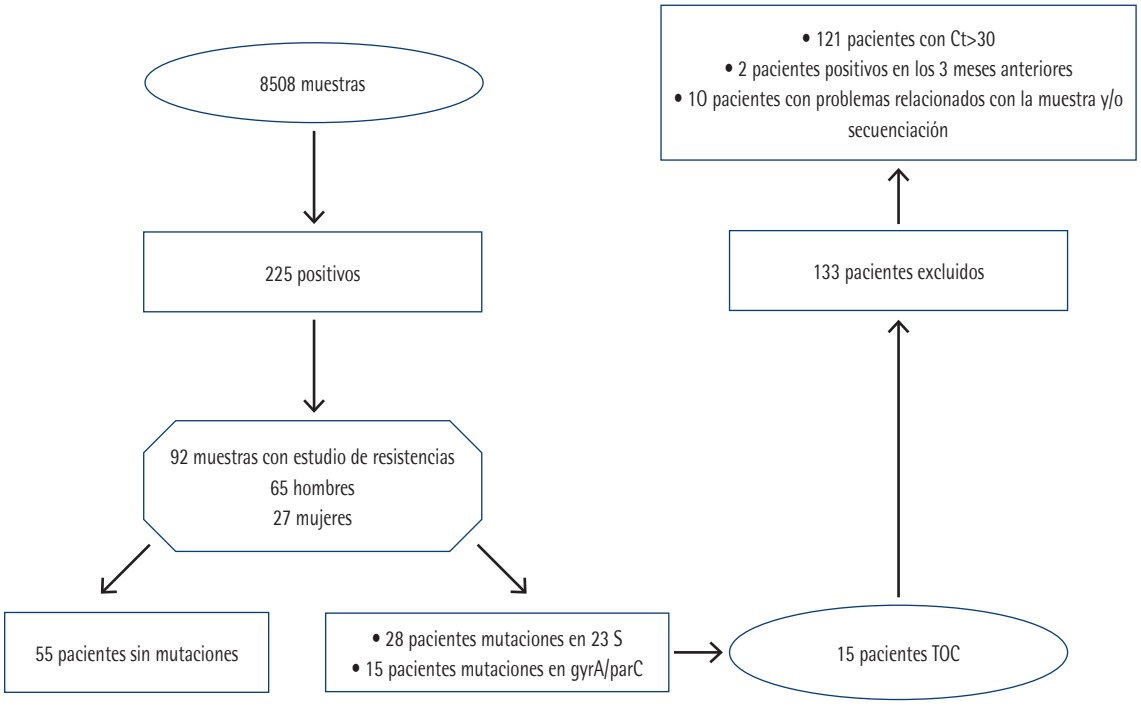

Figura 1 | **Diagrama de flujo del procesamiento de las muestras.**

Tabla 1 **Mutaciones detectadas en macrólidos (dominio V 23s) y quinolonas (*gyr*A y *par*C).**

Macrólidos: dominio V 23S rRNA	Nº muestras[a]	Hombres	Mujeres	Relevancia clínica
A2058T	1 (1,09%)	1(1,54%)		sí
A2058G	10 (10,87%)	10 (15,38%)		sí
A2059G	17 (18,48)	16 (24,61%)	1 (3.7)	sí
Quinolonas				
*par*C				
C184T(P62S)	9 (9,78%)	7 (10,17%)	2 (7.40%)	no
G248T(S83I)	1 (1,09%)	1 (1,54%)		sí
G248A (S83N)	1 (1,09%)	1 (1,54%)		sí[b]
G259T (D87Y)	3 (3,26%)	3 (4,61%)		sí
A281T (G94L)	1 (1,09%)	1 (1,54%)		no descrita
*gyr*A				
G286A(A96T)	1 (1,09%)	1 (1,54%)		no descrita
G295A (D99N)[d]	1 (1,09%)	1 (1,54%)		sí[c]

[a]Datos sobre población total a la que se le han realizado resistencias.
[b]Características similares a C284T (S83I).
[c]Asociado a mutaciones en *par*C.
[d]Asociada a la mutación G248T(S83I) en *par*C.

El estudio de resistencias se basó en analizar el dominio V del gen *23S rRNA* (283pb) [7] para determinar la resistencia frente a macrólidos y la región determinante de resistencia a quinolonas (QRDR) de los genes *gyrA* y *parC*, causantes de resistencia a fluoroquinolonas [8].

Los amplicones fueron secuenciados mediante tecnología Sanger BigDye Terminator v3.1 Cycle Sequence Kit (Applied Biosystems, Foster City, CA) en un secuenciador ABI 3500 (Applied Biosystems).

Las mutaciones detectadas frente a la cepa de referencia *Mycoplasma genitalium G37* (NC_000908.2) fueron registradas para estudiar si suponían un cambio aminoacídico relacionado con las resistencias descritas en las diferentes bases de datos.

Las historias clínicas de los pacientes fueron revisadas recopilando datos demográficos, tratamiento antibiótico utilizado, realización de test de cura, nueva consulta en el centro o persistencia de los síntomas.

RESULTADOS

Durante el periodo estudiado, 225 muestras fueron positivas para MG (2,64%), con una prevalencia mayor en hombres (3,59%) que en mujeres (1,68%). La mediana de edad fue 38,5 años (rango 14-68).

Después de aplicar los criterios de exclusión se les realizó el estudio de resistencias a 92 muestras (40.88%), de las cuáles 65 (70.65%) correspondían a hombres y 27 (29,34%) a mujeres (Figura 1).

En las mujeres la muestra de elección fue el exudado endocervical (92.6%), mientras que en los hombres fue el exudado uretral (83,07%) y el rectal (9,23%). También se detectaron 4 casos en orina y 5 en otras localizaciones.

En lo relativo al estudio genotípico, 28 pacientes presentaban mutaciones que confieren resistencias a macrólidos (30,43%). Las más habituales fueron A2058T (1.09%), A2058G (10.87%) y A2059G (18.48%).

Para las quinolonas, en el gen *parC* fueron detectadas mutaciones en 15 pacientes. Sin embargo, sólo 5 de ellos (5,43%), presentaban resistencias con demostrada relevancia clínica. Así, encontramos 1 mutación G248T(S83I) (1.09%),1 G248A (S83N) (1.09%) y 3 G259T (D87Y) (3.26%). En relación a las mutaciones en *gyrA*, cabe destacar a un paciente que presentaba la mutación G295A (D99N) asociada a G248T(S83I) en *parC*.

El resto de polimorfismos únicos de nucleótido (SNP) no descritos en la bibliografía o sin demostrado significado clínico aparecen recogidos en la Tabla 1.

Con respecto a la antibioterapia, se realizó TOC a 30 pacientes (32.6%), de los cuales 11 presentan resistencias únicamente a macrólidos y 4 a macrólidos y quinolonas.

Tabla 2 **Tratamiento empírico, tratamiento de segunda línea y evolución de los pacientes con mutaciones detectadas que realizaron test de cura.**

Paciente	Tratamiento previo	Mutación 23 s	Mutación *parC*/*gyrA*	Test de cura	Tratamiento dirigido	Resolución del cuadro
1*	Azitromicina + Doxiciclina	A2059G		-	-	sí
2*	Azitromicina	A2059G		+	Levofloxacino	sí
3*	Peniciclina G + azitromicina	A2058T		-	-	sí
4	Azitromicina	A2059G	C184T	+	Moxifloxacino	sí
5	Azitromicina	A2059G		+	Doxiciclina	sí
6	Azitromicina	A2058G		+	ND	ND
7	Azitromicina	A2058G	G248T/ G295A	+	ND	No (minociclina)
8*	Penicilina G+ ceftriaxona + azitromicina	A2059G		+	Moxifloxacino	sí
9	ND	A2059G	G248A	+	ND	ND
10*	Penicilina G	A2059G		-	-	sí
11	ND	A2058G		+	ND	ND
12	Azitromicina	A2059G		-	-	sí
13	Azitromicina	A2059G		+	Moxifloxacino	sí
14	Azitromicina	A2059G		+	Moxifloxacino	sí
15	Azitromicina	A2058G	G259T	+	Moxifloxacino	sí

-: Negativo; +: Positivo; ND: no disponible.

***Paciente 1: coinfección con *Neisseria gonorrhoeae*. Paciente 2: cobertura empírica. Paciente 3 y 10: coinfección con *Treponema pallidum*. Paciente 8: coinfección con *Neisseria gonorrhoeae*, *Chlamydia trachomatis* y *Treponema pallidum*.**

En la tabla 2 se describen los tratamientos empíricos y el tratamiento dirigido post test de cura de los pacientes con alguna mutación.

Por otro lado, 13 pacientes a los que se les detectó resistencias (13/28) no acudieron a consulta o no realizaron test de cura. Se obtuvo información acerca del tratamiento en 5 de ellos; dos pacientes resolvieron el cuadro clínico con tratamiento empírico con doxiciclina y al resto se les modificó el tratamiento empírico por persistencia de síntomas (en una ocasión se cambió a eritromicina y en los otros 2 se utilizó moxifloxacino).

DISCUSIÓN

Los resultados de nuestro estudio evidencian una prevalencia y una tasa de resistencias a los principales antibióticos implicados en el tratamiento de MG semejantes a lo descrito en la bibliografía [3].

Con respecto a las mutaciones asociadas a la resistencia a macrólidos, los resultados son similares a los publicados en otras regiones del país, siendo la mayoritaria la A2059G (17/28). [9,10]. En las muestras que presentaron mutaciones, en cuatro pacientes se observó tratamiento previo con 1,5 gramos de azitromicina; esta pauta se ha relacionado con un aumento de las resistencias a macrólidos [3].

Para las fluoroquinolonas, la ausencia de la mutación S83I en *parC* es altamente predictiva de curación con moxifloxacino [11,12]. Otros SNP con relevancia clínica son S83N, D87N y D87Y, aunque su papel está menos establecido y es necesario profundizar en su importancia en el futuro. El papel del gen *parC* ha sido escasamente descrito en estudios nacionales, como el de De Salazar et al [13].

Solamente 5 de nuestros pacientes presentaban mutaciones relevantes clínicamente. La mutación D87Y se encontró en 3 pacientes. En dos de ellos no se realizó test de cura, por lo que no podemos asegurar que se solventara el cuadro, y en el otro individuo el cuadro se resolvió con moxifloxacino. Un paciente presentaba la mutación S83N, del cual no se pudo obtener datos en relación a la antibioterapia ni a la resolución del caso y el último presentaba la mutación G248T(S83I) en *parC* asociada a G295A (D99N) en *gyrA*. Este paciente presentaba persistencia en los síntomas y finalmente fue tratado con minociclina. Aun-

que en nuestro estudio es un caso aislado, algunas mutaciones en *gyrA* se relacionan con fracaso terapéutico, tal y como sugieren las últimas revisiones al respecto [11,14].

