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Boletín Médico del Hospital Infantil de México

Artículo de revisión

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Hospital Infantil de México Federico Gómez
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REVIEW ARTICLE

Ethics in infectious diseases: latent challenges. Part I

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Abstract

Infectious diseases socially imply individual and community medical problems. Therefore, they require actions aimed at social processes that affect the well-being of the individuals without losing sight of social groups. Faced with this panorama, we ask ourselves: is there a direct relationship between ethics and infectious diseases? To elucidate an answer, let us remember the peak period of the COVID-19 pandemic when guidelines based on ethical principles were issued to facilitate medical decisions on allocating scarce resources in periods of maximum demand. In those moments, since there was no inclusive component of society, the decisions made produced massive criticism. The reactions demonstrated the need to analyze in detail the criteria that had been considered correct. Consequently, we affirm that bioethical principles are transcendental in medical decisions and must be examined, not only for the individual but also with a view to public health. Moreover, the acquired immunodeficiency syndrome (AIDS) epidemic has lived with us for decades, and it continues to show its tragic face in the form of new cases, chronic illnesses, and deaths. Joint United Nations Programme on HIV/AIDS brings us closer to a complex reality where the fight against disease and global health are interrelated with other problems, such as the need to reduce inequality, for which human rights, gender equality, social protection, and the development of research projects, where the ethics committees in research in community processes are constituents.

Keywords: *Fair distribution of scarce medical resources. Ethical principles. Social commitment. Social interventionism. Common good and individuality. Public health ethics.*

Ética en enfermedades infecciosas: retos latentes. Parte I

Resumen

Las enfermedades infecciosas implican problemas médicos individuales y comunitarios, por lo que requieren acciones dirigidas a procesos sociales que incidan en el bienestar de los individuos, sin perder de vista a los grupos sociales. Nos preguntamos: ¿existe relación directa entre la ética y las enfermedades infecciosas? Para dilucidar una respuesta, recordemos el periodo más álgido de la pandemia por COVID-19, cuando se emitieron guías fundamentadas en principios éticos para facilitar las decisiones médicas en la asignación de recursos escasos en periodos de máxima demanda. Al no haber un componente inclusivo con la sociedad, las decisiones que se tomaron produjeron críticas masivas, que demostraron la necesidad de analizar a detalle los criterios que se habían considerado correctos. En consecuencia, afirmamos que los principios bioéticos son trascendentales en las decisiones médicas y deben ser examinados, no solo frente al individuo, sino

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de cara a la salud pública (bien común e individualidad). Por otra parte, la epidemia del SIDA (síndrome de inmunodeficiencia adquirida) convive con nosotros desde hace décadas. ONUSIDA (Programa Conjunto de las Naciones Unidas sobre el VIH/SIDA) nos acerca una realidad compleja, como es que la lucha contra la enfermedad y por la salud global se interrelaciona con otros problemas como la necesidad de reducer la desigualdad, por los derechos humanos, la igualdad de género, la protección social y el desarrollo de proyectos de investigación, donde los comités de Ética en investigación en procesos comunitarios son constituyentes.

Palabras clave: *Distribución justa de recursos médicos escasos. Principios éticos. Compromiso social. Intervencionismo social. Bien común e individualidad. Ética de la salud pública.*

Introduction

Infectious diseases have a special nature of paramount importance in the medical field: they are usually community problems, and their proper management requires actions directed at social processes. These actions usually impact the well-being of individuals and their social groups. In this context, is there really a direct relationship between ethics and infectious diseases? There should be no doubt about this relationship after living through 2 years of the coronavirus disease-19 (COVID-19) pandemic. In this case, we have experienced isolation and social interventionism, together with the ethical dilemmas that arise, for example, in the allocation of scarce medical resources for the treatment of patients who have been infected by the disease, the most important bioethical guiding principle of public health has prevailed: "save the most lives"[1].

Importance of ethics in the study of infectious diseases

As the medical services were overwhelmed during the COVID-19 pandemic, the ethical dilemmas surrounding an infectious disease increased (impacting not only medically, but also sociopolitically), the community began to voice its opinions, and healthcare professionals had to decide between those who should receive life-saving treatment and those who should not. Furthermore, the deliberation took place under the scrutiny of a critical and censorious society. In the same context, it was necessary to confront the stigmatization and criminalization of the lesbian, gay, bisexual, and transgender (LGBT) community and people of African descent, who were unfairly associated with cases of monkeypox or Ebola. This behavior fostered cycles of fear and distanced these communities from health services, hampering efforts to identify cases and encouraging ineffective and highly punitive measures.

During the peak of the COVID-19 pandemic, ethical guidelines were issued in Mexico and other countries to facilitate medical decision-making regarding the allocation of scarce medical resources during periods of peak demand (such resources could be life-saving, particularly invasive mechanical ventilators and hemodialysis machines). The *ethical* guidelines considered, for example, the use of age as a determining factor in decision-making, which some considered as an excuse for unthinkingly slipping into discrimination, while others argued that age was a valid criterion[2].

Despite the warning given by the influenza pandemic a decade ago, the guidelines were exposed to a society that was medically illiterate and even lacking in moral values (where the only thing of value is materialism, money, fame, and fortune). Therefore, in the absence of a genuine altruistic commitment of society, as was to be expected, the criticism was massive and even cruel.

To date, there is no unanimity or social consensus on what would be ideal from a moral point of view, so the debate must remain on the table for decision-makers. After all, the State is a source of guidance and social protection. Hence, the ethics of surveillance require constant evaluation and revision in light of experience (commitment to public health must remain with society to avoid conflict if this situation arises again)[3].

In a pluralistic society, people are likely to disagree about what principles should guide the allocation of scarce resources during an adverse event such as a pandemic, whether a group of people should be isolated to prevent contagion, or even whether it is right to participate in a community trial without obtaining prior informed consent on an individual basis; therefore, careful attention to procedures is critical. Consequently, several aspects of procedural justice should be considered, such as public commitment, transparency in decision-making, reliance on grounds and principles that everyone can accept as relevant, oversight by a legitimate institution, and procedures for appealing and reviewing individual decisions in light of challenges to them[4].

However, health is a basic human right and essential for social and economic development, as stated by the World Health Organization (WHO) in the Jakarta Declaration: "Health promotion is done by and with people, neither imposed nor delivered. It builds the capacity of individuals, groups, organizations, and communities to influence the determinants of health"[5]. Therefore, the contribution of ethics to public health focuses on designing and implementing policies to monitor and improve the health of populations. However, it goes beyond health care by considering the determinants that promote or hinder the development of healthy societies.

It is not surprising that public health surveillance is the foundation for a timely response to epidemics and communicable disease outbreaks, although it is not limited to infectious diseases. When conducted ethically, surveillance is the foundation of any program that seeks to promote wellness at the population level.

This is the case with programs that contribute to reducing inequalities: some causes of unjustified and preventable suffering cannot be addressed without first making them visible. It is important to note that surveillance does not exempt participants from risks; for this reason, surveillance often raises ethical dilemmas, such as issues of privacy, autonomy, equity, and the common good, which must be constantly considered and balanced (this knowledge can be a challenge in practice)[6].

In 2002, WHO Director-General Dr. Gro Harlem Brundtland launched the Ethics and Health Initiative, which has since become a reference for ethics activities across the organization. Most recently, in 2017, the WHO Guidelines on Ethics in Public Health Surveillance were published[6], constituting the first framework to help policymakers and practitioners address the ethical aspects of public health surveillance. In this regard, public health surveillance may limit privacy and other civil liberties. For example, during a pandemic, surveillance may lead to mandatory quarantine, isolation, or confiscation of property, affecting in various ways particular interests for the benefit of the vast majority. In other circumstances, surveillance may include reporting based on names or lifestyles. When the population is aware of all this, it can generate deep concern for invasion of privacy, discrimination, and stigmatization[7]. Therefore, it is necessary to include ethics in all the work carried out by public health as an instrument of the State in the light of preventing infectious diseases.

Principles of equity and justice

For several decades, the lack of resources for research on diseases that constitute a major public health problem has been described. In what is known as the 10/90 distribution, it is estimated that only 10% of the research resources are allocated to diseases that represent 90% of the conditions; if not controlled, these diseases could wipe out the population[8]. This phenomenon is also present in bioethical research, where existing justice problems regarding infectious diseases have not been addressed properly. This situation is linked to the particular interest of a public whose economic and moral condition directs its preferences toward curing diseases that afflict or kill most of the population immersed in a state of worrying poverty. Issues such as euthanasia (even for children), eugenics, abortion, assisted reproduction, pre-natal genetic diagnosis, gene therapy, and the doctor–patient relationship are left on a primary level. In contrast, infectious diseases occupy a secondary place to the agenda of the countries with the greatest potential for global impact.

M. Selgeid pointed out some consequentialist reasons for urgent attention to infectious diseases from an ethical point of view[8]. The main reason is the devastation caused worldwide by the arrival of an infectious disease that becomes a pandemic in a matter of weeks (the death toll will be remembered as evidence that a pandemic can kill more people than two world wars). This underlies health surveillance and ethical dilemmas. To name just a few dilemmas, we find the allocation of scarce resources, social justice, treatment experimentation, voluntary infection of healthy participants for vaccine development, population-based studies without individual informed consent, access to medical care, treatment inequity, forced quarantine and isolation, among others. Finally, the author emphasizes that all these problems arise not only from the biological aspect of the pathogen but also from the social conditions that characterize modernity, such as the condition of vulnerability generated by poverty and inequality worldwide (those who suffer and die most from diseases are those who face this condition). Therefore, the consequentialist vision warns of the risks to carry out correct epidemiological control on a global scale. This implies carrying out various bioethical studies that address the dilemmas without waiting for another infection with the capacity to devastate humanity[8].

Various epidemics are known to have caused the deaths of thousands to millions of people; they have

been some of the worst disasters and have even changed the course of history. The Black Death, which wiped out one-third of Europe's population between 1347 and 1350, was one such epidemic that caused the world to search for solutions and inspired a wide variety of painters, poets, and writers. By changing the mentality of the world's inhabitants, the world did not return to what it was, thus contributing to the arrival of the Renaissance. Another example was when the flu killed between 20 and 100 million people in 1918. Although we have more medical technology today, it does not guarantee total suppression of the constant threat of mass death since there are no vaccines for many deadly diseases with pandemic potential, nor are there hospital beds and ventilators for everybody in the world. This should inspire society to analyze the bioethical aspects of medical decisions to be made in such situations and even to evaluate preventive measures that can sometimes be intrusive for the general population.

Another example is severe acute respiratory syndrome (SARS), a viral respiratory disease caused by the SARS-associated coronavirus (SARS-CoV). SARS was first reported in Asia in February 2003. Within months, the disease spread to more than two dozen countries in North and South America, Europe, and Asia. Before the global outbreak could be contained, 8,098 people worldwide were infected by SARS during the 2003 outbreak, of whom 774 died[9]. Unfortunately, we did not heed the warning, and in 2020, the WHO declared COVID-19 a pandemic, first reported in Wuhan, China, on December 31, 2019. To date, 15 million people have died (estimate for the period January 1, 2020, to May 5, 2022), reflecting the pandemic's impact on many areas (economic, social, emotional, and moral, among others). The world has been paralyzed with fearful and bewildered gazes at something health authorities and citizens saw coming, even if they were unprepared to face it. A new pandemic is inevitable, and the wisest thing to do is to be prepared not only technologically but in terms of the ethical aspects of decision-making that caused so much turbulence and disagreement during that time (Fig. 1).

Another latent pathogen that has been identified as a devastating killer is smallpox. Before its eradication, smallpox ravaged humanity for at least 3,000 years, killing 300 million people in the 20th century alone. Although the WHO declared the disease eradicated in May 1980, humanity is not out of danger, as some countries openly claim to have frozen strains for military purposes (they could be used as biological weapons). In this context, the vast majority of the population is unprotected, as smallpox vaccination has been suspended for 50 years. Smallpox is a historic milestone that underscores the urgent need to invest in global health security and equitable universal health coverage (WHO, December 13, 2019).

Today, the human immunodeficiency virus (HIV)/acquired immunodeficiency syndrome (AIDS) epidemic demonstrates how devastating and unfair an infectious disease can be. According to statistics published by the Joint United Nations Programme on HIV/AIDS, in 2021, 37.7 million (30.2 million-45.1 million) people were living with HIV, of whom 1.7 million (1.2 million-2.2 million) were children (up to 14 years of age), and only 28.2 million people had access to antiretroviral therapy by the end of June 2021. Since the beginning of the epidemic, 79.3 million (55.9 million-110 million) people have been infected with HIV, and 36.3 million (27.2 million-47.8 million) people have died from AIDS-related illnesses. At this point, the problem lies in the inequitable distribution of global resources to care for the sick. It is not the same to contract HIV in sub-Saharan Africa as it is in the United States; ultimately, the prognosis and quality of life are incomparable, further widening the existing inequality gap.

