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RESEARCH ARTICLE

Dietary patterns of Sonoran breastfeeding women are associated to exclusive or partial breastfeeding regimes

*Alejandra Arguelles-López, Omar A. Trujillo-Rivera, and Ana M. Calderón-de la Barca**

Coordinación de Nutrición, Centro de Investigación en Alimentación y Desarrollo A.C., Hermosillo, Sonora, Mexico

Abstract

Background: *During breastfeeding, the maternal diet ensures mothers and infants health. Therefore, it is necessary to update information about the diet of exclusively or partially breastfeeding women in each population. We evaluated the diet of Sonoran breastfeeding women, identified their dietary patterns, and examined their association with the breastfeeding regime.* **Methods:** *In this cross-sectional study, 62 women breastfeeding exclusively (n = 43) or partially (n = 19) participated. The diet was assessed using a food frequency questionnaire, and patterns were identified through principal component analysis.* **Results:** *Overall, fats and sodium intake were higher, while potassium intake was lower than recommended. Two dietary patterns were identified: "regional" (n = 36) and "prudent" (n = 26). Women following the "prudent" pattern consumed more protein, calcium, and potassium than those following the "regional" pattern (p < 0.05). The probability of exclusively breastfeeding women having a "prudent" dietary pattern was higher than that of partially breastfeeding women (adjusted odds ratios = 7.29, p = 0.019).* **Conclusions:** *Exclusive breastfeeding possibly motivated mothers to follow a more prudent diet than those who partially breastfed. Therefore, it is crucial to promote a healthy diet among breastfeeding mothers.*

Keywords: *Breastfeeding. Sonoran women. Dietary patterns.*

Los patrones dietarios de mujeres sonorenses amamantando se asocian con los regímenes de lactancia exclusiva o parcial

Resumen

Introducción: *Durante el amamantamiento, la dieta garantiza la salud materno-infantil. Por esto, es necesario contar con información actualizada sobre la dieta de quienes amamantan exclusiva o parcialmente en cada población. El objetivo de este trabajo fue evaluar la dieta de mujeres sonorenses amamantando, identificar sus patrones dietarios y buscar su asociación con el régimen de lactancia.* **Métodos:** *En este estudio transversal participaron 62 mujeres amamantando de forma exclusiva (n = 43) o parcialmente (n = 19). Se evaluó la dieta con un cuestionario de frecuencia de consumo de alimentos y los patrones se identificaron a través del análisis de componentes principales.* **Resultados:** *En general, la ingestión de grasas y sodio fue superior y la de potasio inferior a las cantidades recomendadas. Se identificaron dos patrones dietarios: "regional" (n = 36) y "prudente" (n = 26). Las mujeres con patrón "prudente" ingirieron más proteína, calcio y potasio que las del patrón "regional" (p < 0.05). La probabilidad de que las mujeres que amamantaban en exclusiva siguieran un patrón dietario "prudente" fue mayor que la de aquellas que amamantaban parcialmente (razón de momios ajustada (AOR) = 7.29, p = 0.019).* **Conclusiones:** *La lactancia exclusiva posiblemente motivó a las madres a seguir una dieta más prudente que la de aquellas que amamantaban parcialmente. Es necesario promover una dieta saludable entre las madres amamantando.*

Palabras clave: *Lactancia materna. Mujeres sonorenses. Patrones dietarios.*

***Correspondence:**
Ana M. Calderón-de la Barca
E-mail: amc@ciad.mx

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Introduction

During breastfeeding, the mother provides all the nutrients and bioactive compounds required to support optimal infant health and growth, and reduce disease risk[1]. The input to sustain this process is the maternal diet, which continues to ensure the infant's health as it did during pregnancy. In parallel to the benefits for the infant, a healthy diet also protects the breastfeeding mother's well-being and helps replenish the maternal nutrient stores used for milk production[2].

Breastmilk is tailored to meet the complex nutritional requirements of infants, and its composition varies according to the infant's age and physiological needs[3]. The infant requirements and milk production take priority over the needs of the mother, and even in cases of maternal malnutrition, high-quality milk is produced to meet the nutritional and immunological requirements of the infant[4]. Nevertheless, several authors have found that dietary patterns influence the concentration and composition of different nutrients in breast milk, including fatty acids, Vitamins B1, B2, B6, C, carotenoids, and others[5-7].

Changes in breast milk composition may influence the health and development of breastfed infants[8]. As diet and other environmental factors are particular to each population and region, it is important to study specific dietary patterns of breastfeeding mothers to find solutions to address negative outcomes for infants and mothers for future interventions.

The only study about the diet of breastfeeding women in Sonora, Mexico, was conducted two decades ago[9]. It showed that breastfeeding mothers had a high intake of energy-dense foods and low consumption of vegetables and fruits[9]. A more recent study of middle-aged women in the same location coincides with the high intake of energy-dense foods[10].

Although breastfeeding is the gold standard for infant nutrition, in Mexico, only 28.6% of infants under 6 months old are exclusively breastfed, while 22.5% of mothers provide partial breastfeeding in conjunction with formula and other types of milk[11]. Evidence suggests an association between exclusive breastfeeding and healthy dietary habits[12]. Hence, it is possible that dietary patterns differ between mothers providing exclusive or partial breastfeeding to their infants. Therefore, we evaluated the dietary intake of Sonoran breastfeeding women, identified dietary patterns, and examined the association between exclusive or partial breastfeeding regimes and dietary patterns.

Methods

We conducted a cross-sectional study including breastfeeding women. Convenience sampling with the snowball method was conducted in Hermosillo, Sonora, Mexico. Women were invited to participate through breastfeeding support groups on social media platforms and daycare centers. Women who followed a restricted diet or had not lived in Sonora for the past 5 years were excluded. Women following an exclusive breastfeeding regime comprised one group; those who provided infant formula alongside breastfeeding were in the partial breastfeeding group. All the participants signed an informed consent, and the study protocol was approved by the institute's Ethics Committee (CEI/002/2022).

During home visits, sociodemographic and health data were collected using questionnaires. The level of marginalization was assessed through household location according to a social marginalization map of Hermosillo, Sonora[13]. Maternal weight and height were measured using an electronic scale (A&D FG-150KBM) and a portable stadiometer (SECA 213). Body mass index (BMI) was calculated for each participant.

Dietary intake was evaluated using a validated food frequency questionnaire (FFQ) modified for the study[14]. The dietary data were coded and analyzed using Ortega et al.[15] and Food Data Central[16] databases. The dietary intake assessment included energy, total protein, total fat, saturated fat, cholesterol, total carbohydrates, fiber, calcium, folate, iron, phosphorus, potassium, sodium, zinc, and Vitamins A, B2, B6, B12, C, and E. The 110 items of the FFQ were assigned to 12 food groups based on their similarity and nutrient content, and the quantity (g) of each food group consumed by each participant was calculated.

Statistical analysis

Data are presented as mean and standard deviation for continuous variables or sums (percentages) for categorical variables. The Kurtosis, Skewness, and Shapiro–Wilk tests were used to verify variable normality. Dietary intake was energy-adjusted using the residual method. Differences in BMI and dietary intake between dietary patterns were evaluated using the t-test for independent variables. Statistical significance was set at $p < 0.05$.

Dietary patterns were identified using principal components analysis (PCA) with orthogonal transformation (varimax rotation). To determine the adequacy of PCA,

we used the Kaiser-Meyer-Olkin (KMO) and Bartlett's sphericity tests; the KMO value was 0.61, and Bartlett's p-value was < 0.001, which supported the model validity. Before PCA, variables were normalized (mean = 0, standard deviation = 1). The number of patterns included was based on visual interpretation of the scree plot of eigenvalues and the percentage of total variance explained by each pattern. Food groups with a factor loading ≥ 0.19 were included in the dietary pattern. The sum of grams consumed of each food group was pondered by its factor load to assign a dietary pattern to each subject.

A logistic regression analysis was conducted to examine the association between dietary patterns and potential predictors, such as breastfeeding regime, sociodemographic, and health factors. The logistic regression model was fitted using maximum likelihood estimation. A model fit was assessed through the Hosmer–Lemeshow goodness-of-fit test and the Akaike Information Criterion. Confounding and effect modification were assessed through stratified analysis and model comparison, respectively. Variables with a p-value ≤ 0.20 in the bivariate analysis were included in the initial logistic regression model. A backward step-wise elimination approach was used to identify the final model, with variables retained in the model if they were statistically significant or improved the model fit. The results are presented as adjusted odds ratios (AOR) with p-value. All statistical analyses were conducted using the Stata 17 MP edition (Stata Corp, College Station, Texas).

Results

Sixty-four breastfeeding women were interested in participating in the study, and 62 met the eligibility criteria and were included in the study. The mean age of the women was 31.6 years old; 51.6% were overweight or obese, 59.7% had a cesarian section delivery, and 69.3% of the women provided exclusive breastfeeding (Table 1). Given the characteristics of our sampling method, all the women in this study lived in areas of very low marginalization.

Table 2 presents women's energy and selected nutrient daily intake compared to the Dietary Recommended Intakes[17]. Women had a high fat intake, accounting for 37.4% of their daily energy consumption, reflecting a high cholesterol intake. Furthermore, women had a high sodium and low potassium consumption, while the rest of their micronutrient intake was adequate. Women who partially breastfed had a higher intake of energy, fiber, folate, iron, sodium, zinc, and Vitamin B2, B6, and B12 than those who exclusively breastfed (p < 0.05). In contrast, women who exclusively breastfed had higher protein intake than women who partially breastfed (p < 0.05).

Table 1. Characteristics of Sonoran breastfeeding women (n = 62)

Characteristics	n (%)	Mean ± SD
Age (years)		31.63 ± 4.0
Weight (kg)		68.70 ± 13.48
Height (m)		1.63 ± 0.06
BMI (kg/m^2)		25.82 ± 4.31
Underweight	3 (4.84)	
Normal weight	27 (43.55)	
Overweight	20 (32.26)	
Obese	12 (19.35)	
Parity		
Primiparous	32 (51.61)	
Multiparous	30 (48.32)	
Delivery mode		
Vaginal	25 (40.32)	
Cesarian	37 (59.68)	
Breastfeeding regime		
Exclusive	43 (69.35)	
Partial	19 (30.65)	
Dietary supplement intake	48 (77.42)	

BMI: body mass index; SD: standard deviation.

Dietary patterns

Two dietary patterns that explained 43.1% of the data variability were identified. The "prudent" pattern was characterized by consuming vegetables, fruits, fats and oils, rice, oats, potatoes, and corn, and no consumption of sweetened drinks. The "regional" pattern was characterized by consuming meat and deli, wheat-based products, legumes, sugar, candies and pastries, and sweetened drinks (Table 3).

Fifty-eight percent of the women had a "regional" dietary pattern, while 41.9% had a "prudent" pattern (Table 4). Women with the "regional" pattern had a higher BMI than women who followed the "prudent" pattern (p = 0.026). In terms of dietary intake, women with the "prudent" pattern had a higher daily intake of protein, calcium, phosphorous, potassium, Vitamin A, and Vitamin C than women in the "regional" pattern (p < 0.05).

Odds-ratio for dietary patterns

Table 5 presents a logistic binary regression analysis, and it reveals that women who exclusively breastfed

Table 2. Energy and selected nutrient daily intake of Sonoran breastfeeding women compared to the Dietary Reference Intake (n = 62)

Nutrient*	Daily intake (mean ± SD)			Requirement†
	All women (n = 62)	Exclusive breastfeeding (n = 43)	Partial breastfeeding (n = 19)	
Energy (kcal)	2025.9 ± 560.6	1838.4 ± 463.5	2450.3 ± 538.6	-
Total protein (E%)	19.1 ± 2.5	19.6 ± 2.6	18.0 ± 1.9	10-35
Total fat (E%)	37.5 ± 4.9	31.8 ± 4.8	36.9 ± 5.2	20-35
Saturated fat (E%)	13.6 ± 2.0	13.5 ± 1.9	13.7 ± 2.4	As low as possible
Cholesterol (mg)	359.9 ± 132.2	346.3 ± 103.7	390.8 ± 180.8	As low as possible
Total carbohydrates (E%)	50.8 ± 5.6	50.9 ± 5.36	50.7 ± 0.6.3	45-65
Fiber (g)	29.5 ± 9.7	27.9 ± 8.6	33.3 ± 11.3	29 (AI)
Calcium (mg)	1015.7 ± 361.6	1007.7 ± 384.2	1033.7 ± 313.4	1000
Folate (μg)	491.3 ± 184.8	454.5 ± 157.8	574.5 ± 217.0	500
Iron (mg)	18.3 ± 5.9	16.7 ± 5.1	22.1 ± 6.1	9
Phosphorus (mg)	1032.6 ± 313.3	977.3 ± 272.8	1157.6 ± 367.9	700
Potassium (mg)	3487.6 ± 997.9	3425.1 ± 963.8	3629.1 ± 1084.7	5100
Sodium (mg)	2914.2 ± 1052.3	2538.5 ± 832.4	3764.4 ± 1017.5	2300 (UL)
Vitamin A (μg)	1564.1 ± 878.7	1612.4 ± 730.9	1454.9 ± 1162.6	1300
Vitamin B_2 (mg)	2.6 ± 0.8	2.4 ± 0.7	2.9 ± 0.9	1.6
Vitamin B_6 (mg)	3.2 ± 1.1	2.9 ± 0.9	3.9 ± 1.3	2
Vitamin B_{12} (μg)	6.4 ± 4.0	5.4 ± 2.03	8.7 ± 5.9	2.8
Vitamin C (mg)	188.6 ± 112,64	199.3 ± 107.4	164.3 ± 123.2	120
Vitamin E (mg)	9.4 ± 3.5	9.1 ± 3.8	10.2 ± 2.8	19 (AI)
Zinc (mg)	12.4 ± 3.3	11.1 ± 2.3	15.1 ± 3.7	12

*Nutrient intake was energy-adjusted using the residual method.
†Recommended Dietary Allowances, unless specified otherwise.
Dietary Reference Intake refers to a set of reference values that represents the approach adopted by the Food and Nutrition Board (2005). AI: adequate intake; E%: percentage of total energy; SD: standard deviation; UL: tolerable upper intake levels.

were 7.3 times more likely to have a "prudent" dietary pattern than women who partially breastfed (AOR, p = 0.019). Maternal BMI was neither associated with the dietary pattern (AOR = 0.96, p = 0.071) nor maternal age (AOR = 0.95, p = 0.462).

Discussion

This study found that the dietary intake of Sonoran breastfeeding women can be grouped into two dietary patterns. Most women (58%) showed a "regional" pattern, which included a higher consumption of ultra-processed foods than the "prudent" pattern. This finding is significant because an ultra-processed dietary pattern during breastfeeding may be associated with negative outcomes for the mother and infant, such as an increase in weight gain and adiposity measures and early weaning[18].

The dietary patterns of Sonoran breastfeeding women were previously studied. Caire-Juvera et al. (2002) found that the typical dietary pattern was characterized by the consumption of foods of animal origin, wheat-based foods, legumes, and soft drinks[9]. This pattern is similar to the "regional" pattern found in our study. In addition, our study also found a "prudent" pattern characterized by the intake of vegetables and fruits. This discrepancy could be attributed to differences in the level of

Table 3. Dietary patterns of Sonoran breastfeeding women (n = 62)

Food groups	Pattern 1: Regional*	Pattern 2: Prudent*
Fruits	–0.0130	**0.4715**
Vegetables	0.0197	**0.5244**
Dairy products	0.0676	**0.2752**
Rice, oats, potatoes, and corn	**0.3042**	**0.3439**
Wheat-based products	**0.4761**	–0.0036
Poultry, fish, and eggs	**0.2359**	0.1995
Meat and deli	**0.4813**	0.0136
Legumes	**0.3842**	–0.1329
Fats and oils	–0.1543	**0.4484**
Sugar, candies, and pastries	**0.3438**	0.0305
Sweetened drinks	**0.3087**	**–0.2174**
Chips and snacks	0.0588	–0.0422
Explained variance (%)	24.81	18.34

Values in the table are the factor loadings for each food group in each dietary pattern.
*Food groups with factor loadings > | 0.19 | were included in each dietary pattern and are highlighted in bold.

marginalization between the two population samples. Most women in the study of Caire-Juvera et al. had a low socioeconomic status and lived in areas with medium and high levels of marginalization[9,13]. Evidence suggests that socioeconomic status is a key factor in determining diet quality in the Mexican population[19]. However, even though mothers in our study lived in areas with very low levels of marginalization, 42% of them had a "prudent" dietary pattern, suggesting that other factors besides socioeconomic status influence the diet quality of participants. In addition, the difference between the two studies, with this study conducted two decades after the study by Caire-Juvera et al.[9], could also contribute to the observed differences.

Our findings suggest that exclusive breastfeeding may be associated with a healthier dietary pattern among mothers. One possible explanation is that women are more likely to consciously consume healthy foods to provide optimal nutrition for their infants. A study of Spanish women found that concern about promoting infant health during breastfeeding was one of the factors that facilitated the adoption of healthy dietary habits[20]. In addition, according to a study with Bangladeshi mothers, nutrition counseling during pregnancy was associated with a healthier diet and exclusive breastfeeding[12], suggesting a link between healthy food choices and exclusive breastfeeding.

In our study, maternal BMI and age were not significant predictors of maternal dietary patterns. In contrast, a study evaluating dietary habits in pregnant women in the United States found that BMI was associated with healthier dietary habits[21]. It is possible that other factors, such as socioeconomic status, education, and culture, may have a stronger influence on maternal dietary patterns than BMI and age[19].

Regarding body composition, three of the women were underweight, while 32.2% and 19.3% were overweight and obese, respectively. These findings are similar to those reported nationally, where 32.3% of Mexican women between 30 and 39 years old were overweight[11]. Women with the "regional" dietary pattern had a higher BMI than those with the "prudent" pattern. Although there were no significant differences in energy intake between the two groups, it is possible that there were differences in physical activity, which was not assessed in this study. In addition, there is evidence of an association between healthy eating habits and physical activity[22].

Regarding dietary intake, the mean fat consumption was higher than recommended (< 35% of total energy intake), which is associated with negative outcomes for mothers and infants[17]. High fat intake is associated with the development of non-communicable diseases[18]. In addition, fat content in breast milk increases with dietary fat intake, and high-fat content in breast milk may have negative outcomes on the breastfed infant[23]. Women had high sodium and a low potassium intake, which is significant because it is associated with hypertension[24], a condition present in 26.4% of Mexican women[11].

Most of the women in this study (59.7%) had a cesarean section delivery. This characteristic is noteworthy, given that this procedure is associated with a longer recovery after delivery, which could compromise breastfeeding and influence the maternal diet[25]. The delivery mode was considered a variable that could affect maternal diet in this study. However, it was not a significant predictor of maternal dietary patterns.

Most women in our study provided exclusive breastfeeding (69.3%) since they were recruited through breastfeeding support groups. Therefore, it is important to know that the sample may not be representative of the general population. In Mexico, only 28.6% of mothers breastfeed exclusively in the first 6 months postpartum, and the regional prevalence is even lower[11].

This study has some limitations. The representativeness of the study sample was limited due to the sampling method utilized. Including women from areas with

Table 4. Body mass index, energy, and selected nutrient daily intake of Sonoran breastfeeding women by dietary pattern (n = 62)

Variable	Regional pattern* (n = 36)	Prudent pattern* (n = 26)	p-value
BMI (kg/m^2)	26.8 ± 0.7	24.4 ± 0.8	0.026
Energy (kcal)	2099.4 ± 88.6	1924.2 ± 116.4	0.228
Total protein (E%)	18.2 ± 0.4	20.3 ± 0.5	0.001
Total fat (E%)	37.0 ± 0.8	38.2 ± 0.9	0.364
Saturated fat (E%)	13.7 ± 0.3	13.4 ± 0.4	0.623
Cholesterol (mg)	362.6 ± 24.5	356.2 ± 21.8	0.749
Total carbohydrates (E%)	50.1 ± 0.9	51.8 ± 1.1	0.239
Fiber (g)	29.9 ± 1.6	29.0 ± 1.9	0.410
Calcium (mg)	947.0 ± 47.9	1110.8 ± 84.9	< 0.001
Folate (µg)	510.4 ± 30.6	464.8 ± 36.6	0.917
Iron (mg)	18,3 ± 0.8	18.3 ± 1.4	0.974
Phosphorous (mg)	1007.1 ± 46.7	1067.8 ± 69.9	0.031
Potassium (mg)	3305.9 ± 144.7	3739.1 ± 220.2	< 0.001
Sodium (mg)	3084.1 ± 158.2	2678.9 ± 227.0	0.373
Vitamin A (µg)	1325.0 ± 125.6	1895.3 ± 185.3	0.001
Vitamin B_2 (mg)	2.6 ± 0.1	2.7 ± 0.2	0.798
Vitamin B_6 (mg)	3.4 ± 0.2	3.1 ± 0.2	0.079
Vitamin B_{12} (µg)	6.5 ± 0.7	6.4 ± 0.7	0.802
Vitamin C (mg)	154.6 ± 15.7	235.6 ± 23.7	< 0.001
Vitamin E (mg)	9.1 ± 0.5	9.8 ± 0.8	0.066
Zinc (mg)	12.8 ± 0.6	11.8 ± 0.6	0.841

*Nutrient intake was energy-adjusted using the residual method.
Data is presented as mean ± standard error. E%: percentage of total energy; SE: standard error. $p \leq 0.05$.

Table 5. Association between breastfeeding regime and the "prudent" dietary pattern

Predictor variable*	Adjusted odds ratio	p-value
Exclusive breastfeeding (yes)	7.29	0.019
Maternal BMI (kg/m^2)	0.96	0.071
Maternal age (age)	0.95	0.462

*The dependent variable is the "prudent" dietary pattern.

medium and high levels of marginalization would enhance the external validity, identify potential disparities in health and nutrition, and help to understand the influence of socioeconomic factors on diet. Furthermore, the principal component analysis would benefit from a larger sample size, and including women from areas with higher marginalization levels would have increased the represent ability of the data. In addition, the assessment of diet using FFQ may have limitations. Combining FFQ with other methods, such as 24-h recall or food records, would provide more accurate data on nutrient intake.

Despite limitations related to sample size and method, this exploratory research may lead to further studies with larger sample sizes and rigorous methods for dietary assessment of breastfeeding women. Furthermore, we expect that the information presented will motivate the development of future programs and interventions to improve the diet of this population.

In conclusion, the diet of Sonoran breastfeeding women was categorized into two dietary patterns: "regional" and "prudent." Our study found that women

who exclusively breastfed were more likely to follow a "prudent" dietary pattern than those who partially breastfed. Therefore, promoting healthy dietary patterns among Sonoran breastfeeding women is crucial for improving maternal and infant health outcomes. Further studies are required to confirm our findings and explore the underlying association mechanisms between the breastfeeding regime and maternal dietary patterns.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Relationship between skin-to-skin contact during the first hour of life and duration of exclusive breastfeeding

*Alejandra Prian-Gaudiano, Daniela Horta-Carpinteyro, and Andrea Sarmiento-Aguilar**

Centro Médico ABC Campus Santa Fe, Mexico City, Mexico

Abstract

Background: *Exclusive breastfeeding (BF) has the greatest potential impact on child mortality of any preventive intervention. Skin-to-skin contact (SSC) during the first hour of life is beneficial for initiating BF; however, routine separation of mother and infant is still common. This work aimed to demonstrate that SSC during the first hour of life is associated with a greater frequency and duration of exclusive BF.* **Methods:** *This is an observational case–control study. We reviewed the medical records of patients born between 2016 and 2022 classified as cases or controls based on the history of SSC in the first hour of life. Statistical analysis was performed using SPSS version 28.* **Results:** *We included 362 medical records, of which 200 (55.2%) had SSC and were considered cases; the 162 (44.8%) who did not have SSC were considered controls. Those who received SSC were more likely to receive exclusive BF at 3 (163 [81.5%] vs. 94 [58%], p < 0.001) and 6 months of age (147 [73.5%] vs. 83 [51.2%], p < 0.001).* **Conclusions:** *Patients who received SSC in the first hour of life were more likely to receive exclusive BF at 3 and 6 months of age. Promoting and respecting this practice is essential to increase the possibility of a newborn to be exclusively breastfed for the first 6 months of life.*

Keywords: *Skin-to-skin contact. Breastfeeding. Exclusive breastfeeding.*

Relación entre el contacto piel con piel durante la primera hora de vida y la duración de la lactancia materna exclusiva

Resumen

Introducción: *La lactancia materna exclusiva (LME) es la intervención preventiva con mayor impacto en mortalidad infantil. El contacto piel con piel (CPP) durante la primera hora de vida es un periodo crítico para establecer la lactancia; sin embargo, la separación rutinaria del recién nacido de su madre es frecuente. El objetivo de este trabajo fue demostrar que el CPP durante la primera hora se asocia con mayor frecuencia y duración de LME.* **Métodos:** *Se llevó a cabo un estudio observacional de casos y controles. Se revisaron expedientes de pacientes de nuestra consulta pediátrica que nacieron entre 2016 y 2022. Se clasificaron como casos y controles de acuerdo con el antecedente de haber recibido CPP durante la primera hora de vida. Se realizó el análisis estadístico en SPSS version 28.* **Resultados:** *Se incluyeron 362 expedientes, de los cuales 200 (55.2%) recibieron CPP en la primera hora de vida y fueron considerados casos; los 162 (44.8%) que no lo hicieron fueron considerados controles. Aquellos que recibieron CPP tuvieron con mayor frecuencia LME a los 3 (163 [81.5%] vs. 94 [58%], p < 0.001) y 6 meses de edad (147 [73.5%] vs. 83 [51.2%], p < 0.001).*

***Correspondence:**
Andrea Sarmiento-Aguilar
E-mail: dra.andreasarmiento@gmail.com

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Conclusiones: *La frecuencia con la cual los pacientes lograron tener lactancia materna exclusiva a los 3 y 6 meses es mayor en aquellos en los que se respeta el CPP en la primera hora de vida. Promover y respetar esta práctica es fundamental para incrementar las probabilidades de que los lactantes reciban LME durante sus primeros 6 meses de vida.*

Palabras clave: *Contacto piel con piel. Lactancia. Lactancia materna exclusiva.*

Introduction

Breastfeeding (BF) is universally recognized as a human right for all women and children. It is considered the most cost-effective intervention for reducing child mortality and promoting the health of the mother and the breastfed infant[1]. For this reason, the World Health Organization (WHO) recommends breast milk as the only food a newborn should receive from birth to 6 months of age, defined as exclusive BF (EBF)[2]. Many actions are being taken every day to increase EBF rates worldwide; however, many social, cultural, environmental, and economic barriers impact, resulting in global EBF rates of around 38%[3].

It is now recognized that the first hour after birth is a critical period for the establishment and continuation of BF. At this time, the newborn exhibits feeding and survival behaviors[4] that, together with the sudden drop in maternal progesterone due to placental expulsion and the concomitant peak in prolactin[5], allow the newborn to be fed. This is considered the optimal initiation of BF[6]. For direct BF to occur due to these biological processes, direct contact of the newborn with the mother is invariably required within the first hour of life, which has important immediate and long-term implications[7]. Among the many components of the first hour of life (which vary depending on the gestational age and condition of the newborn) are skin-to-skin contact (SSC) and the initiation of BF[4]. The initiation of BF in the first hour of life is one of the most important and determining factors in the continuation of BF in the following months; however, other factors such as maternal age, marital status, education, mode of delivery, history of previous BF counseling, and previous BF experience also have a strong influence[8-10].