En la población estudiada la mayoría de los casos son hombres (65/92) y además suponen prácticamente la totalidad de los positivos con mutaciones (27/28 para macrólidos y 5/5 en las mutaciones clínicamente relevantes para fluoroquinolonas). Entre ellos destacan los episodios de uretritis, siendo el exudado uretral la muestra más frecuente (83% de los casos).

Entre las limitaciones de este estudio se encuentran la difícil amplificación de los genes propuestos cuando la carga bacteriana obtenida en la PCR era insuficiente (Ct >30) y la imposibilidad de obtener un antibiograma para correlacionar los resultados fenotípicos con las mutaciones detectadas. También creemos que sería necesario acortar el tiempo de respuesta incorporando una PCR dirigida a SNP concretos, ya que las resistencias a macrólidos están bien descritas y podríamos obtener información rápida.

Además, aunque el tratamiento de segunda línea con fluoroquinolonas en los pacientes con resistencia a macrólidos supuso la resolución del cuadro en la mayoría de nuestros pacientes, la falta de información desde atención primaria en relación al tratamiento y la no realización del test de cura (30/92 secuenciados) impiden tener unos datos concluyentes sobre la efectividad de los tratamientos.

A pesar de estas limitaciones, los resultados de este estudio son de un valor importante, debido a la gran cantidad de casos secuenciados, el acceso a la información de la mayoría de los tratamientos junto a la evolución clínica de los pacientes, y la adición del estudio del gen *gyrA*.

En conclusión, la elevada tasa de resistencias en nuestro entorno evidencia la necesidad de realizar una terapia dirigida por el estudio genotípico de resistencias a macrólidos, apoyándonos en la detección de mutaciones en *parC* (especialmente S83I) y *gyrA* para predecir la susceptibilidad a quinolonas y en el uso del test de cura para evaluar la respuesta al tratamiento.

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CONFLICTO DE INTERESES

Los autores no presentan ningún conflicto de intereses.

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Letter to the Editor

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Pulmonary nocardiosis after covid-19 infection: case report and literature review

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Sir,

An increasing number of opportunistic infections in COVID-19 patients are being described especially for patients with underlying diseases and those who received immunosuppressive therapy. Among these opportunistic infections, fungal infections account for most case reports in COVID-19 patients (mainly *Aspergillus*). Other associated pathogens are viral, protozoa, helminth, and bacterial infections. Regarding these last prospective cohort study in England, Scotland, and Wales analyzed data from COVID-19 inpatients showing that the most common pathogens causing early respiratory coinfections are *Staphylococcus aureus* and *Haemophilus influenzae*. Indeed *S. aureus* and Enterobacteriaceae are also the most common secondary respiratory infections [1].

Nocardia is a gram-positive, ubiquitous, soilborne bacterium that belongs to the family of aerobic actinomycetes that seem like branching, filamentous rods on microscopy. This genus *Nocardia* includes more than eighty species, thirty of which could affect humans. In retrospective studies, *N. asteroides* and *N. farcinica* have often been identified as the predominant species over the years [2].

Most patients with nocardial infection are immunocompromised with cell-mediated abnormalities. Their most common causes are malignancy, organ and hematopoietic stem cell transplantation, and HIV infection. Glucocorticoid therapy has traditionally been linked to nocardiosis. Recently a matched retrospective study conducted at a tertiary hospital in central Israel of sixty hospitalized consecutive adult patients with nocardiosis showed that systemic corticosteroid therapy was strongly associated with pulmonary nocardiosis (matched OR 4.69, 95% CI 2.45–8.99, $p < 0.001$) [3].

Immunosuppressive therapy has been used to alleviate hyperinflammation and cytokine storm syndrome in COVID-19 patients. In fact, a recent meta-analysis confirmed that systemic corticosteroids were associated with lower 28-day all-cause mortality compared with usual care or placebo in COVID-19 patients who received oxygen or invasive mechanical ventilation [4].

Other conditions that have been associated with nocardiosis include diabetes mellitus, alcoholism, chronic granulomatous disease, alveolar proteinosis, structural lung disease, tumor necrosis factor-alpha inhibitor (e.g., infliximab) therapy, inflammatory bowel disease, chronic obstructive pulmonary disease, and tuberculosis.

In one review of 1050 cases [5] main clinical presentations of nocardiosis were systemic (32 %); pulmonary (only) 39 %; CNS (only) 9 %, cutaneous or lymphocutaneous (8 %) and single site extrapulmonary (egg, eyes, bone) 12 %. The onset of pulmonary nocardiosis may be acute, subacute, or chronic and is not distinguished by any specific signs or symptoms. Fever, night sweats, fatigue, anorexia, weight loss, dyspnea, cough, hemoptysis, and pleuritic chest pain have all been described.

Here-in we report a case of a patient initially admitted and treated for COVID-19 pneumonia who was subsequently readmitted due to persistent worsening dyspnea. Pulmonary nocardiosis after further evaluation was diagnosed. An English literature review showed only other five reports of these associations. Data regarding these cases are shown [6-10].

An 86-year-old man infected with SARS-CoV-2 was admitted to the hospital for productive cough and dyspnea on minimal exertion. He was already suffering from multiple health conditions, including type 2 diabetes mellitus, hypertension, and atrial fibrillation treated with dabigatran. He was receiving corticosteroid therapy and daily oral cyclophosphamide because IgG lambda multiple myeloma. Among other medical conditions, a chronic kidney disease IIIB2A stage diabetic nephropathy and non-exacerbator COPD were remarkable features. The patient received acute inpatient care in a

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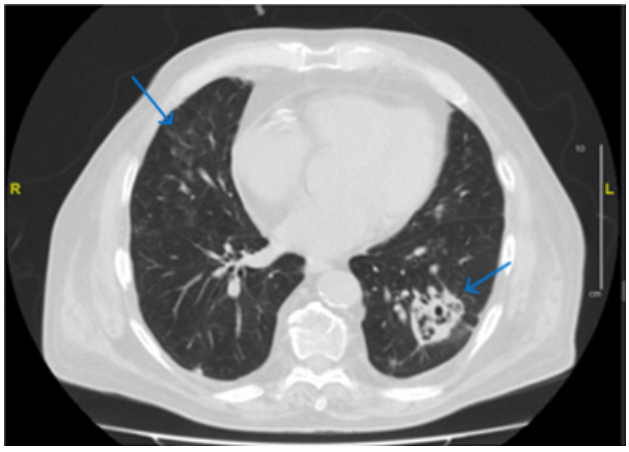

Figure 1 Multifocal and bilateral caviated condensations. Ground glass pattern areas and distal bronchial thickening.

Table 1 Risk factors and clinical characteristics of *Nocardia* COVID-19 coinfected patients.

Author (year) [reference]	Sex & Age	Risk factors	Days after COVID-19 diagnosis	Clinical picture	CT scan features
Colaneri (2021) [6]	Woman, 45 years	Untreated HIV/HCV IDU	5 days	Fever, coughing, dyspnea, fatigability (10 days). Oxygen saturation at room air: 94%	Multiple necrotic core lesions in both lungs, kidneys and soft tissues with peripheral contrast enhancement
Laplace (2021) [7]	Male, 86 years	Type 2 DM, COPD, Crohn´s disease	13 days	Acute dyspnea, fever, productive cough	Dense consolidation with air bronchograms in lower lung lobes
Atemnkeng (2021) [8]	Male, 63 years	Morbid obesity, Type 2 DM	32 days	Worsening shortness of breath. Oxygen saturation at room air: 77%	Near-complete opacification of the left hemithorax with minimal sparing of the apical region MRI: multiple bilateral ring-enhancing lesions in the brain
Arif (2021) [9]	Woman, 61 years	Type 2 DM, hypertension, HF	10 days	Dyspnea	Right upper lobe 3.3 x 3.2 cm mass and a left upper lobe 1.9 x 1.5 cm nodule
Driscoll (2022) [10]	Male, 16 years	Bronchiectasis Pseudomonas aeruginosa infection	6 days	Fever, dyspnea, cough, and lethargy	Left lower lobe opacification but no necrosis or pulmonary embolus
Ortiz (2023) [Present case]	Male, 86 years	Type 2 DM, hypertension, myeloma, COPD, atrial flutter, CKD	11 days	Increased productive cough, dyspnea Oxygen saturation at room air: 82%	Multifocal and bilateral cavitated condensations. Ground glass pattern areas and distal bronchial thickening

Type 2 DM: type 2 diabetes mellitus. COPD: Chronic obstructive pulmonary disease. CKD: Chronic kidney disease. HF: heart failure. HIV/HCV: chronic hepatitis C virus & HIV coinfected. IDU: Injecting drug user. SLE: Systemic lupus erythematosus.

hospital for ten days including high-flow oxygen, oral dexamethasone, and ceftriaxone. Oral cyclophosphamide was temporarily stopped.

The patient had been in his usual state of health until 5 days before this new admission (11 days after he was discharged), when fever developed. He noted shortness of breath at rest and dyspnea on exertion. He was brought to the emergency department of our hospital for further evaluation.

On examination, the temperature was 36.7°C, the blood pressure 107/62 mm Hg, the pulse 111 beats per minute, respiratory rate twenty-eight breaths per minute, and oxygen saturation 82% while the patient was breathing ambient air. Respiratory rate decreased to twenty-two breaths per minute and the oxygen saturation improved to 95% with the administration of supplemental oxygen through a nasal cannula at a rate of four liters per minute. Inspiratory crackles could be heard at the lung bases. The heart sounds were regular, with tachycardia but no murmur. There was no tenderness on palpation of the abdomen and no pitting edema were present in the legs.

Laboratory test results at admission were: leukocytes 8.9 10e9/l (3.5-12.0), lymphocytes 0.08 10e9/l (1.30-4.00); monocytes 1.70 10e9/l (0.20-1.00); hemoglobin 9.9 g/dl (13.5-17.5); hematocrit 29.5% (41- 53); platelets 119 10e9/l (140-450); neutrophils/lymphocytes ratio 89.00 (<3.13 covid-19 more favorable prognosis >3.13 COVID-19 less favorable prognosis); prothrombin time 17 sec (9.40-12.50); Quick index 57% (70.00-100.00); INR 1.4 ratio (0.5-1.5); D-dimer 2,171 ng/ml (0.00-500.00); urea 85 mg/dl (18-44); creatinine 1.67 mg/dl (0.53-1.18); albumin 2.89 g/dl (3.50-4.60); C-reactive protein 17.39 mg/dl (0.00-0.50); procalcitonin 0.91 ng/ml (0.00-0.50). His arterial blood gas analysis (ABG) revealed: arterial pH 7.495 pH (7.34 - 7.44); arterial pO2 50.1 mmHg (75.0-100.0); arterial HCO3- 26.7 mmol/l (22.0-26.0); arterial O2 saturation 86.3% (95.0 -98.0).