It is estimated that just over half of the world's people living with HIV live in sub-Saharan Africa, and a very high percentage of the world's AIDS deaths occur in this region. Most people in these countries live in extreme poverty and, therefore, do not have access to new medications to fight HIV/AIDS. However, the problem extends to other areas of public health, as people in the region lack access to medicines to prevent and control common diseases such as malaria, tuberculosis, cholera, dysentery, typhoid, and meningitis; in fact, 50% of the population in these countries lack access to medications as basic as aspirin or acetaminophen, not only vaccines.

Misfortune or injustice? The problem is not only HIV/AIDS and other deadly infectious diseases but also access to the other components of health, such as living conditions, labor, undocumented migrants, poor education (where it exists), prostitution, and poor nutrition; each contributes to the AIDS epidemic, and each is at least in part the result of historical practices related to racist and abusive colonial oppression (certainly the AIDS epidemic in South Africa should be attributed in large part to historical social injustice).

The current head of WHO, Tedros Adhanom Ghebreyesus (2022), emphasizes the urgent need for all countries to invest in more resilient health systems

Figure 1. Thousands to millions of people have died from epidemics.

that can maintain essential health services during crises, including robust information systems. The question is how. No amount of money is enough for rich countries, much less for those in emerging and developing countries. Ultimately, the problem does not end them. Consequently, everyone is responsible for working together for the good of all, even across borders, according to ethical principles of justice and equity.

Monitoring individuals or groups who are particularly vulnerable to disease, harm, or social injustice is critical and requires careful consideration to avoid imposing unnecessary additional burdens on those already affected. Vulnerability may be generalized, affecting large communities (entire countries) with limited economic development, limited access to health facilities, educational deficiencies, occupational hazards, or greater social disadvantage. Thus, to promote equity, public health surveillance should focus on the specific problems of those vulnerable communities that are particularly vulnerable to disease, harm, or injustice (such as homosexuals and undocumented migrants) and that are at greater risk of experiencing other burdens, such as discrimination and stigma, as a result of surveillance activities. Therefore, a plan should be implemented to reduce, eliminate, or compensate for any harm from these activities[6].

Some countries may not have the capacity to establish and maintain public health surveillance of sufficient quality, even for high-priority goals that could significantly reduce health inequalities and improve the health of their populations due to severe resource constraints. The principles of equity, justice, and solidarity provide the ethical basis for requests for international assistance. The global community – international health organizations, non-governmental organizations, major foundations, and countries playing a leading role on the world stage – has an ethical responsibility to work with and support these countries in public health surveillance and subsequent interventions. This global justice requirement aims to reduce health inequities among countries and improve global health for the benefit of all, including high-income countries. Since disease outbreaks and risk factors do not respect borders, the global community should also be interested in having sustainable surveillance systems

in place, even in countries that do not have the resources to establish and maintain them[10].

Surveillance may require not only technical support but also formal ethical evaluation and improvement on a systematic basis, as demonstrated by international support for research ethics training. Where countries fail to protect the fundamental rights or interests of vulnerable individuals and populations in public health surveillance, international support should be conditioned to the correction of such violations and breaches. International humanitarian organizations have expressed deep concern that surveillance often responds to the needs of high-income countries, creating ambiguity about the primary beneficiaries of surveillance[11]. For example, malnutrition may be a priority in a poor-resource country (such as those in Latin America or Africa), while international donors may consider it a lower priority than an infectious disease outbreak. In other words, they may not be as concerned about children starving to death as they are about Ebola or multidrug-resistant tuberculosis not spreading to their country because of the potential impact on their population (and economy). While famine does not perpetuate diseases that can cross borders, poverty contributes directly. True partnerships may require reforms in global health governance to shift the priority from security, political, and trade interests to "universal health values"[12].

The problem is the global lack of equity and justice in the right to health, given that the greatest investments in preventive interventions are made in countries that have more capital (they can contain the spread of disease). For this reason, WHO member states must create conditions that allow all people to live as healthy as possible.

Health problems tend to affect vulnerable and marginalized groups to a greater extent, so States must take steps to move toward realizing the right to health following the *principle of progressive realization*. This means that once the State has provided the minimum necessary for everyone, it must take deliberate, concrete, and specific measures to maximize its available resources. These resources include those provided by the State and those derived from international assistance and cooperation, continuously taking the necessary steps to move as rapidly as possible toward the full and effective enjoyment of each of the economic, social, and cultural rights (ESCR).

States recognize the right of everyone to the highest attainable standard of physical and mental health. Therefore, as an acquired right, following the basic floor and for the sake of the principle of progressive realization, the State is internationally obliged to increase the necessary measures to achieve the highest standard of the right to health, which cannot be achieved in a short period. In this regard, flexibility is needed to reflect the realities of the world and the difficulties each country faces in ensuring its effectiveness.

The principle of progressive realization should be understood as a gradual and constant advance whereby States, based on their international commitments, take the necessary and appropriate measures to progressively achieve the full realization of ESCR, investing to the maximum of their available resources without taking regressive steps. Therefore, the protection achieved concerning the human right to health must be respected and strengthened based on the principle of progressivity since States have an absolute obligation to ensure the right of everyone to the enjoyment of the highest attainable standard of physical and mental health[13].

The common good and individuality

An individual with a communicable disease threatens the health of those around. Prevention and control measures are necessary to stop its spread, including mandatory testing, vaccine administration, health department notification, contact notification, isolation, quarantine, travel restrictions, and many others. Any of these measures may violate human rights, the principle of autonomy, and the individual's freedom. This ethical dilemma seems easy to resolve if one is inclined to defend that public health is the greater good because it is communitarian and above individual rights, including the privacy of subjects and non-maleficence over an individual's autonomy. For example, if a patient is found to have multidrug-resistant tuberculosis, all contacts should be tested to detect other cases and interrupt the spread. In this case, it should not be an option to go to the clinic to have everything done and be treated. However, it is assumed that in a free and tolerant country, an individual should be allowed to refuse tests to rule out or diagnose an infectious disease that could harm society.

For many philosophers, public health experts, economists, and bioethicists, to find a balance between the legitimate rights of the sick individual and the social conflict represented by the risk of spreading the disease is challenging. Knowing oneself to be free and autonomous implies being respectful of the freedom of others and acting conscientiously. The State has the obligation to respect our choices as long as they do not

violate other people's rights. The State's obligation is to protect the civil rights of citizens: to live, practice their beliefs, and have lifestyles as they see fit without harming others. Even if they are not "best practices," the idea that should prevail is that all citizens, regardless of their lifestyles, should live together in complete equality, respecting the rights of others. This idea would be the threshold from tolerance to respect for individual rights and the preservation of a democratic society. However, reaching the threshold would not be practical.

The answer is not simple. For example, implementing a quarantine policy would be accepted differently in each community, depending on the conditions of democracy, cultural plurality, and social inequality. In some countries, failure to comply with isolation or quarantine rules is considered a crime; in other countries, quarantine could be carried out with voluntary cooperation and conditions as unrestrictive as possible, but social participation is essential in both cases. Vaccines pose a similar problem: some countries enforce the use of vaccines, while others respect the choices of individuals, even though their choices puts their health and that of the rest of society at risk, increases the cost of care, and limits public health resources. Why shall we sacrifice individuality? The short answer is for the common good (from the Latin, *bonum commune*), which generally refers to the well-being of all members of a community and also to the public interest, as opposed to private benefit and particular interest. Although many theories justify the common good, it is not the purpose of this text to explain them in detail; however, they all seek the welfare of the community for the good of all its members, with the participation of all.

Since the early modern period, the common good has been conceived in contractual terms (initially defined in terms of the social contract: for Hobbes, the securing of peace; for Locke, the protection of fundamental rights and individual property; for Rousseau, the general welfare and the preservation of the good condition of the members of society). However, these and other purposes of the common good require the consent of the members of society.

Liberalism produces social integration only formally and through the law, but not through goods defined by their communitarian character or the common good. Consequently, it constructs political legitimacy only through procedures rather than communication among citizens about common goods. Communitarians emphasize a person's connection to the community: his or her existence is essentially defined by his or her social roles, interactions, and interpersonal relationships, while his or her identity is primarily shaped by shared understandings, that is, the culture and historical traditions of the community in which he or she was born and lives. Communitarians believe in creating order by blending the impartiality of the liberal rule of law and the universality of human rights that transcend gender, race, ethnicity, and political beliefs with the partiality of the common good or community goals as defined within the community itself.

How, then, does the community deal with dissidents and cultural minorities? It grants them the right to dissent regarding opinions and ways of life since "the struggle for recognition can find only one satisfactory solution, which is a regime of mutual recognition among equals"[14,15].

The principle of accommodation suggests that some individuals (usually minorities) should sometimes be exempted from certain laws of general application on the grounds of conscientious objection. The scope is much debated, but it is clear that some degree of accommodation is necessary to protect the equality of minorities.

This amplified discrimination may affect some members of the community more than others, particularly women, indigenous peoples, children, persons with disabilities, older adults, and LGBT intersex (LGBTI) people[6]. It is, therefore, essential to implement an age, gender, and diversity approach to meet the commitment to ensure that all health protection activities, including durable solutions, are accessible to and inclusive of all minorities.

Minorities are vulnerable to violations of their rights to identity, non-discrimination, and effective participation. These principles must also be guaranteed in forced displacement and isolation situations, as they may be socioeconomically and physically isolated. A high level of protection can only be achieved through an inclusive and participatory approach. The involvement of members of minority and indigenous groups in policy formulation and consultation processes is key to the development and implementation of appropriate solutions to the problems they face. Consultation and participation are essential in all phases of crisis and prolonged situations. The State's duty is to ensure that these minorities have the necessary information for their participation to be meaningful and consistent with the common good[16].

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 no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Histological transitional zone pull-through in Hirschsprung disease. Postoperative functional results and current recommendations

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Abstract

Background: *Surgeons create a neorectum to repair patients with Hirschsprung's disease (HD), which should be formed from a normoganglionic bowel. However, the neorectum is occasionally created with a transition zone (TZ) bowel. A neorectum created with a TZ has been postulated as a cause of postoperative enterocolitis or constipation. This study compares the incidence of enterocolitis and constipation in patients with TZ neorectum and normoganglionic bowel.* **Methods:** *We conducted a retrospective review of patients with rectosigmoid HD who underwent primary pull-through. Patients were divided into normoganglionic neorectum (NNR) and TZ neorectum. The diagnosis was based on the final histopathologic report of the proximal margin. The incidence of enterocolitis and constipation was compared between these two groups.* **Results:** *A total of 98 HD patients were analyzed. Seventy-one patients fulfilled the inclusion criteria. 65 (92%) had a NNR, and six patients (8%) had a TZ neorectum. From these patients, 42 (59%) presented with enterocolitis or constipation. However, there was no significant difference between both groups.* **Conclusion:** *The present study showed no difference in the incidence of enterocolitis or postoperative constipation in HD patients with normoganglionic or TZ neorectum. These results suggest that TZ neorectum does not cause postoperative obstructive symptoms.*

Keywords: *Hirschsprung disease. Transition zone. Hirschsprung-associated enterocolitis. Hypertrophic nerves. Pull-through.*

Descenso en zona de transición histológica en la enfermedad de Hirschsprung. Resultados funcionales postoperatorios y recomendaciones actuales

Resumen

Introducción: *Los cirujanos crean un neo-recto para tratar a los pacientes con enfermedad de Hirschsprung (EH), que debe formarse con intestino normogangliónico; sin embargo, en ocasiones el neo-recto se forma con intestino de la zona de transición. Se ha postulado que un neo-recto en zona de transición causa enterocolitis o estreñimiento postoperatorio. El objetivo de este estudio fue comparar la frecuencia de enterocolitis y estreñimiento en pacientes con neo-recto en zona de transición y con neo-recto normogangliónico.* **Métodos:** *Se llevó a cabo una revisión retrospectiva de pacientes con EH recto sigmoideo*

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que se sometieron a descenso primario. Los pacientes se dividieron en el grupo neo-recto normogangliónico y el grupo con neo-recto en zona de transición. El diagnóstico del neo-recto se estableció con el informe histopatológico definitivo del margen proximal. Se comparó la frecuencia de enterocolitis y estreñimiento entre estos dos grupos. **Resultados:** *Se analizó un total de 98 pacientes con EH, de los cuales 71 pacientes cumplieron los criterios de inclusión; 65 (92%) con neo-recto normogangliónico y seis (8%) con neo-recto en zona de transición. Posteriormente, 42 (59%) pacientes presentaron enterocolitis asociada a Hirschsprung (HAEC) o estreñimiento; sin embargo, no hubo diferencia significativa entre ambos grupos.* **Conclusiones**: *El presente estudio no demostró una diferencia en la frecuencia de HAEC o estreñimiento postoperatorio en pacientes con EH con neo-recto normogangliónico o en zona de transición. Estos resultados sugieren que un neo-recto en zona de transición no causa síntomas obstructivos postoperatorios.*

Palabras clave: *Enfermedad de Hirschsprung. Zona de transición. Enterocolitis asociada a Hirschsprung. Nervios hipertróficos. Descenso.*

Introduction

In patients with Hirschsprung's disease (HD), there is a segment of the bowel called the histologic transition zone (TZ), which is located between the aganglionic and normoganglionic bowel and is ≤ 5 cm in length[1] (Fig. 1).