SSC refers to the practice of placing the exposed newborn in a prone position directly on the mother's chest, without any barrier, immediately after birth or as soon as possible[11]. It was first described in 1970 as "extra contact"[12] and later in Bogotá, Colombia, where it was called the "kangaroo method"[11]. The benefits of this practice have become so widespread that it is now considered a fundamental part of the Baby-Friendly Hospital Initiative (BFHI) of the WHO and the United Nations Children's Fund (UNICEF)[13].

In Mexico, the National Health and Nutrition Survey (ENSANUT, for its Spanish acronym) reported in 2018 that 28.8% of the country's children receive EBF during the first 6 months of life[14]. Although this figure has doubled compared to what was reported in 2012 (14.4%)[15], it still represents a serious public health problem, as it means that 71.2% of Mexican children are not exclusively breastfed. This information becomes particularly important when we consider that suboptimal BF practices contribute to 11.6% of mortality in children under 5 years of age[2].

In Mexico and many other parts of the world, it has become a common practice to separate newborn babies from their mothers within the first hour of birth[7]. The newborn is placed in a special crib or incubator that provides warmth and helps monitor their breathing patterns to prevent heat loss and ensure their safety[6]. Unfortunately, this practice has detrimental effects on many aspects of infant and maternal health, particularly the establishment and duration of BF[4]. Considering that there is no reason why we cannot monitor the physiological transition of newborns without separating them from their mother, the importance of changing our routine practices can be emphasized when we realize that 820,000 deaths of children under 5 years of age could be avoided each year if all children were properly breastfed[13].

Studies have shown that SSC during the first hour of life is significantly associated with optimal initiation and longer duration of EBF[7]. This work aimed to demonstrate that SSC is associated with a greater frequency and duration of EBF in a Mexican population. The publication of the results obtained will contribute to the medical literature to promote the generalization of this practice in the country[16]. In this way, we will contribute to the WHO goal of increasing the rate of EBF in the first 6 months of life to at least 50% by 2025[2].

Methods

We conducted a case–control observational study. All records of patients in Dr. Alejandra Prian's pediatric practice who were born between January 2016 and January 2022 were reviewed using a data collection

sheet. Files that did not have the required information for the two main variables of the study were excluded from the study: history of SSC at birth during the first hour of life and duration of BF. The following data were collected: sex of the newborn, age, education and marital status of the mother, vaginal or cesarean delivery, and history of SSC in the first hour of life (60 min). The number of months that the infant was breastfed was recorded. The variable was then divided into categories based on whether the patient was exclusively breastfed up to 3 or 6 months of age. In addition, whether or not the mother had previous experience with BF and received prenatal counseling on BF was noted. The study also recorded the number of children to which this birth corresponded. The data were then added to a database created in Microsoft Excel for export and analysis in SPSS version 24. Patients were initially divided into cases and controls according to whether or not they had received SSC during the first hour of life. The description of the studied variables was performed using frequencies and percentages for categorical variables; for numerical variables, the Kolmogorov–Smirnov normality test was performed (the test was chosen because the population studied was > 50). Subsequently, the median was used as a measure of central tendency and the range as a measure of dispersion since the variable had an abnormal distribution.

The difference between the variables studied was examined by comparing cases and controls, using χ^2 for categorical variables and Mann-Whitney's U test for numerical variables with an abnormal distribution.

Results

Of a total of 362 patients, 190 (51.6%) were male while 172 (46.7%) were female. Of all the patients, 201 were delivered vaginally (54.6%), and 161 (43.8%) were born through a cesarean delivery. From the total, 162 patients (44%) did not receive SSC during the first hour after birth, while 200 patients (54.3%) received it. Table 1 presents the frequency of each variable studied concerning the history of receiving or not receiving SSC in the first hour of life.

Patients with a history of vaginal delivery were more likely to receive SSC in the first hour of life than those with a history of cesarean delivery (122 [61%] vs. 79 [48.8%], p = 0.02). Similarly, at the first assessment at 3 months of age, patients with a history of SSC were more likely to continue EBF than those who did not receive SSC (163 [84%] vs. 94 [58.8%], p < 0.001), as shown in Fig. 1. Moreover, a higher proportion of mixed feeding was found in those who did not have SSC (55 [34.4%] vs. 25 [12.9%], p < 0.001). In a second assessment at 6 months, there were more patients with EBF in the group that received SSC than in those that did not (147 [77.8%] vs. 83 [52.9%], p < 0.001) (Fig. 2). However, the proportion of patients with mixed feeding was still higher in the group that did not receive SSC (51 [32.5%] vs. 31 [16.4%], p < 0.001). At this cut-off point, the difference between patients fed exclusively with formula was significantly higher in patients who did not receive SSC (23 [14.6%] vs. 11 [5.8%], p = 0.007). Similarly, the frequency of patients who received prior BF counseling (164 [82.4%] vs. 80 [49.7%], p < 0.001) and who continued BF until the end of the study (80 [44%] vs. 35 [23.2%], p < 0.001) was higher in the group that received SSC than in the group that did not.

Discussion

Our results show that the frequency of EBF at 3 and 6 months of age is higher in those who receive SSC in the first hour of life. In Mexico, 71.2% of Mexican infants do not receive EBF by 6 months[14]. Although evidence of the benefits of SSC in the first hour of life[17] and its influence on BF initiation[18] continues to grow, routine separation of newborns from their mothers remains common, and BF rates remain low[3].

In this study, patients who underwent vaginal delivery were more likely to receive SSC in the first hour of life than those who underwent cesarean delivery (122 [61%] vs. 79 [48.8%], p = 0.02). It has been previously published that SSC after a cesarean delivery can be challenging, particularly in cases of emergency cesarean delivery[16,19]. This practice requires the involvement of not just pediatricians but also anesthesiologists, obstetricians, and nurses. Unfortunately, opposition or interference from medical personnel is common due to a lack of awareness regarding the benefits of SSC[20].

At 3 (163 [84%] vs. 94 [58.8%], p < 0.001) and 6 (147 [77.8%] vs. 83 [52.9%], p < 0.001) months of age, patients in this study with a history of SSC were more likely to continue EBF than those who did not receive SSC. This observation confirms many of the findings previously published in the literature where the establishment and duration of BF are recognized as one of the multiple benefits of SSC[18]. At 3 months of age, the highest proportion of patients with mixed feeding was found in those who did not have SSC (55 [34.4%] vs. 25 [12.9%], p < 0.001), indicating that in the group of patients who did not receive SSC, there were mothers who intended to breastfeed and continued with mixed

Table 1. Description of the variables studied according to the history of receiving or not SSC in the first hour of life

Studied variable	SSC, n = 200 (%)	No SSC, n = 162 (%)	p
Sex			0.668
Female	93 (46.5%)	79 (48.8%)	
Male	107 (53.5%)	83 (51.2%)	
Mode of birth			0.02*
Vaginal delivery	122 (61%)	79 (48.8%)	
Cesarean section	78 (39%)	83 (51.2%)	
Feeding at 3 months			
Exclusive breastfeeding	163 (84%)	94 (58.8%)	< 0.001†
Mixed feeding	25 (12.9%)	55 (34.4%)	< 0.001†
Exclusive formula	6 (3.1%)	11 (6.9%)	0.099
Missing data	6 (3.1%)	2 (1.2%)	
Feeding at 6 months			
Exclusive breastfeeding	147 (77.8%)	83 (52.9%)	< 0.001†
Mixed feeding	31 (16.4%)	51 (32.5%)	< 0.001†
Exclusive formula	11 (5.8%)	23 (14.6%)	0.007†
Missing data	11 (5.8%)	5 (3%)	
Previous breastfeeding experience	38 (19.1%)	20 (12.4%)	0.087
Previous breastfeeding counseling	164 (82.4%)	80 (49.7%)	< 0.001†
Continued breastfeeding at the end of the study	80 (44%)	35 (23.2%)	< 0.001†
Number of birth			0.174
First child	155 (77.9%)	138 (85.2%)	
Second child	38 (19.1%)	22 (13.6%)	
Third child	7 (3.5%)	2 (1.2%)	

*p ≤ 0.05.
†p ≤ 0.001.
SSC: skin-to-skin contact.

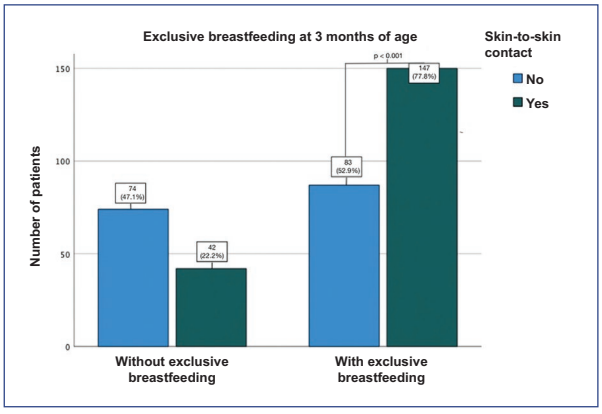

Figure 1. Exclusive breastfeeding at 3 months of age in patients with and without a history of skin-to-skin contact during the first hour of life.

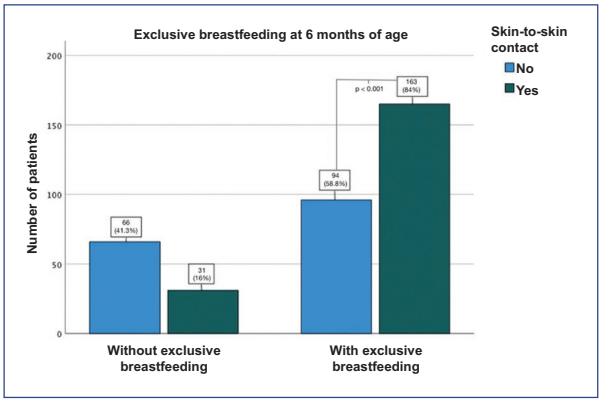

Figure 2. Exclusive breastfeeding at 6 months of age in patients with and without a history of skin-to-skin contact during the first hour of life.

feeding; however, the lack of SSC probably influenced their ability to return to EBF. Although this is a speculation not intended to be proven by the design of this study, it invites us to conduct future research to show how the lack of support from health-care personnel affects the outcome of BF[21]. Reinforcing the same idea, at 6 months after birth, in addition to the proportion of patients with mixed feeding remaining higher in the group that did not receive SSC (51 [32.5%] vs. 31 [16.4%], p < 0.001), the difference between patients fed

exclusively with formula became statistically significant in favor of those who did not SSC (23 [14.6%] vs. 11 [5.8%], p = 0.007). Similarly, we can highlight that there are more patients who continued BF until the end of the study in the group that received SSC compared to the group that did not (80 [44%] vs. 35 [23.2%], p < 0.001).

The effectiveness of BF counseling and its effects on BF initiation and duration have been recognized in the literature[22]. This study confirms that more patients who received previous BF counseling had SSC (164 [82.4%] vs. 80 [49.7%], p < 0.001). Consequently, patients who receive information about the benefits of this practice are more likely to choose health-care professionals who support this practice and to request hospital support to achieve it.

Currently, the benefits of SSC at birth are widely recognized in the medical literature[17]; however, this is not new information. Since 1998, the WHO has recommended that SSC should be performed as soon as possible after birth[2]; the Norma Oficial Mexicana (official Mexican standard) NOM-007-SSA2-2016 recommends that BF should be initiated within the first hour of life[23], and the BFHI recognizes SSC as one of the necessary steps to establish BF. As a result, great efforts have been made to promote this practice, as in the Instituto Nacional de Perinatología[24] (National Institute of Perinatology) case, which reports that SSC was provided in the first hour of life in 78.91% of term newborns. However, despite the lack of medical literature describing the prevalence of this practice nationwide, the author's personal experience is that health-care workers who devote sufficient time to ensuring SSC and promoting exclusive BF of newborns are still a minority.

The situation of EBF in Mexico is far below the target set by the WHO for 2025, where at least 50% of infants should be exclusively breastfed[2]. Similarly, the frequency of SSC and initiation of BF within the first hour of life is unknown. Therefore, the publication of the present results contributes to the medical literature to demonstrate the significant benefits of these practices in establishing and maintaining BF in the Mexican population. In doing so, we expect to contribute to generalizing this practice[16], which is essential to increase the possibility that Mexican infants will be exclusively breastfed during the first 6 months of life.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Analysis of the changes in the management of preterm newborns born in a Spanish third-level hospital in the past 10 years

*María Santiago-Souto[1], Rafael García-Mozo[2], and Marta Costa-Romero[2,3]**

[1]Medicina de Familia y Comunitaria, Hospital Universitario de Cabueñes, Gijon; [2]Unidad de Cuidados Intensivos Neonatales, Hospital Universitario de Cabueñes, Gijon; [3]Departamento de Medicina, Universidad de Oviedo. Asturias, Spain

Abstract

Background: *Preterm newborns require the use of the best and most current strategies to treat and prevent both acute pathology and associated sequelae. This study aimed to compare the differences in the management of preterm newborns over 10 years in a tertiary hospital in Spain and its impact on height, weight, and neurological development in the medium term.* **Methods:** *We conducted a retrospective, observational, and analytical study examining the management and clinical variables in preterm newborns under 32 weeks of gestational age who were born in our hospital in 2011 and 2021.* **Results:** *Twenty-six newborns were included in the study. Significant differences in magnesium sulfate use, continuous positive airway pressure immediately after birth, and non-invasive mechanical ventilation during hospitalization were observed. Differences were found in the use of parenteral nutrition and the timing of initiation of enteral feeding. We did not observe differences in the neurological or weight evolution in the medium term.* **Conclusions:** *Significant differences in managing preterm newborns in these 10 years were observed. Lower mortality and alterations in central nervous system ultrasound and, significantly, less growth retardation during admission in 2021 have been observed; however, it does not manifest with improvement in long-term somatometrics or neurological prognosis.*

Keywords: *Preterm newborn. Neonatology. Surfactant. Parenteral nutrition. Postnatal malnutrition.*

Análisis de los cambios en el manejo de recién nacidos prematuros nacidos en un hospital español de tercer nivel en los últimos 10 años

Resumen

Introducción: *La inmadurez de los recién nacidos pretérmino (RNP) requiere el empleo de las mejores y más actuales estrategias para tratar la patología aguda y prevenir sus eventuales secuelas asociadas. El objetivo planteado es comparar las diferencias en el manejo de RNP a lo largo de diez años en un hospital de tercer nivel en España y su impacto en el desarrollo neurológico y póndero-estatural a medio plazo.* **Métodos:** *Estudio retrospectivo, observacional y analítico examinando variables del manejo y clínicas de todos los RNP menores de 32 semanas de edad gestacional nacidos en nuestro hospital (nivel III-A) en 2011 y en 2021.* **Resultados:** *Se incluyeron 26 infantes (2011: 10 niños, 2021: 16 niños). Observamos diferencias significativas en el uso prenatal de sulfato de magnesio, mayor uso de presión positiva continua en la vía aérea (CPAP) al ingreso y ventilación mecánica no invasiva durante el ingreso, retraso en el uso de surfactante, empleo de alimentación intravenosa e inicio precoz de la alimentación enteral. Existe una menor tasa de mortalidad y desnutrición postnatal en 2021. No observamos diferencias en la evolución neurológica o ponderal a medio plazo.*

***Correspondence:**
Marta Costa-Romero
E-mail: costamarta@uniovi.es

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Conclusiones: *Existen diferencias en el manejo de los prematuros en estos 10 años con mayor ajuste a las guías nacionales e internacionales vigentes. Esto se relaciona con menor mortalidad y alteraciones en la ecografía del sistema nervioso central y, significativamente, con un menor retraso en el crecimiento durante el ingreso en 2021; no se demostró mejoría del pronóstico somatométrico o neurológico a largo plazo.*

Palabras clave: *Recién nacido pretérmino. Neonatología. Surfactante. Nutrición parenteral. Desnutrición postnatal.*

Introduction

According to the World Health Organization, a preterm newborn (PNB) is born before 37 weeks of gestation[1,2]. Three categories are described that classify PNB based on their gestational age:

- Extreme preterm or extremely low birth weight preterm (< 1000 g): born before 28 weeks.
- Very preterm or very low birth weight preterm (< 1500 g): born between 28 and 32 weeks.
- Moderate and late preterm: born between 32 and 37 weeks.

Worldwide, an estimated 15 million neonates are born prematurely each year. Of those who survive, a significant number face lifelong cognitive, motor, or sensory disabilities[2].

PNBs have pathologies inherent to their immaturity and require careful and specific management in the neonatal intensive care unit (NICU), as described in books and systematic reviews[2-8]. Medical advances continue to be made, some modified previous concepts, and others confirmed classical theories and approaches. Table 1 shows the established recommendations in 2011 and 2021, indicating the practices followed in those years[9-29].

The changes in management, improvements in the training of neonatal staff, and state-of-the-art medical equipment have led to a significant increase in the survival of preterm infants and a decrease in the prevalence of severe neurological disability[30,31]. However, other types of less severe neurological problems have increased, such as neuropsychological (autism spectrum disorder, attention deficit hyperactivity disorder, and conduct disorder), motor, and learning disorders. Nutritional support assessment is also relevant, as postnatal malnutrition correlates with future neurological, weight/height alterations. Mid- to long-term follow-up of preterm infants should be coordinated by a multidisciplinary team of pediatricians, rehabilitation specialists, physiotherapists, occupational therapists, and psychologists[31,32].

Therefore, the present study aimed to compare the differences in the management of PNBs born in a tertiary level hospital in 2011 and 2021 and to check whether the changes made have an impact on the neurological development and the weight/height of the children in the medium term.

Methods

We conducted a retrospective, observational, and analytical study to examine clinical and NICU management variables of all infants born before 32 weeks of gestation in a Level III-A hospital in 2011 and 2021. Data were obtained from medical record reviews and recorded in an anonymized database designed for the study. Families were contacted at hospital visits and provided verbal consent for review of their children's records. Those who were not followed up at the hospital were contacted by telephone.

Variables were described as mean and standard deviation, median and interquartile range or percentage according to their characteristics. Statistical tests were used according to the type of variable and according to whether the variables fit the normal (Student's t-test) or non-normal (Mann-Whitney's U) distribution. The χ^2 test was used for percentage analysis. The statistical analysis program SPSS v.22 was used. Significance was considered at $p < 0.05$.

The diagnosis of patent ductus arteriosus (PDA) and retinopathy of prematurity (ROP) required the involvement of pediatric cardiologists and ophthalmologists, respectively, using 2011[33,34] and 2021[35,36] guidelines. The diagnosis of bronchopulmonary dysplasia was based on dependence on oxygen or mechanical ventilation at 36 weeks of age corrected, according to the 2011[37] and 2021[38] definitions.

The percentiles of the somatometric data were obtained from http://www.webpediatrica.com[39] and adjusted for gestational age and sex. Data on post-discharge development were obtained from examinations at the hospital outpatient clinic and the health center. The diagnosis of behavioral disorders was based on DSM-5 criteria[40].

Results

All patients born in our hospital with gestational age < 32 weeks were included in the study: 10 born in 2011

Table 1. Comparison of PNB management and diagnoses in 2011 and 2021

Variable	2011 (n = 10)	2021 (n = 16)	p-value
Respiratory			
CPAP assistance at admission n (%)	5 (50%)	10 (62.5%)	0.420*
Surfactant administration n (%)	8 (80%)	8 (50%)	0.218*
LISA s n (%)	0%	2 (12.5%)	0.467†
Surfactant timing (hours of life) Mean ± SD	0.66 ± 0.73 h	1.8 ± 1.1 h	0.032‡
Duration of non-invasive ventilation (days) Mean ± SD	5.9 ± 6.11 days	7.46 ± 9.82 days	0.728‡
Median (p25-p75)	4 (0.5-8.75)	4 (0.62-9)	0.787§
Duration of any type of mechanical ventilation (days) Mean ± SD	5.9 ± 6.1 days	16.4 ± 25.2 days	0.452‡
Median (p25-p75)	6 (4-11)	4.1 (3-28)	0.783§
Hemodynamic			
PDA n (%)	1 (10%)	3 (20%)	0.626†
Medical or surgical treatment of PDA n (%)	0	1 (7.1%)	1†
Nutrition			
Intravenous feeding n (%)	1 (10%)	15 (93.7%)	0.001†
Start of IV feeding	24 h	9.86 ± 7 h	0.073‡
Start of enteral feeding (hours of life)	1.1 ± 0.56	2 ± 0.94	p = 0.02‡
Breastfeeding/mixed at discharge n (%)	6 (75%)	10 (64.3%)	0.394†
Neurological			
Altered cerebral ultrasound at admission n (%)	4 (40%)	3 (18.7%)	0.369†
Kangaroo care n (%)	0	15 (100%)	0†
Infectious			
Antibiotics at admission n (%)	9 (90%)	3 (18.7%)	0.001†
Nosocomial sepsis n (%)	6 (60%)	4 (28%)	0.211†
Hematological			
EPO n (%)	8 (80%)	5 (33%)	0.041†
Transfusions n (%)	5 (50%)	6 (40%)	0.622†
Ophthalmological			
ROP n (%)	0	1 (7.1%)	1†
Others			
Umbilical vein cannulation at admission n (%)	5 (50%)	14 (87.5%)	0.048†
Mortality n (%)	2 (20%)	2 (12.5%)	0.625†

*χ^2.
†Fisher's exact test.
‡Student's t-test.
§Mann-Whitney's U-test.
p25-p75: 25th and 75th percentile.
CPAP: continuous positive airway pressure; EPO: erythropoietin; IV: intravenous; LISA: less invasive surfactant administration; N: number; PDA: patent ductus arteriosus; PNB: premature newborn; ROP: retinopathy of prematurity; SD: standard deviation.

and 16 born in 2021. The mean gestational age was 29.05 ± 2.4 weeks, varying between 24 and 32 weeks. The surviving lowest gestational-age infants were born in 2021 (their gestational ages were 24 and 25 weeks).

Table 2 shows the epidemiologic data and prenatal management of PNBs in our hospital in 2011 and 2021. We found significant differences between both groups only in the administration of magnesium sulfate.

Regarding respiratory management, we observed fewer infants treated with surfactant and a delay in its administration in 2021 (Fig. 1). Notably, two patients received surfactant in the delivery room in 2011 but none in 2021. Five of the seven infants with conventional mechanical ventilation in 2021 (84% of infants) were ventilated with volume control strategies, but none in 2011 ($p < 0.05$).

Since the breast milk bank of our Autonomous Community was inaugurated in 2017, no child born in 2011 received donated breast milk; instead, all children born in 2021, except for one patient at the expressed wish of the family, received donated breast milk during the first days of life. The analysis of weight development during admission showed no significant differences in the percentage of weight lost (14 ± 5.5% vs. 13 ± 8.2%, p = 0.72). However, we observed a higher mean percentile of weight (20.7 ± 27 vs. 6.3 ± 7.2, p = 0.081)

Table 2. Epidemiological data and prenatal management among premature newborns (PNBs) in 2011 and 2021

Variable	2011 (n = 10)	2021 (n = 16)	p-value
Gestational age Mean ± SD (min-max)	25 ± 2.4 weeks (25-32)	29.3 ± 2.5 weeks (24-32)	0.505‡
Birth weight Mean ± SD (min-max)	1206.5 ± 257.8 g (680-1490)	1246 ± 477 g (610-2320)	0.783‡
Height at birth Mean ± SD (min-max)	38.5 ± 4.4 cm (29-45)	37.8 ± 4.7 cm (29.5-44)	0.932‡
Cranial perimeter at birth Mean ± SD (min-max)	28 ± 4.7 cm (23-40)	28 ± 4.6 cm (22-41)	0.988‡
Gender (males)	90%	37.5%	0.014*
Lung maturity	80%	87.5%	0.625*
Magnesium sulfate	0%	75%	< 0.005†
Cesarean section	50%	56.2%	1
Intensive resuscitation at birth (orotracheal intubation, compressions and/or adrenaline)	50%	37%	0.689*
Apgar score at 1 min Mean ± SD	5.5 ± 2.4	5.5 ± 2.3	0.918‡
Apgar score at 5 min Mean ± SD	8.1 ± 1.45	7.5 ± 1.9	0.385‡

*χ^2.
†Fisher's exact test.
‡Student's t-test.
PNB: premature newborn; SD: standard deviation.

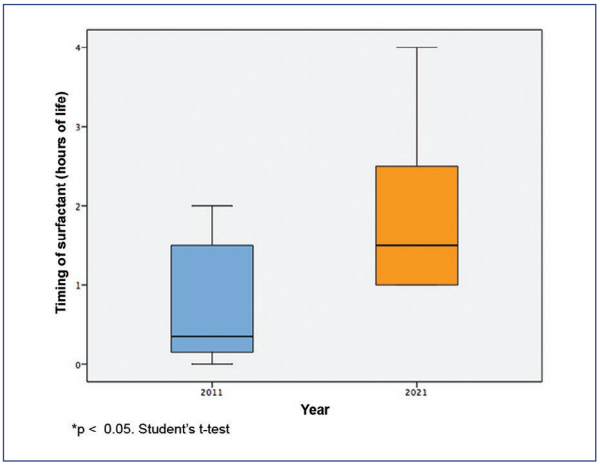

Figure 1. Comparison of the timing of surfactant administration (hours of life).

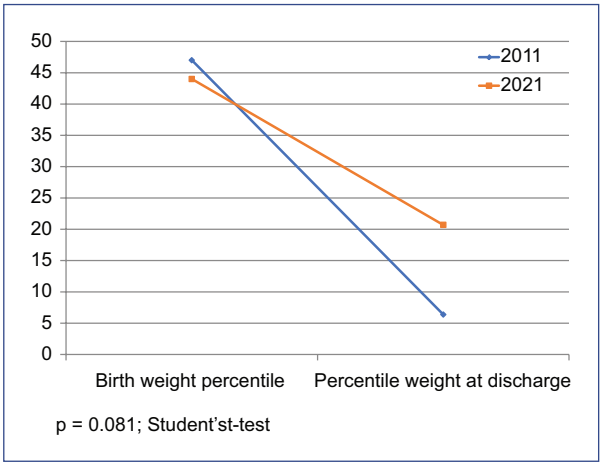

Figure 2. Comparison between birth and discharge weight percentiles in 2011 and 2021.

(Fig. 2) and height (13 ± 20 vs. 5 ± 4.5, p = 0.206) at discharge in 2021 compared to 2011.

Table 1 shows the percentage of children who required specific treatments and had specific diagnoses each year. Two patients died in each group, representing 20% of children in 2011 and 12.5% in 2021 (p = 0.625).