Chest x-ray revealed dense consolidations with air bronchograms in the lower lung lobes. Both SARS CoV-2 antigen and rT-PCR in nasopharyngeal sweep were positive (Ct = or < 30 expressing high viral load). The patient was started on empirical meropenem, oxygen supplementation through nasal prongs, and intravenous remdesivir.

A thoracic CT scan (Figure 1) revealed multifocal and bilateral cavitated condensations. Ground glass pattern areas and distal bronchial thickening. The sputum culture from day five showed abundant leukocytes and no acid-alcohol resistant Gram-positive branching rods in gram stain compatible with *Nocardia* species.

He was initially treated with broad-spectrum antibiotics (meropenem and vancomycin) and thereafter treatment was changed to intravenous imipenem for 4 weeks. We ruled out the use of cotrimoxazole or linezolid due to the foreseeable toxicity at the kidney and bone marrow level in this specific patient.

The patient was discharged home on oral minocycline 100 mg every 12 hours for 6 months.

While corticosteroids have been shown to have varying effects on T lymphocytes, high doses can cause a rapid depletion of circulating T cells by redistribution of circulating cells to other body compartments. In addition, they cause inhibition of interleukin (IL)-2, a cytokine that is essential for the function, differentiation, and proliferation of T-cells. They can also induce apoptosis of T-lymphocytes, which further depletes the total pool of mature functioning T-cells. All these mechanisms result in a profound immunosuppressive state that promotes the development of opportunistic infections.

It has been previously demonstrated that due to the downregulation of various proteins associated with immune function, the immune system is suppressed early during COVID-19 [11]. There is now a growing body of evidence that supports that COVID infection can lead to significant dysregulation of the immune system. Severe COVID infections have been characterized by lymphocytopenia, which is currently used as a prognostic indicator of clinical deterioration and poor outcomes.

We identified only five published case reports (6 overall including our case) of adult patients with a mean age of 59 years (16-86). Main risk factors and clinical characteristics of Nocardia COVID-19 coinfected patients are shown in table 1. Four patients were male (66%). Well-known risk factors were present in all six patients (type 2 diabetes as the main factor). Nocardia infection was diagnosed at a median of 13 days after diagnosis of Covid 19 (5-32 days). Main clinical features were acute o worsening dyspnea, acute respiratory failure, and productive cough. Radiological imaging tests showed mainly lobar or multilobar consolidation and lung cavitating lesions.

Table 2 summarizes microbiological and treatment features and outcomes of Nocardia COVID-19 coinfected patients. As described in the literature *Nocardia cryiacigeorgica*, *Nocardia asteroides* and *Nocardia farcinica* were predominating species. Patients received appropriate combined Nocardia treatment including trimethoprim/sulfamethoxazole, meropenem, linezolid or ceftriaxone. In hospital mortality was 33%.

Empiric antimicrobial treatment included intravenous administration of at least two agents that represent the first-line therapy (either amikacin, imipenem, or a third-generation cephalosporin) and should trimethoprim sulfamethoxazole [12]. After a minimum of 3 weeks of intravenous therapy, patients can be switched to oral treatment.

In summary, severe COVID-19 lung infection, SARS-CoV-2 induced dysregulation of the immune system and widespread use of steroids in COVID 19 can favor Nocardia as an opportunistic infection. We believe that these cases should serve as an example of potential threats of high steroid exposure in this patient population. We would like also to point out the relevance of early attention to opportunistic infections in patients with recent COVID infections.

Table 2 **Microbiological and treatment features and outcome of *Nocardia* COVID-19 coinfected patients.**

Author (year) [reference]	*Nocardia* species	Sample	COVID treatment	*Nocardia* treatment	Outcome
Colaneri (2021) [6]	*Nocardia cyriacigeorgica*	Blood culture	PIP/TAZ TMP/SMX	Linezolid, TMP/SMX and Ceftriaxone (one year)	Cure
Laplace (2021) [7]	*Nocardia cyriacigeorgica*	Sputum	DXM 6 mg/24h, enoxaparin, cefotaxime	Imipenem and TMP/SMX	In hospital death
Atemnkeng (2021) [8]	*Nocardia asteroides*	BAL	Azithromycin, ceftriaxone, REM, DXM y enoxaparin	Meropenem/linezolid TMP/SMX (one year)	Cure
Arif (2021) [9]	*Nocardia farcinica*	Lung biopsy	DXM 4mg oral	TMP/SMX Meropenem/linezolid	Discharged
Driscoll (2022) [10]	*Nocardia farcinica*	Bronchial secretion	Tobramycin, ceftazidime DXM	Linezolid	In hospital death
Ortiz (2023) [Present case]	*Nocardia* spp	Sputum	REM (10 días), ceftriaxone DXM	Imipenem Ceftriaxone	Discharged

COVID-19: Coronavirus disease 2019. PIP/TAZ: Piperacillin/tazobactam. TMP/SMX: Trimethoprim/sulfamethoxazole. DXM: dexamethasone. BAL: bronchoalveolar lavage. CSF: Cerebrospinal fluid. REM: remdesivir.

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CONFLICT OF INTEREST

Authors declare no have conflict of interest.

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Letter to the Editor

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Fungal corneal abscess caused by *Exophiala dermatitidis*

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Sir

Exophiala dermatitidis is a saprophytic black yeast. It is widely distributed in the natural environment and it has the capacity to grow in extreme conditions. Although human infections caused by *E. dermatitidis* are rare, this fungus can occasionally cause subcutaneous and systemic infections. Factors that contribute to pathogenicity are its ability to produce biofilm and melanin, which forms part of the cell wall of black yeasts [1,2]. Here, we present a case of corneal infection by *E. dermatitidis*.

A 68-year-old woman was admitted to the Emergency Department for pain and red eye of one week of evolution. She had undergone a protected penetrating keratoplasty a year ago. Biomicroscopy revealed conjunctival hyperemia, transparent corneal button, brownish corneal foreign body with rubbery paracentral aspect with perilesional corneal thinning. Corneal foreign body was removed and a sample was sent to our laboratory. The patient was initially treated with moxifloxacin eye drops and oral doxycycline and later the treatment was changed to vancomycin and ceztazidime eye drops and oral doxycycline.

The sample obtained was incubated in blood, chocolate and Sabouraud agar and thioglycolate broth. There was growth of dark colonies after 48 hours of incubation at 37°C in the three media and in the reseed of thioglycolate (Figure 1A). The Gram staining of these colonies is shown in Figure 1B.

The identification of the microorganism isolated was realized by matrix-assisted laser desorption/ionization-time-of-flight-mass spectrometry (MALDI-TOF MS) (Maldi Biotyper®Bruker Dal-tonics) resulting in *E. dermatitidis* with a score value of 2.4.

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Antifungal susceptibility testing was performed by microdilution (Sensititre YeastOne, Thermo Fisher). The minimum inhibitory concentrations (MIC) of amphotericin B (0.50 mg/L), itraconazole (0.12 mg/L), voriconazole (0.03 mg/L), and posaconazole (0.03 mg/L) against the pathogenic strain were found to be low. However, MIC of fluconazole (8 mg/L), micafungin (>8 mg/L), caspofungin (>8 mg/L) and anidulafungin (>8 mg/L) were high. Based on these results, voriconazole eye drops for two months and oral voriconazole during three weeks were administered with good clinical evolution.

Reviewing the literature, we have only found a few cases of eye infection by *E. dermatitidis* [1,3-6]. However, this yeast is involved in diverse pathologies such as central line infection [7], pneumonia [8], meningoencephalitis [9] or skin and soft-tissue infections [10] among others.

Regarding susceptibility, there are no defined breakpoints for any species in the genus. Our strain had high MIC to fluconazole and echinocandins. These data are in line with other reported cases [1, 4]. It is necessary to study large number of cases in order to obtain representative data of the antifungal susceptibility of this species.

The case presented here confirm the ability of *E. dermatitidis* as an opportunistic pathogen especially in patients with ocular trauma, pre-existing ocular disease or immunocompromised states.

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CONFLICT OF INTEREST

Authors declare no have conflict of interest.

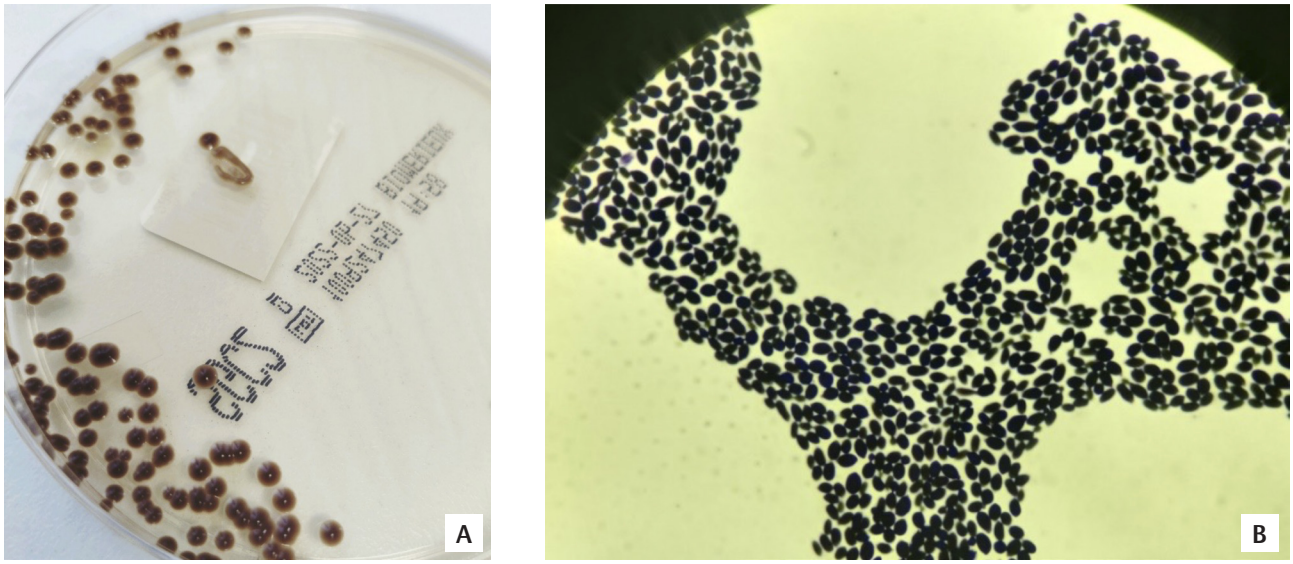

Figure 1 | **A) Image of brownish colonies of *E. dermatitidis* in Sabouraud agar. B) Gram staining of *E. dermatitidis* colonies**

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Carta al Director

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Concordancia entre el GeneXpert y el Life Real Detection Kit en el diagnóstico de las infecciones respiratorias agudas

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Estimado Editor:

Los nuevos protocolos de manejo clínico de los pacientes con infección respiratoria aguda necesitan el diagnóstico rápido de las infecciones por SARS CoV-2, gripe y virus respiratorio sincitial por lo que los Laboratorios de Microbiología deben disponer de los medios adecuados para dar respuesta a esta demanda durante las 24 horas de los 7 días de la semana.