Seven histologic abnormalities have been described in TZ: plexuses with ganglion cells with hypertrophic nerves[2], myenteric hypoganglionosis[3], hyperganglionosis of the submucosal plexus[3], partial circumferential aganglionosis[4], ectopia of ganglion cells in the seromuscular layer and lamina propria[5], ganglioesclerosis[1], and fibromuscular dysplasia of the adventitial layer[6].

Resection of the entire aganglionic bowel and TZ is one of the goals in the surgical repair of HD. This disease always involves the rectum, and therefore, its resection is part of the treatment. The normoganglionic bowel is then pulled-through and anastomosed to a small segment of the aganglionic rectum measuring approximately 5-10 mm, i.e., the anastomosis is made proximal to the dentate line. The descending bowel forms the "neorectum." The edge of the bowel that anastomoses to the rectum is called the *proximal margin*. Based on the histology of the proximal margin, there are three types of neorectum. The normogangliónic neorectum (NNR) is composed of a bowel that covers the entire circumference of the proximal margin, has ganglion cells in the submucosal and myenteric plexuses and has no nerve trunk hypertrophy (Fig. 2). The transition zone neorectum (TZNR) has at least one of the following three histologic changes at the proximal margin: partial circumferential aganglionosis, myenteric hypoganglionosis, or hypertrophy of the submucosal nerve plexuses (Fig. 3)[1,4,7]. Finally, the third type is the aganglionic neorectum (ANR), which has a proximal border without ganglion cells in the myenteric and submucosal plexuses (Fig. 4).

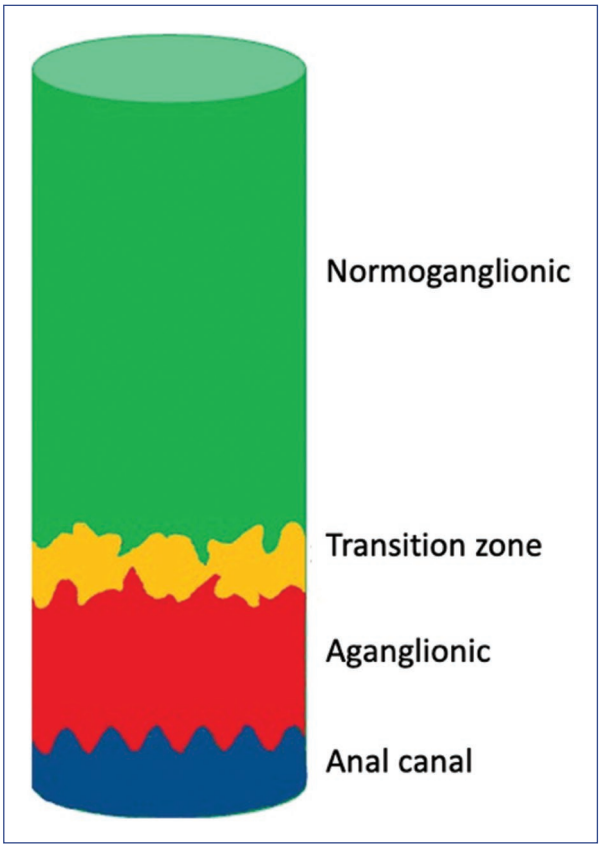

Figure 1. Diagram of a rectum and sigmoid colon with Hirschsprung's disease.

In a pull-through procedure, the surgeon requests a histopathologic study of the proximal margin to ensure the creation of an NNR. Pathologists perform the study of this segment twice and under different conditions. The first time is the intraoperative study, in which frozen tissue, usually stained with hematoxylin and eosin, is evaluated, and the result is reported to the surgeon within minutes during surgery. The second time is known as definitive evaluation and consists of embedding the tissue in

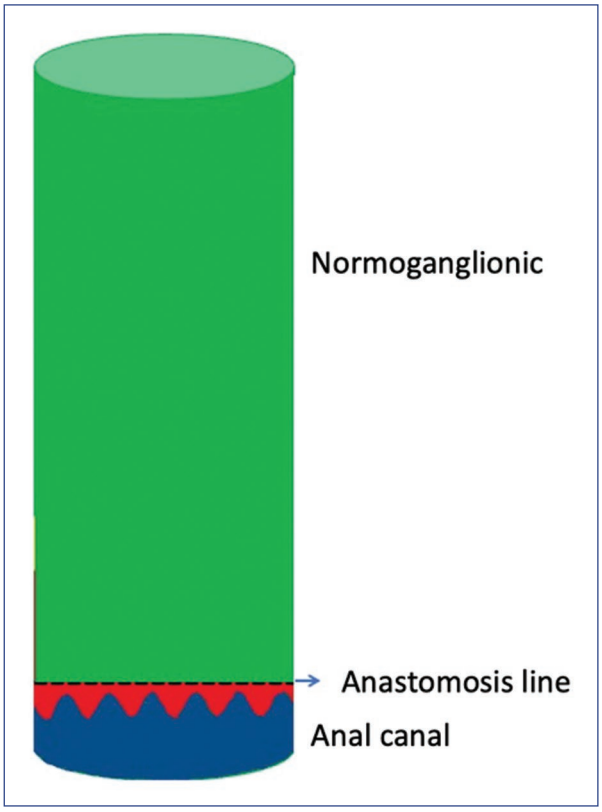

Figure 2. Diagram of a normoganglionic neorectum.

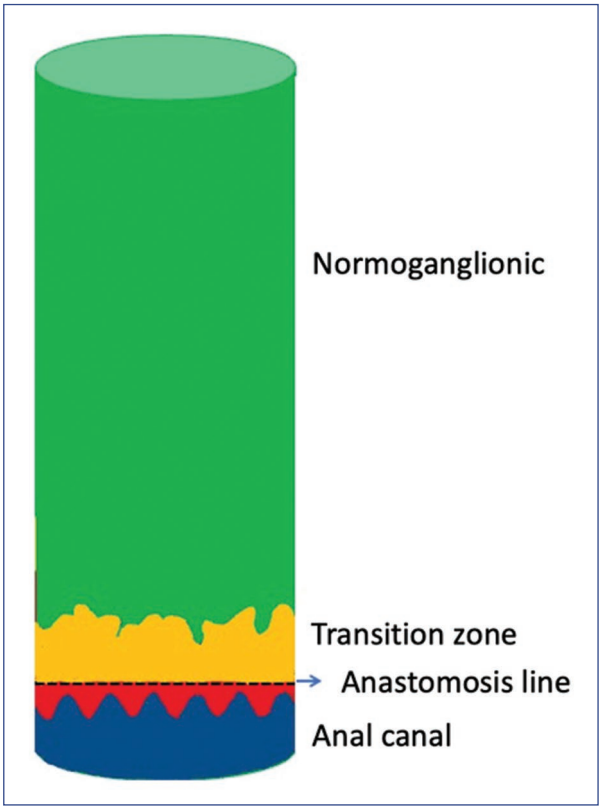

Figure 3. Diagram of a transition zone neorectum.

paraffin, which provides the pathologist with a higher quality for analysis. In addition, this procedure uses different stains and auxiliary methods, such as immunohistochemistry, to facilitate its evaluation, and the result is reported days after the pull-through. Therefore, the result of the intraoperative evaluation may differ from the final result[8,9].

Hirschsprung's associated enterocolitis (HAEC) and postoperative constipation remain a common problem. In recent years, it has been hypothesized that these problems result from a descending bowel in the TZ[10] and that reoperation is necessary to resect this zone and perform a redo pull-through[11].

The present study aimed to evaluate the presence of HAEC or postoperative constipation and to correlate it with the histopathology of the proximal margin in patients with rectosigmoid HD who underwent a primary pull-through.

Methods

Research methodology

We conducted a retrospective study of all HD patients at Children's Hospital Colorado (CHCO) from January 2010 to June 2020. Patients with rectosigmoid HD who underwent a pull-through procedure and had clinical follow-up at CHCO during the study period were included. Patients who had surgery or follow-up at another hospital, patients with mechanical obstruction, patients with ANR, syndromic patients, patients with long-segment aganglionosis, and patients with total colonic aganglionosis were excluded from the study. The study was approved by the Colorado Institutional Review Board (IRB #: 20-1891).

Data collection

Patients with HD and a pull-through procedure were identified using the Colorectal Center database and electronic medical records. A review of each patient's entire record was performed to confirm that they met the inclusion criteria. Demographic and clinical information was then collected: date of birth, sex, race/ethnicity, age at the pull-through procedure, date and type of the procedure. A detailed analysis was performed to determine postoperative outcomes and to identify asymptomatic patients, patients with HAEC events, and constipation.

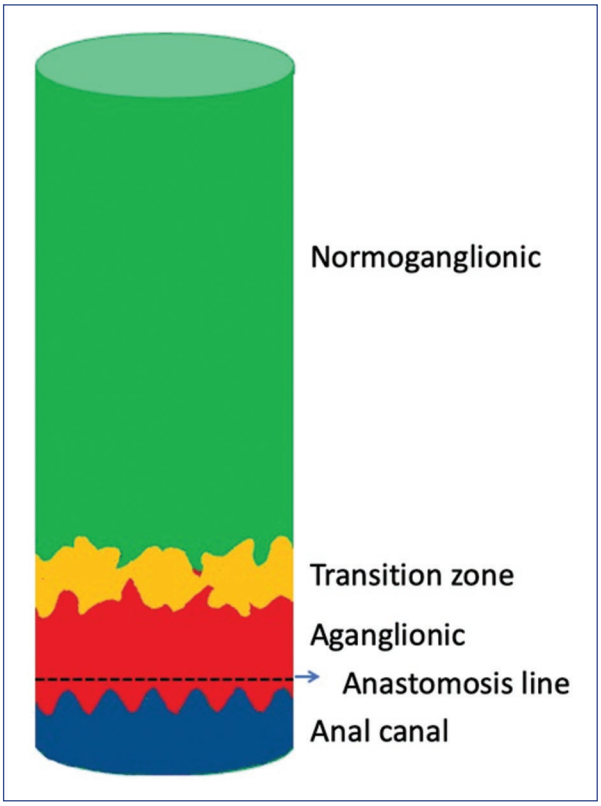

Figure 4. Diagram of an aganglionic neorectum.

Operational definitions

Postoperative HAEC was defined when the patient required a program of rectal irrigation and oral or intravenous metronidazole after the pull-through in the setting of low functional bowel obstruction, with smelly diarrhea, fever, explosive bowel movements, distension of the distal colon on a plain abdominal radiograph, or air-fluid levels.

Constipation was defined as decreased, irregular, or absent bowel movements and the need for laxative therapy.

An asymptomatic patient was defined as one who did not require a laxative regimen, had no episodes of HAEC, and had spontaneous bowel movements.

Histopathologic groups

At CHCO, it is a standard practice to send the resected bowel to evaluate the circumference of the proximal margin. Patients' intraoperative and final reports were reviewed. NNR was defined when the final report described the presence of ganglion cells in the myenteric and submucosal plexuses and the absence of nerve plexus hypertrophy or other neuroanatomic abnormalities of the transitional zone over the entire circumference of the proximal margin.

TZNR was defined when the final report described at least one of the following three features: (1) ganglion cells in both plexuses with hypertrophy of the submucosal nerve plexuses; (2) absence of ganglion cells in at least one-eighth of the circumference (circumferential partial aganglionosis); (3) myenteric hypoganglionosis.

ANR was defined as the absence of ganglion cells in both plexuses over the entire circumference of the proximal border.

Nerve plexus hypertrophy was defined as submucosal nerve trunks > 40 μm. Nerve diameter was measured with an optical micrometer in all cases. Two pediatric pathologists with expertise in HD independently re-examined the proximal margin if the final report described the presence of ganglion cells but no other neuroanatomic abnormalities of the TZ (i.e., an inconclusive report of the TZ).

Data management

Patients were grouped based on the final histopathologic report of the proximal margin. Postoperative outcomes of these groups were analyzed for HAEC and constipation.

Statistical analysis

Data were presented as frequencies and percentages. Student's t-test and χ^2 or Fisher's exact test were used to compare groups. A $p < 0.05$ was considered statistically significant. Statistical analysis was performed with SPSS® version 22; biostatistical analysis was blinded.

Results

Participants

A total of 98 records of patients with HD diagnosis were retrospectively analyzed. Twenty patients were excluded because of long-segment aganglionosis, total colonic aganglionosis, or syndromic HD. In addition, one patient was excluded because the pull-through procedure was performed at another hospital, and six patients were excluded because of anastomotic stenosis; there were no patients with ANR.

A total of 71 patients remained for analysis. Intraoperative diagnosis of the proximal margin revealed ganglion cells

in the myenteric and submucosal plexus without nerve trunk hypertrophy over the entire circumference in all 71 patients. The final diagnosis of the proximal margin was normoganglionic in 63 patients and TZ in four patients due to the presence of nerve trunk hypertrophy. The remaining four reports did not describe the presence or absence of hypertrophic nerves or other histopathologic features of TZ. On review by pathologists, two were reported as normoganglionic and two with marked hypertrophy of submucosal nerve plexuses. Therefore, 65 patients had NNR, and six patients had TZNR. None of the six proximal margins diagnosed with TZ showed other neuroanatomical abnormalities described in TZ besides truncal hypertrophy. The concordance between intraoperative and final reports was 91.5%. There were no patients with ANR.