Regarding the evolution after discharge, we did not observe significant differences in weight development or a significant relationship between somatometric data at discharge from neonatology and subsequent evolution. Only six patients (27.3%) had alterations in psychomotor development (Table 3). No significant relationship was found between weight development

Table 3. Relationship between results of neonatal cerebral ultrasound performed during admission and neurological disorders developed by the children subsequently and age at diagnosis

Year	Neonatal cerebral ultrasound	Diagnosis	Age at diagnosis
2011	Germinal matrix hemorrhage.	Autism spectrum disorder Grade 2	18 m
2011	Right periventricular cystic leukomalacia	Spastic triplegic cerebral palsy	12-15 m
2011	Intraventricular hydrocephalus secondary to Grade III intraventricular hemorrhage and Grade II cystic leukomalacia.	Mild left hemiparesis	15 m
2021	Grade II periventricular leukomalacia+ex vacuo hydrocephalus	Spastic diplegic cerebral palsy	19 m
2021	Germinal matrix hemorrhage.	Mild global developmental delay	18 m
2021	Grade II intraventricular hemorrhage	Mild global developmental delay	18 m

Diagnoses according to DSM-5 criteria[39]. m: months.

at discharge and alterations in psychomotor development. However, it was observed that all children with altered psychomotor development had alterations in the central nervous system (CNS) ultrasound performed at admission.

Discussion

The medical records of 26 neonates born at a gestational age of < 32 weeks and admitted to the NICU of our hospital (level III-A) between 2011 and 2021 were analyzed. Although the sample size is small, the analysis of the records showed the changes that have occurred in the care of preterm infants over a decade.

Although we did not find significant differences between the two groups in gestational age and somatometric data, we observed that infants of lower gestational age (24 and 25 weeks) who survived were born in 2021. These patients had a high number of complications, longer mechanical ventilation duration, and longer hospital stays. It is noteworthy the high rate of males born in 2011, when, according to data from the Spanish National Statistics Institute (*Instituto Nacional de Estadística español*), the percentage of males born that year in our Autonomous Community was similar to that of females (51.9% males vs. 48.1% females)[41]. The analysis of prenatal management showed only differences in the administration of magnesium sulfate, which was expected since it was not until the mid-2010s that its use became widespread in Spain following the publication of its role as a neuroprotectant[42].

There are three fundamental points in which we have observed changes in the management of these patients in our NICU that have allowed greater harmonization with international guidelines. First, we observed differences in several aspects of respiratory management, particularly in the reduced use of surfactant, a significant delay in administering the first dose, and the generalization of less invasive administration techniques such as surfactant administration[16]. Similarly, we observed a trend toward greater use of noninvasive ventilation, especially continuous positive airway pressure, at admission and during hospitalization, and modalities with tidal volume control in the case of invasive mechanical ventilation, both strategies in line with the latest published evidence[16,43]. It is noteworthy that the duration of mechanical ventilation was longer in neonates born in 2021. This is secondary to the fact that this year, there were two patients of extreme gestational age (24 and 25 weeks) who required respiratory support for 85 and 61 days, respectively.

Second, we noted the early and widespread initiation of optimized parenteral nutrition in 2021, as indicated by national and international recommendations[20,22,23], in addition to the significantly earlier initiation of enteral nutrition based on breastfeeding from the milk bank. Both factors have allowed these neonates' weight and height percentiles at discharge to be higher than in 2011. However, we could not demonstrate a relationship between weight development and neurological development as has been published[44].

Third, thanks to the internationally recommended rational use of antibiotics[26,27], rates of empiric antibiotic therapy decreased significantly in 2021 without an increase in early mortality due to sepsis of vertical transmission or an increase in the rate of nosocomial sepsis. In this context, the reduced use of erythropoietin, as

recommended[27,29], was also confirmed, being used only in selected patients without an increase in transfusion rates.

In contrast, we did not observe significant differences in the rates of PDA, ROP, and brain lesions, problems that are very common in the first weeks of life of extremely preterm infants[6-8]. As for PDA and ROP, there were more cases of both in 2021 because the youngest gestational-age infants in the study were born in that year, although their incidence was lower than that published in the literature[32]. The rate of brain lesions observed at each stage was also lower than other reports[30,31,45-47], but has a subsequent neurological impact. Based on our results and large international series[30-47], we can correlate the alteration of the neonatal cerebral ultrasound with alterations in psychomotor development during early childhood. In this sense, although the differences are not significant, the most severe pictures correspond to children born in 2011 and are characterized by severe motor problems secondary to intraventricular hemorrhage.

Finally, although not statistically significant, the mortality rate is much lower in 2021, which is consistent with review articles relating improved care to increased survival of patients, especially those with extreme gestational age[45-47].

As limitations, we consider that despite including all preterm infants born in our hospital in 2011 and 2021, the total sample size was small. This fact has limited the achievement of statistical significance in some comparisons but gives more value to those comparisons that have achieved it. Although there is a decade between both years studied, the changes may need more time to be evaluated. Therefore, in subsequent studies, we will consider analyzing years that are further apart in time.

There are differences in the management of preterm infants over 10 years, with greater adherence to current national and international guidelines.

Lower mortality and fewer CNS ultrasound changes, and significantly less growth retardation were observed in neonates born in 2021; however, no improvement in long-term somatometrics or neurological prognosis were demonstrated so far.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Usefulness and description of the intestinal bypass technique in children with short bowel syndrome: report of a Mexican cohort

Eustorgio S. García-Cárdenas[1], Isela Nuñez-Barrera[1], América L. Miranda-Lora[2], Juan J. Bolaños-Pérez[1], Rosalinda López-Rodríguez[3], Norma Briseño-Chavarria[3], and Salvador Villalpando-Carrión[1]*

[1]Departamento de Gastroenterología y Nutrición; [2]Unidad de Investigación Epidemiológica en Endocrinología y Nutrición; [3]Clínica Colorrectal de Heridas y Estomas. Hospital Infantil de México Federico Gómez, Mexico City, Mexico

Abstract

Background: *Short bowel syndrome (SBS) is one of the most frequent causes of intestinal failure, needing parenteral nutrition to maintain an energy-protein and water-electrolyte balance. At the Hospital Infantil de México Federico Gómez (HIMFG), the formation of two stomas is a technique used for intestinal rehabilitation, where the use of residue through the bypass technique (BT) helps to maintain gastrointestinal functionality, water-electrolyte, and nutritional stability. This study aimed to describe the technique of using intestinal residue through BT as a treatment strategy in intestinal rehabilitation and its effect on the biochemical and nutritional status of pediatric patients with SBS.* **Methods:** *An analytical and retrospective cross-sectional study was performed in patients hospitalized at HIMFG with SBS who underwent BT during their hospital stay between 2019 and 2020 and then followed up for 8 weeks.* **Results:** *A total of 10 patients were included in this study, with a mean age of 24 months; 50% were female. BT was able to reduce the inflammatory process in the liver caused by the continuous use of parenteral nutrition; enteral caloric intake increased from 25.32 kcal/kg/day to 72.94 kcal/kg/day, but it was insufficient to improve their nutritional status.* **Conclusions:** *BT is a safe and effective alternative in intestinal rehabilitation in patients with SBS to stimulate trophism and intestinal functionality, allowing a progression of enteral feeding and a decrease in the hepatic inflammatory process that occurs in these patients with prolonged parenteral nutrition.*

Keywords: *Short bowel syndrome. Intestinal failure. Prolonged parenteral nutrition. Intestinal bypass technique. Pediatric population.*

Utilidad y descripción de la técnica de puenteo intestinal en niños con síndrome de intestino corto: reporte de una cohorte en México

Resumen

Introducción: *El síndrome de intestino corto (SIC) es una de las causas más frecuentes de insuficiencia intestinal que requiere del uso de nutrición parenteral para mantener un balance energético-proteico e hidroelectrolítico. En el Hospital Infantil de México Federico Gómez (HIMFG) la formación de dos estomas es una técnica empleada para la rehabilitación*

***Correspondence:**
Eustorgio S. García-Cárdenas
E-mail: eustorgiogarcia1@hotmail.com

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intestinal, donde con el aprovechamiento de residuo mediante la técnica de puenteo (TP) se ayuda a mantener la funcionalidad gastrointestinal, equilibrio hidro-electrolítico y estabilidad nutricional. El objetivo de este estudio fue describir la técnica del aprovechamiento de residuo intestinal mediante TP como estrategia de tratamiento en la rehabilitación intestinal y su efecto en el estado bioquímico y nutricional de pacientes pediátricos con SIC. **Métodos:** *Se llevó a cabo un estudio transversal analítico y retrospectivo en pacientes hospitalizados en el HIMFG con SIC en quienes se realizó la TP durante su estancia intrahospitalaria entre 2019 y 2020.* **Resultados:** *Se incluyeron 10 pacientes en este estudio, con una edad promedio de 24 meses, y el 50% de sexo femenino. La TP logró disminuir el proceso inflamatorio hepático ocasionado por el uso continuo de nutrición parenteral; la ingesta calórica por vía enteral incrementó de 25.32 kcal/kg/día a 72.94 kcal/kg/día, pero fue insuficiente para mejorar el estado nutricional.* **Conclusiones:** *La TP es una alternativa segura y efectiva en la rehabilitación intestinal en pacientes con SIC para estimular el trofismo y funcionalidad intestinal, permitiendo una progresión de la alimentación enteral y disminución del proceso inflamatorio hepático que se presentan en estos pacientes con nutrición parenteral prolongada.*

Palabras clave: *Síndrome de intestino corto. Insuficiencia intestinal. Nutrición parenteral prolongada. Técnica de puenteo intestinal. Población pediátrica.*

Introduction

Short bowel syndrome (SBS) is a complex condition caused by the anatomical or functional loss of part of the small intestine. This condition results in severe metabolic, electrolyte, and nutritional disturbances due to a reduction in the effective absorptive surface of the bowel[1]. According to Nightingale, a patient is considered to have SBS when the length of the intestine is insufficient to allow adequate absorption of nutrients, fluids, and electrolytes, which interferes with proper growth and development[2].

SBS is one of the most common causes of intestinal failure requiring parenteral nutrition to maintain energy-protein and water-electrolyte balance, a term introduced by Pironi et al.[3].

The term 'intestinal failure' was coined by Fleming and Remington in 1981 to describe a decrease in functional intestinal mass resulting in impaired digestion, absorption, or both[4]. The American Gastroenterological Association defines it as a condition resulting from obstruction, dysmotility, bowel resection, congenital defect, or disease associated with loss of absorption and characterized by an inability to maintain an adequate balance of fluids and electrolytes, proteins, and micronutrients[5].

The incidence of intestinal autonomy, defined as the ability of the gastrointestinal tract to be maintained without parenteral nutrition for more than three consecutive months, is estimated to range from 42% to 86% in cases of short bowel[6-8]. According to the Pediatric Intestinal Failure Consortium, in a study of 272 patients under 12 months of age with intestinal failure who received parenteral nutrition for more than 60 consecutive days, 44% achieved intestinal autonomy within 3 years, 26% died, and 23% required intestinal transplantation[7]. However, intestinal autonomy is not always achieved. Therefore, the introduction and combination of new intestinal rehabilitation therapies focusing on controlling and improving intestinal failure have enhanced intestinal adaptation and reduced the need for intestinal transplantation. These therapies include serial transverse enteroplasty, a surgical procedure to lengthen the intestine; optimization of total parenteral nutrition to prevent hepatopathy associated with intestinal failure through the use of omega-3 lipid emulsions and lipid minimization; and ethanol seals used to prevent recurrent catheter-related infections, sepsis, and bacterial overgrowth, as well as to treat intestinal dysmotility[9]. In patients with enterostomies, performing an enteral anastomosis can sometimes be challenging, which prolongs the use of the ostomy and affects the functionality of the distal bowel. At the Hospital Infantil de México Federico Gómez (HIMFG), we create two stomas in these cases to preserve gastrointestinal functionality proximally and distally. In addition, at HIMFG, we have experience in intestinal rehabilitation using the bypass technique (BT) to utilize the residuals and improve the patient's situation.

The nutrition protocol for these patients begins with total parenteral nutrition to meet their nutritional needs. Enteral nutrition is then initiated by continuous infusion, with the volume of formula increased as tolerated by the patient. Gastrointestinal status, hemodynamic and water-electrolyte balance, and stool output are monitored to decrease parenteral nutrition and increase enteral nutrition gradually. The ultimate goal is to provide all energy and nutrition through the enteral route, eliminating parenteral nutrition and continuous infusion of enteral nutrition[10].

This study aimed to describe the use of BT as part of the treatment for intestinal rehabilitation and its impact on the biochemical and nutritional status of pediatric patients with SBS.

Methods

An analytical and retrospective cross-sectional study was conducted by reviewing the records of pediatric patients treated at HIMFG diagnosed with SBS who underwent the BT between November 2019 and June 2020, with a follow-up of 8 weeks. The STROBE checklist was used for this cross-sectional observational study.

Inclusion criteria

We included patients under 18 years of age who met the following characteristics:

– Diagnosis of SBS, defined as insufficient intestinal length to allow adequate absorption of nutrients, fluids, and electrolytes, which interferes with proper growth and development.
– Presence of external shunting of the small intestine by two or more stomas, without metabolic or systemic complications that prevent the use of the enteral route.
– Patients undergoing bypass surgery as described below.

Exclusion criteria

Patients without complete clinical records, imaging studies, and reports, and those with infectious processes, water-electrolytic or metabolic alterations, or intestinal obstructions that prevented adequate intestinal transit during the BT. We used dependent variables such as anthropometry, indicators of nutritional status, biochemical parameters of hepatic and intestinal function, and data on intestinal functionality, and as an independent variable, the type of intestinal resection.

For data collection, an electronic tool in Excel (TPeIC) was created with four sections: (a) identification card (age, sex, diagnosis, and hospital record); (b) birth data (gestational weeks, weight, height, and head circumference); (c) surgical data (pre- and post-operative diagnosis, length and location of bowel resection, length of residual bowel, and number of stomas, presence/absence of ileocecal valve); and (d) weekly evolution sheet with anthropometric, nutritional, and biochemical data. The anthropometric measurements (weight, height, brachial perimeter, and triceps fold) were taken as follows: for weight, a SECA® 20 kg digital scale was used, placed on a flat surface, and tared before the patient was placed unclothed; several measurements were taken until two coincident ones were obtained.

For standing patients, a digital ONROM® scale was used, with several measurements taken until two equal measurements were obtained; the measurement was taken in underwear or with the minimum amount of clothing, maintaining the same conditions for subsequent measurements. Length was measured in centimeters with a SECA® infantometer; for standing patients, a clinical scale was used with a BAME® stadiometer in centimeters. To obtain weight-for-height and height-for-age indicators, we compared them with CDC growth charts, adjusted for sex and age. Nutritional status was classified according to Waterlow parameters. Arm circumference was measured in centimeters with a HERGOM® anthropometric tape using the ISAK technique. The triceps fold was measured with a LANGE® plicometer in neonates and HARPENDEN® in pediatrics, using the ISAK technique. Frisancho constants and formulas were used for lean mass and adipose reserve indicators according to sex and age. Clinical, biochemical, and anthropometric data were collected from the case files. Finally, anthropometric and biochemical data and oral and enteral caloric intake were analyzed.

Bypass technique

Once the permeability of the distal bowel has been confirmed through a contrast study, BT involves infusing the contents of the proximal stoma through the distal stoma. The aim is to utilize the gastrointestinal secretions and enzymes, intraluminal absorption of nutrients to stimulate and maintain villous length, and hormonal regulation of intestinal adaptation, including hormone action on intestinal trophism[7,11].

An ostomy collection system is placed in the proximal stoma to store the proximal bowel contents to a minimum of 20 ml, an amount that can be infused through the distal stoma with a 20 ml syringe using a 3-5 cm latex or silicone tube (Fig. 1). This tube should be connected to a smaller caliber feeding tube for continuous administration with a venoclysis set in an infusion pump until the collected contents exceed 60 ml, delivering the same amount and rate to the distal bowel.

This infusion through the distal stoma must be slow and continuous < 1 h from collection to avoid bacterial proliferation. It does not require a sterile technique, and

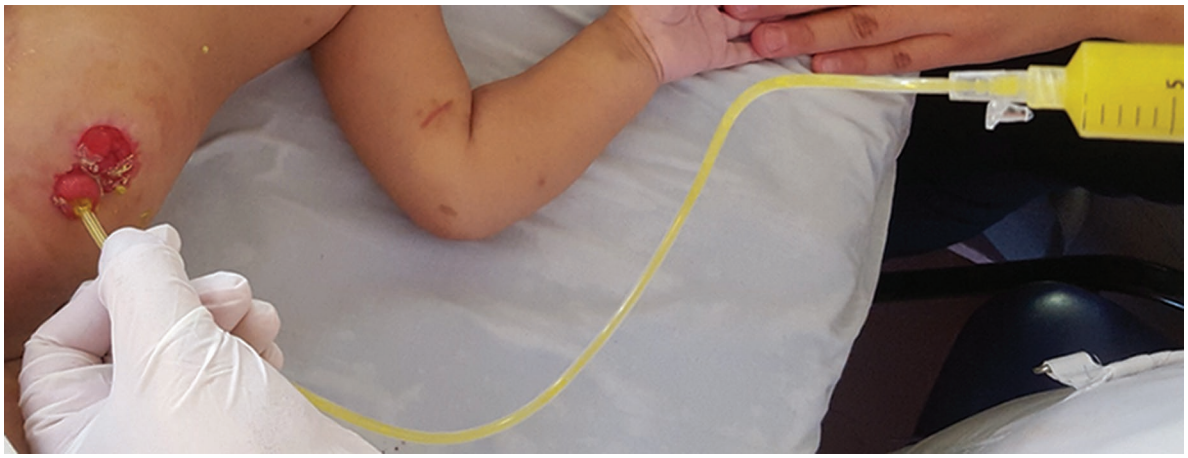

Figure 1. Application of bowel residue collected from the proximal portion of the bowel to the distal portion using a probe.

the process is repeated as many times as necessary to infuse all of the contents of the proximal stoma into the distal stoma as it is collected.

At the end of the procedure, the tube is removed with strict attention to abdominal symptoms such as pain, bloating, and vomiting. For clinical follow-up, the technique's functionality is evaluated with the fecal output, whose volume should be less than the initial infusion of the distal stoma, translating the absorption of nutrients and fluids. An increase in rectal output would indicate clinical instability or intolerance to the procedure.

Statistical analysis

Descriptive analysis of the participant characteristics was performed using frequencies for dichotomous variables and medians, minimums, and maximums for quantitative variables. For these variables, tests of difference of medians were performed. The p-value was calculated using Friedman's test.

Ethical considerations

As this was a retrospective documentary investigation without intervention or intentional modification of variables, the study was considered free of risk, and informed consent was not obtained. The confidentiality of the data and the anonymity of the participants were maintained. Due to its nature, the study has no ethical implications.

Results

Over a period of 7 months, ten patients met the selection criteria. There was no gender predominance (50% female and 50% male). The mean age at surgery was 24 months. The pathologies causing SBS were intestinal malrotation and volvulus (4/10), necrotizing enterocolitis (2/10), intestinal atresia (1/10), gastroschisis (1/10), and others (2/10) (Table 1). In 8/10 patients, more than 100 cm of bowel was resected, while in two patients, the length was not recorded, only the site (Table 1).

The initial nutritional diagnosis was acute malnutrition in 70% of the patients and stunted growth due to short stature in 30%. At the end of the study, 20% were found to be eutrophic: 50% had weight/height harmony despite short stature, and 30% had acute malnutrition. It should be noted that one of the patients had four stomas, and the length of the residual intestine was unknown, so the limitation of intestinal absorption in the presence of BT should be considered (Table 1).

Basal lean tissue reserve was 69.19%, with no significant improvement, and fat tissue reserve was 67.68% (Table 2). Liver function tests showed a decrease in aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels: (154 U/L vs. 69 U/L) and alanine aminotransferase (ALT): (131 U/L vs. 79 U/L). When compared, the p-value was 0.03 for AST and 0.04 for ALT (Table 3).

The caloric intake of parenteral nutrition decreased by 25% on average from baseline (79.36 kcal/kg/day to

Table 1. Demographic and clinical characteristics of the patients

Patient	1	2	3	4	5	6	7	8	9	10
Age (months)	2	3	157	3	154	170	2	1	1	4
Gender	Female	Female	Male	Male	Female	Female	Male	Male	Male	Female
Diagnosis	Gastroschisis	NEC	Not Specified	Intestinal volvulus	Intestinal volvulus	Not specified	Intestinal volvulus	Intestinal atresia	NEC	Intestinal volvulus
Length Resected	Not Specified	> 100 cm	> 100 cm	> 100 cm	> 100 cm	> 100 cm	> 100 cm	> 100 cm	> 100 cm	Not Specified
Resection Site	Duodenum-jejunum	Multiple Segments	Ileum	Ileum	Ileum	Ileum	Multiple segments	Ileum-colon	Multiple segments	Multiple segments
IVC	+	+	+	+	+	+	-	-	+	+
Stomas	2	2	2	2	2	2	2	2	2	4
Initial feeding	Mixed	Mixed	Mixed	Mixed	Mixed	TPN	TPN	Mixed	Mixed	Mixed
Feeding at 8 weeks	Enteral	Mixed	Mixed	Enteral	Mixed	Mixed	TPN	Mixed	Mixed	Mixed
Initial nutritional status	Low birth weight	Low birth weight	Severe acute malnutrition	IUGR	Mild chronic malnutrition	Compensated chronic malnutrition	Low birth weight	Low birth weight	Low birth weight	Severe acute malnutrition
Nutritional status at 8 weeks	Growth delay	Growth delay	Moderate acute malnutrition	Eutrophic	Compensated chronic malnutrition	Eutrophic	Growth delay	Growth delay	Growth delay	Severe acute malnutrition

IUGR: intrauterine growth retardation; IVC: ileocecal valve; NEC: necrotizing enterocolitis; TPN: total parenteral nutrition.

Table 2. Anthropometric indicators

Weekly follow-up	Weight (kg)	Z-score weight	Height (cm)	Z-score height	Lean tissue reserve (%)	Fat tissue reserve (%)
Basal	3.21	–2.01	44.7	–1.97	69.19	67.68
	(3.8-49.5)	(–4.49-0.05)	(45-145.5)	(–5.15-0.58)	(50.9-86.5)	(32.5-106.6)
Week 2	2.86	–1.91	40.4	–1.83	69.69	66.75
	(3.8-40.5)	(14.11-0.1)	(47-145.5)	(15.06-0.70)	(39.37-86.6)	(38.5-106.6)
Week 3	11.13	–2.14	45.4	–1.67	67.15	71.78
	(2.7-51.25)	(–3.93-0.13)	(52-145.5)	(– 4.69-0.70)	(49.4-90.2)	(50-106.2)
Week 4	36.61	–2.22	39.5	–2.22	73.71	71.75
	(2.73-51.6)	(–4.83-0.16)	(52-145.5)	(–4.6-0.7)	(53-90.3)	(52.5-107.5)
Week 8	37.1	–2.56	50.8	–2.56	72.19	66.16
	(2.64-50.6)	(–4.9-0.03)	(53-145.5)	(–4.14-0.62)	(49.8-94.18)	(45-110)
p-value	0.098		0.099			

Values expressed as mean, minimum and maximum respectively.

Table 3. Evolution of liver enzymes

Liver enzyme	Basal	Week 2	Week 3	Week 4	Week 8	p-value*
AST (U/L)	154 (27-947)	91 (33-278)	67 (32-217)	117 (39-465)	69 (17-252)	0.033
ALT (U/L)	131 (23-741)	113 (35-351)	86 (15-269)	148 (19-493)	79 (11-325)	0.043

Values given as means, minimum and maximum respectively.
*p-value Friedman's test.
ALT: alanine aminotransferase; AST: aspartate aminotransferase.

Table 4. Amount of kilocalories administered by enteral and parenteral nutrition

Daily caloric intake and mode of nutrition	Basal	Week 2	Week 3	Week 4	Week 8	p-value*
EN kcal/kg/day	25.32 (2.17-82.63)	34.87 (0.10-96.6)	28.90 (24.70-73.86)	40.59 (0.37-89.39)	72.94 (49.90-134.83)	0.034
PN kcal/kg/day	79.36 (38.80-143.50)	76.88 (46.47-108.12)	72.81 (45.10-109.60)	75.59 (43.95-113.34)	59.62 (31.87-76.50)	0.66

Values given as means, minimum and maximum respectively.
*p value Friedman's Test.
EN: enteral nutrition; PN: parenteral nutrition.

59.62 kcal/kg/day). Moreover, the caloric intake of enteral nutrition increased by 28% from baseline (25.32 kcal/kg/day to 72.94 kcal/kg/day), with a p-value of 0.034. The energy density of the enteral formulas varied between 0.67 and 0.95 kcal/ml (Table 4). In 80% of patients, the BT was performed at a capacity of 100%, while in the remaining 20%, output of 20% of the capacity was achieved. At the end of the follow-up period, 90% of the patients received 100% of the achieved output, while the remaining 10% received 70% output.

Discussion

After bowel resection, the remaining bowel attempts to compensate and maintain nutritional homeostasis through physiological, cellular, and molecular mechanisms. This adaptation begins as soon as the resection is performed and can last between 1 and 3 years[6,8,12].

This is the first study to report the BT procedure with residue recovery as an alternative treatment in the intestinal rehabilitation of pediatric patients. With this

intestinal rehabilitation technique, an improvement in nutritional status was demonstrated in 50% of the patients; 20% (n = 2) became eutrophic patients and 30% improved weight for height, remaining in compensated chronic malnutrition. There is little evidence regarding malnutrition in patients with SBS. However, it is known that it is difficult to maintain proper growth and development in a child whose intestine has a reduced absorptive surface and a decrease in digestive enzymes and transporter proteins. This may explain the variations in the percentages of lean and adipose tissue reserves seen in our patients since the limitation of nutrient absorption is reflected in tissue synthesis. In a series of three cases with SBS presented by Galiano et al., it was found that only two patients had an adequate weight/height gain, while one remained below the mean value[13].

In our series, eight out of ten patients received mixed nutrition (enteral and parenteral) at the beginning of treatment; one patient received enteral stimulation until week 4, and another was dependent on parenteral nutrition without being able to initiate enteral nutrition. With this technique, a progression of enteral nutrition was achieved with a consequent decrease in parenteral nutrition, suggesting that this technique reduces the duration of parenteral nutrition, with a consequent reduction in associated complications.

Predictors have been sought to assess bowel autonomy, with residual bowel length being a primary determinant of bowel function and the most consistent indicator. It has been suggested that a residual bowel length of 35 cm is associated with a 50% chance of not requiring parenteral nutrition[14]. A residual length > 40 cm significantly decreases the likelihood of continuing to require parenteral nutrition. However, a residual length of only 15-40 cm has been associated with intestinal adaptation when resection occurs in term neonates[15].

There are other factors associated with prognosis and evolution, such as the extent and portion of the resected segment, the associated diagnosis, the functionality of the residual bowel, the presence of an ileocecal valve, the age of the patient at the time of resection, and the presence of a stoma versus primary closure[16]. Regarding the latter, at 8 weeks after initiation of treatment with the bypass technique, 50% of the population underwent surgical closure. At 12 weeks of follow-up, 80% of the patients were reconnected, and at 16 weeks, only one patient had a stoma. Other important factors include the presence of cholestasis secondary to parenteral nutrition[15,17]. In this regard, at biochemical level, we found that AST and ALT levels were significantly reduced, suggesting that bypass may be a protective factor against the development of hepatopathy associated with prolonged use of parenteral nutrition.