Desde el punto de vista clínico, la detección rápida de las infecciones respiratorias agudas producidas por SARS CoV-2 y gripe ayuda a seleccionar el tratamiento antiviral en los pacientes vulnerables o con indicación del mismo y dado que dicho tratamiento es más efectivo en función de la precocidad de la administración, la rapidez del diagnóstico contribuirá a un tratamiento más eficaz, en la elección del antiviral correcto y su administración precoz. En cuanto al VRS, en población muy seleccionada, contribuirá a la indicación del tratamiento, y en población no susceptible de tratamiento, a evitar tratamientos antibióticos en cuadros de infección respiratoria de vías altas. Además, de la importancia del diagnóstico rápido en el manejo de los pacientes, es importante a la hora de aplicar medidas de prevención y control de infecciones de forma rápida, como la rápida gestión de aislamientos y camas en función del virus identificado [1,2].

En este marco, hemos evaluado la concordancia de uno de los sistemas de diagnóstico rápido más utilizados en la práctica clínica asistencial (Genexpert® Xpert Xpress CoV-2/Flu/RSV plus, Cepheid) con un nuevo sistema que acaba de llegar al mercado (Life Real (2019-nCoV/Influenza/RSV Nucleic Acid (RNA) Detection Kit, HangZhou Lifereal Biotechnology).

Hemos analizado en paralelo las primeras 80 muestras recibidas durante el periodo estudiado (octubre y noviembre de 2022); 20 positivas para SARS CoV-2, 20 positivas para gripe y 20 positivas para virus respiratorio sincitial. No hay ningún caso de infección mixta por estos virus. También hemos procesado las primeras 20 muestras negativas para los tres virus. En este periodo, la variante circulante más prevalente en nuestro medio es Omicron (Linaje BA.5) y todos los casos de gripe son causados por influenza A [3].

Ambas técnicas tienen formato individual y la prueba evaluada es fácil y rápida de realizar (mezclar 10µl de Magnetic Beads y 200µl de muestra al cartucho de PCR que viene incluido en el kit y cargar en el aparato) por lo que el tiempo técnico de ambas técnicas es similar (menor de 5 minutos por muestra). Como desventaja frente a la técnica de referencia, no permite diferenciar entre influenza A y B, el tiempo de procesamiento de la técnica es más largo (84 versus 36 minutos) y se trata de una técnica cualitativa.

El análisis de concordancia muestra un elevado índice kappa (98% para SARS CoV-2 y 95% para gripe y virus respiratorio sincitial) ya que la única discrepancia detectada es la existencia de 1 falso negativo para el primer virus y 2 falsos negativos para los otros dos virus estudiados. Considerando como patrón de referencia los datos aportados por el Genexpert /Cepheid) la sensibilidad de la prueba es: SARS CoV-2 95%, Gripe 90% y VRS 90% con una especificidad del 100% en todas ellas. Todas estas muestras discrepantes tenían baja carga viral (Ct superiores a 35) por el sistema de referencia y por tanto, con baja capacidad de transmisión del proceso; esta disminución de la sensibilidad también se produce en otras técnicas como las basadas en RT-LAMP (reverse-transcription loop-mediated isothermal amplification) [4].

La disponibilidad de varios métodos diagnósticos que ofrezcan resultados en menos de 90 min basados en la detección del genoma de los tres virus de forma simultánea, aporta importantes ventajas para el manejo de estos pacientes en relación con la detección de antígenos virales, técnicas que muestran una menor sensibilidad especialmente frente a

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algunas variantes virales (hasta el 50%) y que habitualmente ofrecen información exclusivamente sobre la presencia de SARS CoV-2, lo que limita su utilidad en la práctica clínica asistencial en los próximos meses de convivencia de los tres virus en nuestro entorno [5-8].

Aunque hemos realizado una evaluación preliminar, nuestros datos muestran que la técnica evaluada puede ser una alternativa válida como complemento de las herramientas ya disponibles en el mercado teniendo en cuenta que es recomendable disponer de varios métodos diagnósticos de estos procesos que puedan paliar posibles roturas de stocks, problemas técnicos de los equipos, etc [9].

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses

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Letter to the Editor

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Kikuchi-Fujimoto Disease: a rare type of lymphadenopathy and its plausible relationship with human papillomavirus vaccines

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Sir,

Kikuchi-Fujimoto Disease (KFD) or histiocytic necrotizing lymphadenitys is a rare, benign self-limited disorder characterized by subacute necrotizing regional lymphadenopathy. It was thought that it commonly affected young Asian adults, mainly females. However, further research has shown that males and females are equally affected, and different cases have been reported all over the world [1,2].

KFD is usually presented as painful cervical nodes and is frequently associated with fever, headache, night sweats, nausea, vomiting and sore throat. Cervical lymphadenopathy is evidenced in 60-90% of cases, with concomitant involvement of axillary and/or supraclavicular lymph nodes [1,2]. Extranodal locations are uncommon [3]. Systemic symptoms like splenomegaly and hepatomegaly occur in less than 5% of cases [1]. Most patients have normal laboratory findings. Analytical abnormalities in some patients include elevated serum lactate dehydrogenase and aminotransferases. Leukopenia has been detected in 50% of KFD patients [4,5].

Etiology of KFD is still unknown. Two main theories have been postulated: infections and autoimmune origin. Numerous viruses and other infectious agents have been proposed as etiologic agents of KFD: Epstein-Barr virus; herpes simplex virus; varicella zoster virus; human herpesviruses 6, 7, and 8; parvovirus B19; paramyxovirus; parainfluenza virus; rubella; cytomegalovirus; hepatitis B virus; human immunodeficiency virus; *Brucella* spp., *Bartonella henselae, Yersinia enterocolitica, Toxoplasma gondii, Entamoeba histolytica,* and *Mycobacterium* spp. [6]. KFD seems to be related to an overactive T-cell-mediated immune response [2, 3]. Patients diagnosed with KFD frequently have human leukocyte antigen (HLA) class II alleles, specifically HLA-DPA1 and HLA-DPB1, which are more prevalent among Asians and rare or absent in Caucasians [7].

KFD diagnosis is based on histopathological analysis. The disease may resolve spontaneously without treatment. NSAIDs or paracetamol are first line of treatment for symptomatic control. Despite the overall prognosis is satisfactory, symptoms can last up to weeks or months [8,9]. In chronic, recurrent or complicated cases; corticosteroids, intravenous immunoglobulins and hydroxychloroquine can represent an alternative [10].

The human papillomavirus (HPV) is a known etiological agent of cervical cancer and other types of cancer, reason why vaccination campaign is established for certain population groups. There are three different marketed vaccines that differ in the number of serotypes they contain; the bivalent vaccine (HPV2), which protects against HPV types 16 and 18; the tetravalent vaccine (HPV4), which protects against types 16, 18, 6, and 11; the 9-valent vaccine (HPV9), which protects against types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

It is already widely proven that vaccines are effective, cost-effective and safe [11]. However, there have been reports of subacute course or complicated lymphadenopaties associated with HPV vaccination [12,13]. KFD associated to HPV vaccination has only been reported in the literature once [14].

Recently, there have been reports of KFD related to vaccination, mainly to COVID-19 vaccines [15]. Due to this growing increase, the immunomodulatory mechanism of vaccination and the underdiagnosis of KFD, a literature and adverse events databases search has been conducted to assess the possible relation between HPV vaccines and KFD.

A search in the Spanish adverse events database (FEDRA) and the European adverse events database (Eudravigilance) was carried out. To be aware of KFD cases, search criteria were "*HPV Vaccines; Gardasil® and Cervarix®*" **and** the diagnosis *"Histiocytic necrotising lymphadenitis"*, as well as a search of *"Histiocytic necrotising lymphadenitis"* for any drug. To know the cases with any other lymphadenopathy a new search with

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Table 1 HPV vaccines associated KFD cases in Eudravigilance

Case	Sex	Country	Vaccine	Other immune disorders*	Outcome**	Seriousness
1	F	Germany	Gardasil (16,18)®	Lymphadenopathy	Recovered	No
2	F	Japan	Cervarix®	Lymphadenopathy	Not recovered	Hospitalization
3	F	Japan	Cervarix®	Lymphadenopathy Splenomegaly Elevated aminotrasnferases	Recovered	Hospitalization
4	F	Japan	Cervarix® Encevac®	Painful lymphadenopathy	Recovered	Hospitalization
5	F	Portugal	Gardasil (6,11,16,18)®	Lymphadenopathy	Recovering	Hospitalization

*** Other reported AE apart from KFD. **At time of notification**

the criteria "*lymphadenopathy and linphadenitis*" for the same vaccines was conducted. According tothe Medical Dictionary for Medical Activities version 25.0 (MedDRA). All adverse events registered as September 18th 2022 were included.

The study was conducted in accordance with the ethical standards established in the Declaration of Helsinki. Since FEDRA and Eudravigilance are anonymized, no informed consent was required.

FEDRA encompassed only three KFD adverse reports, one related to methotrexate, other to elasomeran (Spikevax®) and the other to tozinameran (Comirnaty®). No case of KFD associated to HPV vaccines was found. On the other hand, Eudravigilance included a total of 62 KFD cases, of which 5 were associated to HPV vaccines (table I) and 19 to other vaccines.

Regarding HPV vaccines associated reports, 3 cases occurred after Cervarix® vaccination [one case also had the Japanese encephalitis vaccine as suspected drug, Encevac®, and two after Gardasil®. Median age was 13 (range 12-26). Out of the 5 cases, four required hospitalization and in all five cases other lymphadenopathy was also notified.

In case 2, screening for influenza A and B viruses was negative. In case 3, the following serologies were negative: adenovirus, CMV, enterovirus, VEB, VHA, VHB, toxoplasma and mycoplasma. In both cases 2 and 3, Quantiferon test was also negative. In case 4, serologies for VEB, VIH, VHB, VHC and parvovirus B19 were negative.