Demographic characteristics

Both groups were predominantly males: 47 (72%) in the NNR group and four (67%) in the TZNR group. The mean age of the 71 patients at the time of primary repair was 11 months. There was no significant difference in mean age between both groups (NNR = 11 months and TZNR = 7 months). Soave-type pull-through was performed in 69 patients, Swenson in one, and Duhamel in one. The median follow-up for the NNR group was 6.80 years (interquartile range [IQR]: 5.82-10.63 years), and for the TZNR group was 5.77 years (IQR: 0.39-10.80 years). All demographic characteristics of both groups are summarized in table 1.

Postoperative outcomes

Overall, of the 71 patients, 42 (59.1%) had HAEC, constipation, or both; 38 had NNR, four had TZNR ($p = 0.818$). Moreover, 29 (40.8%) patients were asymptomatic. All patients with HAEC or constipation, regardless of neorectum type, received medical treatment, and none underwent reoperation.

Of the 65 patients with NNR, nine had constipation, 17 had HAEC, and 12 had both problems at different times. Twenty-seven patients were asymptomatic.

Of six patients with TZNR, one patient had constipation, one had HAEC, and two patients had both problems at different times. Two patients were asymptomatic. There were no statistically significant differences regarding the number of patients with HAEC, constipation, or asymptomatic presentation ($p = 0.853$, $p = 0.960$ and $p = 0.360$, respectively) between both groups. No patient required reoperation (Table 2).

Discussion

HAEC and constipation remain two common postoperative problems in HD. In the present study, more than half of the patients had one or both, but we observed no difference in the frequency of these problems between patients with NNR or TZNR. These results suggest that HAEC and constipation cannot be attributed only to the TZ pull-through. However, it is undeniable that it is in the best interest of the patient to perform a complete resection of the aganglionic bowel and TZ bowel and perform a pull-through with the normoganglionic bowel.

Receiving an intraoperative result of the proximal margin as normoganglionic and, days later, receiving the final report as a TZ creates a dilemma. In this circumstance, the question is: Do we need to perform a reoperation to resect the bowel of the TZ? Based on the present study, the answer would be no. We suggest waiting and seeing the patient's progress. If HAEC or constipation is present, medical treatment should be initiated in the same manner as patients with NNR who present with HAEC or postoperative constipation. Consistent with our findings and suggestions, Shankar et al.[12] reported 10 patients (8.7% of a cohort of 114), and Ghosh et al.[13] reported eight patients (16% of a cohort of 50) with TZ neorectum. Both authors reported successful outcomes with medical management, and no patients underwent reoperation. Furthermore, these authors suggested not to reoperate these patients due to the high incidence of fecal incontinence in reoperations.

It is recommended to resect an additional 5-10 cm from an intraoperatively reported full-thickness biopsy with ganglion cells without nerve trunk hypertrophy to avoid creating a neorectum in the TZ when performing a pull-through procedure in circumstances where the entire circumference of the proximal margin cannot be assessed with an intraoperative study[14].

Another scenario is to evaluate a patient with HAEC or constipation after a pull-through who was operated on in another hospital, and the histopathology of the proximal margin is not known. In this situation, there is a possibility that the patient has an ANR. Ideally, the resected specimen should be requested to examine the proximal margin. If access to this tissue is unavailable, a full-thickness biopsy of the neorectum should be performed. This biopsy should be taken proximal to the anastomotic line, so its identification is essential (Fig. 5). A neorectal biopsy helps diagnose ANR by observing submucosal and myenteric plexuses without ganglion

Table 1. Demographic characteristics of groups with NNR and TZNR

	Type of neorectum		
	NNR (n = 65)	TZNR (n = 6)	p-value
Sex			1.00
Female	18 (28%)	2 (33%)	
Male	47 (72%)	4 (67%)	
Race			N/A
African American	5 (8%)	0 (0%)	
Asian	3 (5%)	1 (17%)	
Alaskan Indian/Alaskan Native	1 (1%)	0 (0%)	
White	40 (62%)	5 (83%)	
More than one race	1 (1%)	0 (0%)	
Unknown	13 (20%)	0 (0%)	
Other	2 (3%)	0 (0%)	
Ethnicity			1.00
Hispanic or Latino	9 (14%)	1 (17%)	
Not Hispanic or Latino	53 (82%)	5 (83%)	
Unknown	3 (4%)	0 (0%)	
Age at surgery (years)	0.96 (2.51)	0.61 (0.47)	0.74

NNR: normoganglionic neorectum; TZNR: transition zone neorectum.

Table 2. Distribution of 71 patients with Hirschsprung's disease by type of neorectum and postoperative evolution

	Type of neorectum			
	Normoganglionic (n = 65)	Transition zone (n = 6)	Number of patients	p-value
Constipation	9 (13%)	1 (16.6%)	10	0.960
HAEC	17 (26%)	1 (16.6%)	18	0.853
HAEC and constipation	12 (18%)	2 (33.3%)	14	0.818
Asymptomatic	27 (41%)	2 (33.3%)	29	0.304

*HAEC: Hirschsprung's associated enterocolitis.

cells, truncal hypertrophy, and negative calretinin. It is very important to mention that if the biopsy is taken below the line of the anastomosis, that is, in the residual rectum, the report of "absence of ganglion cells" will be obtained. However, this result is a false positive.

According to the guidelines of the Hirschsprung Disease Interest Group, when a patient presents with HAEC or constipation after descent, it is necessary to rule out that the patient has ARN or TZNR. Consequently, these patients should undergo a biopsy of the neorectum. This group recommends a new pull-through if the neorectum biopsy shows a TZ because the specimen has ganglion cells, but there is hypertrophy of the nerve trunks. However, this recommendation was invalidated since 2016, when Kapur et al. demonstrated that submucosal nerve plexus hypertrophy in neorectum biopsies with ganglion cells should not be considered evidence for diagnosing TZNR[15,16]. Therefore, after the pull-through, biopsy of the neorectum is useful only to diagnose an aganglionic neorectum.

The goal of performing a new pull-through procedure justified by the diagnosis of TZNR should be to relieve HAEC, constipation, or both. If this decision is made, a critical step is to protect the entire anal canal to prevent fecal incontinence. Several authors have published their experience with reoperations in patients with TZNR diagnosed by neorectum biopsy. Unfortunately, most reports do not include postoperative functional outcomes. The few authors who have reported them mention improvement of HAEC or constipation, but the patients showed fecal incontinence[17-29]. Reoperation increases the likelihood of performing a low anastomosis, (i.e., an anastomosis across the anal canal). Damage to the anal canal is the main cause of fecal incontinence in Hirschsprung's

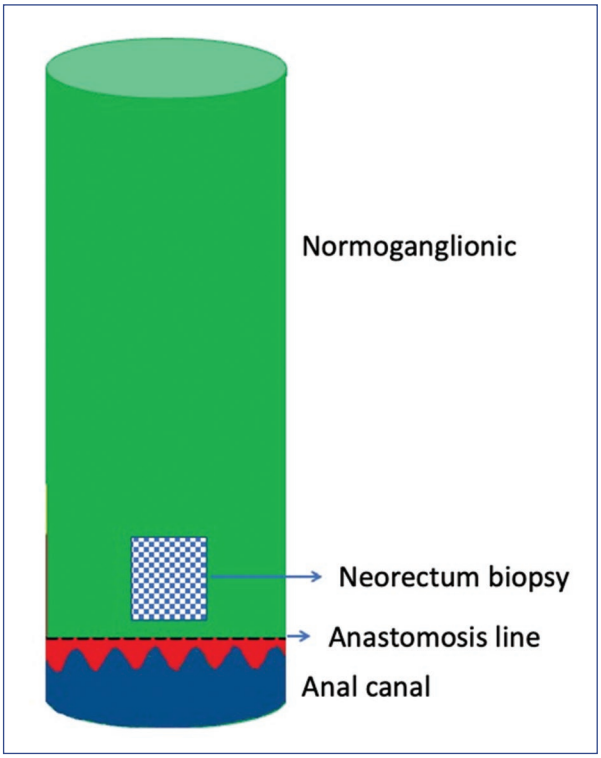

Figure 5. Diagram of a normoganglionic neorectum showing the site where the neorectum biopsy should be taken above the anastomosis line.

patients[30-32]. Furthermore, a redo pull-through does not guarantee the resolution of obstructive symptoms[17-29]. The evidence presented here suggests that medical management should be attempted in patients with HAEC or postoperative constipation before reoperation is proposed[12,13].

The pull-through procedure requires an intraoperative histologic study to confirm that the descent is in a normoganglionic bowel. The pathologist's experience is important to ensure that the intraoperative study is consistent with the final study. It has been reported that the concordance of the intraoperative report with the final report is 89%[8,9]; in this study, it was 91.5%. The literature reports an incidence of neorectum in the TZ of 18%[18]; in this study, it was 8.4%.

A limitation of our study is the difference in the number of patients in each group: there are more NNRs than TZNRs. This outcome is expected and even normal. Regardless of the sample size, there will always be more patients with NNR than TZNR in HD sigmoid rectum. Another limitation is that, despite the prospective or retrospective nature of this type of study, HD is a rare pathology with an incidence of 1:5,000 newborns[14].

In order to create a homogeneous cohort, we only included patients with rectosigmoid HD, as this is by far the most common form that is primarily operated on and in which the proximal margin is examined intraoperatively. We excluded longer or total segments and syndromic HD, which have a higher incidence of HAEC compared to sigmoid rectus and non-syndromic HD[33,34]. Finally, we conclude the following:

- –HAEC and postoperative constipation occur in patients with rectosigmoid HD with normoganglionic neorectum and TZ neorectum
- –Since there is no difference in the frequency of enterocolitis and constipation between patients with TZ pull-through and normoganglionic pull-through, these obstructive symptoms may have another cause
- –Our results cannot be generalized to patients with long-segment HD, total colonic aganglionosis, and syndromic HD. Therefore, further studies should be performed to validate our findings.

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).

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

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RESEARCH ARTICLE

Vulnerability in women primary caregivers of children in palliative care due to intimate partner violence in a pediatric hospital in Mexico

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Abstract

Background: *Women are the primary caregivers of children in palliative care. Research has shown that the presence of intimate partner violence at home exacerbates the vulnerability of the caregiver. Current statistics indicate a high prevalence of violence in Mexico present in the intersectionality between intimate partner violence and the role of the primary caregiver. This study aimed to describe the frequency of intimate partner violence among primary palliative caregivers at the Hospital Infantil de México Federico Gómez.* **Methods:** *We conducted a cross-sectional and prospective study with convenience sampling; no sample calculation was performed. All female primary caregivers of children in the palliative care unit were invited to participate. The Scale of Violence and Index of Severity of Violence was used as the measuring instrument.* **Results:** *One hundred women participated in the study by submitting their survey in a designated mailbox. No sociodemographic data or patient diagnoses were collected. The frequency of intimate partner violence was 28%, of which 16% were considered severe cases. Women reported psychological violence (36%), sexual violence (23%), and physical violence (22%).* **Conclusions:** *Almost one-third of female primary caregivers of pediatric patients at the Hospital Infantil de México Federico Gómez have been victims of some form of violence by current partners. This study highlights a previously unreported problem and opens the door for studies to correlate intimate partner violence among primary caregivers and the quality of life of children in palliative care.*

Keywords: *Intimate partner violence. Palliative care. Pediatric patients. Primary caregivers.*

Vulnerabilidad en mujeres cuidadoras primarias de menores en cuidados paliativos debida a violencia de pareja en un hospital de niños en México

Resumen

Introducción: *Las mujeres son las principales cuidadoras de los niños en cuidados paliativos. Las investigaciones han demostrado que la violencia de pareja en el hogar exacerba la vulnerabilidad del cuidador. Las estadísticas actuales sobre violencia en México indican una alta prevalencia presente en la interseccionalidad entre la violencia de pareja y el rol de cuidador principal. El objetivo de este estudio fue describir la frecuencia de violencia de pareja entre los cuidadores primarios*

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del Hospital Infantil de México Federico Gómez (HIMFG). **Métodos:** *Se llevó a cabo un estudio transversal y prospectivo con muestreo por conveniencia; no se realizó ningún cálculo de muestra. Se invitó a participar a todas las mujeres cuidadoras primarias de niños en la Unidad de Cuidados Paliativos. Se utilizó como instrumento la Escala de Violencia e Índice de Severidad de la Violencia.* **Resultados:** *Cien mujeres participaron en el estudio; no se recogieron sus datos sociodemográficos ni diagnósticos. La frecuencia de violencia de pareja fue del 28%: 16% se consideraron casos graves. Las mujeres reportaron violencia psicológica (36%), violencia sexual (23%) y violencia física (22%).* **Conclusiones:** *Alrededor de la tercera parte de las mujeres cuidadoras principales de pacientes pediátricos del HIMFG han sido víctimas de algún tipo de violencia por parte de sus parejas actuales. Este estudio destaca un problema no informado previamente y abre la puerta a estudios para correlacionar la violencia de pareja íntima entre los cuidadores primarios y la calidad de vida de los niños en cuidados paliativos.*

Palabras clave: *Violencia de pareja. Cuidados paliativos. Pacientes pediátricos. Cuidadores primaries.*

Introduction

Palliative care is defined as a medical approach that improves the quality of life of patients and their families facing the problems associated with life-threatening illnesses. It prevents and relieves suffering through early identification, assessment, and treatment of pain and other physical, psychosocial, and spiritual problems[1]. Pediatric palliative care addresses life-threatening or life-limiting illnesses in children and involves a multidisciplinary team focusing on the patient's entire social environment. Most primary caregivers are women[2]. Society assumes that caring for a sick family member is part of the so-called "domestic work" and, as such, is associated with a particular gender role: "a woman's job"[3]. Caregivers may face challenges in daily caregiving that place them in a situation of multidimensional (emotional, economic, and structural) vulnerability.