To evaluate the functionality of the technique, we quantified fecal output, which should be less than that infused through the distal stoma. To date, there are no published studies to determine normal stool output in patients with SBS and stomas. This is because the proximal stoma output may correspond to an output that exceeds oral, gastric, or transpyloric intake, as endogenous gastric, pancreatic, biliary, and intestinal secretions constitute a significant portion of both stoma and fecal output. In this context, the proximal output may be 3 or 4 ml/kg/h despite an intake of only 1 or 2 ml/kg/h. Therefore, the amount of nutrients administered enterally should be given as a continuous infusion at a slow but controlled flow rate, for example, 1 ml/kg/day. In addition, stoma and rectal volumes should be monitored to keep them at < 40-50 ml/kg/day. This is because higher outputs put the patient's water status at risk and may require water and electrolyte replacement[9,18,19].

In our study, the initial average proximal output was 32.37 ml/kg/day, increasing to 52 ml/kg/day at the end of the study. The initial average fecal output was 9.91 ml/kg/day, increasing to 11.5 ml/kg/day at the end of the study. This represents an absorption of 78% of the initial infusion. These results are consistent with those published by Aragón et al., in which the average fecal output in stable children with SBS was 31.5 g/kg/day[10].

There are therapies aimed at promoting and achieving intestinal sufficiency through dietary modifications and pharmacological interventions. Enteral nutrition is the most important stimulus for intestinal adaptation[16] because it stimulates the secretion of gastrointestinal hormones and gastric and pancreatic secretions. It also causes direct stimulation of enterocyte hyperplasia through the interaction of the intestinal epithelium with intraluminal nutrients[20,21]. In addition, enteral nutrition stimulates bile flow and intestinal motility, reducing the risk of bacterial overgrowth and providing a protective effect against cholestasis[22]. At histologic level, this translates into hyperplasia of the intestinal epithelium; such hyperplasia includes increased microvilli height and crypt depth, as well as intestinal elongation and dilatation[23,24].

The use of residuals with the BT as an alternative treatment in intestinal rehabilitation aims to achieve intestinal adaptation by early transition from parenteral to enteral nutrition. The goal is to maintain adequate nutritional status and limit morbidity and mortality.

In conclusion, intestinal rehabilitation with residue utilization and BT can help to achieve greater intestinal autonomy and adaptation, morphologically and

functionally. This is achieved by favoring intestinal tropism and allowing the use of the absorptive capacity of the residual intestine, reducing the risk of malnutrition and maintaining an adequate water-electrolytic balance.

This procedure also helps to maximize enteral nutrition early and reduce the use of parenteral nutrition. This may reduce the risk of developing hepatopathy associated with prolonged use of parenteral nutrition.

The use of residue by the BT may also improve the nutritional status of patients and help to optimize the weight/height ratio.

The main limitations of this study are the sample size, its descriptive nature, and the retrospective analysis of cases. However, the study represents a starting point for future work on managing these patients.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. This study involved a retrospective review of medical records, for which approval was obtained from a formally constituted review board (Institutional Review Board or Institutional Ethics Committee).

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Changes in Neonatal Intensive Care Unit statistics during the COVID-19 pandemic

David Rodríguez-Medina[1], Luis M. Avalos-Huizar[2], Wendy Bolio-Pontigo[1], Ma. Guadalupe Soto-Castañeda[3], Julio C. Cárdenas-Valdez[4], and Claudia K. Medina-Ríos[5]*

[1]Unidad de Cuidados Intensivos Neonatales; [2]División de Neonatología; [3]Dirección General; [4]Dirección Médica; [5]Departamento de Neonatología. Hospital de Gineco obstetricia, Centro Médico Nacional de Occidente "Lic. Ignacio García Téllez", Instituto Mexicano del Seguro Social, Guadalajara, Jalisco, Mexico

Abstract

Background: *With the identification of COVID-19 disease in China, a pandemic began that affected health-care systems. The Neonatal Intensive Care Unit (NICU) of the Hospital de Ginecobstetricia del Centro Médico Nacional de Occidente experienced an increase in patient flow as part of the COVID-19 strategy of the Instituto Mexicano del Seguro Social (IMSS). This study aimed to analyze the impact of the COVID-19 pandemic on neonatal care and mortality indicators in our unit.* **Methods:** *We conducted a retrospective study to compare the number of hospital births, pre-term newborns (PTNB), NICU admissions, and deaths. Changes in frequencies between 2019 and 2021 were analyzed using Poisson distribution. Changes in PTNB births, proportion of admissions, and deaths/NICU discharges were analyzed by z-test for two proportions.* **Results:** *Between 2019 and 2021, the number of births increased by more than 2-fold. NICU admissions increased from 770 in 2019 to 1045 in 2021 ($p < 0.01$). The ratio of deaths/discharge from the service was 16.9% in 2019 and 13.1% in 2021 ($p = 0.02$).* **Conclusions:** *Mortality indicators in the NICU decreased from 2019 to 2021, even with the increase in the number of patients admitted during the COVID-19 pandemic.*

Keywords: *Newborn. Neonatal intensive care. Statistical distributions. Coronavirus infections.*

Cambios en las estadísticas de una Terapia Intensiva Neonatal durante la pandemia COVID-19

Resumen

Introducción: *Con la identificación de la enfermedad por COVID-19 en China, inició una pandemia que afectó a los sistemas de salud. La Unidad de Cuidados Intensivos Neonatales (UCIN) del Hospital de Ginecobstetricia del Centro Médico Nacional de Occidente del Instituto Mexicano del Seguro Social (IMSS) vio incrementado su flujo de pacientes como parte de la Estrategia COVID-19 del IMSS. El objetivo fue analizar el impacto de la pandemia COVID-19 en los indicadores de atención y mortalidad neonatal en nuestra unidad.* **Métodos:** *Se realizó un estudio retrospectivo para comparar el número de nacimientos en el hospital, nacimientos de recién nacidos prematuros (RNPT), ingresos a UCIN y defunciones. Se analizaron los cambios en frecuencias entre los años 2019 a 2021 mediante la distribución de Poisson. Los cambios en nacimientos de RNPT, proporción de ingresos y defunciones/egreso en UCIN se analizaron mediante prueba Z para dos proporciones.*

***Correspondence:**
David Rodríguez-Medina
E-mail: davirome@gmail.com

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Resultados: *Entre los años 2019 a 2021, el número de nacimientos incrementó más de 2 veces. Los ingresos a UCIN aumentaron de 770 en 2019, a 1045 en 2021 (p < 0.01). La proporción de defunciones/egreso del servicio fue de 16.9% en 2019, y 13.1% en 2021 (p = 0.02).* **Conclusiones:** *Los indicadores de mortalidad en la UCIN disminuyeron de 2019 a 2021, aun con el incremento en el número de pacientes atendidos durante la pandemia COVID-19.*

Palabras clave: *Recién nacido. Cuidado intensivo neonatal. Distribuciones estadísticas. Infecciones por coronavirus.*

Introduction

COVID-19 was first identified in December 2019 in Wuhan, China[1]. The COVID-19 pandemic has pressured health systems and social and economic dynamics globally[2]. As a result, health authorities in various countries have adopted strategies to protect patients and health workers and mitigate the pressure on health systems[3-6].

Neonatal intensive care unit (NICU) services also faced challenges of a different nature. These included changes in patient flow associated with health policy adjustments. Some of the consequences of these changes have been reported as an increase in the frequency of deaths[7] or a lack of necessary supplies for neonatal care[8].

Developed countries have reported reductions in neonatal mortality[9], cesarean births, pre-term births, and NICU admissions[10-15].

The NICU of the Hospital de Ginecobstetricia (HGO) of the Centro Médico Nacional de Occidente (CMNO) of the IMSS cares for patients who, due to associated maternal conditions or characteristics of the product of pregnancy, require management with specialized equipment and personnel. The HGO-CMNO is located in the city of Guadalajara, Jalisco, Mexico. This High Specialty Medical Unit (UMAE) cares for pregnant women who, due to their complex conditions, are referred from different units in the western part of the country.

As an essential part of the IMSS COVID-19 strategy, hospital restructuring was implemented to reorganize hospital infrastructure, medical equipment, and health personnel to face the health emergency. To provide adequate medical care, several types of health units were established, such as 100% COVID hospitals, hybrid hospitals, temporary medical units, expansion medical units, and early opening units. Each of these units had specific dynamics and logistics for their operation, as well as the financial and administrative resources necessary for their operation[16].

The HGO, a highly specialized medical unit for the care of high-risk pregnant women and their critical newborns, adapted its infrastructure and human resources to accept pregnant patients without evidence of COVID-19 disease, thus avoiding their care in pandemic-adapted units. This change resulted in an increased influx of patients with complex pregnancies who had not previously been cared for in pandemic-adapted units. As a result, the number of patients in the NICU also increased. Therefore, it is essential to analyze the behavior of statistical indicators related to neonatal mortality in the NICU to understand the impact of this increase in patient load on these indicators.

The main objective of this study was to analyze the impact of the COVID-19 pandemic on neonatal care and mortality indicators in our unit.

Methods

With the approval of the IMSS Local Health Research Committee No. 1310, a retrospective, observational, and analytical time series analysis was performed. The objective was to evaluate the difference in the number of patients seen at the HGO before the onset of the COVID-19 pandemic and during the period of support to the reconverted units. Changes in mortality indicators were also analyzed. All live newborns in the unit were included in birth statistics, regardless of gestational age and diagnosis at birth. For the analysis of neonatal mortality, all patients who died in the NICU were included, regardless of birth weight, extrauterine life, or gestational age at birth as well as those with congenital malformations.

The pre-pandemic period was defined as the period from December 26, 2018, to December 25, 2019. During the pandemic, two periods of care for the eligible population were identified from December 26, 2019, to December 25, 2020, and from December 26, 2020, to December 25, 2021.

To determine whether there were significant differences between these periods, we employed Poisson regression to analyze frequencies and the z-test to compare proportions. We also measured the risk of death in patients admitted to the NICU using the odds ratio, presenting the results with 95% confidence intervals.

The statistics collected and analyzed in this unit are routinely published for annual surveillance, so the study was not submitted to the local health research committee.

Table 1. Distribution of indicators in NICU from 2019 to 2021

Indicator	Year 2019	2020	2021
Births per year	3402	6272	7589
Average weight at admission (SD)	1960 (± 763)	2050 (± 854)	2101 (± 852)
Maximum and minimum weight at admission (g)	351-4425	359-5484	385-5335
Average gestational age at admission (SD)	32.9 (± 5.7)	33.4 (± 3.7)	33.8 (± 3.6)
Maximum and minimum gestational age at admission (weeks)	22-41	24-42	24-41
Pre-term newborns (PNB) (%)	1307 (38.3)	1514 (24.1)	1422 (18.7)
NICU admissions per year (%)	770 (22.6)	1005 (16.0)	1045 (13.8)
NICU discharges per year (%)	732 (21.5)	993 (15.8)	1043 (13.7)
Deaths	124	153	137
Other deaths	85	110	100
PTNB deaths (%)	102/1307 (7.8)	125/1514 (8.2)	96/1422 (6.7)
Deaths per discharge (%)	124/732 (16.9)	153/993 (15.4)	137/1043 (13.1)

NICU: neonatal intensive care unit; PTNB: pre-term newborns; SD: standard deviation.

Results

During the period from 2019 to 2021, a total of 17,263 live newborn births were registered in the HGO-CMNO UMAE. Table 1 shows the distribution and characteristics of these births during the study period. It also shows the distribution of pre-term births and NICU admissions and discharges. In addition, the frequency of deaths is detailed, and the indicators of PTNB deaths in relation to total deaths and deaths in relation to discharges are calculated. Other deaths are described, which include cases with severe congenital malformations, gestational age < 28 weeks, or birth weight < 1000 g.

In 2020, there was an 84% increase in the number of births compared to 2019, which is considered the pre-pandemic period. By 2021, this increase was 120% compared to 2019 and 21% compared to 2020.

The number of PTNB births increased in 2020 compared to 2019 but experienced a decrease in 2021, although it remained at a higher level compared to 2019.

Although the number of deaths increased from 2019 to 2020, a significant decrease was observed in 2021, although at a lower level than in 2019. In the NICU, the ratio of deaths to discharges decreased each year.

Poisson regression analysis was used to assess whether increases or decreases in incidence were due to chance. The results showed that the increase in the number of births between 2019, 2020, and 2021 was statistically significant.

NICU admissions and PTNB births increased significantly from 2019 to 2020 and from 2019 to 2021, although no significant change was observed between 2020 and 2021 (Table 2).

In the NICU, a significant increase in the number of deaths overall, particularly PTNB deaths, was observed from 2019 to 2020. Although there was no significant change in the overall frequency of deaths from 2020 to 2021, a significant decrease in PTNB deaths was observed during this period. Notably, the incidence of deaths in 2021 was similar to that in 2019, as shown in Table 3.

Table 4 shows the comparison of the proportions of NICU admissions, births, and deaths (unrefined) between 2019, 2020, and 2021. The comparison between each of these years is detailed.

Despite the increase in the frequency of PTNB births, their proportion decreased significantly between 2019 and 2020.

A non-significant decrease in the ratio of deaths to NICU discharges was observed in 2020 compared to 2019. In 2021, despite the significant increase in births, NICU admissions, and discharges, the ratio of deaths to discharges also decreased significantly.

Table 5 shows the magnitude of the risk of death by year of admission. The risk of death for patients admitted to the NICU decreased from 1.16 (0.93-1.46) in 2019 to 0.82 (0.65-1.02) in 2021.

Table 2. Probability of occurrence of births and NICU admissions from 2019 to 2021 (Poisson)

Variable	2019	2020	2021
Hospital births 2019 2020	(n = 3409) NA NA	(n = 6272) p < 0.0001 NA	(n = 7589) p < 0.0001 p < 0.0001
NICU admissions 2019 2020	(n = 770) NA NA	(n = 1005) p < 0.0001 NA	(n = 1045) p < 0.0001 p = 0.11
PTNB births 2019 2020	(n = 1307) NA NA	(n = 1514) p < 0.0001 NA	(n = 1422) p < 0.001 p = 0.01

NICU: neonatal intensive care unit; PTNB: pre-term newborns.

Table 3. Probability of occurrence of NICU deaths from 2019 to 2021 (Poisson)

Variable	2019	2020	2021
NICU deaths 2019 2020	(n = 124) NA NA	(n = 153) p < 0.01 NA	(n = 137) p = 0.13 p = 0.10
NICU PTNB deaths 2019 2020	(n = 102) NA NA	n = 125 p = 0.02 NA	(n = 96) p = 0.30 p < 0.01

NICU: neonatal intensive care unit; PTNB: pre-term newborns.

Table 4. The difference in proportions (z-test) of NICU indicators from 2019 to 2021

Variable	2019	2020	2021
% Admissions to NICU 2019 2020	22.6% (770) NA NA	16.0% (1005) p ≤ 0.001 NA	13.8% (1045) p ≤ 0.001 p ≤ 0.001
% PTNB births 2019 2020	38.3% (n = 1307) NA NA	24.1% (n = 1514) p = < 0.001 NA	18.7% (n = 1422) p ≤ 0.001 p ≤ 0.01
% of deaths/NICU discharges 2019 2020	16.9% (124/732) NA NA	15.4% (153/993) p = 0.40 NA	13.1% (137/1043) p = 0.02 p = 0.14

NICU: neonatal intensive care unit; PTNB: pre-term newborns.

Table 5. Distribution of the risk of death among patients admitted to the NICU between 2019 and 2021

Year	Deaths	Alive discharge	OR (95% CI)
2019	124	646	1.16 (0.93-1.46)
2020	153	852	1.07 (0.86-1.33)
2021	137	908	0.82 (0.65-1.02)

CI: confidence interval; NICU: neonatal intensive care unit; OR: odds ratio.

Discussion

In our unit, the number of births increased by more than 100% between 2019 and 2021. This increase is attributed to the increase in the flow of obstetric patients seeking care at the HGO UMAE, which represents an important support for the converted hospital units as part of the IMSS COVID-19 strategy.

Contrary to what has been reported by other authors[10,17-20], it was observed that the number of pre-term births increased from 2019 to 2020 but decreased in 2021. Even though the total number of births increased significantly and more were attended at term and without additional pathology, the percentage of PTNBs increased significantly from 2019 to 2020 and then decreased in 2021 to even lower levels than in 2019. This decrease in the proportion of pre-term births was probably due to mothers working from home, which reduced the stress and chances of complications due to lack of rest, as has also been suggested by some authors in Israel[21].

From 2019 to 2020, there was an increase in the frequency of NICU admissions, although it decreased as a proportion of the total number of births. This was due to the increased number of term patients seen at birth. Although the number of deaths increased from 2019 to 2020, the number of patients dying in the NICU decreased in 2021, even to a lower level than in 2019. The decrease in mortality from 2020 to 2021 was statistically significant.

The ratio of deaths to NICU discharges showed a steady decrease from 2019 to 2021. Although the decrease was not statistically significant from 2019 to 2020, it was statistically significant from 2019 to 2021 and 2020 to 2021.

During the COVID-19 pandemic, there was an expectation that NICU mortality might increase due to increased patient flow, and some authors were concerned about a lack of supplies in the NICU[8] or possible difficulties in staff collaboration due to increased patient flow[22,23]. Despite monthly occupancy rates consistently exceeding 100% during the pandemic, the mortality rate relative to discharges decreased significantly. This finding contrasts with other authors who reported no change in neonatal mortality[24] or even an increase in neonatal mortality[25].

We attribute this success to the dedicated efforts of the health-care staff, including physicians, nurses, biomedical engineers, social workers, assistants, laboratory personnel, cabinet staff, hygiene and cleaning teams, utilities, and general services, among others. It is also important to highlight the work of the administrative staff who managed the increase in NICU staffing and ensured that despite the support provided by the health system to the ICUs and units converted to COVID-19, there was no shortage of supplies and resources for the care of critical newborns in our NICU.

The IMSS HGO-CMNO UMAE showed a significant increase in the number of births and the number and frequency of PTNBs cared for as part of the COVID-19 strategy implemented by the IMSS. However, the frequency of deaths remained constant, and the ratio of deaths to NICU discharges decreased in 2019, 2020, and 2021.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Comparison between the KARVI scale and the Child Development Evaluation test (EDI) as a screening tool for suspected neurodevelopmental delay

Carolina Tovar-Moreno[1], Miguel A. Karlis-Rangel[2], Susana A. Villarreal-Guerra[3], Fernanda P. García-Ayón[1], Jesús Santos-Guzmán[1], and Belinda Carrión-Chavarría[1]*

[1]Escuela de Medicina y Ciencias de la Salud, Instituto Tecnológico y de Estudios Superiores de Monterrey (ITESM); [2]Hospital Regional Materno Infantil, Secretaría de Salud de Nuevo León; [3]Unidad de Especialidades Médicas (UNEME) Pediátrica, Secretaría de Salud de Nuevo León. Monterrey, Nuevo León, Mexico

Abstract

Background: *Early detection of suspected neurodevelopmental delay allows for timely diagnosis and appropriate intervention, for which numerous screening tests have been developed. However, most are complex and impractical for health-care workers at the community level.This study aimed to validate the KARVI scale in the neurodevelopment assessment of children under 1 year of age.* **Methods:** *We conducted an observational, longitudinal, comparative, inferential, and prospective study. Healthy children without risk factors for developing neurodevelopmental delay from 0 to 12 months of age were evaluated remotely using the Zoom® application. The Child Development Evaluation Test and the KARVI scale were applied once a month for four consecutive months.* **Results:** *Fifty individuals were analyzed, with a predominance of males in 52%. Adequate percentages for a screening test were obtained in the first evaluation with a sensitivity of 70% (confidence interval [CI] 95% 34.75-93.33) and a specificity of 75% (CI 95% 58.8-87.31), and in the fourth evaluation with a sensitivity of 100% (CI 95% 29.4-100) and a specificity of 78.72% (CI 95% 64.34-89.3), being significant in both evaluations (p = 0.007 and p = 0.001, respectively).* **Conclusions:** *The KARVI scale has the elements to be an effective screening test for suspected neurodevelopmental delay, but more extensive studies are needed to obtain more reliable results.*

Keywords: *Neurodevelopment. Screening. Growth. Development.*

Comparación entre la escala KARVI y la prueba de Evaluación del Desarrollo Infantil (EDI) como tamizaje para la sospecha de retraso en el neurodesarrollo

Resumen

Introducción: *La identificación temprana de retraso en el neurodesarrollo permite un diagnóstico oportuno y una intervención apropiada. Para ello, se han creado diversas pruebas de tamizaje; sin embargo, la mayoría son complejas y poco prácticas para el personal de la salud a nivel comunitario. El objetivo del estudio fue realizar la validación de la escala KARVI en la valoración del neurodesarrollo en niños menores de un año.* **Métodos:** *Se realizó un estudio observacional,*

***Correspondence:**
Carolina Tovar-Moreno
E-mail: caro.tovar02@gmail.com

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longitudinal, comparativo inferencial y prospectivo, en el cual se evaluaron, vía remota mediante la aplicación Zoom®, niños sanos de 0 a 12 meses de edad sin factores de riesgo para desarrollar retraso en el neurodesarrollo. Se aplicaron la prueba EDI (Evaluación del Desarrollo Infantil) y la escala KARVI una vez al mes por cuatro meses consecutivos. **Resultados:** *Se analizaron 50 individuos, con predominio del sexo masculino en el 52%. Se obtuvieron porcentajes adecuados para una prueba de tamizaje tanto en la primera evaluación, con sensibilidad de 70% (IC 95% 34.75-93.33) y especificidad de 75% (IC 95% 58.8-87.31), como en la cuarta, con sensibilidad de 100% (IC 95% 29.4-100) y especificidad de 78.72% (IC 95% 64.34-89.3), con significación estadística en ambas evaluaciones (p = 0.007 y p = 0.001, respectivamente).* **Conclusiones:** *Se considera que la escala KARVI cuenta con los elementos para considerarla como una prueba de tamizaje efectiva para detectar retraso del neurodesarrollo, sin embargo. Sin requieren estudios más extensos para obtener resultados más confiables.*

Palabras clave: *Neurodesarrollo. Tamizaje. Crecimiento. Desarrollo.*

Introduction

Growth and development begin during pregnancy and continue throughout the years[1]. Neurodevelopment is an interactive process between children and their environment[2], influenced by genetic, environmental, biochemical, and physical factors[3]. Its ultimate goal is the maturation of the nervous system, achieving the development of brain functions and personality formation[4]; there are critical periods with conditions for acquiring skills[5].

The World Health Organization (WHO) estimates that 10% of a country's population shows some form of developmental delay[2]. According to the Pan American Health Organization, approximately 250 million children (43%) under the age of five in developing countries are at greater risk of not reaching their full development due to poverty, constituting a public health problem[2]. In Mexico, a prevalence of 6% of children with disabilities has been reported, and approximately 25% of children under the age of five have a developmental delay[2].

The American Academy of Pediatrics recommends neurodevelopmental evaluations at 9, 18, 30 months, and 4-5 years of age in the absence of risk factors[6]. This assessment evaluates developmental milestones[7] and identifies warning signs such as regression or persistence of patterns that should have disappeared[8]. As the pediatrician's clinical judgment is not sufficient, it is necessary to use screening tools that assess different areas of development[9]. Several international screening tests are described below (Table 1)[8,10-14].

The available screening tests are very complex and lengthy, making them impractical for health workers at the community level. Therefore, neurodevelopmental assessment is often omitted from the well-child visit[15]; a standardized clinical test is needed to make a timely diagnosis[4]. A screening test identifies individuals with suspected disease in an apparently healthy population[16]; it should have a sensitivity and specificity >70%[16]. In the review of the literature, we found tests developed and validated in Mexico, highlighting the *Evaluación del Desarrollo Infantil* (EDI), with the lowest bias, and the *Valoración Neuroconductual del Desarrollo del Lactante* (VANEDELA), with the most documented validation process[9]; the EDI is the most widely used[16] (sensitivity 76.1% and specificity 59.1%)[17] (Table 2)[15,17-19].

This study aimed to provide a screening tool for detecting suspected neurodevelopmental delay in children under 1 year of age that is practical and can be used by health professionals and caregivers. It is not intended to replace the existing ones but to be a filter that easily identifies those patients at risk who require more extensive and detailed evaluation.

The test is the KARVI scale, created by Dr. Miguel Angel Karlis Rangel, which evaluates children from 0 to 12 months in five areas: sensory (proprioceptive and fine motor), auditory, visual, emotional (socio-affective), and motor (gross motor). It has two achievements per area per month, which are scored as "Yes" (achieved) or "No" (not achieved), leaving a total of 10 items for each month. The test is composed of observational and verbal items. Each domain is scored individually, resulting in a total score that is classified into four categories: optimal development (two achievements reached), standard development (one achievement reached), lack of developmental stimulation (no achievement reached in 1 month of evaluation in a single domain), and developmental delay (none of the achievements reached in at least 2 consecutive months of evaluation). If no achievement is reached in a certain area, the evaluation of the previous and current month of that individual activity is repeated the following month. The results are color coded (traffic lights) to highlight their importance (blue = optimal, green = standard, yellow = lack of stimulation, and red = developmental delay) (Table 3). Among the advantages of

Table 1. Characteristics of existing screening tests at international level

Test	Battelle developmental inventory	Bayley scales of infant and toddler development III	Denver scale II	Milani comparetti test	Ages and stages questionnaire 3
Areas evaluated	Cognitive, adaptive, motor, communication and socio-personal development	Cognitive, language, motor, social-emotional, and adaptive	Personal social, adaptive fine motor, gross motor, and language	Postural behavior, spontaneous motor, and stimulation-induced movement patterns	Communication, fine and gross motor, problem-solving, and social-personal
Ages evaluated	0-96 months	1-42 months	0-72 months	0-24 months	1-66 months
Items	100 items	91 items	125 items	27 items	30 items
Application time	30-90 minutes	50-90 minutes	20-25 minutes	15-25 minutes	10-15 minutes
Special material	Yes	Yes	Yes	Yes	No
Previous training	Yes	Yes	Yes	Yes	No

Table 2. Characteristics of the tests developed and validated in Mexico

Test	EDI	VANEDELA
Areas evaluated	Gross motor, fine motor, language, social development, and cognition	Cognitive, language, motor, socio-emotional, and adaptive
Ages evaluated	1-60 months (14 groups)	1-24 months (6 groups)
Formats	Areas of development, warning and alarm signs	Somatometry, developmental behaviors, developmental reactions, and warning signs
Application time	10-15 min	10-15 min
Special material	Yes	Yes
Previous training	Yes	Yes

EDI: Child Development Evaluation; VANEDELA: Neurobehavioral Assessment of Infant Development.

Table 3. Interpretation of results obtained on the KARVI scale

Achievements	1 month	2 consecutive months
0 achievements per area	Delayed stimulation (yellow)	Developmental delay (red)
1 achievement per area	Standard development (green)	-
2 achievements per area	Optimal development (blue)	-

this test are its duration of 5-10 min, its straightforward language, and the fact that it does not require any special material but uses objects that are familiar to the child. A limitation is that it is only used in children under 12 months of age.

During our study, we faced several problems, including that in March 2020, the WHO declared a severe acute respiratory syndrome coronavirus 2 pandemic, which triggered an epidemiological emergency that forced governments to take measures such as social isolation[20]. As a result, face-to-face consultations were reduced, pathology checks were postponed, treatments were interrupted, and social activities were restricted, increasing problems in early childhood development[21]. Studies that analyze the impact of the pandemic on neurodevelopment have emerged. In Spain, a decrease of up to 15% in neurodevelopmental consultations has been reported[22]; in Italy, it is mentioned that paying more attention to children with risk factors for developing neurodevelopmental delays is important[23]. This information represents a major challenge for physicians, who must focus on early detection[24].