Concerning "*lymphadenopathy and linphadenitis*", 7 cases for Cervarix® and 16 for Gardasil® were found in FEDRA. Whereas 108 and 547 cases were found for Cervarix® and Gardasil®, respectively, in Eudravigilance.

In relation to other vaccines, 15 cases of KFD related to COVID-19 vaccines were found. Moreover two reports of KFD disease connected to tetanus, diphtheria, pertussis, and polio disease vaccine, one case of KFD related the flu vaccine was reported, and other one with bacilli Calmette-Guerin. Median age was 30 (range 10-52). Six of these cases had another type of lymphadenopathy as well. Eight of them were serious and seven required hospitalization.

KFD is a rare entity, which real incidence is unknown. Due to its self-limited course and its common symptoms, it is often mistaken with other lymphadenopathies, and is probably underdiagnosed [6].

The current incidence of lymphadenopathy with HPV vaccines is not clearly established. Data Sheets of bi and tetra-valent vaccines describe the frequency of lymphadenopathy as "not known", whilst in the 9-valent vaccine it is described as "rare". Underreporting and the fact that the data reported in pharmacovigilance databases may be incomplete, are a clear limitation to assess a relationship.

In the Spanish national adverse events database, 25 events categorized under the MedDRA term *"Lymphatic system disorders"* have been reported for bi, tetra and 9-valent vaccines. This means that some of these cases could have been KFD and might have not been properly diagnosed.

According to table 1, 3 of 5 cases correspond to female of Asian origin, which fits the data available. The literature review shows that KFD frequently presents concomitantly with other lymphadenopathies [1], and in the five cases described, any lymphadenopathy was also reported apart from KFD. The T-lymphocyte-mediated immune response at the lymph node level post-vaccination could also contribute to the development of KFD [1]. In three of five cases, negative microbiological test were available. Taking into account the infectious origin of KFD and the immunomodulated mechanisms, plausible causal relationship may be reinforced, although more research is required.

Symptoms of KFD may be confused with lymphomas, making proper diagnosis mandatory to avoid unnecessary clinical tests. Four cases required hospitalization. Knowledge of KFD could have avoided prolonged hospitalization as well as reduced health care costs.

KFD is an entity of probably multifactorial origin and re-

search is needed to understand the origin of the disease. Reporting of suspected adverse events is essential to assess the real incidence and to optimize patient management presenting with lymphadenopathy of subacute course or with some complication.

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CONFLICT OF INTEREST

Authors declare no have conflict of interest.

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Carta al Director

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Bacteriemia por *Solobacterium moorei* en paciente con sinusitis

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Estimado editor: *Solobacterium moorei* es un bacilo Gram-positivo anaerobio estricto que forma parte de la microbiota oral y fecal y juega un papel en la halitosis [1]. Sin embargo, también puede ser un patógeno oportunista, causando bacteriemia, infecciones de herida u otros cuadros [2]. Presentamos un caso de bacteriemia por *S. moorei*, con foco probable en una sinusitis.

Una mujer de 19 años acudió al Servicio de Urgencias por dolor en zona maxilar izquierda de 24 horas de evolución, acompañado de fiebre, edema y eritema palpebral en hemicara izquierda. A su llegada la paciente estaba febril (39,6ºC), taquicárdica (144 lpm) e hipotensa (97/55 mmHg). Se realizó TC, donde se observaron hallazgos compatibles con sinusitis aguda con ocupación de la totalidad del seno maxilar y celdillas etmoidales izquierdas. Se extrajeron hemocultivos e ingresó a cargo del Servicio de Otorrinolaringología con pauta de amoxicilina-clavulánico (1g/8h iv), metronidazol (500mg/100ml/12h iv) y corticoide (20mg/8h iv).

Un TC realizado el cuarto día de ingreso (Figura 1) mostraba una sinusitis izquierda con patrón de obstrucción de unidad osteomeatal complicada con absceso subperióstico que improntaba a la grasa extraconal orbitaria. Debido a la mala evolución, se realizó abordaje quirúrgico mediante cirugía endoscópica nasosinusal, logrando drenar el seno maxilar, las celdillas, etmoidales y el absceso subperióstico adyacente. Se tomaron muestras del material purulento para cultivo.

Los hemocultivos recogidos en el Servicio de Urgencias se remitieron al Servicio de Microbiología en frascos aerobios y anaerobios y fueron incubados en el equipo BD Bactec Fx (Becton Dickinson, Franklin Lakes, USA). Tras 64 horas de incubación se detectó crecimiento en un frasco anaerobio, cuya tinción de Gram mostró bacilos Gram-positivos. Se realizaron subcultivos en agar sangre y Schaedler, incubándose el primero en atmósfera enriquecida con CO_2 y el segundo en anaerobiosis. A las 72 horas se observaron unas colonias grisáceas de pequeño tamaño (aproximadamente 0,5mm de diámetro) únicamente en las placas incubadas en anaerobiosis. La espectrometría de masas (MALDI-TOF MS [Bruker, Billerica, USA]) realizada a partir de las colonias identificó el microorganismo como *S. moorei* (score 2,33).

La concentración mínima inhibitoria (CMI) obtenida mediante tiras de gradiente (Liofilchem, Roseto degli Abruzzi, Italia) de penicilina, amoxicilina-clavulánico y metronidazol fue de 0,19, 0,094 y 0,094 mg/L respectivamente. El aislado era sensible a todos ellos según los puntos de corte de CLSI (M100 ED32:2022) y EUCAST (v11.0).

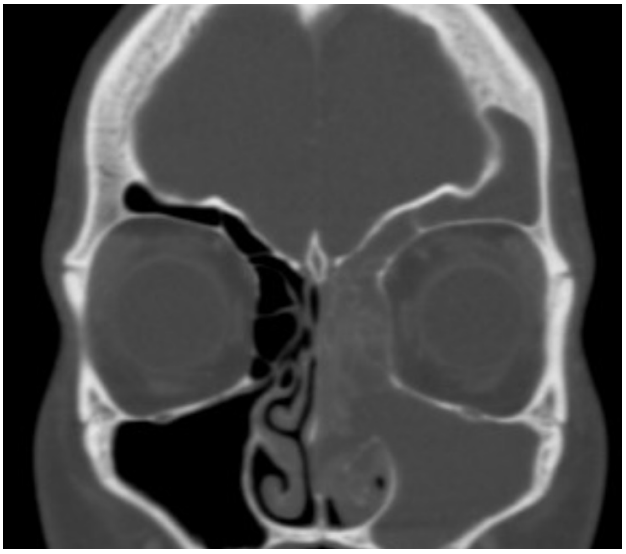

Figura 1 TC en el que se aprecia ocupación de los senos izquierdos.

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En las muestras de pus creció abundante microbiota mixta aerobia y anaerobia, entre la cual se hallaba *S. moorei*.

El cuadro clínico mejoró tras el drenaje quirúrgico y la paciente fue dada de alta tras 11 días de ingreso, manteniendo el tratamiento con amoxicilina-clavulánico 875/125mg/8h durante 7 días más.

S. moorei forma parte de la microbiota oral y fecal, pero la muestra clínica en la que más frecuentemente ha sido aislado es la sangre [2,3]. Esto podría deberse, entre otras causas, a un mayor esfuerzo por parte de los microbiólogos para alcanzar la identificación a nivel de especie en este tipo de muestra. Además, es frecuente que *S. moorei* forme parte de infecciones polimicrobianas [2,4,5], lo cual dificulta establecer cual es realmente su papel patógeno en esas ocasiones.

El caso que describimos se presentó como un cuadro séptico derivado de una sinusitis, en el que se pudo identificar *S. moorei* como único microorganismo presente en la sangre de la paciente, aislándose también junto a abundante flora mixta en las muestras del pus drenadas de la sinusitis, lo que sugiere que pudiera ser el origen de la bacteriemia. Es el primer caso de bacteriemia por *S. moorei* publicado cuyo foco probable fue una sinusitis. Otros estudios mencionan como posible foco infecciones bucales, colangitis o translocación de flora intestinal [2,6].

Hasta el momento, los casos descritos de bacteriemia por *S.moorei* se habían descrito en pacientes con patología de base, enfermedad hematológica u oncológica [2,3,5], siendo este el primero publicado en una paciente joven sin enfermedades de base.

S. moorei es un patógeno oportunista poco frecuente, de crecimiento lento y de difícil identificación. La identificación mediante secuenciación del gen 16S rRNA es lenta, costosa y no está disponible en todos los laboratorios. En nuestro caso, la identificación se realizó gracias a la espectrometría de masas, una herramienta ampliamente empleada hoy en día en los laboratorios de Microbiología que permite identificar patógenos de manera rápida y fiable [2,5,7,8]. Las mejoras en las bases de datos han aumentado el número de microorganismos que pueden ser identificados, como es el caso de los anaerobios [9]. El empleo de estas técnicas podría explicar el mayor número de infecciones por *S. moorei* observadas en los últimos años, cuyo papel como patógeno aún está por determinar.

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de interés.

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Letter to the Editor

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Use of ceftaroline in complex central nervous system infections

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Sir,

Ceftaroline fosamil is a fifth-generation cephalosporin approved for skin and soft tissue infections and pneumonia, but its use in out-off-label indications is increasing, as we have previously reported in this journal [1]. It is particularly valuable in serious infections with participation of resistant gram-positive microorganisms, in which other options as vancomycin, linezolid or daptomycin may be restricted because of adverse effects or low efficacy. Few data are available about its use in central nervous system (CNS) infections.

In the last 5 years, we have recorded 5 CNS infections treated with ceftaroline [1]. We here present two of them which were evaluable.

Case 1

A 67-year-old woman was admitted due to fever and gait instability. She was carrying a ventriculoperitoneal shunt device placed 10 years ago. Blood cultures were obtained, and methicillin-susceptible *Staphylococcus aureus* (MSSA) grew 23 hours later in 2 of 2 sets. MIC to vancomycin was 2 mg/L using microdilution and 1.5 mg/L by E-test. A sample of cerebrospinal fluid (CSF) was obtained from the ventriculoperitoneal shunt reservoir. Gram stain revealed Gram-positive cocci in grape-like clusters and MSSA grew in aerobic culture. Infection of the ventriculoperitoneal shunt was then confirmed and the device was removed. While waiting for definite antibiotic susceptibility testing and confirming microbiological clearance in repeated blood cultures, ceftaroline (600mg every 8 hours) was employed for the first 7 days and then switched to cloxacillin plus linezolid. After 2 weeks of antibiotic treatment, CSF culture was negative, ventriculoperitoneal shunt was replaced, and patient was discharged one week afterwards.