The caregiver's experience is related to training, information, emotional and social support, financial assistance, coping strategies, and the availability of relief care and assistance at home[4]. Deficits in these factors lead to caregiver burnout, which is defined as a state of emotional exhaustion, stress, and fatigue that interferes with leisure activities, social relationships, freedom, and emotional balance. Fatigue can cause anxiety and depression, trigger interpersonal changes, and directly or indirectly affect the caregiver's physical and mental health and subjective well-being[4-7]. In addition, burnout interferes with the management of the patient's disease and its clinical course, leading to episodes of physical and psychological abuse of the patient[8].

Violence against women refers to any harmful act against a female due to their gender, whether done in public or privately[6]. Yugueros García identified three types of intimate partner violence: direct, structural, and cultural[9]. Direct violence can be seen through physical, verbal, or psychological abuse. Structural violence is caused by the social environment, while the cultural dimension is based on symbolic violence originating from traditional values.

Among the traditional values are the belief that women should live for others through multiple duties, including caring for people, and that others should be the priority over the women's well-being.

Violence also results in Years of Healthy Life loss for large segments of the population, particularly women[10,11]. In Mexico the prevalence of women who have experienced violence from their current intimate partner is estimated at 33.3% (2006), of those who have experienced violence from their intimate partner at some point in their lives at 42.9%, and of all forms of domestic violence at 60%[12]. Exposure to gender-based violence in the domestic sphere has a negative impact on the sons and daughters of the abused women, exposing them to direct physical and psychological abuse by both parents or indirect abuse through witnessing acts of violence against their mothers[13]. There is also a relationship between family violence and non-adherence to treatment[14].

Research on professionals' knowledge, barriers, and attitudes toward gender-based violence shows that it is a common and serious problem surrounded by myths and beliefs, but difficult to detect[15]. Among the difficulties cited by professionals as impeding their active participation in recognizing this problem are the lack of training on the subject and the lack of time due to excessive workloads[15].

Studies documenting the relationship between palliative care and violence have focused on caregiver abuse toward patients but have not addressed the gender-based violence experienced by caregivers.

Considering that mostly women take the role of primary caregiver or are forced into this role, it is important to examine the areas that affect their health, including violence. Based on current statistics regarding violence in Mexico, we think that there is a connection between

being a primary caregiver and experiencing intimate partner violence. We view intersectionality as a useful tool for examining and comprehending how gender intersects with other aspects of identity and how these intersections can lead to distinct experiences of privilege and oppression[16].

There are no reports in palliative care on the population of female caregivers of pediatric patients who are abused by their intimate partners. Therefore, we considered documenting this issue to fully address the needs of these women and their children and follow-up with further research sensitive to this issue.

Therefore, we conducted this exploratory study to describe the self-reported frequency of intimate partner violence perpetrated against the primary caregivers of patients in the Palliative Care and Quality of Life Unit of the Hospital Infantil de México Federico Gómez.

Methods

We conducted a cross-sectional and prospective study between May and November 2021. As a convenience sample was used, no calculation was performed. All female primary caregivers of children who attended a palliative care appointment at the Hospital Infantil de México Federico Gómez were invited to participate under anonymity. The study's purpose, data confidentiality, and voluntary participation were explained to them, and verbal informed consent was obtained when their partners were not present to protect them from possible aggression.

Participants then received a printed version of the Scale of Violence and Index of Severity of Violence questionnaire, which included 19 questions with four possible answers, to be completed at a convenient time and place. On completion, the surveys were placed in a mailbox in the palliative care unit and then collected and analyzed.

No sociodemographic characteristics, patient names, or diagnoses were collected to maintain confidentiality, given the potential risk that responding to this survey posed to the participants.

Surveys that were not (fully) completed were eliminated.

Instrument

The Scale of Violence and Index of Severity of Intimate Partner Violence was used as the measuring instrument, which has been validated in a Mexican population[17]. This scale measures intimate partner violence with a severity index composed of four factors: psychological violence, sexual violence, physical violence, and severe physical violence (Supplementary data).

For this study, we defined intimate partner violence as any behavior within an intimate relationship that causes or is likely to cause physical, psychological, or sexual harm to its members[18]. The definitions on which the scale used is constructed are the following:

- Psychological violence. Any of the following: insulting, belittling, or humiliating the partner; frightening or intimidating her (for example, by destroying things); threatening to harm her or someone important to her; threatening to abandon her, take her children away, or withhold financial support.
- Sexual violence. Any of the following: forcing the partner to have unwanted sexual relations, forcing her to perform other unwanted "sexual acts," forcing her to have unwanted sex because of fear of what the husband/partner will do if she refuses.
- Physical violence. Any of the following: slapping, shaking, throwing objects at the partner, pushing, twisting her arm, or pulling her hair; hitting her with a fist or an object that could hurt her; kicking, dragging, or striking her; choking or burning her (actually doing so or attempting to do so); threatening or injuring her with a knife, gun, or other type of weapon.

The violence scale consists of 19 validated questions grouped into four factors: psychological violence, physical violence, severe physical violence, and sexual violence. These factors measure the frequency of violent acts in the past 12 months on a Likert scale: never, once, a few times, and many times. Each of the possible answers to the 19 questions has a weight that was previously assigned during the validation of the instrument by expert judgment (Appendix 1). The questions were scored as follows: 0 for "never", 4-9 for "once", 8-18 for "a few times" and 12-27 for "many times".

The final assessment was made using an overall index of the severity of intimate partner violence, considering the different dimensions assessed: psychological, physical, and sexual. This index allows for the inclusion of dimensions of severity, such as the frequency with which acts of violence are perpetrated against women over a year and the severity of such acts.

The severity index was constructed based on the results of the sample studied. We calculated the mean and standard deviation to obtain the value of the Index of Severity of Partner Violence, grouping the cases as follows:

Table 1. Values of categorization for defined cases

Values	Non-case (nc)	Case (c)	Severe case (sc)
Sexual violence	< 5.95	5.95-18.16	> 18.16
Psychological violence	< 15.01	15.01-35.6	> 35.6
Physical violence	< 9.2	9.2-28.37	> 28.37
Index of Severity of Intimate Partner Violence	< 30.16	30.16-78.19	> 78.19

Cutoff points for the categorization: Non-cases (nc): as any score less than the mean of the factor studied in our population; Cases (c): any score greater than or equal to the mean of the factor studied; Severe cases (sc): any value greater than the mean plus one standard deviation of the factor studied.

Table 2. Frequencies by type of violence and by the Likert scale of responses

Type of violence	Never	Once	A few times	Many times
Sexual violence	236 (78.66%)	37 (12.33%)	16 (5.33%)	11 (3.66%)
Psychological violence	315 (63%)	84 (16.8%)	45 (9%)	56 (11.2%)
Physical violence	414 (82.8%)	57 (11.40%)	17 (3.40%)	12 (2.4%)
Severe physical violence	579 (96.5%)	19 (3.16%)	0	2 (0.33%)

Number of responses that were given in the surveys grouped by types of response. The corresponding frequency of responses is provided next to the total.

- Non-cases: values from 0 to below the mean.
- Cases: values from the mean to one standard deviation.
- Severe cases: values greater than one standard deviation above the mean.

Results

One hundred women participated in the study by delivering their survey in the mailbox described in the methodology section. Due to the nature of the study, in which confidentiality was essential to ensure the women's safety and the data quality, sociodemographic characteristics and diagnoses of the children in their care were not collected for correlation.

After scoring the surveys using the weights assigned to each question, we identified three groups: "non-cases," defined as any score less than the mean of the factor under study in our population; "cases," defined as any score greater than or equal to the mean of the factor under study in our population and up to one standard deviation; and "severe cases," defined as any score greater than the mean plus one standard deviation of the factor under study. Cases were defined according to the values shown in table 1.

As we can see in table 2, which describes the frequencies by type of violence using the Likert scale of responses, the most common types of violence were as follows: 36% of the women underwent psychological violence, of which 17% was classified as severe and 19% as non-severe. The frequency of sexual violence was 23%, of which 10% were considered non-severe and 13% severe. The frequency of physical violence was 22%, with a marked difference between severe 17% and non-severe 5% (Table 3).

An estimated 28% of participants reported experiencing intimate partner violence, of which 12% were considered cases and 16% severe cases.

Discussion

In this study, the incidence of intimate partner violence among primary caregivers of children in palliative care was 28%, indicating a prevalent problem among female primary caregivers.

The frequency found in this study was higher than that reported in the general population in Mexico according to a 2020 national survey, which reported an overall prevalence of 25.6% of women who had experienced intimate partner violence[19]. Similarly, the National Survey on Violence against Women (ENVIM 2003), reported a prevalence of 21.5% of current intimate partner violence[20], suggesting that despite the

Table 3. The Index of Severity of Intimate Partner Violence based on the information collected in the surveys and their analysis

Types of violence	Total	Non-severe	Severe
Psychological violence	36.00%	19%	17%
Sexual violence	23%	10%	13%
Physical violence	22%	5%	17%
Index of Intimate Partner Violence	28%	12%	16%

Frequencies obtained following the analysis of data regarding the construction of indices of severity in each factor and the Index of Severity of Intimate Partner Violence constructed from the sum of the factors.

limitations of this study, intimate partner violence is a major problem. The difference of 6.5% between the ENVIM 2003 and our results could be explained by the additional vulnerability experienced by women in the role of caregivers. Our study found a frequency of psychological violence of 36%, compared to a prevalence of 19% reported in the ENVIM 2003, a difference of 17%, which could be explained by the stress generated in families with a child facing a life-threatening diagnosis.

The most significant differences between severe and non-severe violence were observed in physical and sexual violence. The frequency of severe physical violence was higher than non-severe physical violence, at 16% and 12%, respectively; the frequency of sexual violence was similar, with 10% experiencing non-severe violence compared to 13% experiencing severe violence. Such figures should alert us to the danger in which these women find themselves because they live in a stressful and violent environment and experience violence that puts their lives in imminent danger.

Assigning the role of caregiver to women is considered one of the main structural barriers to economic stability for a significant portion of the population. Thus, the fact that economic violence against women was not measured in the instrument used leads us to believe that intimate partner violence has been underestimated since economic violence has a prevalence of up to 4.4% in Mexico[13].

Furthermore, women may have underreported situations of violence due to shame, fear, reprisals, or the phenomenon known as the normalization of violence. This phenomenon is defined as predispositions consistent with subjection to a social context favored by being predominantly male and tolerant of various forms of misogyny[21].

Furthermore, vicarious violence against women is underreported. This type of violence is directed at people, objects, and possessions important to women to harm them vicariously. Unfortunately, the ultimate expression of it is the murder of their daughters and sons. The perpetrator knows that by harming her children, the mother will never recover from this trauma. This extreme level of harm[22] could be an important reason why women do not dare to speak out about or report the violence they experience. In addition, the children they care for are already in such a vulnerable situation that they would not be able to survive without their care if their abusers were to separate them.

Limitations

This study has some limitations. First, its cross-sectional design. In addition, given the inability to measure sociodemographics or support network variables, among others, it was not possible to identify other factors associated with violence. Second, the type of instrument used, which could explain the underestimation of intimate partner violence. The Scale of Violence and the Index of Severity of Intimate Partner Violence lacks items that can provide information on economic violence, which were excluded due to validation problems in the original study.

Despite the limitations, our results provide evidence for the creation of specific interventions in the health sector, as current legislation prioritizes interventions in the legal and criminal fields. Routine monitoring of this issue and, better yet, creating a service to address gender-based violence in hospital units, such as the palliative care unit, would be considered a priority strategy to address this problem. Awareness-raising and training of healthcare personnel for the detection, early intervention, or, if necessary, referral to facilities for timely treatment of this type of violence should also be prioritized[23].

It is known that the greater the number of questions asked about violence and its various manifestations, the higher the prevalence in the female population studied. In this case, we preferred to protect the integrity of women by using a short scale as a preliminary approach to the problem to later create a network of timely care.

Based on our findings, we conclude that three out of ten female primary caregivers of pediatric patients at the Hospital Infantil de México Federico Gómez have been victims of some form of violence by their current

partners. Having a patient in the palliative care program represents an enormous emotional burden for women caregivers. One of the fundamental difficulties in providing adequate help is that society tends to ignore the existence of aggression. Therefore, we emphasize that these results should set a precedent for further research to estimate the prevalence of violence against this population, and also to correlate it with the quality of life of children in palliative care and with the repercussions of their treatment.