Studies of remote neurological assessment using telemedicine, defined by the WHO as "The delivery of health services using information and communication technologies for the exchange of information for the diagnosis, treatment, and prevention of disease," were identified in the literature[25]. Telemedicine removes the barriers of time and distance by reaching remote locations and reducing waiting times[26]. The Internet and electronic devices are helpful in monitoring and diagnosing clinical conditions[27]; thus, the evaluations performed by telemedicine are not inferior to those performed in person in terms of patient and health professional satisfaction[28]. There have been publications in which telemedicine has been used to evaluate neurological disorders, and this field of telemedicine has been called "teleneurology"[29]. In Australia in 2016, a study was conducted to determine whether a mobile phone application could identify the risk of neurodevelopmental delay using the General Movements Assessment scale and concluded that the application facilitated identification[30]. In Iowa in 2014, parents of children with neurological conditions concluded that telemedicine consultations were as effective as in-person consultations[31]. The world has seen the current situation as an opportunity to develop an alternative to continue neurodevelopmental assessment[32]. In Spain, a 63% increase in pediatric consultations through telemedicine was demonstrated from March to June 2020, maintaining the follow-up of patients with neurodevelopmental disorders and minimizing the risk of contagion[22]. After reviewing these studies, we developed the idea of continuing our project through teleneurology.

Methods

We conducted an observational, longitudinal, comparative, inferential, and prospective study to determine the sensitivity of the screening test (KARVI scale) in the neurodevelopment assessment in children under 1 year of age. We decided to compare our KARVI scale (screening test) with the EDI test (gold standard), a test developed and validated in Mexico for detecting neurodevelopmental problems[33]. The study hypothesis (alternative) was "The screening tool (KARVI scale) is as sensitive as the EDI test for the timely detection of suspected neurodevelopmental delay in children under 1 year of age," while the null hypothesis was "The screening tool (KARVI scale) is not as sensitive as the EDI test for the timely detection of suspected neurodevelopmental delay in children under 1 year of age."

The study was approved by the Research Ethics Committee of the ITESM School of Medicine (No. P000253-EKARVI2019-CEIC-CR003). Pediatricians and neonatologists in the metropolitan area of Monterrey, Nuevo León, were informed of the project; individuals who met the inclusion criteria were identified and, with prior authorization from the physician, were invited to participate. Informed consent was given to each caregiver, and a signed consent form was obtained before the assessments. Participants were recruited between October 2020 and October 2021.

Inclusion criteria were individuals aged 0-12 months, born at term, previously healthy, without apparent risk factors for neurodevelopmental delay (metabolic or genetic diseases, tumors, cranioencephalic trauma, or neurological infections with sequelae), attending well-child visits and referred by their physicians, whose caregivers and physicians agreed to participate in the evaluation, and who had the means to conduct sessions remotely. Exclusion criteria were individuals older than 12 months, pre-mature births, caregivers who did not wish to participate in the study, children with a previously diagnosed disease associated with any neurodevelopmental delay (metabolic and genetic diseases), healthy children whose neurodevelopment could be affected by a previous disease (tumors, cranioencephalic trauma, and neurological infections with sequelae), incomplete evaluations, and children who did not come for follow-up or who did not have the means to conduct sessions through remote access.

We worked with qualitative variables grouped as positive test (abnormal) or negative test (normal) to obtain dichotomous variables. Optimal development (blue) in the KARVI test and normal development (green) in the EDI test were identified as equivalent variables and were considered negative. Standard development (green), delayed stimulation (yellow), and developmental delay (red) in the KARVI test and developmental delay (yellow) and risk of developmental delay (red) in the EDI test were considered positive.

The following formula was used to calculate the sample size:

$$n = \frac{z^2 PQ}{d^2}$$

$$n = \frac{(1.98)^2 (0.20)(1-0.20)}{(0.05)^2} = 250$$

Legend: z = 1.98, d = 0.05, P = prevalence of neurodevelopmental problems, Q = 1-p

The following parameters were used:

Table 4. Demographic variables for each application

Evaluation	Age (months)	Weight (kg)	Length (cm)	HC (cm)	BMI (kg/m^2)
Evaluation 1					
Range	1-9	3.8-10.6	51-74	36-46	12.18-20.54
Mean (SD)	4.7 (2.4)	7.08 (1.5)	64 (5.5)	41.68 (2.22)	17.1 (1.65)
Median	5	6.9	64	42	17.12
Mode	5	5.3	62	42	15.86
Variance	5.7	2.2	30.76	5.07	2.7
Evaluation 2					
Range	2-10	5-10.6	55-74	37-47	13.87-20.11
Mean (SD)	5.7 (2.4)	7.7 (1.36)	67.17 (4.8)	43.01 (2.01)	17.11 (1.62)
Median	6	7.7	68	43	17.12
Mode	6	7	68	43	16.56
Variance	5.7	1.8	23.77	4.07	2.64
Evaluation 3					
Range	3-11	5.6-10.8	57-77	38-48	14.28-20.26
Mean (SD)	6.7 (2.4)	8.33 (1.28)	68.95 (4.48)	44 (1.99)	17.45 (1.48)
Median	7	8.32	70	44	17.59
Mode	7	7.2	67	44	17.59
Variance	5.7	1.66	20.07	3.97	2.21
Evaluation 4					
Range	4-12	6.3-11.4	60-79	40-48	14.91-20.15
Mean (SD)	7.7 (2.4)	8.87 (1.21)	71.21 (4.54)	44.89 (1.84)	17.45 (1.43)
Median	8	8.85	72	45	17.39
Mode	8	9	70	44	18
Variance	5.7	1.47	20.68	3.42	2.05

BMI: body mass index; HC: head circumference; SD: standard deviation.

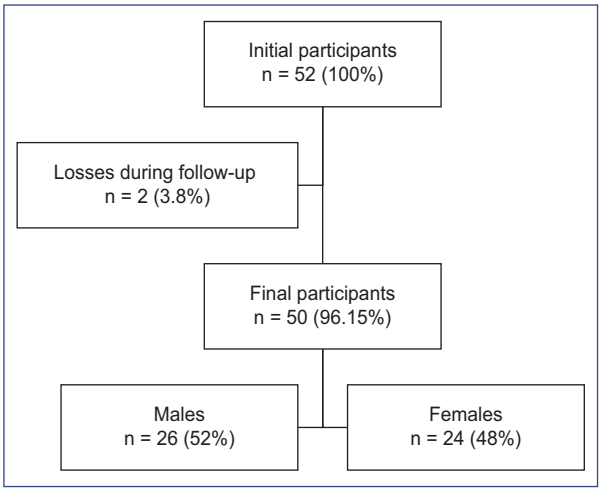

Figure 1. Total number of participants during the study.

95% confidence level (C), prevalence of neurodevelopmental problems of 20% (P), and absolute precision of 5% (d).

This gave us a total sample of 250 individuals. However, this sample was modified by the pandemic, making it impossible to conduct the sessions in person. Therefore, it was decided to conduct them remotely using the Zoom® application, avoiding any physical exposure. A total of 52 children were recruited, two of whom dropped out of the protocol, leaving us with 50 individuals who were evaluated remotely using the Zoom® application by physicians (pediatric residents and interns) who had been previously trained in using both tests. Four monthly Zoom sessions were conducted to obtain age and anthropometric data; the WHO charts were used to obtain percentiles of weight, height, head circumference (HC), and body mass index. The KARVI scale and the EDI test were then applied, and the results were registered into the database.

Results

Fifty-two children were recruited, of which 3.8% (2/52) dropped out of the study due to lack of time to attend the sessions. In the end, the remaining 96.15% (50/52) constituted our final sample for analysis. Participants were 52% male (26/50) and 48% female (24/50) (Fig. 1).

Results were analyzed using IBM SPSS Statistics® version 28 software. Descriptive statistics were used to

Table 5. Results of the four evaluations performed with the KARVI test

Evaluation	P	Se (95%CI)	Sp (95%CI)	PPV (95%CI)	NPV (95%CI)	FP (95%CI)	FN (95%CI)
1	0.007	70% (34.75-93.33)	75% (58.8-87.31)	41% (18.44-67.08)	90% (75.67-98.08)	25%	30%
2	0.091	57.1% (18.41-90.1)	74.4% (58.83-86.48)	26% (7.79-55.1)	91% (76.94-98.2)	25.6%	42.9%
3	0.063	62.5% (24.49-91.48)	71.4% (55.42-84.28)	29.4% (16.88-46.09)	90.9% (80.02-96.15)	28.6%	37.5%
4	0.001	100% (29.4-100)	78.7% (64.34-89.3)	23.08% (14.76-34.21)	100% (0-0)	21.3%	0%

CI: confidence interval; FN: false negative; FP: false positives; NPV: negative predictive value; P: significance; PPV: positive predictive value; Se: sensitivity; Sp: specificity.

analyze demographic variables and obtain measures of central tendency (Table 4), followed by 2 × 2 and Pearson's χ^2 tables to compare the degree to which a test can discriminate between individuals with and without neurodevelopment problems. Inferential or comparative statistics were used for parameter estimation and hypothesis testing.

Four consecutive monthly evaluations of the EDI standard test and the KARVI test were performed using digital media: Zoom®, Skype®, and Whatsapp®, by one of the doctors in the study, with a duration of approximately 15-20 min, in which the EDI test was applied through the electronic platform and the KARVI test through Google® forms. Sensitivity, specificity, false negative/type II error, false positive/type I error, positive predictive value, and negative predictive value of both tests were determined in each evaluation. In evaluation 1, sensitivity was 70% (confidence interval [CI] 95% 34.75-93.33) and specificity was 75% (CI 95% 58.8-87.31); in evaluation 4, sensitivity was 100% (CI 95% 29.4-100) and specificity was 78.72% (CI 95% 64.34-89.3), both of which were significant (p = 0.007 and p = 0.001, respectively). A sensitivity of 57.1% (CI 95% 18.41-90.1) and a specificity of 74.4% (CI 95% 58.83-86.48) were obtained in evaluation 2 and a sensitivity of 62.5% (CI 95% 24.49-91.48) and a specificity of 71.4% (CI 95% 55.42-84.28) were obtained in evaluation 3, without being significant (p = 0.091 and p = 0.063, respectively) (Table 5).

Table 6. Sample size and gender distribution of the validated tests in Mexico compared to the KARVI test

Test	n	Age	Female (%)	Male (%)
KARVI	50	1-12 months	24 (48)	26 (52)
EDI	438	1-60 months	190 (43)	248 (57)
VANEDELA	379	1-24 months	183 (48)	196 (52)

Discussion

Neurodevelopmental disorders are a major problem in developing countries, affecting child morbidity and public health. Their assessment at the point of care is essential but is not always possible due to factors such as the complexity of existing screening tests and, more recently, the isolation caused by the pandemic. Therefore, simpler tests are needed. During our study, we confirmed that the screening tool KARVI scale is as sensitive as the EDI test for timely detection of suspected neurodevelopmental delay in children under 1 year of age, as we obtained sensitivity percentages > 70% in scores 1 and 4, and specificity percentages > 70% in all 4 scores. However, we recognize that our study did not reach the ideal sample size for this type of scale, resulting in an inability to perform psychometric analysis and obtain wide CIs adequately. In addition, although Pearson's χ^2 test was performed with significant results in evaluations 1 and 4, given that it is very sensitive to the sample size, we could face errors in its interpretation, overestimating the test's usefulness. Therefore, it is recommended that the study should be reproduced in a larger population.

Among our limitations are the age of the patients, since only patients from 0 to 12 months were included; the recruitment process, referred by physicians from the metropolitan area of Monterrey; the follow-up of the patients, because it was only carried out for 4 months; the interpretation of the results, since the EDI test has three groups, while KARVI scale has four, which made it difficult to compare the results. Lastly, the application, since the same person performed both tests, which could lead to bias when knowing the result of the other test. In addition, it is necessary to consider the limitations resulting from the pandemic since the isolation prevented to conduct a face-to-face assessment of the patients, which affected the size of the sample and

Table 7. Comparison of results of the EDI test validation process in 2013 with that of the KARVI test in 2020

Test	Se (95%CI)	Sp (95%CI)	PPV (95%CI)	NPV (95%CI)
EDI modified	74% (65-82)	60% (51-68)	61% (53-70)	72% (63-81)
KARVI Evaluation 1	70% (34.75-93.33)	75% (58.8-87.31)	41% (18.44-67.08)	90% (75.67-98.08)
KARVI Evaluation 2	57.1% (18.41-90.1)	74.4% (58.83-86.48)	26% (7.79-55.1)	91% (76.94-98.2)
KARVI Evaluation 3	62.5% (24.49-91.48)	71.4% (55.42-84.28)	29.4% (16.88-46.09)	90.9% (80.02-96.15)
KARVI Evaluation 4	100% (29.4-100)	78.7% (64.34-89.3)	23.08% (14.76-34.21)	100% (0-0)

EDI: Child Development Evaluation; NPV: negative predictive value; PPV: positive predictive value; Se: sensitivity; Sp: specificity.

made it difficult to find caregivers willing to conduct sessions through remote access to electronic media and privacy issues, as well as communication problems and lack of understanding of the items by the child's caregivers.

In the literature, we found several validation studies of neurodevelopmental screening tests, highlighting the EDI test conducted in 2013 by Rizzoli et al. and the VANEDELA test conducted in 2011-2012 by Sanchez et al. their sample sizes and distribution by gender are shown in Table 6[17,19].

Our results were compared with those obtained with the modified version of the EDI test in children under 16 months of age during its validation process. In conclusion, KARVI is more specific than EDI, i.e., it is better at obtaining a negative result in healthy patients (Table 7). Despite the conditions, we had a diverse sample in terms of age and sex, representative of the general population; however, it is suggested to expand the sample to obtain more significant results.

The KARVI scale has the elements to be an effective screening test to detect suspected neurodevelopmental delay since it has adequate sensitivity and specificity (> 70%). In addition, it does not require special materials, caregivers can use it without prior training, and its use requires less time than other tests. However, we faced some limitations in the present study, such as the sample size. therefore, a study with a larger number of patients and recruitment sites should be conducted. Both tests should be administered in person, and more personnel should be available to administer the tests separately and minimize bias. Finally, the results are satisfactory under the circumstances in which this study was conducted. We will continue the validation process and implement the electronic scale project.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Frequency of hand contact with hospital surfaces in hospitalized pediatric patients

José F. Mier-de Leija[1], Daniela de la Rosa-Zamboni[2], Juan J.L. Sienra-Monge[3], Horacio Márquez-González[4], and Solange G. Koretzky[4]*

[1]Infectious Diseases; [2]Comprehensive Patient Care Department; [3]Ambulatory Pediatrics; [4]Clinical Research. Hospital Infantil de México Federico Gómez, Mexico City, Mexico

Abstract

Background: *Hand hygiene (HH) is an important strategy for preventing health-care-associated infections (HAIs). Few programs focus on HH for family members and primary caregivers but fewer for patients. This study aimed to estimate the frequency with which hospitalized pediatric patients have hand contact with hospital surfaces.* **Methods:** *We conducted a cross-sectional descriptive observational study consisting of three phases: the first was the creation of an observation and data collection tool, the second was the training of the monitors, and the third was the observational study of hand contact and HH opportunities in hospitalized pediatric patients.* **Results:** *Over 3600 minutes of observation, 2032 HH opportunities were detected, averaging 33.8/h (SD 4.7) as determined by hand contact with hospital surfaces of hospitalized pediatric patients. In our study, infants and preschool children had the highest frequency of hand contact.* **Conclusion:** *The high frequency of hand contact of hospital surfaces by children suggests that hourly hand disinfection of patients and caregivers, objects and surfaces around the patients may be prevention measures that could be incorporated to reduce HAIs in pediatric hospitals.*

Keywords: *Pediatrics. Hand hygiene. Infection control. Health-care-associated infection.*

Frecuencia de contacto de manos de pacientes pediátricos hospitalizados

Resumen

Introducción: *La higiene de manos es una estrategia importante para la prevención de infecciones asociadas a la atención sanitaria. Existen pocos programas centrados en la higiene de manos para los familiares y cuidadores primarios, y aún menos para el paciente. El objetivo de este estudio fue cuantificar la frecuencia con la que los pacientes pediátricos hospitalizados tienen contacto manual con superficies hospitalarias.* **Métodos:** *Se llevó a cabo un estudio observacional descriptivo transversal que constó de tres fases: la primera fue la creación de una herramienta de observación y registro de datos; la segunda fue la capacitación de los monitores y la tercera fue el estudio observacional del contacto manual y de las oportunidades de higiene de manos en pacientes pediátricos hospitalizados.* **Resultados:** *Durante los 3600 minutos de observación, se detectaron 2032 oportunidades, con una media de 33.8 (DE 4.7) por hora de oportunidades de higiene de manos establecidas por contacto manual con superficies de pacientes pediátricos hospitalizados. Los lactantes y los niños en edad preescolar presentaron la mayor frecuencia de contacto manual.* **Conclusiones:** *La alta frecuencia de contacto manual por parte del niño indica que medidas como la desinfección de las manos cada hora del paciente y del cuidador,*

***Correspondence:**
Daniela de la Rosa-Zamboni
E-mail: rzdaniela@hotmail.com

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así como de los objetos y superficies alrededor del paciente, podrían ser medidas útiles que deberían incluirse para prevenir las infecciones asociadas a la atención de la salud en los hospitales pediátricos.

Palabras clave: *Pediátricos. Lavado de manos. Control de infección. Infecciones relacionadas con la asistencia sanitaria.*

Introduction

Health-care-associated infections (HAIs) are the most frequent adverse events associated with providing health-care services. According to the World Health Organization (WHO), approximately 1.4 million people worldwide acquire an HAI each year. However, in developing countries[1], the risk of acquiring an HAI can be as much as 20 times greater than in developed countries. The prevalence of hospitalized patients who acquire one or more HAIs in developed countries ranges from 3.5% to 12%. In contrast, in developing countries, the HAI prevalence varies between 5.7% and 19.1%, with some studies reporting over 25% of hospitalized patients being affected[2].

According to the General Directorate of Epidemiology, in 2011, the prevalence of HAIs in general hospitals in Mexico was 21%, which is higher than international statistics[3]. In the pediatric population, the global incidence rate for nosocomial infections is 8.8-17.5/1000 patient days in developing countries[4]. In 2014, it was reported that the HAI incidence rate for our hospital was 19.64 HAIs per 1000 patient days[5].

Hand hygiene (HH) is the most important strategy for preventing HAIs. In 2009, the WHO integrated the HH Guide for Global Health in Healthcare guidelines[6]. Since then, remarkable progress has been made in reducing HAIs rates, accompanied by various studies and programs that confirm and support this initiative. These programs implement specific measures that healthcare workers must follow to break the chain of microbial transmission among hospitalized patients. As outlined in the WHO Five Moments, adherence to HH practices significantly reduces the risk of patients acquiring HAIs[6]. Most programs initiated by various health agencies focus primarily on promoting HH among healthcare workers.

It is widely recognized that children have frequent hand contact with the environment, people, and their mucous membranes during development. Furthermore, emphasizing hand washing among children is an important public health measure to reduce various types of infections[7]. Surprisingly, little attention has been paid to HH opportunities for patients, with most studies focusing on adult patients[8]. The timing of proper HH practice among hospitalized pediatric patients has not been studied. There is not enough information about the participation of hospitalized pediatric patients in the chain of transmission of microorganisms for the prevention of HAIs. This study aimed to estimate the frequency with which hospitalized pediatric patients have hand contact with hospital surfaces and could intervene in the chain of transmission of microorganisms by hand contact. These moments could eventually be turned into patient HH opportunities or be useful in developing other prevention strategies for hospitalized children.

Methods

Study design

We conducted a cross-sectional descriptive observational study conducted in a 290-bed national pediatric referral teaching hospital.

The research, ethics, and biosafety committees approved the protocol.

Settings

The research study consisted of three phases: the first was the development of a data collection form, the second was the training of the monitors, and the third was the observational study of HH opportunities of hospitalized pediatric patients.

Phase 1: Development of the data collection form. Based on the WHO 2009 Guidelines for HH in Health Care and consultation with specialists in pediatric neurodevelopment, pediatricians, hospital epidemiologists, and infection control nurses, the situations in which the hospitalized patient could transmit pathogens through their own hands were identified. According to this review, four categories of contact were considered: mucosal or surgical wound contact, invasive devices, people, and objects outside the patient's area. The tool is shown in Table 1.

All the moments were placed in a format along with general patient data, date, start and end time of the observation, and duration of the observation. In the format, the number of times the patient had any of the contacts was scored. One contact was considered

Table 1. Tool to measure hand contact in hospitalized children

	Register of hand contact of the pediatric patient	Total
Category 1: Objects outside the patient/'s area Cellphone or tablet Toys Crib or bed railing Dresser or urinal Food tray Others		
Category 2: People Healthcare personnel Primary caregiver Others		
Category 3: Mucous membranes or surgical wounds Ears Nostrils Eyes Mouth Anus Genitals Surgical Wounds Others		
Category 4: External objects Peripheral venous accesses Central venous catheter Urinary catheter Body drains (ileostomies, colostomies) Tracheostomy Others		

if the patient touched the area in question once or several times without touching another area. For example, it was considered a single moment if the patient touched a toy several times without touching the caregiver, mucous membranes, or other objects or devices. On the contrary, if the patient touched a toy, then touched the caregiver, and returned to the toy, two contacts were considered for the first moment and one for the second.

Phase 2: Training of the monitors. A group of medical students and pediatric residents was trained through a workshop. The workshop included the following topics: transmission of healthcare-associated pathogens through the hands according to the WHO HH guidelines[6], WHO moments of HH, the importance of HAIs and the benefits in their prevention, and filling out the data collection form of Phase 1. The instruction was face-to-face with slides and videos; the trainers were a pediatrician and a hospital epidemiologist. Five 1-h training sessions were held in groups.

Phase 3: Execution. Prior informed consent of the parents and assent of those over 8 years of age, both requested by the principal investigator, the observers went to pediatric hospitalization services. They stood outside the patient's room while simulating doing another activity. Covert observation was facilitated since the patient rooms have transparent glass walls, and every room has 2-5 patients with their respective caregivers.

Study size

According to what is considered a minimum to make comparisons in HH, 200 opportunities[6] and considering an average of one opportunity every 5 min and 20% of invalid observations, a time observation sample size was calculated in 1200 min. A monitor observed the participants at 20-min intervals from 8:00 to 12:00 in the morning.

Participants

Hospitalized patients from 1 month to 18 years of age were included in the study. Patients whose primary caregivers did not give informed consent or children > 8 years of age who did not give an asset, patients under the effects of sedation, and patients with a serious medical condition according to the record or in a critical situation during the visit were excluded from the study. The study was immediately stopped, and the nurse and attending physician were informed if the patient manipulated the central venous catheter, peritoneal dialysis catheter, or hemodialysis catheter, touched a surgical wound without HH, or had unintentional removal of any device.

The age groups were as follows: infants (0-3 years), preschool (3-5 years), school-age (6-12 years), and adolescents (13-18 years).

Variables

- Mucous membranes or surgical wounds: contact with ears, nostrils, mouth, anus, genitals, eyes, surgical wounds, and others were considered.
- Invasive devices: peripheral venous accesses, central venous catheters, urinary catheters, body drains (ileostomies, colostomies), tracheostomies, and

others (open section to describe another object not included in the category).
– People: refers to those who enter the patient's area, that is, health-care personnel, primary caregiver, or other (open section to describe another object not mentioned in the category).
– Objects outside the patient's area: cell phone or tablet, toys, crib or bed rail, dresser or urinal, food tray, and other (open section to describe another object not mentioned in the category).

Statistical methods

Statistical analyses were performed using SPSS (Statistical Package for the Social Sciences) version 20 software (SPSS Inc.) and Excel. Frequencies, percentages, means, and medians were used for descriptive analysis. The description of the frequency of missed moments of HH in hospitalized pediatric patients was based on these estimates: incidence of contacts/observation time, variability of contacts by age groups, by category, and by items within each category.

Results

A total of 3600 minutes of observation were performed in 60 patients of whom 34 (56.6%) were females. The time of observation was distributed as follows: 1800 min (50%) in infants, 900 minutes (25%) in school-age patients, 780 min (22%) in preschoolers, and 120 min (3%) in adolescents. The distribution of services was 22 (36.7%) in pediatric internal medicine and 17 (28.3%) in gastroenterology; the rest was observed in cardiology (10; 16.7%), infectious diseases (9; 15%), and endocrinology (2; 3.33%). Half of the patients (30, 50%) were infants, and about a quarter were schoolchildren (15, 25%). Moreover, there were 13 preschoolers (21.7%) and two adolescents. During the 3600 min of observation, 2032 opportunities were detected, and the mean of incidence of contacts was 33.8 SD 4.7/h.

Differences by age group

Significant differences in the frequency of hand contact per hour were observed between age groups. The most frequent age group was infants, with 37 occasions per hour, as opposed to adolescents, with < 1 occasion per hour. It is observed that the older the age, the lower the frequency of hand contact (Fig. 1).

Differences by category

Among the categories, "Objects outside the patient area" was the most common, with 20 contacts per hour. The least common category was invasive devices, with < 2 contacts per hour (Table 2).

Differences by subcategory

For the subcategories, the mouth was the most frequently touched site; for invasive devices, the peripheral venous catheter was the most frequently touched one; for contact with people, contact with the primary caregiver was almost 5 times more frequent than contact with health-care personnel; finally, in the category of external objects, the subcategory "other" was the one with the highest number of contacts.

Comparison of hand contacts between age groups and categories

For all categories evaluated in this study, the preschool group is the group with more hand contacts in each category ($p = 0.001$), followed by the school-age group, and then the infants. The results are shown in Table 3.

Discussion

The safety of the patient environment in the public sector is compromised by its communal nature, as it is a shared space with other patients and their caregivers. This communal environment increases the likelihood of exposure to various pathogens, thereby increasing the risk of HAIs. Therefore, monitoring interactions with hospital surfaces and developing risk-reduction strategies are critical. Particular attention should be paid to contact with medical devices as they serve as direct entry points for pathogens. Therefore, it is imperative that healthcare workers who care for pediatric patients are supported in maintaining clean hands.

In this study, we found interesting and scarcely published information about hand contact by hospitalized pediatric patients. First, on average, children make contact with their hospital environment, themselves, or caregivers more than once every 2 min, potentially participating in the chain of microbial transmission. Second, infants and preschool children had a higher incidence (about once every minute and a half) and a higher variability of contacts.