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Case 2

A 77-year-old man was admitted due to traumatic brain injury with a subdural hematoma. A craniotomy was performed. 2 months later cranioplasty with autologous bone was made, and 1 week afterwards patient developed a subdural empyema in surgical site. Re-intervention was performed, collection was removed, and culture showed polymicrobial growth of EBSL-producing *Escherichia Coli, Enterococcus faecalis*, methicillin-resistant and linezolid-resistant (MIC > 4 mg/L) *Staphylococcus epidermidis* and *Corynebacterium amycolatum*. Treatment was initiated with meropenem and vancomycin. Nevertheless, CT scan performed 2 weeks later revealed worsening of the epidural collection with data suggestive of cerebritis. Surgical debridement was made again and autologous bone plasty was removed. Antibiotic therapy was changed to meropenem + ceftaroline (600mg every 8 hours) and maintained for 4 weeks. CT scan then showed resolution of the collection.

These two cases show the usefulness of ceftaroline for complicated CNS infections in which resistant-gram positive microorganisms' participation is suspected. The first case is an infection of ventriculoperitoneal shunt by MSSA with secondary bacteriemia. While waiting for susceptibility test, daptomycin was considered inappropriate as first-line therapy because of its low penetration in CSF, as it was linezolid for its bacteriostatic effect in bacteriemia. The second case is a complex patient with post-surgical epidural empyema with multi-resistant isolations. Here, ceftaroline was used against methicillin-resistant *S. epidermidis* after clinical failure with vancomycin, being linezolid ruled out because of resistance.

Available literature in this scenario is scarce. A large retrospective study conducted by Britt et al. evaluated ceftaroline in 764 patients, 2% of which had meningitis. Mortality was low (6%), but microbiological etiology or causes of death were not provided [2]. Martin-Cerezuela et al performed a retrospective study involving patients with *Streptococcus pneumo-*

niae penicillin-susceptible meningitis, comparing ceftaroline (n=5) and standard therapy (n=20). There was a non-statistically significant lower mortality in ceftaroline group (0% vs 40%, P=0,016) despite of being more severe cases [3]. Most experience comes from case series, including some regarding ceftaroline use in epidural abscess, mainly due to MRSA, with promising results [4-6]. Skoulas et al described 5 patients with gram positive bacterial meningitis (4 due to *S. pneumoniae,* of which one was penicillin-resistant, and 1 MSSA). Four of them treated with 600mg of ceftaroline fosamil every 8 hours were successful whilst the other one with 600mg very 12 hours failed [7]. Both cases reported here were treated with 600mg every 8 hours.

Little is known about CSF penetration of ceftaroline. Chauzy et al reported a mean of 9% in a series of 11 patients with external ventricular drain, but without meningeal inflammation [8]. However, this penetration can be enhanced with meningeal inflammation, as showed by Helfer et alt [9]. In fact, animal models of meningitis show variable rates from 15 to 51%. Ceftaroline was no-inferior to vancomycin in an animal study of meningitis by SARM and was superior to ceftriaxone in meningitis by penicillin-susceptible *S. pneumoniae* and to combination of ceftriaxone plus vancomycin in penicillin-resistant pneumococcal meningitis [10-11].

In summary, ceftaroline fosamil administrated 600mg iv every 8 hours is an attractive option in CNS infections. Although there is little experience in meningitis by penicillin-resistant *S. pneumoniae* or MRSA, its penetration in CSF is like other third-generation cephalosporins and better to vancomycin, which together with its higher in vitro activity makes it an interesting option in this scenario. In neurosurgical infections by linezolid-resistant *S. epidermidis* – an emerging problem with taxes of 17% in our center- ceftaroline could be the best choice, as it was in our second case.

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CONFLICTS OF INTEREST

Authors declare no conflict of interest

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Ajuste posológico de linezolid por interacción con rifampicina en endocarditis infecciosa

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Estimado Editor:

Presentamos el caso de una mujer de 60 años con antecedentes de hipertensión arterial, espondilitis anquilosante, meningiomatosis múltiple y síndrome de seno cavernoso. Acudió a urgencias por imposibilidad para movilizar los miembros inferiores y desorientación. Ingresó en UCI por shock séptico, dónde se inició tratamiento empírico con meropenem (2g c/8h) en perfusión extendida tras extracción de hemocultivos. Se aisló *Staphylococcus aureus* sensible a meticilina (SASM) y se realizó ecocardiografía que confirmó endocarditis infecciosa sobre válvula nativa (EIVN) tricúspidea, por lo que se modificó el tratamiento a daptomicina (750 mg c/24h) y cloxacilina (2000 mg c/4h) [1].

En el día +7 de ingreso, es trasladada a medicina interna manteniendo episodio febril por lo que se asoció linezolid (600 mg c/12h) para ampliar la cobertura debido a la aparición de émbolos sépticos pulmonares, así como por persistencia de SAMS en hemocultivos seriados. En el día +10 estaba afebril y negativizó los hemocultivos. Transcurridos siete días se retiró la daptomicina y se mantuvo la asociación de linezolid/cloxacilina.

Pese a que la asociación de rifampicina sólo está recomendada en endocarditis infecciosa sobre válvula protésica [2], debido a la progresión de las lesiones cardíacas observadas mediante PET-TAC el día +30 y a la presencia de *clips* quirúrgicos por una reciente meningioblastectomía, se decidió asociar rifampicina (600 mg c/24h).

En el día +36 se realizó monitorización farmacocinética (TDM) del linezolid debido a la potencial interacción con rifampicina, obteniéndose una concentración plasmática (Cp) indetectable, por lo que se decidió administrar el linezolid en perfusión contínua (PC) con dosis de 1200 mg c/24h. Ante persistencia de Cp indetectable en el día +40 se suspendió la rifampicina y se asoció fosfomicina (4.000 mg c/8h). A partir de este momento, se realizaron controles periódicos de linezolid en los que la Cp continuó indetectable pese a los incrementos de dosis y la interrupción de la rifampicina (Figura 1). En el día +49 con una dosis de 1.800 mg c/24h en PC se detectó por primera vez presencia del fármaco (1,77 mg/L). Posteriormente, el día +57 se alcanzó valores terapéuticos (3,56 mg/L) junto con la disminución de un 90,9% de la proteína C reactiva (PCR) respecto del valor inicial al comenzar la TDM (Figura 2). Durante el seguimiento, no se observaron reacciones adversas al linezolid y tanto la creatinina sérica como la bilirrubina, ambos factores predictivos de eliminación para linezolid [3], se mantuvieron constantes (Figura 2). Finalmente, en el día +64 fue dada de alta.

La Cp indetectable se puede atribuir a una interacción entre linezolid y rifampicina ya que no se identificó otra posible interacción con el tratamiento instaurado. La disminución de la Cp de linezolid por la rifampicina es conocida [4], pero los mecanismos subyacentes no están del todo definidos. El linezolid se metaboliza mediante reacciones de oxidación del anillo de morfolina. Las enzimas implicadas eran desconocidas, por este motivo se denominó como "metabolismo oxidativo no enzimático". Sin embargo, un estudio reciente demuestra la participación del sistema microsomal (CYP450) mediante las enzimas CYP2J2, CYP4F2 y CYP1B1 [5]. El metabolismo se iniciaría con la formación de 2-hidroxilinezolid y finalizaría con desetilenlinezolid, aunque se forman también otros metabolitos. De estos citocromos, el CYP2J2 es el que mayor importancia tiene en el metabolismo, tanto en la reacción inicial como en las sucesivas. Está presente en el hígado, pero predomina en el miocardio, donde representa la mayor parte de los CYP450 de este tejido [6]. Además, el miocardio dispone de una vía de síntesis de ácidos epoxieicosatrienoicos (AEET) [6] con actividad antiinflamatoria en la que el CYP2J2 es una enzima implicada en la síntesis de dichos mediadores. En presencia de estrés oxidativo, el CYP2J2 está sobreexpresado en el tejido miocárdico [6], por

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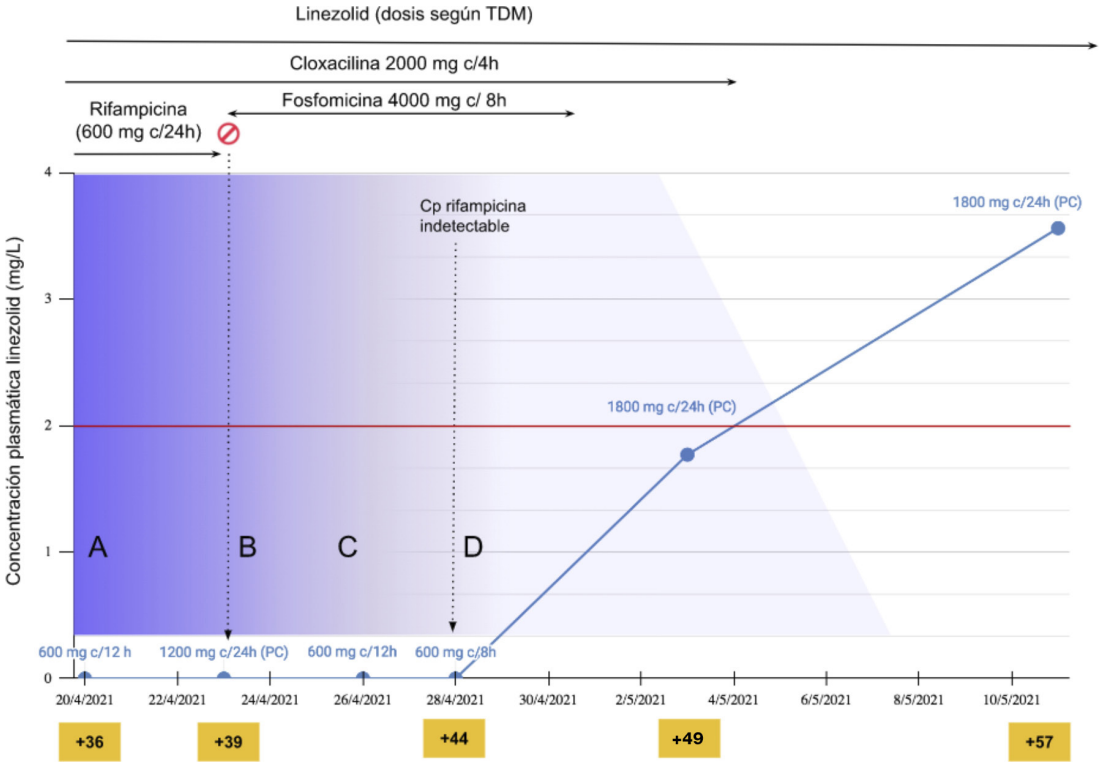

Figura 1 | **Concentración plasmática de linezolid (mg/L) medida a lo largo del seguimiento.**

Las dosis de linezolid se muestran adjuntas sobre cada monitorización (línea azul). El gradiente morado intenta representar de forma teórica el efecto inductor de la rifampicina, donde se consideran cuatro escenarios: (A) efecto inductor total; (B) semivida de la rifampicina (3-4h); (C) posible tiempo de acumulación por colestasis; (D) posible tiempo de inducción diferida una vez eliminada la rifampicina. La línea roja en 2 mg/L representa el límite inferior del intervalo terapéutico para linezolid. En amarillo se indican los días tras el ingreso.

lo que es razonable pensar que también podría estarlo en el caso de endocarditis.