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 no patient data appears in this article.

Right to privacy and informed consent. Due to confidentiality and the difficulty of emotional openness, a mailbox strategy was implemented to submit anonymous surveys. For this reason, direct informed consent was not obtained, although verbal consent was obtained. In addition, women signed an informed consent form when they entered the palliative care service as part of research projects.

Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary data

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RESEARCH ARTICLE

Prevalence of alcohol, tobacco, and illicit drugs consumption during teenage pregnancy: an observational, prospective, and cross-sectional study

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Abstract

Background: *Teenage pregnancy is a significant public health issue in Mexico; its prevalence oscillates around 20% of all pregnancies. Concurrently, alcohol, tobacco, and illicit drug use have become more common in this age group.* **Methods:** *To estimate the prevalence of substance exposure in a population of pregnant teenagers, we conducted a prospective, observational, and cross-sectional study. The protocol was approved by the institutional review board. On informed consent, we asked 420 consecutive pregnant youngsters cared for at the outpatient obstetric service of a tertiary public regional women's and children's hospital in Nuevo León, in northeast Mexico, to answer a previously validated questionnaire to estimate the prevalence of alcohol, tobacco, or illicit drugs use during pregnancy.* **Results:** *Of the 420 participants, 317 (75.5%) consumed at least one substance during pregnancy. Alcohol, either alone or in combination, was consumed by 300 (71.7%) participants. Tobacco was used by 117 (27.8%) participants, almost always in combination with other substances, while marijuana and other illicit drugs were consumed by 92 (21.9%) participants. Approximately one-fourth of the participants, 102 (24.1%) reported no substance use during pregnancy.* **Conclusions:** *In this series, the reported prevalence of alcohol, tobacco, and illicit drugs consumption during pregnancy, explored with a validated instrument, is higher than that previously reported in our country. This fact offers a worrying picture of another set of factors adding to the burden of teenage pregnancy.*

Keywords: *Pregnancy in adolescence. Alcohol drinking. Tobacco. Illicit drugs.*

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Prevalencia del consumo de alcohol, tabaco y drogas ilícitas durante el embarazo en adolescentes: un estudio observacional, prospectivo y transversal

Resumen

Introducción: *El embarazo en la adolescencia ha adquirido gran importancia en la salud pública en México; su prevalencia oscila alrededor del 20% de los embarazos. Paralelamente, el consumo de alcohol, tabaco y drogas ilícitas en este periodo es cada vez más común en estas jóvenes.* **Métodos***: Para estimar la prevalencia de exposición a estas substancias en adolescentes embarazadas, se llevó a cabo un estudio prospectivo, observacional y transversal. El protocolo fue aprobado por los Comités de Ética e Investigación. Previo consentimiento informado, se solicito a 420 jóvenes embarazadas atendidas en la clínica prenatal del hospital materno-infantil más grande en Nuevo León, que respondieran un cuestionario previamente validado para estimar la prevalencia del consumo de substancias.* **Resultados:** *De 420 participantes, 317 (75.5%) consumieron al menos una de estas sustancias durante el embarazo. El alcohol, solo o en combinación, fue consumido por 300 (71.5%). El tabaco fue usado por 117 (27.8%), casi siempre en combinación con otras sustancias, mientras que la mariguana y otras drogas ilícitas fueron consumidas por 92 (21.9%) participantes. Alrededor de una cuarta parte del grupo estudiado (24.1%) reportó no haber consumido ninguna de estas substancias en su embarazo.* **Conclusiones:** *En nuestra serie, la prevalencia de consumo de alcohol, tabaco y drogas ilícitas durante el embarazo, explorada con un instrumento validado, es mayor de la reportada en estimaciones previas en nuestro país. Estos datos ofrecen un panorama preocupante de una serie de factores que se agregan a la carga del embarazo en la adolescencia.*

Palabras clave: *Embarazo en la adolescencia. Consumo de alcohol. Tabaco. Drogas Ilícitas.*

Introduction

Teenage pregnancy (also referred to as adolescent pregnancy) is one of Mexico's current significant public health issues; nationwide, its prevalence has been estimated around 18.8% in 2010, 19.4% in 2013, and 15.3% in 2021[1,2]. In a retrospective analysis, from 1992 to 2016, other authors found that, although the birth rate for teenage pregnancies for this period was 17.6%, this percentage was exceeded in at least three of the 32 states in Mexico, reaching 19.93%[3]. The official adolescent pregnancy rate in our state, Nuevo León, in the Northeast of Mexico, was 16.9% in 2010, 15.2% in 2018, and 12.7% in 2021[1]. However, it may be even higher in the lower socio-economical strata and has been a government concern since 2002.

Poverty, discrimination, violence against women, inadequate schooling, difficulty in accessing health services, and poor knowledge about reproductive planning methods have increased the number of unplanned pregnancies during adolescence[2,4]. In 2015, these factors gave origin to a government strategy , known as ENAPEA (for its Spanish acronym), aimed at diminishing births from teenagers between 10 and 14 years of age and halving by 50% the fecundity rate of those teenagers between 15 and 19 years of age by the year 2030, which is still ongoing[5].

Another problem affecting Mexican teenagers is the increase in alcohol, tobacco, and illicit drug use during pregnancy, which, unfortunately, has scarcely been addressed in scientific studies. In 1988, the Mexican General Directorate of Epidemiology and the Mexican Institute of Psychiatry carried out the first National Survey on Addictions. Through a multistage probabilistic sample from 5234 women from the urban population (ages 12-65 years), who reported having ever been pregnant, alcohol consumption during pregnancy was estimated by self-reporting: they found a percentage of consumption between 9.7% and 17.2%, the last figure associated with low-birth weight in the offspring[6]. However, age-related differences were not explored. A retrospective study in a big metropolitan area, which included 78,871 births from 1991 to 1998, revealed a self-reported prevalence of alcohol consumption during pregnancy of 2.42%, with an apparent increase from 1.97% in 1991 to 2.8% in 1998[7]. Another retrospective, descriptive, and observational study in 2016, which included 608 teenage pregnancies cared for during an 18-month period, reported that 60.2% had consumed alcohol, 53.6% had consumed tobacco, and 1.8% had consumed illicit drugs during pregnancy[8]. Due to insufficient information on the current prevalence of use of alcohol, tobacco, and illicit substances in the pregnant adolescent population in Mexico, we conceived an observational, prospective, cross-sectional study aimed at determining the self-reported prevalence and

calculating relative risks for these exposures in a public third-level hospital in Northeast Mexico. We focused on estimating the prevalence of alcohol use by pregnant adolescents seen at the study hospital and exploring potentially predictive variables for substance use during pregnancy in this population. As a secondary objective, we aimed to establish the prevalence of tobacco and illicit drugs in the same population.

Methods

The study cohort included 420 pregnant adolescents. Inclusion criteria were maternal age between 12 and 18 years, signing the informed consent or assent document, not being currently under legal prosecution, and not having any cognitive or psychiatric limitation that would limit their free will to participate. The study protocol was reviewed and approved by Institutional Review Boards at Escuela de Medicina y Ciencias de la Salud del Instituto Tecnológico y de Estudios Superiores de Monterrey, registered at CONBIOETICA-19-CEI-011-20161017, as well as at the study site. Recruitment was done while the eligible participants were attending the Perinatal High-Risk Clinic for prenatal evaluation (all teenage pregnancies are referred to this clinic by local health policy), and the participants were followed through delivery care until discharge at Hospital Regional Materno-Infantil of the State of Nuevo León in Mexico, from March to August 2018. Upon acceptance, we applied a questionnaire created by the WHO Research and Reporting Project on the Epidemiology of Drug Dependence, further validated by the Comisión Nacional Contra Adicciones, Centro Nacional para la Prevención y Control de las Adicciones and Instituto Nacional de Psiquiatría Ramón de la Fuente Muñiz, to all the participants[9,10]. This instrument has been used in previous surveys in the Mexican adolescent population and was adopted for assessing the use of illicit substances, alcohol, and tobacco consumption. We also collected sociodemographic and anthropometric data, as well as APGAR and Capurro neonatal assessment, and data on the intra-hospital destination of the neonate once he/she was born.

Statistical analysis

We used IBM® SPSS® Statistics v26 for the statistical analysis. The information was initially tabulated in Excel and further imported into SPSS. Continuous variables with normal distribution were expressed as means and standard deviations and analyzed with the *t*-test. Continuous variables with non-normal distribution were expressed as medians and interquartile ranges (IQR) and analyzed with the Mann–Whitney's U test. Categorical variables were expressed as frequencies and proportions and analyzed with the χ^2 test. We explored Kendall's tau b correlations among a set of independent variables and the dependent outcome variables and for those with a statistically significant association (Supplementary Table 1). Those independent variables with a statistically significant association to any of the main study outcomes and an Event Positive Value >10 in the outcome group with the lowest frequency were included in a binary logistic regression model analysis to obtain the most stable model, as previously published recommendations[11,12].

The outcome variables selected for the logistic regression analysis were "*Substance consumption during pregnancy*," coded as "Yes" or "No"; "*Exclusive alcohol consumption during pregnancy*," coded as "Yes" or "No", and "*Consumption of other substances (except alcohol) during pregnancy*," coded as "Yes" or "No." The logistic regression approach was based on the conditional backward method. We considered statistical significance when the p-values of the applied tests were < 0.05, and, for the odds ratios or Exp[β], as long as the corresponding 95% confidence interval (CI) did not contain or cross 1.

A sample of 420 subjects would give our study a power of 90%, with an alpha error of 0.05, to detect a 5% difference with the published prevalence of alcohol use in adolescents in Mexico[9]. The decision not to attempt an estimation of sample size regarding the prevalence of tobacco and illicit drug use was made since no reliable data were available for these outcomes involving the study population.

The flowchart of the study population is outlined in figure 1. We report results for the group of 420 subjects recruited. Table 1 reports the sociodemographic data of the study participants.

Most of the interviewees, 376 (89.5%), reported being dedicated to housekeeping activities; 29 (6.9%) declared being students; 11 (2.7%) were working, and four (1%) reported being unemployed, not working, and not in school. Regarding schooling of 136 participants, almost one-third (32.4%) had completed only grade school; most of our study population, 249 (59.3%) had graduated from high school; 20 (4.8%) had already finished their baccalaureate, 3 (0.7%) had a technical degree, and only 12 (2.9%) reported having dropped-out before finishing primary school. During the year before giving birth, 305 (72.6%) were not attending school, while 115 (27.4%) were still attending school

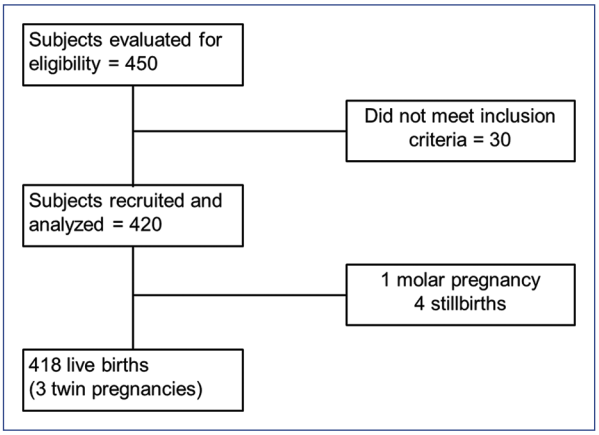

Figure 1. Study flow diagram for prevalence of alcohol, tobacco, and drugs consumption during teenage pregnancy.

Table 1. Sociodemographic characteristics of the study population of pregnant teenagers

Characteristics (n = 420)	Median	IQR
Age (years)*	17	16-18
Sexually active since (years)*	15	14-16
Number of sexual partners*	1	1-2
Age of current partner (years)*	19	18-21
Main occupation		
Housewife†	376	89.4
Student†	29	6.9
Employee†	7	1.7
Independent†	4	1.0
None†	4	1.0
Marital Status		
Unwed†	320	76.2
Single†	95	22.6
Married†	4	1.0
Separated†	1	0.2
Perinatal history		
Molar pregnancy†	1	0.25
Stillbirth†	4	0.95
Born alive, preterm†	48	11.4
Born alive, term†	370	87.4

*Values expressed as median and interquartile range.
†Values expressed as frequencies and percentages.

despite being pregnant. A third of the study subjects (142, 33.8%) reported having paid work during the year before giving birth, while the majority (278, 66.2%) did not have paid work during the referred period.

Sexually transmitted infections (STI) occurred in 17 participants during pregnancy, for an overall prevalence of 4%. The most frequently reported STI was human papillomavirus (9 cases, 2.1%), followed by cervicitis and vaginitis (5 cases, 1.2%), and syphilis, HIV infection, and trichomoniasis (one report each, 0.2% each). We did not find any association between the occurrence of STI and the reported number of sexual partners.

Slightly over one-third of the study population (152, 36%) reported living with their partner as a couple, although most of them remained unwed; 126 (30%) were living with a consanguineous relative, while 71 (16.9%) were living with both a consanguineous relative and their partner, and 69 (16.4%) were living with their partner and his family. Only 3 (0.7%) had been relocated to a state-managed refuge.