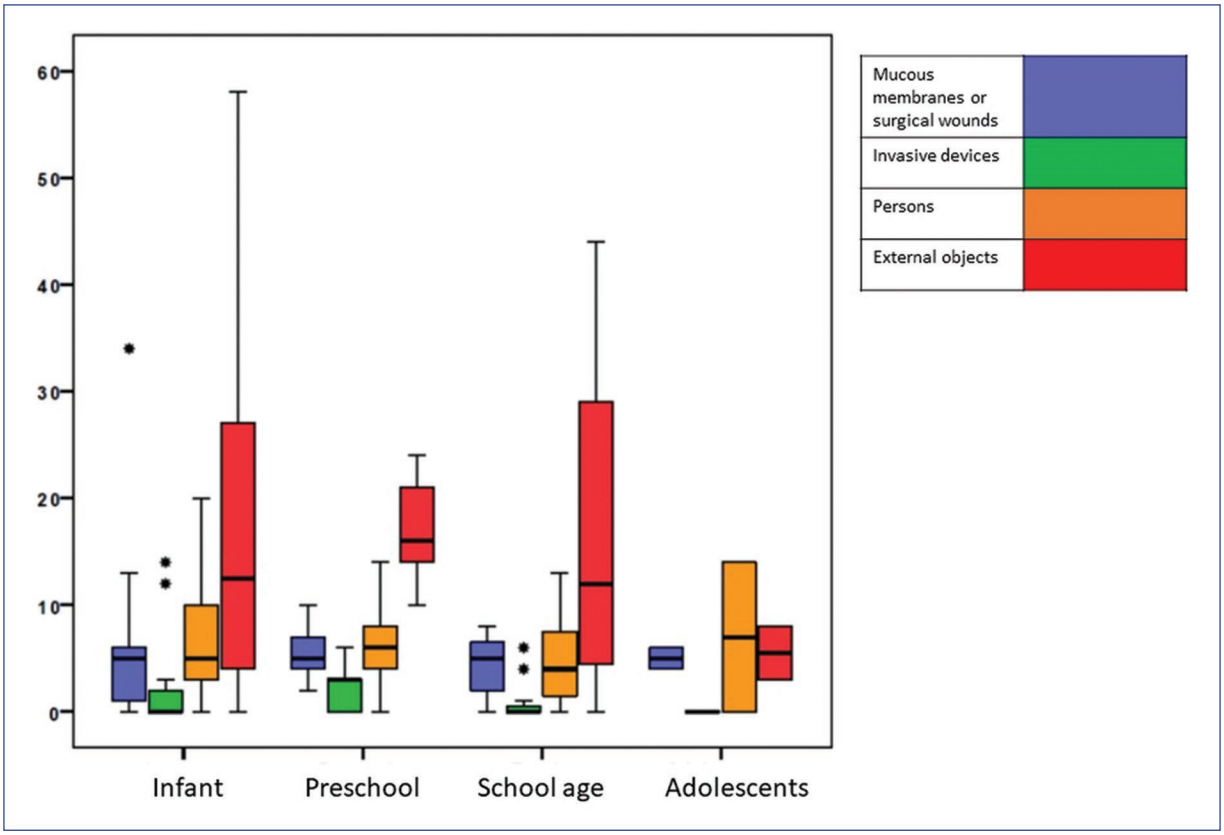

Figure 1. Hand contacts by age and category. *Outlier.

In pediatric populations, it is crucial to consider age groups. In this study, we observed that pediatric patients are exposed to various infectious risks depending on their age and their interactions with the environment and themselves.

During infancy and preschool years, the spectrum of pathogens and other microorganisms changes; after neonates, this group has the highest risk of HAI mortality. In adolescents, the risk of HAI mortality is similar to that of adults but with fewer comorbidities. The study looked at four age groups, with infants having the highest incidence, followed closely by preschoolers with 37 and 34 hand contacts per patient hour, respectively. Within the age groups, the most common category was external objects, primarily the "other" item. This can be explained by analyzing the stage of psychomotor development according to age group. A preschooler has reached a motor and cognitive development level that allows more frequent interaction with the environment. In addition, preschoolers are in a psychosocial stage dedicated to actively exploring their surroundings[9].

Therefore, it is crucial to emphasize the increased risk of acquiring a HAI faced by patients in these age groups. This happens through perpetuating the transmission chain of hospital microorganisms when they fail to perform HH during risky times. In the school-age group, the frequency of contact with external objects is higher compared to other categories; however, it occurs less frequently than in infants and preschoolers.

The sample for adolescents is scarce, but it is observed that the contact with other people was greater in this group, which can be explained by their high capacity for social interaction.

Several authors have examined the incidence of HAIs concerning the admission service, devices used, or age group. According to one report, bacteremia accounts for 20% of infections in pediatric care, but this figure can rise to 36% in pediatrics and 45% in neonatology[4].

The category recording the highest frequency of hand contacts was external objects, with 1200 instances noted during 60 h of observation. Within this category, the "others" subcategory was the most frequent. Monitors observed various items in this subcategory, including venous access lines, monitoring cables, bedding, and hygiene products, among others.

Table 2. Frequencies of hand contacts between age groups

Categories	Age group									
	Infant		Preschooler		School-age		Adolescent		Total	
	Total	Event/ time	Total	Event/ time	Total	Event/ time	Total	Event/ time	Total	Event/ time
Mucous membranes or surgical wounds	163	5.43	68	5.23	87	5.8	10	5	328	5.47
Ear	14	0.47	11	0.85	13	0.87	4	2	42	0.7
Nose	20	0.67	15	1.15	23	1.53	2	1	60	1
Mouth	102	3.4	28	2.15	34	2.27	4	2	168	2.8
Anus	3	0.1	1	0.08	1	0.07	0	0	5	0.08
Eyes	17	0.57	8	0.62	4	0.27	0	0	29	0.48
Genitals	6	0.2	5	0.38	12	0.8	0	0	23	0.38
Wound	1	0.03	0	0	0	0	0	0	1	0.02
Invasive devices	59	1.97	31	2.38	13	0.87	0	0	103	1.72
Venoclysis	45	1.5	28	2.15	12	0.8	0	0	85	1.42
Central Venous Catheter	11	0.37	2	0.15	0	0	0	0	13	0.22
Urinary Catheter	0	0	0	0	0	0	0	0	0	0
Stoma	0	0	1	0.08	0	0	0	0	1	0.02
Tracheostomy	0	0	0	0	0	0	0	0	0	0
Others	3	0.1	0	0	1	0.07	0	0	4	0.07
People	219	7.3	85	6.54	83	5.53	14	7	401	6.68
Primary Caregiver	176	5.87	67	5.15	71	4.73	4	2	318	5.3
Health workers	43	1.43	18	1.38	12	0.8	10	5	83	1.38
External objects	677	22.57	264	20.31	248	16.53	11	5.5	1200	20
Mobile phone	22	0.73	12	0.92	10	0.67	1	0.5	45	0.75
Toys	110	3.67	61	4.69	53	3.53	0	0	224	3.73
Bed Rail	162	5.4	79	6.08	95	6.33	2	1	338	5.63
Bedpan	2	0.07	0	0	0	0	0	0	2	0.03
Food	57	1.9	28	2.15	7	0.47	0	0	92	1.53
Utensils	0	0	0	0	0	0	0	0	0	0
Others	324	10.8	84	6.46	83	5.53	8	4	499	8.32
Total	1119	37.30	448	34.46	431	7.18	35	0.58	2032	33.87

Each hospital unit should implement a strategy to minimize the exposure of hospitalized pediatric patients to potentially contaminated external objects, including microorganisms. While restricting children's exploratory behavior is challenging and not advisable, it is essential to ensure that every object is thoroughly cleaned and disinfected before and after being touched by the child. In addition, an element observed within the patient's area, such as the rails of a bed or crib, must be meticulously cleaned. The patient's unit, whether a bed or crib, requires high-quality cleaning, which is a significant element in the patient's area. If

Table 3. Comparison of hand contacts between age groups and categories

Categories	Infant			Preschooler			School-age			Adolescent			p-value
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	
Total	53.2	30	90	65	51	77	64	38	94	49.5	40	59	0.001
Mucous membranes or surgical wounds	5	1	6	5	4	7	5	2	7	5	4	6	0.5
External objects	0	0	2	3	0	3	0	0	1	0	0	0	0.7
People	5	3	10	6	4	8	4	1	8	7	0	14	0.02
Objects outside the patient´s area	12.5	4	27	16	14	21	12	4	34	5.5	3	8	0.001

not properly maintained, its surface can contribute to the transmission chain of microorganisms.

In a study conducted in a low-income informal settlement in Kisumu, Kenya, Davis et al.[10] reported 264 oral contact events over 142 h of observation of 25 infants. This averaged 1.76 contact events per child per hour, with a mean of 10.6 oral contact events per observation period, or 1.8 events per hour of observation. One of the study's goals was to observe oral contact behavior in infants aged 3-9 months. However, this study was not conducted in a hospital setting. In contrast, we report a total of 3.4 events per hour in the same age group of hospitalized patients, where it is well-known that surfaces can be contaminated with various types of microorganisms.

In 2015, Sunkesula et al.[11] published "Four Moments for Patient HH: A Patient-Centered, Provider-Facilitated Model for Improving Patient HH." Before conducting an observational study, they proposed four critical moments for HH in hospitalized adult patients: before and after touching devices and probes, before eating, upon entering or leaving their room, and after using the toilet. Out of 606 observations of HH opportunities, only 59 patients (approximately 10%) practiced HH. Specifically, HH was observed in 52 of 389 instances (13%) before meals, in 2 of 160 instances (1%) at room entrance or exit, and in 5 of 60 instances (8%) after using the toilet.

The study mentioned above highlights the low adherence to HH among hospitalized patients despite their understanding of its benefits and prior education about the appropriate times for its practice. This issue is even more complex for pediatric patients, who often rely on the support of their primary caregivers. Special training tailored to each age group is necessary.

In a study published by Lee et al.[12], the overall rate of HH compliance was 10.3% (72 out of 701 observations). Specifically, pediatric patients had an overall HH rate of 4.1% (2 out of 49 observations). The researchers concluded that HH among patients, families, and visitors is significantly suboptimal and should be prioritized for improvement.

Education about the importance of HH is crucial for patient compliance. In 2019, Lary et al.[13] published an article aimed to assess whether interactive educational interventions could increase compliance with HH among children and their visitors. The study reported a 24.4% increase in HH compliance following educational interventions, with a 40.8% increase in children and 50.8% in visitors. The study notes that educational interventions raised awareness about the importance of HH. Another study by Wong et al.[14] concluded that despite these efforts, HH rates among patients and visitors remain low. The study suggests that strategies need to be developed to improve compliance further. While typical multimodal programs have some impact, their effectiveness could be enhanced by incorporating additional change strategies that influence culture and behavior. This is why understanding the opportunities for HH in patients is essential, as recognizing these statistics clearly indicates the need for patient-targeted strategies, particularly age-specific ones, to prevent HAIs.

Pokrywka et al.[15] implemented an intervention to reduce HAIs in a 520-bed tertiary care hospital. Educational pamphlets, HH reminders, and alcohol wipes were distributed to patients with their meal trays. Staff and volunteers also

assisted in handwashing at mealtimes. As a result, the rate of HAIs decreased from 10.45/10,000 patient days in the year before the intervention to 6.95/10,000 patient days during the year of the intervention.

Gagné et al.[16] implemented a hospital intervention that involved meeting with all patients and visitors for 346 days to educate them about the benefits of HH and distributing brochures on HAIs. In addition, staff cleaned patients' hands with hand sanitizer twice daily on weekdays. As a result, methicillin-resistant *Staphylococcus aureus* infections decreased from 10.6/1000 admissions in the 385 days before the intervention to 5.2/1000 admissions during the intervention period. A cost-benefit analysis of the intervention showed a net saving of $688,840, attributed to reductions in nosocomial infections, including sepsis, surgical wound infections, bone and soft-tissue infections, and respiratory tract infections.

The HH practices among hospitalized children need standardization. Children have been implicated in infection outbreaks in hospitals and community organizations, such as schools and nurseries. Therefore, HH in this patient group is essential[17]. Based on the obtained results, we suggest the following HH moments for hospitalized pediatric patients: before and after eating or having contact with food-related objects (cutlery, plates, food trays, bottles), after using the bathroom or commode, and before and after using objects outside the patient's area (electronic devices and toys, among others). Prior cleaning of the device or toy is also strongly recommended as part of the HH routine. It may be logistically challenging to perform HH for the patient before and after every contact, such as every two minutes. We believe that maintaining the described HH moments, disinfecting the objects, and adding HH for both the patient and their caregivers could be feasible and help keep hands disinfected. The present work opens the door to many research opportunities. These opportunities include studying and analyzing the behavior of pediatric patients in the hospital environment and their role in the transmission chain of microorganisms. Maintaining good HH is challenging, which is why there are several strategies to improve adherence. However, as previously mentioned, most strategies focus on health-care personnel since these programs are easier to implement and monitor. Nonetheless, it is not just the hospital staff who are important; patients, caregivers, and visitors constitute a large group that must be involved in adhering to hygiene practices. The challenge of controlling HAIs persists. However, the more people who become aware of the importance of hand washing, the better the infection control rates that could be achieved. As demonstrated in our study, hospitalized pediatric patients are in constant contact with various surfaces, objects, and people. Therefore, implementing HH opportunities for hospitalized patients could help reduce infection rates.

Considering the limited number of studies on HH in hospitalized pediatric patients, which are predominantly from gray literature, there is scant knowledge in this area. One limitation of this study is the non-uniformity of the patient sample. Observations were consistently conducted in the morning, and the study was confined to a single hospital. Following the research committee's recommendation, this project was initiated as a pilot study to validate the instrument developed by the working group. While the monitors' training achieved an acceptable Kappa coefficient, their training program lacks validation from an external institutional body.

As this is the first study focused on estimating the number of times a pediatric patient has hand contact with different hospital surfaces, there were several limitations, such as the lack of records of the sequence of contacts as objects were touched immediately before or after the mouth. Another limitation was that the study was conducted only during the morning shift.

In conclusion, hospitalized pediatric patients, especially those in preschool and infancy, can be significant and frequent contributors to the transmission of microorganisms. Considering the substantial economic costs, the high morbidity, mortality, and disease burden associated with HAIs in children, our findings strongly support the integration of HH practices for patients and their caregivers, along with cleaning of objects and the patient environment, as key components of infection prevention policies to reduce their occurrence.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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REVIEW ARTICLE

Drugs and natural products for the treatment of COVID-19 during 2020, the first year of the pandemic

*Elia G. Jaimes-Castelán[1], Claudia González-Espinosa[2], Gil A. Magos-Guerrero[3], Isabel Arrieta-Cruz[4], Manuel Jiménez-Estrada[5], Ricardo Reyes-Chilpa[5], and Jorge I. Castillo-Arellano[1,5]**

[1]Facultad de Ciencias, Universidad Nacional Autónoma de México; [2]Centro de Investigación y Estudios Avanzados, Instituto Politécnico Nacional; [3]Facultad de Medicina, Universidad Nacional Autónoma de México; [4]Instituto Nacional de Geriatría, Secretaría de Salud; [5]Instituto de Química, Universidad Nacional Autónoma de México. Mexico City, Mexico

Abstract

This work aimed to show which treatments showed efficacy against coronavirus disease 2019 (COVID-19); therefore, the results of 37 clinical trials started in 2020 and completed in 2021 are reviewed and discussed here. These were selected from databases, excluding vaccines, computational studies, in silico, in vitro, and those with hyperimmune sera from recovered patients. We found 34 drugs, one vitamin, and one herbal remedy with pharmacological activity against symptomatic COVID-19. They reduced mortality, disease progression, or recovery time. For each treatment, the identifier and type of trial, the severity of the disease, the sponsor, the country where the trial was conducted, and the trial results are presented. The drugs were classified according to their mechanism of action. Several drugs that reduced mortality also reduced inflammation in the most severe cases. These include some that are not considered anti-inflammatory, such as Aviptadil, pyridostigmine bromide, anakinra, imatinib, baricitinib, and bevacizumab, as well as the combination of ivermectin, aspirin, dexamethasone, and enoxaparin. Nigella sativa seeds with honey have also been reported to have therapeutic activity. On the other hand, tofacitinib, novaferon with ritonavir, and lopinavir were also effective, as well as in combination with antiviral therapies such as danoprevir with ritonavir. The natural products colchicine and Vitamin D3 were only effective in patients with mild-to-moderate COVID-19, as was hydroxychloroquine. Drug repositioning has been the main tool in the search for effective therapies by expanding the pharmacological options available to patients.

Keywords: *Severe acute respiratory syndrome coronavirus 2. Coronavirus disease 2019. Clinical studies. Anti-inflammatory. Antiviral repositioning.*

Fármacos y productos naturales para el tratamiento de la COVID-19 durante 2020, el primer año de la pandemia

Resumen

El objetivo del presente trabajo fue conocer qué tratamientos mostraron efectividad contra COVID-19, para lo cual se revisan y discuten los resultados de 37 estudios clínicos iniciados durante 2020 y concluidos en 2021. Estos fueron seleccionados de bases de datos, excluyendo vacunas, estudios computacionales, in silico, in vitro y con sueros hiperinmunes de pacientes recuperados. Se documentaron 34 fármacos, una vitamina y un remedio herbolario, con actividad farmacológica ante COVID-19 sintomático. Estos redujeron la mortalidad, el progreso de la enfermedad, o el tiempo de recuperación. Para cada

***Correspondence:**
Jorge I. Castillo-Arellano
E-mail: jorge.ivan.df@gmail.com

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tratamiento se presenta identificador y tipo de estudio, la gravedad de la enfermedad, patrocinador, país donde se realizó, así como sus resultados. Los fármacos se clasificaron de acuerdo con su mecanismo de acción. Varios fármacos que redujeron la mortalidad también disminuyeron la inflamación en los casos más graves. Esto incluyendo algunos no considerados antiinflamatorios, como el aviptadil, el bromuro de piridostigmina, el anakinra, el imatinib, el baricitinib y el bevacizumab, así como la combinación de ivermectina, aspirina, dexametasona y enoxaparina. También se reportaron con actividad terapéutica las semillas de Nigella sativa con miel. Además, resultaron efectivos el tofacitinib, el novaferón con ritonavir y lopinavir, así como los antivirales en terapias combinadas como el danoprevir con ritonavir. Los productos naturales colchicina y vitamina D3, solo tuvieron actividad en los pacientes en estado leve a moderado de la COVID-19, así como la hidroxicloroquina. El reposicionamiento de fármacos fue la principal herramienta para buscar terapias efectivas ampliando las opciones farmacológicas accesibles a los pacientes.

Palabras clave: *SARS-CoV-2. COVID-19. Estudios clínicos. Antiinflamatorios. Reposicionamiento antiviral.*

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the coronavirus that causes the infectious disease known as coronavirus disease 2019 (COVID-19). Its global spread led the WHO to declare it a public health emergency of international concern. SARS-CoV-2 is the seventh zoonotic coronavirus to infect humans. Its RNA genome is 80% similar to that of SARS-CoV[1]. It encodes several structural proteins, including spike (S), which regulates viral entry by binding to angiotensin-converting enzyme 2 (ACE2). This cellular receptor is expressed in respiratory epithelium, vascular endothelium, alveolar monocytes, and macrophages, among others[2].

The binding of ACE2 and S proteins triggers a membrane fusion reaction initiated by transmembrane serine protease 2 by cleaving S protein. Subsequently, the virus enters the cell by clathrin-mediated endocytosis[3] and its genetic material is released into the cytosol where it is translated into non-structural and structural proteins. The former assemble in membranes derived from the endoplasmic reticulum and replicate viral RNA. The latter assemble into viral particles and exit the cell through the lysosomal pathway[4].

During infection, the SARS-CoV-2 virus primarily enters type II pneumocytes, where an innate immune response is initiated. Macrophages initiate this response in the pulmonary alveoli, which secrete mediators such as tumor necrosis factor (TNF) and recruit lymphocytes and neutrophils, which release proinflammatory cytokines (interleukin [IL]-1, IL-6, and IL-8) and reactive oxygen species on entry into the alveoli[2].

SARS-CoV-2 can also infect monocytes, macrophages, dendritic cells, and lymphocytes. These cell lines in severe COVID-19 undergo dysregulated cytokine release, or "cytokine storm" syndrome, which dramatically increases leukocyte recruitment and causes endothelial cell and pneumocyte injury. This leads to pulmonary capillary leakage and surfactant abnormalities that compromise alveolar gas exchange, resulting in acute respiratory distress syndrome, multi-organ failure, and, in the worst case, death[2].

As of December 2020, COVID-19 disease had a global case fatality rate of 2.3% and a case fatality rate of 8.8% in Mexico[5]. COVID-19 is a systemic disease that presents with asymptomatic or presymptomatic infection. In symptomatic patients, mild, moderate, severe, very severe and critical disease occurs, as described in table 1, with the most common symptoms being fever, cough, dyspnea, and loss of smell and taste[6,7].

During the 1st year of the pandemic, management of COVID-19 included infection control measures, symptom management, and intensive care support for severe or critical illness[1]. However, clinical trials were also initiated, starting with drug repositioning. As a result of the tremendous effort and guidance on clinical management strategies to deal with COVID-19, numerous clinical trials were completed; however, they encountered various problems, including several that were never completed due to difficulties in patient recruitment or follow-up.

At present, despite the availability of various types of RNA- and DNA-based vaccines, it is still necessary to develop effective therapies to prevent severe cases of COVID-19 and death. For example, in 2022, the mortality rate was 4.7% in Mexico and 1% worldwide[6]. This review identified drugs that showed efficacy in clinical trials for treating SARS-Cov-2 and COVID-19 disease during the 1st year of the pandemic.

Many natural and synthetic compounds have been described and suggested in databases as potential inhibitors of COVID-19 development and progression. However, many of the compound repositioning studies have been performed by *in silico* computational studies without being supported by *in vitro*, *in vivo*, or clinical

Table 1. Clinical phases of COVID-19

Clinical phases	Symptoms	Symptom management
Mild	Fever, cough, altered sense of smell or taste, fatigue, myalgia or arthralgia, expectoration, chest pain, without evidence of pneumonia	Antipyretic/analgesic Outpatient
Moderate	Lower respiratory tract disease. Radiological evidence of pneumonia	Antibiotics. Hospitalized, no oxygen requirement
Severe	Pneumonia, RR > 30, SpO_2 < 90% PI > 50% (PaO_2/ FiO_2) < 300 mmHg	Venous thromboembolism prophylaxis, antibiotics, and corticosteroids. Without oxygen therapy or with low flow
Very severe	PaO_2/FiO_2 < 200 mmHg Hyperinflammation, acute respiratory distress syndrome	Antimicrobial treatment, venous thromboembolism prophylaxis, and pulmonary vasodilator. Non-invasive or high flow oxygenation. Intensive care unit
Critical	Acute respiratory distress syndrome, sepsis, hypoxemic respiratory failure and hemodynamic instability, hypercoagulability, and multiorgan failure. PaO_2/FiO_2 < 150 mmHg	Antimicrobial treatment, venous thromboembolism prophylaxis, pulmonary vasodilator, corticosteroids, endotracheal intubation, and mechanical ventilation. Intensive care unit

COVID-19: coronavirus disease 2019; PaO_2/FiO_2: ratio of arterial partial pressure of oxygen to fraction of inspired oxygen; PI: pulmonary infiltrates; RR: respiratory rate measured in breaths per minute; SpO_2: blood oxygen saturation levels[7,8].

studies to demonstrate their activity. Therefore, such results were excluded from the present review. Similarly, papers on the use of hyperimmune immunoglobulin from patients who have developed COVID-19 disease were excluded due to the complexity of evaluating each patient from whom the anti-SARS-CoV-2 sera were obtained. Studies related to vaccine development were also excluded because this type of biologic is classified as a prophylactic treatment rather than a drug for treating patients with COVID-19.

Methods

A search was performed in specialized databases available at UNAM and open access databases, using the following search strategy in the Title, Abstract, and Keywords fields: (sars AND cov 2 AND inhibitor AND NOT [docking OR *"in silico"* OR "virtual screening" OR computational OR antibody OR antibodies OR plasma OR "network model" OR immunoinformatics OR epitope]).

The following types of studies were included in this work: Adaptive clinical, randomized, non-randomized, cross-assignment, placebo, blinded, double-blind, triple-blind, quadruple-blind, exploratory, interventional, longitudinal, observational, parallel, prospective, retrospective, single-center, multicenter, single-group, and triple-group studies describing the activity of drugs against SARS-CoV-2 and COVID-19 and their effect on reducing mortality, respiratory failure, viral load, disease progression, hospitalization, or recovery time. Only full-length articles in English and Spanish in which the study started between December 31, 2019, and December 31, 2020, were considered, and the results of these studies were reviewed until November 01, 2021. The search procedure is shown in Fig. 1.

After obtaining a total of 1387 articles, we eliminated duplicates, leaving a total of 991 unique articles. A selection was then made based on the title and abstract, excluding studies related to hyperimmune sera from recovered patients and those focused on vaccine development. Computational, *in silico*, and *in vitro* studies were also excluded because they used different terms to define the type of research, making it difficult to identify them using Boolean operators. In the final screening stage, 152 relevant articles were identified. However, 90 studies that were not completed by November 2021 and 25 drug-related studies that showed no activity were excluded. As a result, a total of 37 articles were included in this review.

Results

Effective treatments

Drugs, an herbal remedy, and a vitamin were documented; 24 were used alone, and 12 in combination with others. These successfully reduced mortality, hospitalization, respiratory failure, viral load, disease progression, or recovery time in patients with COVID-19. Most are available internationally and have been identified in

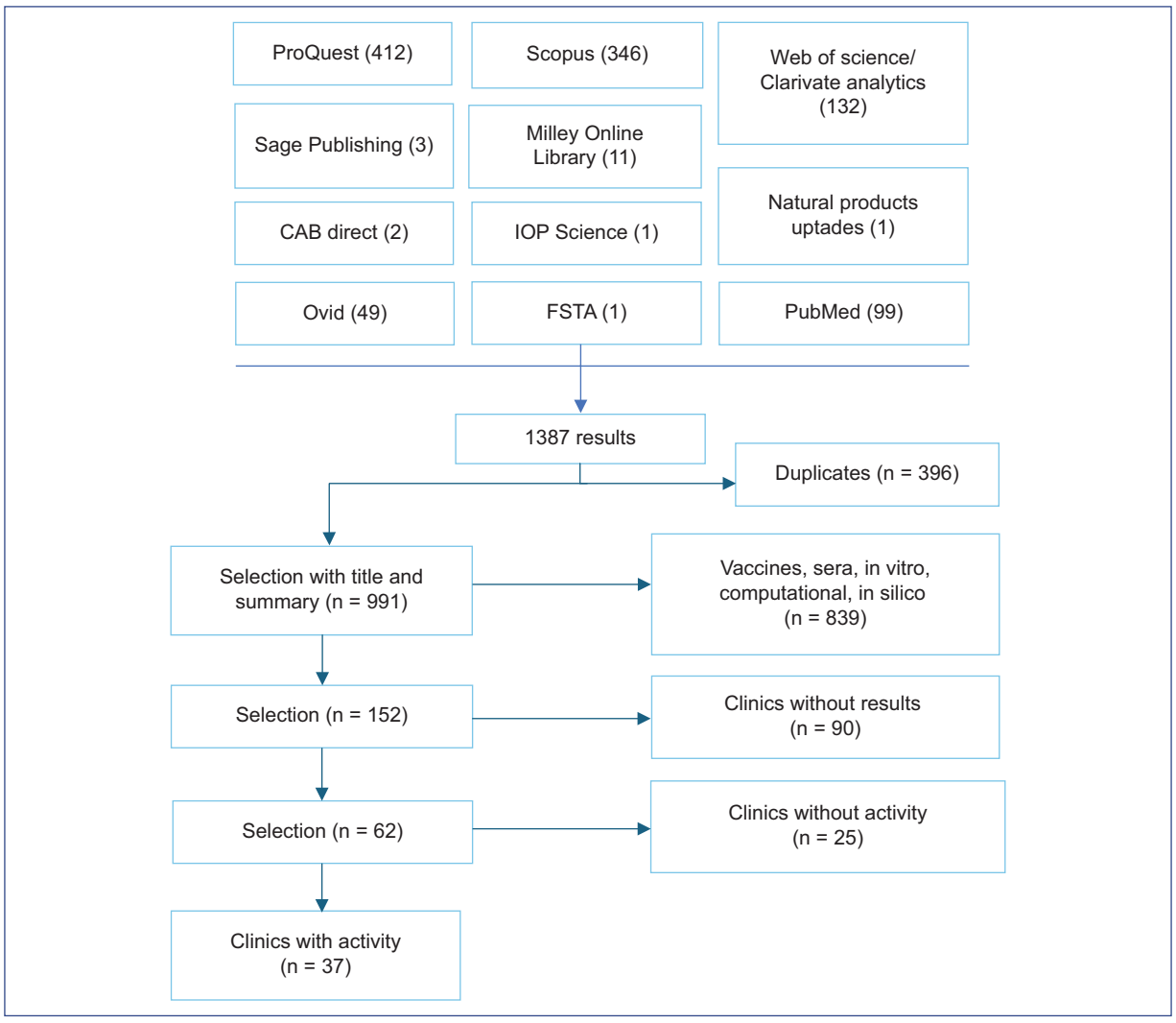

Figure 1. Summary of the design for articles selection and results.

repositioning studies. Table 2 lists the drugs, vitamins, and remedies that were administered individually, while table 3 lists the combined therapies. For each treatment, the identifier and type of trial, the severity of the disease, the sponsor and country in which the trial was conducted, and the trial results are presented.