Por otro lado, la rifampicina posee una gran capacidad inductora del metabolismo oxidativo, aunque parece que no afecta significativamente al CYP2J2 [6]. El 80% de la rifampicina se elimina en forma desacetilada en la bilis por lo que la persistencia de la interacción pese a la suspensión de la rifampicina se puede explicar por una eliminación disminuida de ésta (Figura 1C) ya que la paciente presentó un patrón colestásico objetivado por valores de GGT elevados (Figura 2). Hay que considerar que el efecto inductor del metabolismo puede prolongarse hasta dos semanas tras la suspensión del tratamiento [7]. Este efecto explicaría la ausencia de linezolid pese a Cp de rifampicina indetectables en el día +48 (Figura 1D).

La interacción entre linezolid y rifampicina es relevante y requiere de TDM. Además, debido a la importancia del CYP2J2 en el metabolismo y la poca evidencia disponible actualmente, parece lógico pensar que en cualquier endocarditis tratada con linezolid debería realizarse TDM independientemente del tratamiento concomitante con rifampicina, ya que su metabolismo podría estar aumentado por la sobreactivación de la vía de los AEET.

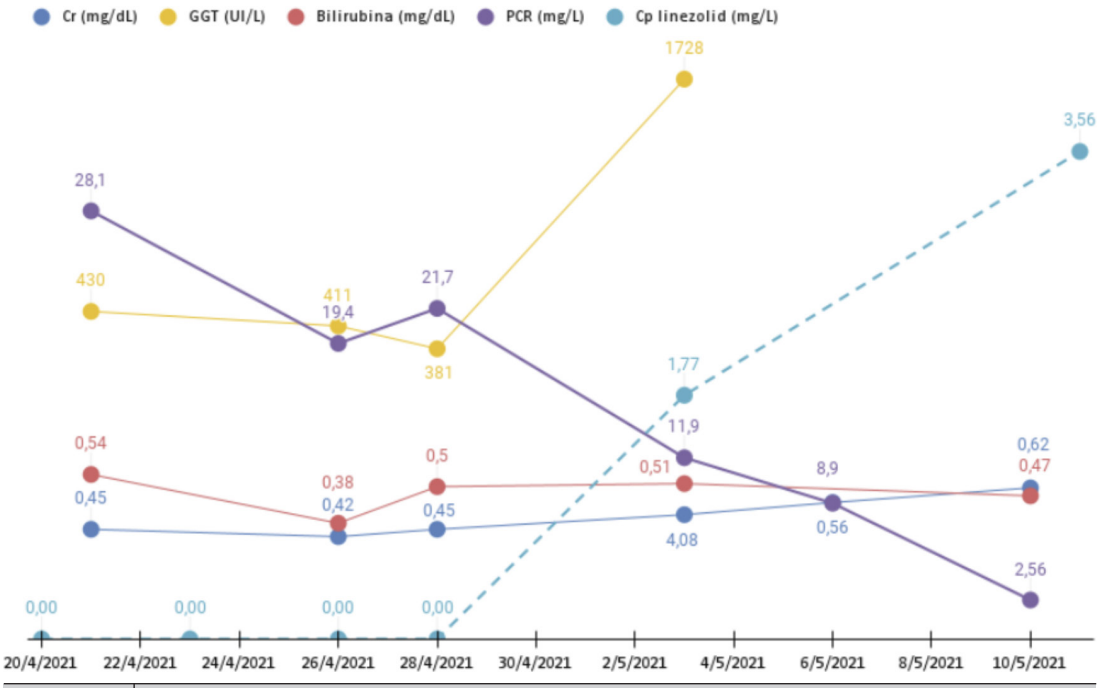

Figura 2 | **Representación de la evolución de diferentes valores bioquímicos durante el seguimiento. Para facilitar la interpretación, se ha anotado sobre cada determinación el valor obtenido, ya que son de magnitudes diferentes.**

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CONFLICTO DE INTERESES

Los autores declaran no tener conflicto de intereses.

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Letter to the Editor

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Two cases of *Prevotella oris* causing serious pleuropulmonary infections

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Sir,

The genus *Prevotella* is a group of obligate anaerobic Gram-negative bacteria that includes more than 50 species, many of them associated with the human microbiota, where they are commensals of the upper respiratory tract and the genitourinary system. *Prevotella oris* was isolated for the first time in 1982 in a patient with periodontitis being named *Bacteroides oris* and reclassified years later as *P. oris* [1]. In this manuscript, we describe two cases of serious pleuropulmonary infections, a necrotizing pneumonia and a pneumonia associated with pleural empyema.

Case 1

A 4-year-old patient with a history of sickle cell anemia presented with fever up to 39ºC associated with cough and purulent expectoration of 19 days of evolution. At the beginning of the clinical picture, the patient was diagnosed as a respiratory viriasis due to Influenza A virus by PCR. On examination, no alarm signs were observed and the blood analysis showed 20,680 leukocytes with 81% neutrophils and a C-reactive protein of 210 mg/L. A Pulmonary ultrasound showed condensation in the right upper lobe (Figure 1A) and the patient was admitted for study and IV antibiotic treatment with 1 g/6 h of ampicillin, obtaining bronchoaspirate, bronchoalveolar lavage and bronchial brushing samples, ruling out *Mycobacterium tuberculosis* by PCR with the GeneXpert MTB/RIF panel (Cepheid, California, USA).

After two days of hospitalization, a computed tomography scan was conducted with data consistent with necrotizing pneumonia (Figure 1B). In the aerobic culture of the bronchoaspirate sample, *Lautropia mirabillis* (oral cavity commensal previously isolated from children with HIV) was isolated, while *Prevotella oris* was identified by 16S rRNA gene sequencing of bronchial brushing and bronchoalveolar lavage samples with an homology percentage of 99.50% and 99.82%, respectively. The second sequence was registered in GenBank with accession number OP601405. After switching to IV 1 g/8 h cefotaxime and 260 mg/6 h vancomycin, the patient improved until resolution of the infection 18 days after admission (Figure 1C).

Case 2

A 13-year-old patient with a history of Glanzmann's thrombasthenia and allergic asthma came to the emergency department for left flank pain radiating to the shoulder and respiratory distress. Examination showed hypoventilation in the left lung base and blood tests showed a C-reactive protein of 180 mg/L, 25,340 leukocytes/µL with 22,280 neutrophils/µL. Chest X-ray (Figure 2A) showed condensation in the left lung base, being admitted with IV antibiotic treatment with 2 g/6 h of ampicillin. The patient had daily febrile fever for 5 days until reaching a fever of 39ºC, at which time lung ultrasound was performed (Figure 2B) and the presence of bilateral pleural effusion was confirmed. The pleural effusion was drained by evacuating thoracentesis and sent to the laboratory for microbiological studies and cultures. The treatment was changed to IV 2 g/8 h of cefotaxime, 1 g/8 h of vancomycin and 500 mg/8 h of clindamycin.

The fluid was compatible with empyema presenting 396,000 leukocytes/µL with 74% neutrophils, LDH of 5,447 U/L and glucose of 0 mg/dL. In microbiological cultures there was no growth after 5 days, being performed sequencing of the 16S rRNA gene with *P. oris* with a homology percentage of 98.94%. The sequence was registered in GenBank with accession number OP601436. After 5 more days of treatment the patient was discharged with good evolution (Figure 2C).

The occurrence of oral commensals as a cause of pulmonary infections is invariably related to aspiration of food or other secretions, which together with dental procedures constitute the most likely cause of these infections. In addi-

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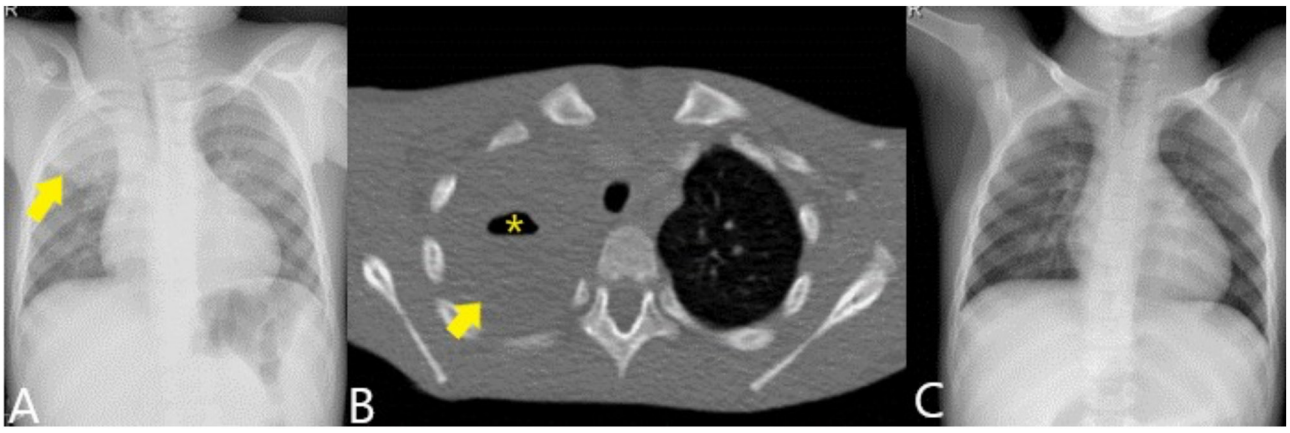

Figure 1 | **Chest X-ray (A) showing condensation in the right upper lobe (arrow). Contrast-enhanced CT (B) shows the condensation (arrow) with the presence of an air level suggestive of cavitary pneumonia (asterisk). The control radiograph (C) shows complete resolution of the picture.**