Table 2 provides a comparative description of the sociodemographic characteristics of participants who self-declared as non-consumers and those who declared themselves as consumers of any substance during pregnancy. The only sociodemographic characteristic that exhibited a statistically significant difference between non-consumers and consumers was the median and range of the number of sexual partners.

Substance use during pregnancy

Overall, 317 (75.5 %) of the 420 participants reported having consumed at least one substance during their pregnancy. As shown in figure 2, 103 (24.5%) participants were not exposed to addictive substances during pregnancy, and of the 317 that self-reported as consumers, 120 (28.6%) participants reported having never consumed alcohol (data not shown). Alcohol, either alone or in combination with other substances, was the most frequently consumed substance (more than two-thirds of the population). Thus, 300 out of 420 participants (71.4%) reported consumption of alcohol during pregnancy, alone or in any combination. According to published definitions applicable to the study population, they may be classified as heavy drinkers[13]. Of those 300 participants who consumed alcohol during pregnancy, 59 (19.7% of the whole study population) participants may be qualified as binge drinkers. Eight subjects (0.03% of all participants) met the above-mentioned published criteria to be considered heavy drinkers.

Exclusive alcohol consumption was the third most prevalent outcome (158, 37.6% of the participants), followed by combinations of alcohol with tobacco, alcohol, marijuana, and other drugs (Fig. 2 and Table 3).

The median age at first alcohol ingestion was 15 years (range 10-18 years); the median age at onset

Table 2. Comparative of sociodemographic characteristics of the participant pregnant teenagersaccording to substance consumption (n = 420)

Variables	Non consumers, n = 103 (24.5%)		Consumers, n = 317 (75.5%)	
Age (years)*	17	16-18	17	16-18
Sexually active since (years)*	15	14-16	15	14-16
Number of sexual partners*	1	1-1	1	1-2‡
Age of current partner (years)*	19	17-21	19	18-22
Main occupation				
Housewife†	95	92	281	88.6
Student†	6	6	23	7.3
Employee†	-	-	7	2.2
Independent†	2	2	2	0.6
None†	-	-	4	1.3
Marital Status				
Unwed†	78	76	242	76.3
Single†	24	23	71	22.4
Married†	1	1	3	0.9
Separated†	-		1	0.3
Perinatal history				
(418 born alive)	105	100	313	100
Molar pregnancy†	-	-	1	0.35
Stillbirth†	1	1	3	0.95
Born alive, preterm†	16	15.2	35	11.2
Born alive, term†	88	83.8	274	87.5

*Values expressed as median and interquartile range.
†Values expressed as frequencies and percentages.
‡Groups were statistically different, as per Mann-Whitney's U test = 11493.00, Z = –5.124, p = 0.0000003; and Kolmogorov-Smirnov Z test Z = 2.319, p = 0.00004.

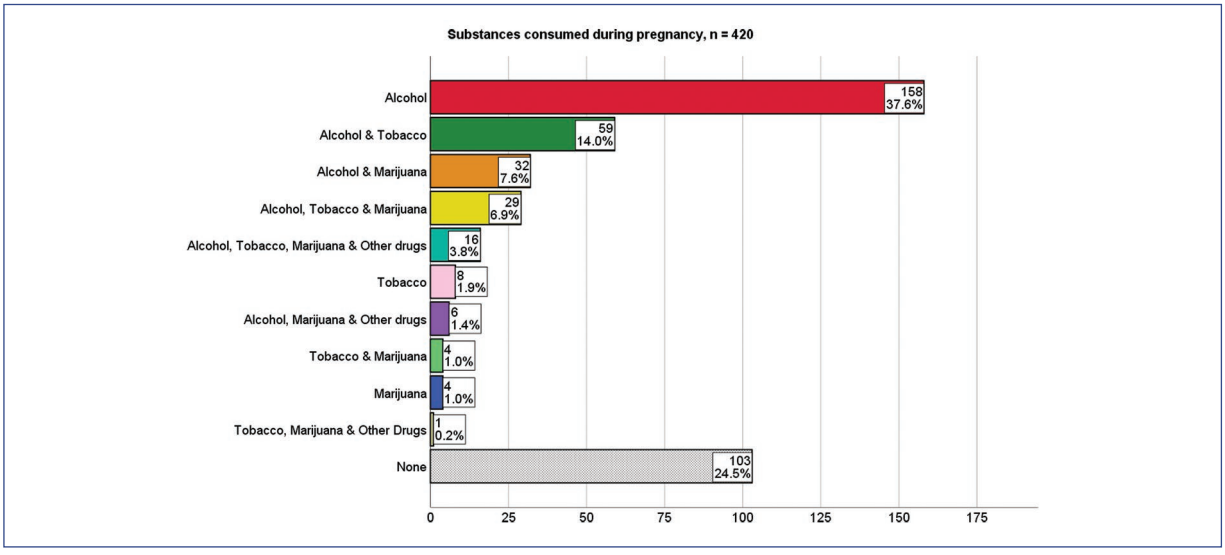

Figure 2. Frequencies and percentages of the different substances consumed during pregnancy in 420 consecutively enrolled pregnant teenagers.

of sexual activity was 15 years (range 11-18 years). No differences were found between these variables concerning alcohol consumption.

The exclusive use of tobacco was reported by eight (1.9%) participants, while 117 (27.8%) of the total cohort admitted using tobacco during pregnancy, alone or in

Table 3. Bivariate analysis, Pearson's χ^2 with asymptotic two-sided significance, and odds ratio (95% CI) estimation, for independent variables potentially predictive for the specified outcomes, from a study of 420 pregnant adolescents (100%)

Outcome	Independent variables	$\chi 2$	p-value	Odds ratio	95% CI
Consumers of any substance during pregnancy, n = 317 (75.5%)	Having ever had two or more sexual partners	22.360	< 0.001	3.420	2.02-5.80
	Substance use by partner	9.549	0.002	2.15	1.31-3.51
	Living with someone who smokes	10.776	0.001	2.194	1.36-3.53
Exclusive alcohol consumption during pregnancy, n = 158 (37.6%)	Onset of sexual intercourse at 15 years and over	6.728	0.006	1.800	1.15-2.81
	Exclusive alcohol consumption by partner	7.840	0.005	2.271	1.27-4.06
Consumption of other substances (except alcohol) during pregnancy, n = 159 (37.9%)	Onset of sexual intercourse at or before 14 years of age	11.800	< 0.001	2.085	1.36-3.18
	Having ever had two or more sexual partners	22.306	< 0.001	2.638	1.76-3.96
	Substance use by partner	22.299	< 0.001	3.547	2.05-6.12
	Living with someone who smokes	16.367	< 0.001	2.279	1.52-3.40

CI: confidence interval.

diverse combinations with alcohol and drugs. Details on tobacco use alone and tobacco use associated with other substances can be seen in figure 2. The median (IQR) age at first cigarette for the entire cohort who admitted to having ever smoked (n = 255, 60.7%) was 15 (13-15) years) and the median age (IQR) at first cigarette was lower, 14 (13-15) years, in those who continued smoking during pregnancy, (n = 117, 27.8%). However, this difference was not statistically significant.

Exclusive use of marijuana during pregnancy was reported by four subjects (1%), and there were no cases of exclusive use of other drugs not associated with concurrent marijuana use. Marijuana use in combination with another illicit drug was reported by 92 of the 420 participants (21.9%). The different frequencies of marijuana and other illicit drugs during pregnancy are detailed in figure 2. The median age (IQR) of first marijuana use for the entire subcohort who reported this practice was 15 (14-15) years; all marijuana users continued to use marijuana during pregnancy. The most common substance associated with marijuana use was alcohol, followed closely by concurrent use of alcohol, tobacco, and marijuana, and alcohol, tobacco, marijuana, and other drugs. The absolute and relative frequencies of each type of use are detailed in figure 2.

Participants who referred using substances other than alcohol during pregnancy were the second most common group, with 159 (37.9%); this is one of the main outcomes reported in Table 3.

Bivariate analysis and construction of regression models

To investigate the relationship between the main study outcome and independent variables, we conducted a bivariate analysis using χ^2, Kendall's tau-b correlation coefficients, and odds ratio estimation with 95% CIs. The results of this analysis are provided in supplementary tables 1 and 2. We performed a binary logistic regression analysis for the three outcomes presented in Table 3 to explore the relationship between the variables further. For the regression analysis, these outcomes were expressed as dichotomous variables. Supplementary table 2 contains the details of the binary logistic regression process.

Briefly, for the outcome "*Substance consumption during pregnancy*", which was positive in 317 (75.5 %) of the study participants, the intercept model (with no added predictors) correctly identified the outcome in 76.3% of the instances, a minor increase from the previous percentage due to missing data. Among the three potentially predictive variables identified, two remained significant in the model, "*Having ever had two or more sexual partners,*" Exp(β) = 3.173, 95 % C.I. 1.837- 5.482, p < 0.0001, whenever present would increase by 3.2 times the odds of substance consumption in pregnancy; "*Living with someone who smokes,*" Exp(β) = 1.872, 95% C.I. 1.131-3.099, p = 0.015, if present, would

increase by 1.9 times the odds of the outcome. Another potentially predictive variable, "*Substance use by partner"*, lost statistical significance in the model, and its 95 % CI for Exp(β) included 1. Thus, it does not contribute to identify the outcome. However, both significant variables in the model have a negligible contribution to further identifying the outcome, so this model is useless in the clinical setting. Perhaps these variables were affected by a collinearity issue.

For the outcome *"Exclusive alcohol consumption during pregnancy"*, the intercept model correctly identified the outcome in 50% of instances. Among the two potentially predictive variables identified, both remained significant in the model: "*Onset of sexual life at or above 15 years*", Exp(β) = 2.240, 95% CI 1.364-3.678, p = 0.001, whenever present would increase by 2.24 times the odds of the outcome; "*Substance use by partner*", Exp(β) = 2.861, 95% CI 1.588 to 5.156, p < 0.0001, when present, would increase by 2.9 times the odds of exclusive alcohol consumption during pregnancy. This model also had an acceptable goodness of fit, in accordance with the Hosmer and Lemeshow test. The proposed model would explain at least 10% of the variation in the outcome variable, and it would increase the correct identification of the outcome by 8.9% among pregnant teenagers.

For the outcome "*Consumption of other substances (except alcohol) during pregnancy,*" the intercept model correctly identified the outcome in 50.2% of instances. Among the four potentially predictive variables identified, all remained significant in the model, "*Onset of sexual life at or before 14 years*", Exp(β) = 1.953, 95% CI 1.172-3.255, p = 0.010, whenever present would increase almost twice the odds of the outcome; "*Having ever had two or more sexual partners*", Exp(β) = 1.710, 95% CI 1.066-2.744, p = 0.026, when present, would increase by 1.7 times the odds of the outcome; "*Substance use by partner,*" Exp(β) = 2.692, 95% CI 1.466-4.945, p = 0.001, whenever present would increase by almost 2.7 times the odds of the outcome; and "*Living with someone who smokes,*" Exp(β) = 1.620, 95% CI 1.010-2.600, p = 0.046, if present, would increase by 1.6 times the odds of the outcome. This model also had an acceptable goodness of fit, in accordance with the Hosmer and Lemeshow test. The proposed model would explain at least 13.8% of the variation in the outcome variable, and it would increase the correct identification of the outcome by 12%, so it may be useful to identify the consumption of substances other than alcohol during pregnancy in a population akin to ours.

The partners' use of alcohol, tobacco, or illicit drugs was documented in 313 cases (74%), while in 103 cases, the partner did not consume any substance (24.3%), and in six cases (1.4%), these data were unknown for various reasons (non-cohabitation, partner not involved). The substances consumed by the partner are detailed in table 4. The most frequently consumed substances among partners was the combination of tobacco and alcohol, followed by exclusive alcohol and, to a lesser extent, tobacco consumption. A statistically significant coefficient of agreement was observed regarding consumption of toxic substances by the study individuals and their partners (kappa = 0.152, p = 0.002).

All identified cases of substance exposure during pregnancy were followed by brief intervention and referral to treatment, as recommended[14].

Discussion

The main objective of this study was to estimate the prevalence of alcohol consumption during teenage pregnancy in our region. Our findings allowed to identify this behavior as a significant problem since it was reported by 300 out of 420 participants (71.4%). This percentage is higher than we would have expected based on previous estimates. Previous studies have been conducted in the vicinity of our geographic location. In 2008, Galván González et al. conducted a comparative prevalence estimate by directly interviewing 873 participants under the age of 19 who lived in one of two communities on the US-Mexico border. They reported that 15.3% of pregnant adolescents in the Mexican community referred using alcohol, compared with 38.4% of participants in the US county[15]. Chang et al. surveyed a group of 30 young pregnant women and found that nearly one-third of them self-reported using alcohol during pregnancy[16].

Other groups have reported the prevalence of alcohol use during adolescence as a group, and excluding pregnancy status, their prevalence figures are also lower than those found in our study[17].

The prevalence found in the present study also exceeds that reported for pregnant young adults in other countries in our continent[18,19]. It also exceeds the rate of alcohol consumption reported in the general adolescent population in our country[8,20-23] and other American countries[24].

However, a detailed comparison between the studies mentioned above and our results is not possible due to the heterogeneity in the measurement tools used in the studies.