Among the therapies that promoted clinical improvement, we highlight those that reduced the rate or probability of death by 50% or more in patients with severe, very severe, or critical illness. Aviptadil reduced mortality by 50% in critically ill patients. While in patients with very severe disease, the reduction in the rate of mortality was in first place bevacizumab (no mortality), in second place the combination of ivermectin, dexamethasone, aspirin, and enoxaparin (71%), and in third place pyridostigmine bromide (63.3%). In severe patients, *Nigella sativa* seeds with honey also reduced mortality (~70%), followed by low-molecular-weight heparin (64%), the combination therapy of hydroxychloroquine with favipiravir, darunavir, and ritonavir (16-4%), baricitinib (50% and 58% with corticosteroids) and anakinra (50%), as well as the combination of hydroxychloroquine, favipiravir, darunavir, and ritonavir (25%). We also highlight tocilizumab as it significantly reduced the time to clinical discharge (at day 4) (Tables 2 and 3).

However, given that the disease develops in two phases, an initial phase of high viral replication and a second phase of inflammation[7,8], controlling the infection before the hyperinflammatory response is triggered is important. Therefore, we highlight the activity of those treatments that, in mild-to-moderate disease, promoted patient recovery before seven days or significantly reduced viral load, such as danoprevir with ritonavir, hydroxychloroquine with oseltamivir,

Table 2. Clinical studies of individually administered drugs against COVID-19 that showed effectiveness

Drug	Study identifier	Type of study	Sponsor/Country of study	Phase, (Patients), Severity	Results	References
Acalabrutinib	NCT00001467; NCT01200953	IN	Astra Zeneca/US	(19) Severe	Improved lung function and decreased inflammation	47
Anakinra* (Kineret)	NCT04357366	OG, NoR, OL		II (1000) Severe	Reduced respiratory failure and mortality by 50%	11
Aviptadil (Zyesami)	NCT04311697	R, PL, MC	NeuroRx, Inc/US	II (196) Critical	Reduced respiratory failure and mortality	10
Baricitinib	NCT04393051	IN/NRC	Azienda Ospedaliero U. Pisana/ IT	II (126) Moderate-Severe	Reduced inflammation, viral load, clinical worsening, and mortality	38
Bevacizumab*	NCT04275414	IN, OG, OL	Qilu Hospital, Renmin Hospital of Wuhan/CN, IT	II (27) Severe, very severe	Reduced fever, duration of oxygen support, and mortality	70
Pyridostigmine bromide	NCT04343963	IN, R, QB, PL	Instituto Nacional Salvador Zubirán/ MX	II (436) Very severe	Reduced the need for mechanical ventilation and mortality	15
Chloroquine	NCT04323527	IN, R, DB	Fundação Medicina Tropical Dr. H. V. /BR	IIb (81) Critical	At low doses, CQ decreased mortality	19
Colchicine†	NCT04322682	IN, R, DB, PL	Montreal Heart Institute/CA	III (4488) Mild	Reduced mortality and hospital admissions	31
Eculizumab*	NCT04346797	R, PR, OL, OG	Publique Hopitaux de Paris/ FR	II (8) Severe	Six patients improved significantly	32
Favipiravir	CTRI/2020/05/025114	OL, R, OG, PR, MC, TE	IN	III (150) Mild-moderate	The duration of clinical signs and symptoms decreased	61
Favipiravir versus umifenovir	ChiCTR2000030254	PS, OL, MC, R	CN	(240) Moderate	Higher patient recovery rate at day 7 with favipiravir	62
Fluvoxamine	NCT04342663	DB, R, PL	Washington University/ US	II (152) Mild	Reduced disease progression	21
Nitric oxide gas	NCT04305457	IN, R, OL, TE.	Massachusetts General Hospital/ US	II (29) Severe	Reduced respiratory distress and prevented readmissions	72
LMWH	NCT04323761	OB, PS	University Hospital of Pisa/IT	(244) Moderate-severe	Reduced risk of disease progression and mortality	24
Imatinib mesylate	EudraCT 2020-001236-10	IN	Amsterdam Medical Center Foundation/ NL	(385) Very severe	Reduced mortality and duration of mechanical ventilation	37
Nigella sativa oil‡	NCT04401202	IN, R, PR, PS	King Abdulaziz University/SA	II (183) Mild	Significantly reduced recovery time	27

(Continues)

Table 2. Clinical studies of individually administered drugs against COVID-19 that showed effectiveness *(continued)*

Drug	Study identifier	Type of study	Sponsor/Country of study	Phase, (Patients), Severity	Results	References
Nigella sativa and honey‡	NCT04347382	IN, R, PR, PL	Sohaib Ashraf/ PK	III (313) Moderate-severe	Reduced symptoms, viral load, and mortality rate	26
Opaganib	NCT04414618	IN, R, PR, PL.	RedHill Biopharma Limited/US, IL	II (42) Severe	Reduced supplemental oxygen requirement	51
Ravulizumab*	NCT04369469	IN, R, PR, OL	Alexion Pharma /US	III (22) Severe	Reduced terminal complement C5 convertase	34
Remdesivir	NCT04292730	IN, R, PR, OL, ST	Gilead Sciences/ US, CN, FR, DE, HK, IT, JP, KR, NL, SG, ES, SE, CH, TW, GB	III (584) Moderate	The 5-day treatment improved the clinical condition	57
Remdesivir	NCT04280705	IN, R, DB, PL.	Europe, Asia, and America	III (1062) Moderate-Severe	Reduced recovery time	23
Talidomide	NCT04273529	R, PR, QB	H. Wenzhou Medical University/ CN.	II (12) Critical	Recovery in half the time of the control group	17
Tocilizumab*	NCT04331795	NoR, OG, OL	University of Chicago/ US	II (32) Severe	It was associated with clinical and laboratory improvement in patients	22
Tofacitinib	NCT04469114	R, PL, PR	Albert Einstein Israelite Hospital / BR	III (289) Moderate	Reduced mortality	44
Umifenovir		PS, NoR	CN	(62) Mild	Reduced symptoms of fever, cough	63
Vitamin D_3†	NCT04560608	Quasi-experimental	Angers University Hospital/FR	(77) Moderate	Reduced disease progression and mortality	75

*Biologics.
†Natural products or their semi-synthetic derivatives.
‡Herbal remedy.
COVID-19: coronavirus disease 2019; DB: double-blind; IN: interventional; MC: multicenter; NoR: non-randomized; NRC: non-recruiting; OB: observational; OG: one group; OL: open-label; PL: placebo; PR: parallel; PS: prospective; QB: quadruple-blind; R: randomized; ST: standard therapy; TB: triple-blind; SA: Saudi Arabia; BR: Brazil; CA: Canada; CH: Switzerland; CN: China; DE: Germany; ES: Spain; FR: France; GB: United Kingdom; GR: Greece; HK: Hong Kong; IN: India; IL: Israel; IT: Italy; JP: Japan; KR: South Korea; MX: Mexico; NL: Netherlands; PK: Pakistan; SE: Sweden; SG: Singapore; TW: Taiwan; US: United States; LMWH: low-molecular-weight heparin.

the combination of baricitinib with lopinavir and ritonavir, multidrug therapy with lopinavir, ritonavir, interferon (IFN) β-1b, and ribavirin, in addition to, umifenovir, favipiravir, novaferon, tofacitinib, and colchicine (Tables 2 and 3).

Mechanism of action

Regarding the mechanism of action of the drugs, vitamins, and natural products that have shown efficacy in clinical trials have been found to act by inhibiting cytokine release, inflammation, tubulin polymerization, complement system, tyrosine kinases, viral replication, thrombosis, chemotaxis, or promote bronchodilation, or are regulators of innate and adaptive immunity. They are presented below according to their biological activity.

Anti-inflammatory drugs that regulate the release of proinflammatory cytokines

Aviptadil (Zyesami) is a vasodilator neuropeptide with anti-inflammatory and immunomodulatory activity. It binds to the vasoactive intestinal peptide (VIP) receptor type 1

Table 3. Clinical studies of combination therapies against SARS-CoV-2 and COVID-19 that showed efficacy against the disease

Drug	Study identifier	Type of study/ Status	Sponsor/Country of study	Phase, (Patients), Severity	Results	References
Baricitinib and LPV/R		RT, OL, NoR	Ministero "Ricerca corrente"/IT	I (24) Moderate	Reduced symptoms and disease progression	42
Baricitinib and LPV/R	NCT04358614	OB, RT, LN, MC	Hospital de Prato/ IT	II (191) Moderate	Reduced symptoms, viral load, and disease progression	43
Baricitinib and corticosteroid	EUPAS34966	OB, PR, SC	U. General Hospital of Albacete/ES	(112) Moderate - severe	Improved pulmonary function and reduced the need for oxygen	41
Danoprevir and ritonavir	NCT04291729	IN, OG, OL /CM	The Ninth Hospital of Nanchang/CN	IV (11) Moderate	Suppressed viral replication in less than a week	53
HQ and oseltamivir	NCT04303299	IN, R, PR, PL	Rajavithi Hospital/ TH	III(320) Mild	At high doses, viral load decreased compared to the control	65
HQ and oseltamivir	NCT04349241 (-)	R, IN, OL, ST	Ain Shams University/ EG	III (100) Mild-moderate	Decreased viral load in 8 days	64
HQ, FVP, DRV, and ritonavir	NCT04303299	IN, R, PR, ST	Rajavithi Hospital/ TH	III(320) Moderate-severe	Together they had higher viral clearance	65
IV, AAS, DEX, and ENOX*	NCT04425863	OB,PS/ CM	Eurnekian Public Hospital/AR	167 Mild-severe	Reduced mortality and disease progression	78
LPV-R, IFNβ-1b, ribavirine	NCT04276688	IN, MC, PR, OL	The University of Hong Kong/ HK	II (127) Mild-moderate	Significantly reduced viral load	56
Novaferon and or LPV/R	ChiCTR2000029496	R, OL, PR, IN	The First Hospital of Changsha /CN	(89) Moderate-severe	Significantly reduced viral load	46
Remdesivir alone or with baricitinib	NCT04401579	IN, R, PR, DB, MC, PL/ CM	I. Allergy and Infectious Diseases/ US, DK, JP, KR, MX, SG, ES, GB	III (1033) Moderate-severe	Baricitinib with remdesivir reduced recovery time and improved clinical status	58

*Natural products or their semi-synthetic derivatives.
COVID-19: coronavirus disease 2019; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; CM: completed; DB: double-blind; IN: interventional; LN: longitudinal; MC: multicenter; NoR: non-randomized; OB: observational; OG: one group; OL: open-label; PL: placebo; PR: parallel; PS: prospective; R: randomized; Rt: retrospective; SC: single center; ST: standard therapy. AR: Argentina; CN: China; DK: Denmark; EG: Egypt; ES: Spain; GB: United Kingdom; HK: Hong Kong; IT: Italy; JP: Japan; KR: South Korea; MX: Mexico; SG: Singapore; TH: Thailand; US: United States; ASA: Acetylsalicylic acid; DEX: Dexamethasone; DRV: Darunavir; ENOX: Enoxaparin; FVP: Favipiravir; HQ: Hydroxychloroquine; IFN: Interferon; IV: Ivermectin; LPV/R: Lopinavir with Ritonavir. (-): retracted article.

in type II pneumocytes and blocks chromatin condensation and fragmentation by caspases, thus preventing cell apoptosis (Fig. 2)[9]; it also blocks the release of IL-6 and TNFα[10]. When used in COVID-19, Aviptadil reduced respiratory failure and mortality by ~50% when patients were treated with the maximum standard of care in tertiary care hospitals but not in regional secondary care hospitals[10].

Anakinra (Kineret) is a recombinant form of the IL-1 receptor antagonist. It is a disease-modifying antirheumatic drug that inhibits nuclear factor-kappa B (NFκB) translocation (Fig. 2), thereby controlling the production of proinflammatory mediators[11]. It reduced the 30-day mortality by 50% and improved patients' ability to breathe. Pyridostigmine bromide (Mestinon) also

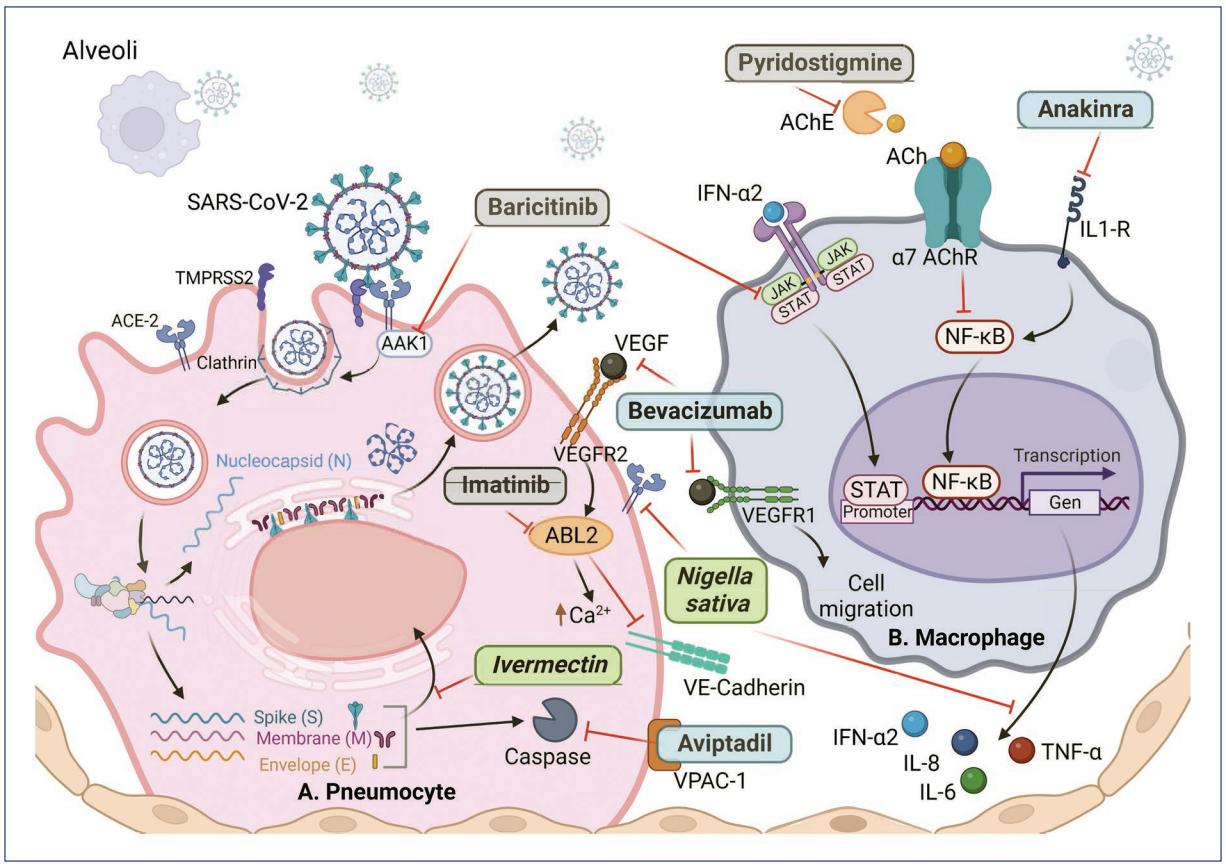

Figure 2. Drugs with greater potential against SARS-CoV-2 and COVID-19. **A:** type II pneumocyte. **B:** macrophage. ACE2: angiotensin 2 receptor; TMPRSS2: transmembrane serine protease 2; AAK1: AP2-associated protein kinase-1; VEGFR2/1: vascular endothelial growth factor receptor; ABL2: ABL tyrosine kinase; JAK: Janus kinase; STAT: signal transducer and activator of transcription; IFN-α2: interferon-alpha-2; AChE: acetylcholinesterase; ACh: acetylcholine; IL1-R: IL-1 receptor; NF-κB: nuclear factor enhancer of activated B-lymphocyte kappa light chains; VE-Cadherin: vascular endothelial cadherin. Natural products in green, biological in blue, synthetic in gray. Figure created on BioRender.com.

inhibits NFκB because it is an acetylcholinesterase inhibitor, and its activity results in an increase in the half-life of acetylcholine, which is critical in the cholinergic anti-inflammatory pathway[12-14] (Fig. 2); its administration reduced the need for mechanical ventilation by 2 days and reduced mortality by 63%[15].

Thalidomide is an anti-inflammatory, immunomodulatory, and anti-angiogenic drug that inhibits the NFκB and interferon regulatory factor 3 (IRF3) pathways[16]. Thalidomide, in combination with glucocorticoids, reduced hospital stay and viral load by ~50%, decreased IFN-γ and IL-6 levels, and the need for mechanical ventilation[17]. In addition, chloroquine, an antimalarial and arthritis drug, inhibits the inflammatory response mediated by IL-6, IL-17, and IL-22 and prevents viral entry by interacting with ACE2[18]. Chloroquine (400 mg, 2 times daily for 4 days) showed a mortality rate of 15% versus 39% in the high-dose group (600 mg, 2 times daily for 10 days)[19]. The mortality rate was similar to that of the thalidomide control group (16%), so its efficacy is questionable, and the use of high doses in critically ill patients is not recommended.

Fluvoxamine is an antidepressant that pharmacologically functions as a selective serotonin reuptake inhibitor. It inhibits the production of TNF-α and IL-6 through the S1R-IRE1 pathway[20]. Patients treated with fluvoxamine experienced no clinical worsening compared to 8.3% in the placebo group[21], while tocilizumab (Actemra), an IL-6 receptor inhibitor, induced recovery of patients requiring supplemental oxygen in a median of 4 days in tertiary care[22], compared to 10 days for patients treated with remdesivir[23]. However, several clinical trials have suggested that tocilizumab may not be effective against COVID-19[11,24,25] because, unlike the drugs above, which inhibit the upstream inflammatory response, tocilizumab only inhibits IL-6 activity.

Treatment with *N. sativa* (*Ranunculaceae*) seeds and honey was evaluated in a study conducted at a tertiary care center in Pakistan. It reduced the time to symptom relief by 50%, accelerated viral clearance, and reduced the mortality rate fivefold (4% vs. 18.8% for placebo)[26], while *N. sativa* seed oil increased the percentage of recovered patients (62%) compared to the control (36%) and reduced the recovery time in a study conducted at a tertiary care center in Saudi Arabia[27].

In both studies, most patients were under 60 years of age, while the average age in the Saudi Arabian group was 36 years. Both studies showed a significant benefit from using *N. sativa* seeds, resulting in remission of symptoms. There were differences in the baseline characteristics of the patients in terms of comorbidities, as the Pakistani group had a higher percentage of hypertension and obesity. In addition, various concomitant treatments were used due to the greater severity of the disease compared to the patients in the Saudi Arabian study, where the use of other medications was not reported (Table 4).

The main phytopharmaceutical of this seed is thymoquinone, which has anti-inflammatory effects by suppressing expression of enzymes that produce prostaglandins and leukotrienes and also blocks ACE2 (Fig. 2)[28]. This species also contains nigellone, which blocks histamine release[29]. The oil showed antiviral activity in a murine cytomegalovirus and H9N2 model and decreased proinflammatory cytokines in a murine allergic asthma model[28].

Antimitotics

Colchicine, an alkaloid derived from the plant *Colchicum autumnale* (*Colchicaceae*), used in the treatment of gout, inhibits tubulin polymerization in leukocytes and acts on the NLRP3 inflammasome[30]. Colchicine-reduced mortality and hospitalization by 24% compared with placebo in patients over 40 years of age with COVID-19 confirmed by polymerase chain reaction (PCR)[31].

Complement system inhibitors

Eculizumab (Soliris) is a monoclonal antibody used to treat autoimmune diseases; it is an inhibitor of complement protein C5b-9[32] and reduces the levels of IL-1, IL-6, and TNFα[33]. In one study, it contributed to the improvement of 6 out of 8 patients[32]. Ravulizumab (Ultomiris), on the other hand, is a complete inhibitor of C5 convertase, which is the initiator of the terminal phase of the complement system[34], so in addition to preventing complement-mediated inflammation, it also blocks cell activation and lysis[35].

Tyrosine kinase inhibitors

Imatinib mesylate, a c-ABL kinase inhibitor used to treat certain cancers, inhibits VE-cadherin dissociation (Fig. 2), preventing capillary leakage and alveolar edema; it also reduces IL-6 and IL-8 secretion[36]. Imatinib mesylate reduced the median duration of mechanical ventilation from 12 to 7 days and reduced the likelihood of death in patients by 49%[37].

Baricitinib (Olumiant), an inhibitor of Janus kinase (JAK) 1 and 2 kinases used in the treatment of rheumatoid arthritis, decreases the expression of ACE2 in human liver cells and the expression of proinflammatory cytokines induced by IFN-α2 through the JAK/signal transducer and activator of transcription (STAT) pathway[38,39]. In addition, it has affinity for the AP2-associated protein kinase-1 and reduces SARS-CoV-2 endocytosis (Fig. 2)[40]. Baricitinib reduced respiratory failure, mortality, and disease progression by 50%[38], and in another study where it was administered with corticosteroids, supplemental oxygen requirements were reduced (25.8% vs. 62% in the methylprednisolone control group), and mortality was ~4% in both groups[41], suggesting that corticosteroid activity reduced mortality. Baricitinib in combination with lopinavir and ritonavir (Kaletra) improved patient status and prevented disease progression[42], and in another study, inhibited mortality, reduced disease progression by 95% (0.88% vs. 17.9% control), and increased hospital discharge rate (9.7% vs. 1.3%)[43].

Tofacitinib as baricitinib, is an inhibitor of JAK1 and 3 kinases and the JAK/STAT pathway used to treat rheumatic diseases. Tofacitinib alone reduced mortality at day 28 by 49% (2.8% vs. 5.5% for placebo) and the cumulative incidence of death or respiratory failure by 37.6% (18% vs. 29% for placebo)[44]. Meanwhile, Novaferon, an antitumor/antiviral protein that interacts with the IFN2 receptor, a JAK/STAT45 signaling pathway[45], with or without lopinavir and ritonavir, had a higher viral clearance rate at day 6 than the lopinavir/ritonavir group (50.0% vs. 24.1% and 60.0% vs. 24.1%, respectively)[46].