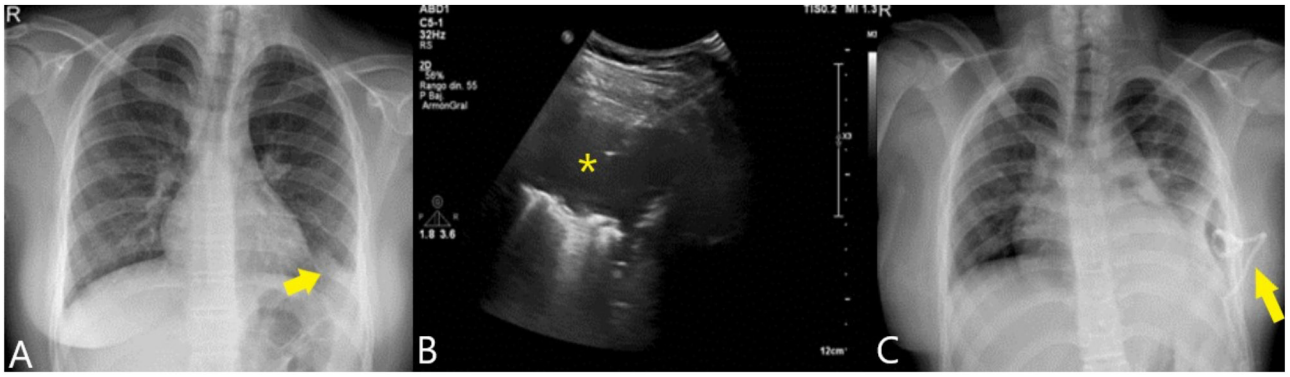

Figure 2 | **Chest X-ray (A) showing a condensation in the left pulmonary base (arrow). Ultrasound (B) showed presence of empyema (asterisk), which was drained with a trocar (arrow). The control radiograph (C) shows the placement of the drainage catheter (arrow) achieving complete resolution of the picture.**

tion, poor oral hygiene or periodontitis increases the growth of mouth commensals such as *P. oris*, favoring severe opportunistic infections to occur [2]. Previously, *P. oris* has been associated with clinical pictures such as abscesses or bacteremia, among others [3,4]. Although rare, it has also been described causing pleuropulmonary infections in the form of pneumonia and pleural empyema in both adult and pediatric populations [2,5-8]. Both the article by Viswanath LS et al. and Cobo F et al. describe cases in which *P. oris* are an unequivocal cause of pleural pathology. These cases and the ones presented here show that *P. oris* should be taken into account in the etiology of pleuropulmonary infections after bronchoaspiration or when there is a history of previous birth procedures with consequent antibiotic coverage.

In terms of diagnosis, the MALDI-TOF mass spectrometer is a rapid tool of great help for the identification of numerous species, however, in the case of *Prevotella* spp. there may be discrepancies. This idea is stated in both the articles by Wybo I et al. and Gürsoy M et al., in which they collect statistics concerning the percentage of strains identified by MALDI-TOF MS at the genus and species level of *Prevotella* spp. [9, 10]. In the first article, out of 102 isolates, the genus was identified in 73.5% and the species in 62.7%, while in the second one, out of 123 isolates, the genus was identified in 100% and the species in 88%. Although MALDI-TOF MS is of great help, the identification should be confirmed by another more accurate technique such as 16S rRNA gene sequencing and expand the MALDI-TOF database to increase the accuracy of identification as stated in the articles of Wybo I et al and Gürsoy M et al. Furthermore, in our experience, we believe that confirmation is necessary in order to avoid misidentifications of some species of Prevotella. In fact, in one case, our Bruker® MALDI-TOF MS identified the isolate as *Prevotella bivia* with a value greater than 2, while 16S rRNA gene sequencing identified it as *P. oris*

with a homology percentage greater than 99% (with a reference strain studied through complete genomic sequence).

In terms of treatment, control of the focus by draining the collections associated with antibiotics would be of choice [5-8]. In recent years, antimicrobial resistance is increasing among anaerobic anaerobic bacteria worldwide. *Prevotella spp.* have traditionally been considered susceptible to penicillin, but an increasing rate of resistance to this drug has been lately documented [11-13]. *Prevotella spp.* are generally susceptible to beta-lactams associated with beta-lactamase inhibitor, metronidazole, tigecycline or cefoxitin. Some strains could be resistant to clindamycin, tetracyclines or moxifloxacin as can be seen, for example, in the multicenter study by Ulger Toprak N et al [13]. On the other hand, metronidazole has been reported as resistant in a case of bacteremia caused by *Prevotella spp.* although this is exceptional, retaining good activity against most strains [14]. Therefore, empirical treatment with penicillin should not be recommended in infections caused by species of the genus Prevotella, whereas beta-lactams associated with beta-lactamase inhibitors, carbapenems or anaerobicides such as clindamycin or metronidazole could be used. In our cases, it was not possible to study the susceptibility of the strains as they were identified only by sequencing of the 16S rRNA gene. This may be due to the fact that the patients had received intravenous antibiotics in the days prior to sampling.

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CONFLICT OF INTEREST

Authors declare no have conflict of interest.

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Carta al Director

Revista Española de Quimioterapia
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Diagnóstico vírico alternativo en las sospechas de viruela del mono

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Las características dermatológicas de las lesiones cutáneas asociadas a la infección por la viruela del mono (VM) son bastante específicas, aunque varían en su proceso evolutivo [1]. Su localización en las palmas y plantas es muy sugerente, pero en la epidemia de 2022 un porcentaje elevado de las lesiones se presentaban además en las zonas genitales. Las lesiones cutáneas junto al comportamiento sexual de las personas afectadas y el contexto epidemiológico, se constituyeron como el principal indicio de sospecha de VM [2].

Durante el período epidémico situado entre el 1 de junio y el 30 de noviembre de 2022 se analizaron 367 muestras cutáneas con sospecha clínica de VM. La detección del virus de la VM se realizó mediante una RT-PCR comercial en tiempo real basada en la proteína de fusión 14-kDA del género Orthopoxvirus (LightMix Modular Orthopox virus; Roche). Las muestras negativas al VM se analizaron mediante una RT-PCR comercial (Meningitis V1/V2 Assay; Seegen) que detecta todos los herpesvirus y enterovirus.

De las 367 muestras analizadas muestras analizadas 293 (79,8%) correspondían al ámbito hospitalario y 74 (20,2%) a atención primaria. De las 141 muestras consideradas como positivas a VM (78,7%), 133 (94,3%) lo fueron en el ámbito hospitalario y 8 (5,7%) de primaria. El virus de la VM se detectó en 133 muestras/159 positivas (83,6%) hospitalarias y en 8/20 positivas (40%) de primaria. De los 38 (21,2%) diagnósticos etiológicos alternativos, el virus varicela-zóster representó el 50% (19 casos). El diagnóstico alternativo vírico más frecuente fue el de VZV, detectándose 12 casos (7,5%) en hospitales y 7 (35%) en primaria. Los virus no-VM representaron el 16,5% en hospitales frente al 60% en primaria. De las lesiones genitales 16 (8,9%) fueron diagnosticadas como alternativa a la VM, correspondiendo 10 a HSV-1 (62,5%) y 6 a HSV-2 (37,5%). Los tres casos de enterovirus correspondían a niños con diagnóstico del síndrome mano-pie-boca, que también presenta lesiones plantares. El resto de virus y su ámbito de detección se presentan en la Tabla 1.

A pesar de las características dermatológicas específica, aunque no siempre, existen otros virus causantes de manifestaciones cutáneas y lesiones muy parecidas a alguna de las fases evolutivas presentes en la VM [3,4]. La principal es el virus varicela-zóster, que en su forma de varicela del adulto puede confundirse como sospecha de la VM. De este modo, hemos confirmado como de las alternativas virológicas a la VM, el virus varicela-zóster ha sido el responsable del 50% de los casos, seguidos del herpes simple tipo 1 (26,3%), herpes simple tipo 2 (15,7%) y los enterovirus (7,8%).

Las infecciones por el VVZ en el adulto son mas severas que en la infancia y asociadas en ocasiones a complicaciones neurológicas. Un estudio realizado en la República Democrática del Congo [5] mostró que en 730 pacientes diagnosticados clínicamente de varicela-zóster, el virus de la VM era el responsable del 3,3% de estas lesiones (confirmación de laboratorio) y otro 7,3% se diagnosticaron de zóster atípico (sin confirmación etiológica); por ello se recomienda la toma muestras y su estudio etiológico viral tanto en África como fuera de este continente. La epidemia de 2022 representó un nuevo reto diagnóstico, aunque sin la endemicidad africana, la sospecha de VM se estableció de una forma prioritaria, mientras que las otras etiologías virales se realizaron de forma secundaria.

En el estudio de Hughes et al.[3] realizado en la República Democrática del Congo en 2021, observan que de 991 muestras cutáneas analizadas en adultos 400 (40,4%) estaban causadas por el VM, 457 (46,1%) por el virus varicela-zóster y 134 (13,5%) eran infecciones mixtas entre ambos virus. Se encontraron diferencias en la gravedad y los síntomas en aquellos con coinfecciones en comparación con aquellos con VM o varicela-zóster solos. Los casos de coinfección presentaban

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Tabla 1 **Principales virus detectados en los casos de sospecha de viruela del mono.**

Número de muestras	Hospitales	Atención primaria	Total
	(293)	(74)	(367)
Viruela del mono	133	8	141
Varicela-Zóster	12	7	19
HSV-1	7	3	10
HSV-2	5	1	6
Enterovirus	2	1	3
Total	159	20	179

más síntomas asociados con la VM y tenían mayor número de lesiones que los casos con varicela-zóster solo. Es posible que la coinfección entre estos dos virus pueda modular no sólo la expresión dermatológica de las lesiones sino incluso la gravedad o complicaciones de la misma [3,4]. En nuestro estudio las muestras positivas a la VM no fueron sometidas a la detección de otros virus cutáneos, con lo que no tenemos datos de las posibles coinfecciones entre ambos virus.

Es destacable el mayor porcentaje de detección de casos de VM en las urgencias hospitalarias frente a atención primaria. Probablemente la existencia de dermatólogos en el hospital haya facilitado esta sospecha. Además es posible que en atención primaria no tengan muchas oportunidades de observar casos de varicela del adulto, que ha sido la primera causa alternativa (35% frente al 7,5% hospitalaria).

Los tres casos de enterovirus correspondían a niños con diagnóstico del síndrome mano-pie-boca, que también presenta lesiones plantares. En un estudio realizado en Argentina sobre 9 casos de sospecha de VM, sólo 3 (33,3%) fueron VM y 4 (44,4%) correspondían a enterovirus [6].

La rápida incorporación de la detección molecular específica frente a la VM ha permitido no sólo establecer un diagnóstico rápido y específico de la infección, sino que ha permitido la adopción de medidas preventivas para contener la epidemia.

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CONFLICTO DE INTERESES

Los autores declaran no tener ningún conflicto de intereses.

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