Acalabrutinib improved lung function and reduced inflammation by targeting BTK tyrosine kinase; BTK is important in activating the innate immune response of blood monocytes[47] by promoting inflammasome and phagocytic receptor activation[48]. In addition, BTK inhibition also blocks nuclear translocation of NFκB, which results in a reduction of the synthesis of proinflammatory cytokines. Also, the activity of opaganib, which is an inhibitor of sphingosine kinase-2. This kinase has been proposed to be a factor in viral replication[49,50], and its inhibition also decreases TNF-α and IL-6. In patients, it

Table 4. Characteristics of clinical studies with individually administered drugs

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Acalabrutinib	NCT00001467; NCT01200953	100 mg PO, BID for 14 days or placebo	Steroids and/or hydroxychloroquine	Median age 61 years, 68% men, hypertension 84%, obesity 68%, and diabetes mellitus 37%	National Institutes of Health Clinical Center (CC). Tertiary	47
Anakinra* (Kineret)	NCT04357366	100 mg SC, QD, for 10 days or placebo	ND	Mean age 63 years, 62.3% men, diabetes 31.5%, hypertension 52.3%	13 centers, tertiary	11
Aviptadil (Zyesami)	NCT04311697	Aviptadil IV, 3 days in titrated doses of 50 pmol, 100 pmol, 150 pmol/kg/h or placebo	ND	62.6% younger than 65 years, 64.9% men	Five centers, secondary and tertiary	10
Baricitinib	NCT04393051	Italy: 4 mg/day for 14 days along with standard of care. Spain: 2 or 4 mg/day for 3-11 days or placebo	Hydroxychloroquine, antibiotics, protease inhibitors, enoxaparin, and steroids	Mean age 80 years, 65.2% men, 73.9% hypertension, 45.7% diabetes	Spain: Complejo Hospitalario Universitario de Albacete. Italy: University of Pisa. Tertiary	38
Bevacizumab*	NCT04275414	Single dose of 500 mg dissolved in 100 mL of saline solution, IV or placebo	Lombardy and Wuhan: antivirals, hydroxychloroquine, antibiotics, steroids, antipyretics, and supportive care. Wuhan: Chinese herbal medicine in all patients	Mean age 62 years, 77% men, 50% hypertension, and 23% diabetes	China: Renmin Hospital of Wuhan University, Wuhan, Hubei Province. Tertiary Italy: Hospital S.p.A. Ospedale Generale di Zona Moriggia Pelascini. Secondary	70
Pyridostigmine bromide	NCT04343963	60 mg/day PO, 14 days or until hospital discharge	Dexamethasone 74.5% and tocilizumab (5.3%)	Average age 52 years, 59.6% men, diabetes 36.2%, hypertension 35.1%, and obesity 43.1%	Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán. Tertiary Instituto Nacional de Cardiología Ignacio Chávez (INCICh). Tertiary	15

(Continues)

Table 4. Characteristics of clinical studies with individually administered drugs *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Chloroquine	NCT04323527	High dose: 600mg BID for 10 days Low dose: 450 mg BID on day 1 and QD for 4 days	Ceftriaxone IV (1g 2 BID for 7 days), azithromycin (500 mg QD for 5 days), oseltamivir (75 mg BID for 5 days) in case of influenza	Mean age 51.1 years, 75.3% male, hypertension 45.5%, alcohol use disorder (27.5%), and diabetes (25.5%)	Hospital e Pronto Socorro Delphina Rinaldi Abdel Aziz. Tertiary	19
Colchicine†	NCT04322682	0.5 mg oral, twice a day for 3 days and then once a day for 27 days	Hydroxychloroquine (0.5%), oral anticoagulant (2.1%), aspirin (8.7%), other platelet agents (1.4%)	Mean age 54 years, 53.9% women. Hypertension (34.9%), respiratory disease (26.1%), diabetes (19.9%)	Eight centers. Secondary and tertiary	31
Eculizumab*	NCT04346797	900 mg every week, 900 mg every 4 days and 3 doses of 1,200 mg on days 1, 4 and 8 showed the most satisfactory results. Intravenous	Enoxaparin, unfractionated heparin, dexamethasone	Hypertension (87.5%), diabetes (37.5%)	Hôspital saintlouis aphp, ND	32
Favipiravir	CTRI/2020/05/025114	1800 mg twice daily 1; maintenance dose of 800 mg twice daily thereafter, maximum 14 days	Antipyretics, cough suppressants, antibiotics, and vitamins.	73.5% men, 77.6% aged 30 to 60 years, 25.9% with diabetes mellitus, hypertension and/ or obesity	AIIMS India. Tertiary. Breach Candy Hospital Trust Secondary. Dr. Balabhai Nanavati ND Hospital. Fortis Hospital Limited, primary to quaternary	61
Favipiravir versus umifenovir (Arbidol)	ChiCTR2000030254	1600 mg, twice on the first day followed by 600 mg, twice daily, for the next few days. Or Arbidol (200 mg, 3 times a day) plus standard care for 7 days	Traditional Chinese herbal medicines, antibiotics, additional antiviral treatment, immunomodulatory drugs, steroids, antipsychotic drugs, nutritional support, cardiovascular drugs, oxygen support, non-invasive positive pressure ventilation (NPPV), or invasive ventilation	In favipiravir group 50.86% men, 75% < 65 years, 31.05 hypertension, 12.07% diabetes. In Arbidol group 42.50% men, 65.83% < 65 years, 25% hypertension, 12.07% diabetes	Zhonghan Hospital of Wuhan University. Tertiary Leishenshan Hospital, field hospital Hospital of Hubei Province, Wuhan, Tertiary	62
Fluvoxamine	NCT04342663	50mg once, 100 mg 2 times a day for 2 days, then 100 mg 3 times	ND	Diabetes 11%, hypertension 19%, 30% male	BJC Belleville. Primary. Washington University	21

(Continues)

Table 4. Characteristics of clinical studies with individually administered drugs *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
		a day as tolerated until day 15			School of Medicine. Tertiary	
Nitric oxide gas	NCT04305457	NO inhaled at 160 ppm for 30 min, twice daily for 14 days or until discharge	ND	Hypertension 41%, diabetes 34.5%, 65.2% male	Massachusetts General Hospital. Tertiary	72
LMWH	NCT04323761	Subcutaneous enoxaparin 40-60 mg daily, or therapeutic 40-60 mg subcutaneously twice daily	Hydroxychloroquine LPV/r or DRV/r, doxycycline dexamethasone, prednisone, methylprednisolone, hydrocortisone), macrolides, baricitinib tocilizumab remdesivir	Hypertension 46.03%, 19.68% diabetes, 76.2% male, mean age 70 years old	University Hospital of Pisa, Italy. Tertiary	24
Imatinib mesylate	EudraCT 2020-001236-10	800 mg oral on day 0 followed by 400 mg daily on days 1-9	ND	Median age 64 years, diabetes 25%, cardiovascular disease 22%, hypertension 37.6%	VU University Medical Center. Tertiary Erasmus MC (Rotterdam). Tertiary, Spaarne Ziekenhuis (Haarlem). Secondary. Haaglanden Medical Center (the Hague) Secondary. Isala Clinic (Zwolle) Primary	37
Nigella Sativa oil‡	NCT04401202	500 mg of *Nigella sativa* oil in capsule, 2 times a day for 10 days	ND	Average age 36 years old, 36% male, 8% diabetes, and 9% hypertension	King Abdulaziz University Hospital. Tertiary	27
Nigella sativa and honey‡	NCT04347382	Honey 1 g/kg/ day and *Nigella sativa* seeds 80 mg/kg per day for 13 days	Panadol, azithromycin, montelukast, LMWH, hydrocortisone, multivitamins, tazobactam+ piperacillin, ivermectin, meropenem, at physician's consideration	56.86% men, 49.84% ≤ 40 years, hypertension 31.62%, and diabetes 36.74%.	Shaikh Zayed Post-Graduate Medical Complex, Services Institute of Medical Sciences, Doctor's Lounge, and Ali Clinic. Tertiary	26

(Continues)

Table 4. Characteristics of clinical studies with individually administered drugs *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Opaganib	NCT04414618	2 × 250 mg of oral Opaganib in capsules or placebo every 12 h for up to 14 days	Remdesivir and/or corticosteroids	Mean age 58 years, 64.3% male	Honor Health Research Institute, Miami Cancer Institute, Tertiary. Oregon Health & Science University, Albany Medical Center, Henry Ford Hospital, Ziv Medical Center, Tertiary	51
Ravulizumab*	NCT04369469	Day 1: 2400 mg, 2700 mg, or 3000 mg if they weighed ≥ 40- < 60 kg, 60- < 100 kg, or ≥ 100 kg, respectively. On days 5 and 10 600 mg if they weighed < 60 kg and 900 mg if they weighed ≥ 60 kg, then 900 mg on day 15	Antivirals such as remdesivir	54.5% men, mean age 66 years, diabetes 50%, hypertension 45.5%	Brigham and Women's Hospital Tertiary, Houston Methodist Hospital, Quaternary, King's College Hospital Tertiary, Washington University School of Medicine. Tertiary	34
Remdesivir	NCT04292730	Intravenous remdesivir 200 mg on day one, followed by 100 mg/day For 5-10 days or standard care	Steroids, hydroxychloroquine/ chloroquine, lopinavir-ritonavir, tocilizumab, azithromycin, aspartate aminotransferase, alanine aminotransferase	Average age 57 years old, 61.13 male, 42.46% hypertension, 39.72% diabetes	105 hospitals in the US, Europe, Asia: Secondary and tertiary	57
Remdesivir	NCT04280705	Intravenous 200 mg on day one and 100 mg daily for up to 9 additional days	Hydroxychloroquine and glucocorticoid	Average age 58.9 years, 64.4% men, 50.2% hypertension, 44.8% obesity, and 30.3% diabetes mellitus	60 centers ND	23
Thalidomide	NCT04273529	100 mg per day for ≥ 7 days, with a median duration of 12 days	Dexamethasone in low doses (40 mg IV every 12 h for 3 days, then every 24 h for 5 days)	66.7% male, median age 65.5 years 50% with comorbidities	First Affiliated Hospital of Wenzhou Medical University. Tertiary	17
Tocilizumab*	NCT04331795	Range of 40, 80, 120 and 200 mg, with possible repetition at 24 or 48 h	Hydroxychloroquine or azithromycin, lopinavir-ritonavir, or systemic corticosteroids	Median age 69 years, 50% men, 62% two or more comorbidities	University of Chicago Medicine. Tertiary	22

(Continues)

Table 4. Characteristics of clinical studies with individually administered drugs *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Tofacitinib	NCT04469114	10 mg oral or placebo 2 times daily for up to 14 days or until discharge	It may have included glucocorticoids, antibiotic agents, anticoagulants, and antiviral agents	Mean age 56 years, 65.1% men, 50.2% with hypertension, and 23.5% with diabetes	Multicenter, 17 locations, Secondary and Tertiary	44
Umifenovir (Arbidol)		2 pills 0.2 g 3 times daily	Interferon, asmeton (compound methoxyphenamine), limonene and pinene, moxifloxacin, ibuprofen, and ambroxol	54.8% men, 17.7% hypertension, 11.3% diabetes. Most between 48 and 63 years old	First Hospital of Jiaxin Tertiary	63
Vitamin D_3†	NCT04560608	Group 1: 50,000 IU per month, 80,000 IU or 100,000 IU every 2-3 months the year before infection. Group 2: 80,000 IU within a few hours of COVID-19 diagnosis	Antibiotics, corticosteroids, and pharmacological treatments for respiratory disorders	Mean age 88 years, 50.6% men. 63.6% hypertension, 54.5% cardiomyopathy	Angers University Hospital Tertiary	75

*Biologicals.
†Natural products or their semi-synthetic derivatives.
‡Herbal remedy.
SA: Saudi Arabia; BR: Brazil; CA: Canada; CH: Switzerland; CN: China; DE: Germany; ES: Spain; FR: France; GB: United Kingdom; GR: Greece; HK: Hong Kong; IN: India; IL: Israel; IT: Italy; JP: Japan; KR: South Korea; MX: Mexico; NL: Netherlands; PK: Pakistan; SE: Sweden; SG: Singapore; TW: Taiwan; US: United States; LMWH: low molecular weight heparin; IV: intravenous; PO: oral; SC: subcutaneous; QD: once daily; BID: twice daily; TID: three times daily; ND: Not described. NO: Nitric oxide.

reduced the need for supplemental oxygen (61.6% vs. 46.7% placebo) and accelerated hospital discharge[51].

Antivirals

Danoprevir is an inhibitor of hepatitis C virus NS3/4a protease, which has high structural similarity to Mpro of SARS-CoV-2[52], while ritonavir increases danoprevir exposure by inhibiting cytochrome P450 isoenzyme 34A. Danoprevir with ritonavir suppressed viral replication in < 1 week and reduced ground glass opacity[53].

Lopinavir and ritonavir are HIV-1 protease inhibitors; ribavirin inhibits normal viral replication, and IFN β-1b induces the synthesis of antiproliferative and immunomodulatory proteins[54]. Meanwhile, lopinavir and ritonavir had no clinical benefit when administered alone[24] or with Arbidol[55]. Treatment with lopinavir and ritonavir with ribavirin and IFN β-1b, administered 7 days after symptom onset, reduced the median time for negative nasopharyngeal swab results compared to the control group (from 12 to 7 days), suppressed viral load at 8 days, relieved symptoms at 4 days, and reduced IL-6 levels[56].

Remdesivir reduced the median recovery time by 10 days (vs. 15 days for placebo) and also reduced mortality (6.7% vs. 11.9% for placebo) in a study conducted in 60 tertiary care hospitals in Europe, Asia, and the Americas in patients with moderate to severe illness[23]. In another study conducted in 105 secondary and tertiary care hospitals in the U.S., Europe, and Asia in patients with moderate illness, 5 days of remdesivir improved the condition of patients compared to placebo. However, the clinical significance was uncertain due to the study design[57]. In another study conducted in 71 centers in eight countries in Europe, Asia, and the Americas, remdesivir was administered alone or in combination with baricitinib, and in the second case, the median recovery time was reduced from 8 to 7 days[58].

The protocols of the three studies were the same in terms of doses. However, there was a difference in the duration evaluated, as the first study found that the 10-day treatment was sufficient to shorten patients' recovery time. In contrast, the second study found that a 5-day treatment was more beneficial than a 10-day treatment. From these data, it can be concluded that a 10-day course provides greater benefit in patients with more advanced diseases (Tables 4 and 5).

We also found two articles that are not included in the results tables. In one, remdesivir was administered for 5 or 10 days and produced a clinical improvement of 2 points or more on the 7-point ordinal scale at day 14 in 64% of patients; however, they found no significant differences between the two groups, in patients with severe disease who did not require mechanical ventilation[59]. In another study in China with critically ill patients, remdesivir did not affect clinical improvement[60]. Therefore, the benefit of remdesivir is uncertain; it appears that its individual activity may not be sufficient to improve clinical status significantly.

Favipiravir is an influenza virus RNA polymerase inhibitor. It has been evaluated in various studies in patients with mild to severe disease in which it did not reduce viral load; it only showed a reduction in the recovery time of patients from 5 to 3 days in a study conducted in India[61] and in a study conducted in China it contributed to 71% of patients recovering before 7 days versus 55% in the group with umifenovir[62]. The latter study used lower doses, with a difference of 200 mg. Both studies were conducted in tertiary care hospitals, and the patients evaluated had similar characteristics in terms of disease status. However, the standard of care differed in that the Chinese study used herbal medicines and additional antiviral treatment. Both studies concluded that favipiravir therapy accelerated patient recovery but had no effect on viral load reduction (Table 4).

On the other hand, umifenovir, a broad-spectrum antiviral[61,63] that prevents the hemagglutinin from switching to its fusion state, thereby inhibiting the entry of the virus, also reduced the recovery time of symptoms such as fever (4.9 vs. 6 days) and dry cough (4.3 vs. 5 days)[63].

Oseltamivir inhibits influenza virus neuraminidases, limiting the spread of infection and inflammation. Patients who received hydroxychloroquine with oseltamivir had a negative reverse transcriptase-PCR (RT-PCR) test in an average of 8.1 days[64] (article retracted due to questionable results). In another study, patients had a negative RT-PCR test 4 days earlier than the control group (7.5 vs. 11.5 days)[65]. This is important because it reduces the period of infectiousness and the risk of disease progression.

Antithrombotics

Low-molecular-weight heparin is an anticoagulant that enhances antithrombin III activity, reduces the risk of coagulopathy and thromboembolism, and interacts with NF-κB by mediating the production of proinflammatory cytokines[66]. It reduced the likelihood of death by 64% and the risk of disease progression and death by 39%[24].

Chemotaxis inhibitors

It is possible that the effect of bevacizumab is related to the secretion of vascular endothelial growth factor (VEGF) by leukocytes in response to a hypoxic environment[67] and that inhibition of VEGF (Fig. 2) prevents its function as a chemoattractant for monocytes and macrophages through its receptor VEGF receptor 1[68]. Bevacizumab reduced fever in the first 72 h, improved respiration in populations from China and Italy, and no patients died. However, a decrease in respiratory capacity was observed only in the control group in Italy throughout the study[69]. This is probably due to the use of Chinese herbal medicine, including Jinhua Qinggan, Lianhua Qingwen, and Xuebijing[70], in the treatment of all control patients in Wuhan, unlike those in Italy[69] (Table 4 for more data on concomitant treatments).

Bronchodilators

Inhaled nitric oxide reduced respiratory rate, improved oxygenation, and prevented hospital readmissions after discharge[71]. In addition to its bronchodilator activity, it is thought to have antiviral activity, as it reduced viral replication by 99% in *in vitro* studies by inhibiting the Mpro protease of SARS-CoV-2[72].

Vitamins

Regular supplementation with Vitamin D_3 during the year before illness significantly reduced mortality; the clinical benefit was not significant in patients who received it after diagnosis[73]. In an extension of this trial, Vitamin D_3 supplementation before, during, or after hospitalization reduced mortality in geriatric patients[74]. Vitamin D regulates innate and adaptive immunity, as its hormonal metabolite (calcitriol) mainly suppresses the production of inflammatory cytokines, induces regulatory T lymphocytes, and has a possible antiviral effect[75].

Table 5. Characteristics of clinical studies of combination therapies

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Baricitinib and LPV/R		Baricitinib 4 mg QD, PO for 14 days. LPV/R 250 mg, PO, BID, 14 days	Hydroxychloroquine 400 mg/QD/PO, LPV/R	83% men, mean age 63.5 years, 20.83% hypertension, 29.16% diabetes	Hospitals in Prato and Alessandria. ND	42
Baricitinib and LPV/R	NCT04358614.	Baricitnib 4 mg, PO, QD, 14 days. LPV/R 250 mg PO BID, 14 days	HQ, LPV/R	62.30% men, mean age 65.5 years, 27.74% hypertension, 16.23% diabetes	7 care centers, ND	43
Baricitinib and corticosteroid	EUPAS34966	Baricitinib 4 mg PO the 1st day, then 2 mg QD or 4 mg QD Methylprednisolone 80, 125 or 250 mg/QD	LPV/R, two tablets PO 200/50 mg BID, 7-10 days HQ 200 mg, PO, BID	Mean age 63 years, 69.6% men, 28.8% hypertension, 18.8% diabetes	Hospital General Universitario de Albacete, Spain, Tertiary	41
Danoprevir and ritonavir	NCT04291729	Danoprevir 100 mg PO, BID, 4-12 days, Ritonavir 100 mg PO, BID	α-interferon, 5 million units, IN BID	Mean age 44 years, 36.4% men, 18.2% hypertension	The Ninth Hospital of Nanchang Tertiary	53
HQ and oseltamivir	NCT04303299	Oseltamivir 300 mg/ QD O 4-6 mg/kg QD; HQ 800 mg QD	Supportive care without experimental treatments	Mean age 32 years, 46.6% male, 6.6% obese	Rajavithi Hospital Tertiary	65
HQ and oseltamivir	NCT04349241 (-)	Oseltamivir PO 75 mg BID 10 days; HQ 800 mg PO day 1, followed by 200 mg BID, days 2-10	ND	Mean age 36.4 years, 50% male, 18% with comorbidities ND	Ain Shams University Hospital, Tertiary y Assiut University Hospital, Tertiary	64
HQ, FVP, DRV yand ritonavir	NCT04303299	HQ 400 mg QD; FVP 6000 mg 1st day, then 2400 mg QD; DRV 1200 mg, QD or 4-6 mg/kg, QD; R 200 mg, QD or 2.5 mg/kg QD	Supportive care with no experimental treatments	Mean age 42 years, 52% men, 30% obese	Rajavithi Hospital Tertiary	65
IVE, AAS, DEX and ENOX*	NCT04425863	IVE PO 24, 36 and 48 mg days 0 and 7; DEX 4 mg IM; ENOX SC; ASA 250 mg PO	ND	Average age 55.7 years, 51.5% men	Hospital Eurnekian Secondary	78
LPV-R, IFNβ-1b, Ribavirine	NCT04276688	LPV 400 mg; R 100 mg BID, 14 days; ribavirin 400 mg BID; IFNβ-1b 8 million IU, TID every other day	Amoxicillin, azithromycin, ceftriaxone, doxycycline, levofloxacin, corticosteroids	Average age 52 years old, 54% men, 13% diabetes, 27% hypertension	6 centers	56
Novaferon and/or LPV/R	ChiCTR2000029496	Novaferon 40 μg TID, IN. LPV/R 200 mg/50 mg PO TID	ND	Average age 46, 50, 37 years in the different groups, 9% diabetes, 10% hypertension	First Hospital of Changsha city, ND	46

(Continues)

Table 5. Characteristics of clinical studies of combination therapies *(continued)*

Drug	Study identifier	Experimental treatment Dose/route/ duration	Accompanying treatment	Demographic and clinical characteristics	Hospital/level	References
Remdesivir alone or with baricitinib	NCT04401579	Remdesivir 200 mg IV day 1, 100 mg day 2-10. Baricitinib 2mg BID 14 days	Standard support with no experimental drugs	Mean age 55 years, 63.1% male, 57% 2 or more coexisting conditions	71 centers	58

*Natural products or their semi-synthetic derivatives.
ASA: Acetylsalicylic acid; DEX: Dexamethasone; DRV: Darunavir; ENOX: Enoxaparin; FVP: Favipiravir; HQ: Hydroxychloroquine; IFN: Interferon; IVE: Ivermectin; LPV/R: Lopinavir with Ritonavir; PO: oral; IV: intravenous; SC: subcutaneous; IN: intranasal; IM: intramuscular; QD: once daily; BID: twice daily; TID: three times daily; ND: not determined; (-): retracted article.

Multi-target combination therapies

The combination of hydroxychloroquine with favipiravir, darunavir, and ritonavir reduced mortality by 25% compared with patients receiving oseltamivir, lopinavir, and ritonavir (4% vs. 16%)[65]. The individual effect of the drugs in this regimen against COVID-19 is inconclusive. However, he efficacy of this regimen is related to the inhibition of different stages of the viral cycle, as it includes antiviral agents, protease inhibitors, polymerase inhibitors, and an antiparasitic agent that may interfere with viral entry.

The combination of ivermectin, dexamethasone, acetylsalicylic acid (aspirin), and enoxaparin covers different aspects of the disease, as ivermectin blocks the IMPα/β1 import heterodimer on which nuclear trafficking of RNA virus proteins depends (Fig. 2)[76]. Aspirin is an antithrombotic agent in mild cases, enoxaparin is an anticoagulant[77], and dexamethasone inhibits transcription factors such as AP-1, NF-κB, and IRF[78], prevents the synthesis of cytokines and chemokines, and induces apoptosis of T lymphocytes and neutrophils[79]. This therapy inhibited disease progression and reduced mortality by 71% compared to the mortality rate in Argentina and 87% compared to the mortality rate in Spain and Italy for hospitalized patients[77].

Fig. 3 shows the molecular structure of the drugs included in clinical trials that were shown to inhibit the processes involved in SARS-CoV-2 infection.

Discussion

The global pharmaceutical industry has relied on developing prophylactic vaccines to reduce transmission through large-scale mass vaccination programs worldwide, aiming to achieve herd protection in the short term. Although highly effective vaccines have been developed, there is still significant mortality, as well as limitations in vaccine availability and the emergence of SARS-CoV-2 variants.

Drug repurposing is an alternative to the traditional drug development and discovery process to address emerging diseases such as COVID-19. In this study, we identified drugs, an herbal remedy, and a vitamin that were administered orally (23), intravenously (6), subcutaneously (3), intramuscularly (2), and inhalational (2). Twenty-four of these were administered alone, and 12 were in combination therapies that were shown to be effective against COVID-19 during the 1st year of the pandemic. Several of these drugs were recommended by the Instituto Mexicano del Seguro Social (Mexican Social Security Institute) for their use in patients with COVID-19 in the Clinical guide for the treatment of COVID-19 in Mexico (Guía clínica para el tratamiento de la COVID-19 en México).

The drugs that showed the best results in reducing mortality and the need for mechanical ventilation in critically ill, very severe and severe patients were those that reduced inflammation even though they were not specifically anti-inflammatory, such as the kinase inhibitors imatinib mesylate and baricitinib, the proinflammatory cytokine regulators aviptadil, anakinra, and pyridostigmine bromide, the monoclonal antibody bevacizumab, the herbal remedy based on *N. sativa* seeds with honey, and the combination of ivermectin, aspirin, dexamethasone, and enoxaparin; also, hydroxychloroquine in combination with favipiravir, darunavir, and ritonavir; and the anticoagulant low-molecular-weight heparin.

In mild-to-moderate cases, the drugs that reduced viral load, mortality, or prevented progression to severe disease were synthetic antivirals such as danoprevir with ritonavir, the combination of lopinavir with ritonavir, IFN β-1b and ribavirin, also umifenovir, favipiravir, the recombinant IFN novaferon, the kinase inhibitor

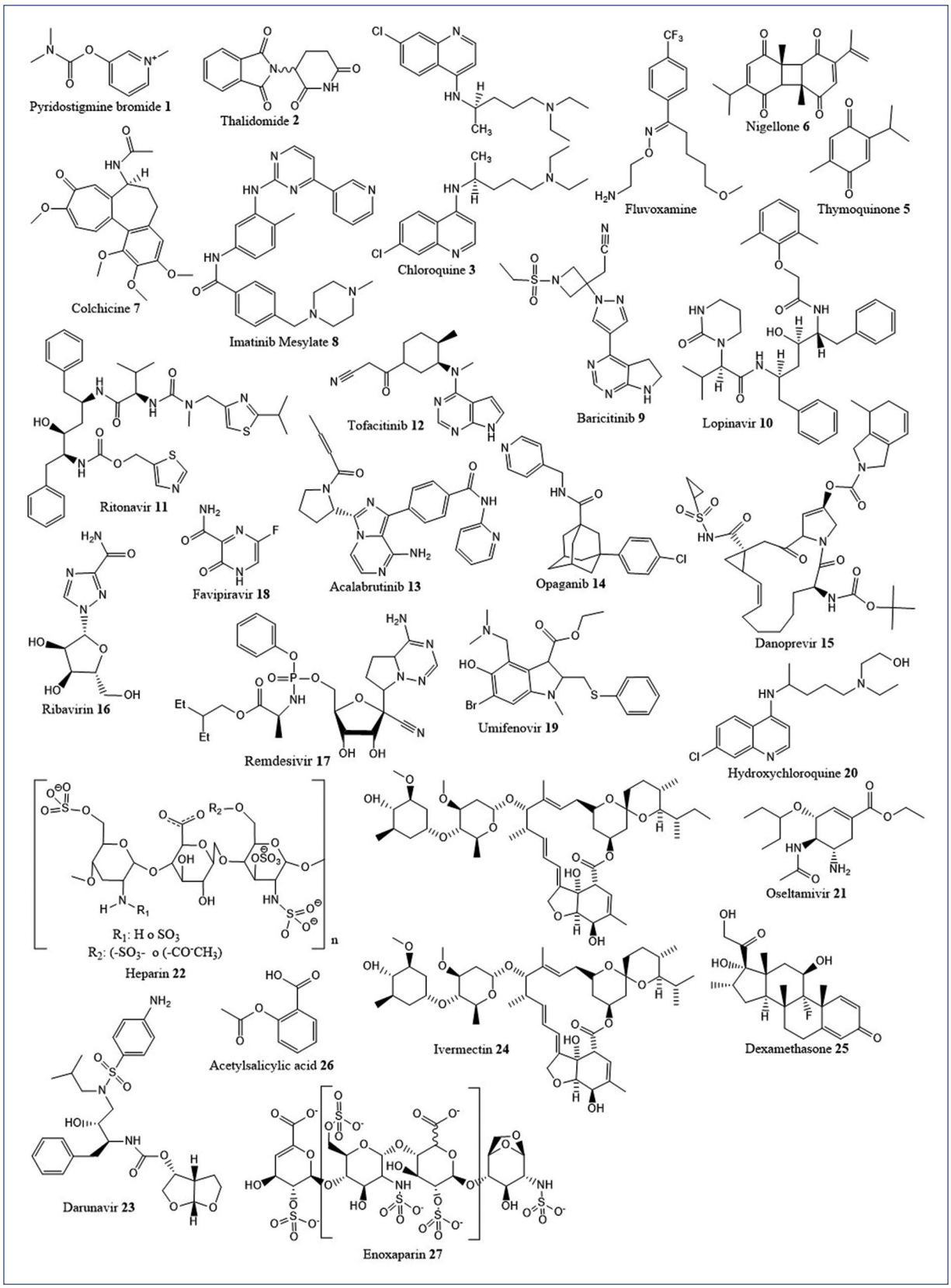

Figure 3. Molecular structure of drugs included in clinical studies that were shown to inhibit the processes implicated in SARS-CoV-2 infection.

tofacitinib, the natural product colchicine, and the semi-synthetic derivative hydroxychloroquine in combination with the antiviral oseltamivir.

We highlight the remarkable responsiveness of the drug repurposing strategy, which allowed clinical trials to be conducted early in the pandemic, reducing mortality, and recovery time; however, it is essential to continue to dedicate efforts to research and development of effective drugs and vaccines to have better, affordable, and easily accessible therapeutic options to face this pandemic and increase preparedness for future epidemics fully.

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that they have followed the protocols of their work center on the publication of patient data.

Right to privacy and informed consent. The authors have obtained the written informed consent of the patients or subjects mentioned in the article. The corresponding author has this document.

Conflicts of interest

The authors declare no conflicts of interest.

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