Table 4. Distribution of the substances consumed by the partners of the pregnant teenagers, (n = 420)

Substance consumed	Frequency	%
None*	103	24.5
Tobacco and alcohol*	147	35.0
Alcohol*	83	19.8
Tobacco*	27	6.4
Marijuana*	12	2.9
Tobacco and marijuana*	5	1.2
Tobacco, alcohol, marijuana, and drugs*	5	1.2
Alcohol and marijuana*	4	1.0
Marijuana and drugs*	3	0.7
Tobacco, alcohol, and drugs*	2	0.5
Alcohol, marijuana, and drugs*	1	0.2
Alcohol and drugs*	1	0.2
Unknown*	6	1.4
Total	420	100

*Values expressed as frequencies and percentages.

According to the CDC definition, any amount of alcohol consumption during pregnancy can be considered as excessive drinking[13]; the same source defines binge drinking for women as consuming four or more drinks in a short period (2 h), while heavy drinking is defined as consuming eight or more drinks per week. Using these measures, our binge drinking rate was 59 out of 300 (19.6%), while 8 of these 300 (0.03%) were classified as heavy drinkers. These figures are similar to those reported for adolescents as a group in both Mexico[22,23] and the United States[24,25].

It should be noted that comprehensive comparisons of alcohol consumption, binge drinking or heavy drinking rates, tobacco use, or drug use rates between our study and previous reports were beyond the scope of our study.

In our study, risk determinants were assessed for substance use during pregnancy, exclusive alcohol intake during pregnancy, and use of other substances except alcohol during pregnancy. The identified risk factors are detailed in table 3. We did not attempt to screen for risk factors for tobacco or other substances, as these were not our primary objectives, and our study design was not adequately powered for these purposes.

The risk factors that remained significantly associated with the outcome "*Substance consumption during pregnancy*" in the logistic regression analysis (see Supplementary Tables 1 and 2) may all be related to lack of information about sexuality, promiscuity, poor family support, family tolerance, and peer pressure[26,27], the last of which has been previously reported as a risk factor for tobacco use[28] but not for alcohol use. This difference may be due to study methodology rather than other reasons.

About "*Exclusive alcohol consumption during pregnancy,*" again, lack of information on sexuality, promiscuity, poor family support, and peer pressure may be involved[26,27] as well as family tolerance[28].

For the outcome "*Consumption of other substances (except alcohol) during pregnancy*", promiscuity, lack of information on sexuality, peer pressure, and family tolerance appeared as consistent risk factors, as previously reported in other countries[26,27] and in Mexico[29].

Regarding tobacco use during pregnancy, our study found a rate of 27.86%, which contrasts with previously reported prevalence rates in Mexico. In an unpaired cases and controls study done in a public hospital in Guadalajara, Jalisco, Mexico, between 2005 and 2006, Ramos Gutiérrez et al. reported a 15.7 % rate of tobacco use among 203 pregnant teenagers[30]. More recently, in 2016, Blanquet-García et al. reported an almost double prevalence rate for tobacco use in 608 teenage pregnancies, (53.6%)[8], while Vazquez-Nava et al., in our same geographical region, reported a prevalence of 21.2% for tobacco use during pregnancy, in 785 cases, similar to our findings[31]. Factors associated with tobacco use during pregnancy in our study seem to be related to peer pressure and a non-intact family structure[26,27,31].

A somewhat more complicated scenario was found concerning illicit drug use during pregnancy. Isolated marijuana use was reported by only four participants (1%), exactly half the frequency of exclusive tobacco use. This low frequency precludes any solid estimation of associated factors.

We should acknowledge that this study had some limitations. First, it was an observational, descriptive, and transversal study and relied mainly on the self-report of pregnant adolescents. Self-report approaches have been criticized, mainly because the epidemiological biases of information, selection, and confusion of participants complicate the documentation of prenatal exposure to illicit substances, tobacco, and alcohol. Moreover, the measurement of the substances or their metabolites in different types of specimens such as

urine, meconium, maternal or neonatal hair, cord blood, breast milk, amniotic fluid, or umbilical cord tissue is rarely available and often unreliable due to the characteristics of the specimens or the inaccuracy of the detection techniques[32,33]. If we had chosen this study model, we would have needed to collect biological samples, thus complicating our work due to regulatory issues. Simultaneously, we emphasize that the survey instrument, equipped with a set of universal screening questions, has been adequately validated in our country. Furthermore, the researcher's approach to these young women allowed for adherence to ethical consideration and observance of the principles of beneficence, non-maleficence, justice, and respect for autonomy, in the search for information, followed by a referral to brief intervention, if necessary[34]. This approach prevented any implicit criminalization of behavior and privileged the possibility of helping those involved. Another limitation was the inability of our study design to discern the burden that sociodemographic issues might have on the observed outcomes.

Based on our findings, self-reported use of alcohol, tobacco, and illicit drugs appears to be increasing in the study population compared with previous data. These findings support the need to establish a mandatory survey to address these exposures and to develop specific strategies aimed at reducing these behaviors. We agree that alcoholism during pregnancy is an underestimated problem in our country[35]. There is a clear need for more in-depth and analytical studies on this issue, and ideally, establishing a specific health registry strategy would facilitate further and more in-depth research on this issue.

In conclusion, our findings on the prevalence of alcohol, tobacco, and illicit drug use during adolescent pregnancy, assessed with a validated instrument, provide a worrying picture of yet another set of factors adding to the burden of teenage pregnancy. Addressing this issue by the perinatal team should be a clinical care priority.

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.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript nor for the creation of images, graphics, tables, or their corresponding captions.

Conflicts of interest

The authors declare no conflicts of interest.

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Supplementary data

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RESEARCH ARTICLE

High-flow nasal cannula and non-invasive mechanical ventilation in pediatric asthma exacerbation: two-year prospective observational study in intensive care

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Abstract

Background: *Asthma is a common cause of admission to the pediatric intensive care unit (PICU). We described and analyzed the therapies applied to children admitted to a tertiary PICU because of asthma. Later, we evaluated high-flow nasal cannula (HFNC) use in these patients and compared their evolution and complications with those who received non-invasive ventilation.* **Methods:** *We conducted a prospective observational study (October 2017-October 2019). Collected data: epidemiological, clinical, respiratory support therapy needed, complementary tests, and PICU and hospital stay. Patients were divided into three groups: (1) only HFNC; (2) HFNC and non-invasive mechanical ventilation (NIMV); and (3) only NIMV.* **Results:** *Seventy-six patients were included (39 female). The median age was 2 years and 1 month. The median pulmonary score was 5. The median PICU stay was 3 days, and the hospital stay was 6 days. Children with HNFC only (56/76) had fewer PICU days (p = 0.025) and did not require NIMV (6/76). Children with HFNC had a higher oxygen saturation/fraction of inspired oxygen ratio ratio (p = 0.025) and lower PCO_2 (p = 0.032). In the group receiving both therapies (14/76), NIMV was used first in all cases. No epidemiologic or clinical differences were found among groups.* **Conclusion:** *HFNC was a safe approach that did not increase the number of PICU or hospital days. On admission, normal initial blood gases and the absence of high oxygen requirements were useful in selecting responders to HFNC. Further randomized and multicenter clinical trials are needed to verify these data.*

Keywords: *Asthma. Pediatric critical care. Children. High-flow nasal cannula. Non-invasive ventilation.*

Cánula nasal de alto flujo y ventilación no invasiva en asma pediátrico grave: estudio observacional prospectivo de dos años de duración en cuidados intensivos

Resumen

Introducción: *El asma es una causa frecuente de ingreso en la unidad de cuidados intensivos pediátricos (UCIP). En este, cuadro el uso de cánula nasal de alto flujo (CNAF) se ha visto extendido. En este trabajo se describe el tratamiento global en la UCIP ante el ingreso por asma en un hospital monográfico pediátrico y se evalúa la respuesta al uso de la CNAF, comparando la evolución de los pacientes con aquellos que recibieron ventilación no invasiva (VNI).* **Métodos:** *Se llevó a cabo un estudio observacional prospectivo (de octubre del 2017 a octubre del 2019). Se describieron epidemiología, clínica, tratamiento y soporte respiratorio. Para la comparación se crearon tres grupos de pacientes: 1) solo CNAF; 2) CNAF y VNI; y 3) solo VNI.*

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Resultados: *Se incluyeron 76 pacientes. La mediana de edad fue de dos años y un mes; la mediana de índice pulmonar fue 5. La mediana de ingreso en UCIP fue de tres días y de ingreso hospitalario, seis días. Los niños con solo CNAF (56/76) mostraron menos días de UCIP (p = 0.025) y no requirieron VNI (6/76). También mostraron mayor $SatO_2/FiO_2$ (saturación de oxígeno/fracción de oxígeno inspirado) (p = 0.025) y menor nivel de PCO_2 (presión parcial de CO_2) (p = 0.032). La VNI se utilizó primero siempre en el grupo que recibió ambas modalidades (14/76). No se encontraron diferencias epidemiológicas o clínicas entre grupos.* **Conclusiones:** *En nuestra serie, el uso de CNAF no aumentó los días de ingreso en la UCIP ni de hospital. Tampoco requirió cambio a VNI. Al ingreso, una gasometría normal y bajo requerimiento de oxígeno permitieron seleccionar a los pacientes respondedores. Se necesitan más ensayos multicéntricos clínicos aleatorizados para verificar estos datos.*

Palabras clave: *Asma. Cuidados críticos pediátricos. Niños. Cánula nasal de alto flujo. Ventilación no invasiva.*

Introduction

Asthma is a common cause of admission to the pediatric intensive care unit (PICU). In addition to pharmacological therapies, respiratory support by non-invasive mechanical ventilation (NIMV) has been the classical approach to help these patients. In recent years, this approach has been complemented and replaced by a high-flow nasal cannula (HFNC)[1]. Both respiratory supports are used to avoid mechanical ventilation (MV), which is helpful but associated with complications[2].

The use of HFNC in children has increased. Certainly, its simplicity and comfort have influenced its implementation[3,4]. Thus, its use has been described in neonatal units[5,6], emergency rooms[7-9], hospital wards[5,10,11], transport[12], or intensive care units[13-15]. Additionally, HFNC has been defined as safe for managing bronchiolitis[16,17] or asthma[1,14,15,18].

However, using HFNC in these different clinical settings is not always supported by consistent clinical evidence[8,19]. In addition, there is concern that HFNC may delay the initiation of other ventilatory strategies with proven efficacy[7]. In asthma, for example, there are doubts about how HFNC might delay NIMV[10,13]. This potential risk should be addressed in children with severe asthma[20].

Therefore, in this short prospective observational monocentric study, we described and analyzed the therapies applied to children admitted to a tertiary PICU due to asthma. Later, we evaluated the use of HFNC in these patients and compared their evolution and complications with those who received non-invasive ventilation.

Methods

Design

We conducted an observational, prospective, longitudinal study in a tertiary PICU (from October 2017 to October 2019). The study was approved by the hospital ethics committee. Data were collected from clinical records following the principles of the Declaration of Helsinki. The parents or caregivers of each patient were informed about the study and were included after obtaining their consent. In addition, patient data were anonymized after discharge.

Inclusion criteria

Patients who met the following criteria were included in the study:

- < 18 years of age.
- Patients with asthma, defined as an acute episode of increased work of breathing with wheezing and prolonged expiratory phase in a previously healthy child or with similar previous episodes.
- Patients admitted to the PICU due to failure to respond to optimized asthma therapies in the Pediatric Emergency Department/Pediatric Unit.
- No major comorbidities or pre-existing conditions other than asthma.
- No criteria for acute bronchiolitis. On physical examination, acute bronchiolitis was defined as the onset of wheezing before 24 months in patients with a viral lower respiratory tract infection and no other explanation for the wheezing.

Study groups

- After the observation period, four groups were created based on their respiratory support: (1) “only HFNC”; (2) “NIMV and HFNC”; (3) “only NIMV”; and (4) Children on MV to evaluate HFNC and compare it against other therapies.

Respiratory support

The respiratory support used was not standardized or randomized. Physicians decided which therapy to use based on their clinical judgment.

- NIMV: bi-level positive airway pressure (BiPAP) Vision V60® (Respironics Philips) with a full-face or oronasal mask. Modalities: continuous positive airway pressure (CPAP) and BiPAP. CPAP was initially set at 5-6 cm H_2O. For BiPAP, inspiratory positive airway pressure was initially set at 8-10 cm H_2O, and end-positive airway pressure was set at 5-6 cm H_2O. Inspiratory and expiratory pressures were titrated in 2 cm H_2O increments based on tidal volume, continuous pulse oximetry, work of breathing, respiratory rate, and subject-ventilator synchrony. The fraction of inspired oxygen (FiO_2) was titrated to maintain SpO_2 > 92%.
- High flow nasal cannula (HFNC): Fisher-Paykel High Flow Nasal Cannula® and Vapotherm® were used. A cannula of a suitable size, an appropriate circuit, a humidifier, and air or oxygen were used. Cannula size was selected based on the subject's weight, and flow rates were initiated at 0.5-1 L/kg/min. The FiO_2 was titrated to maintain a SpO_2 > 92%.

Data

- Demographic characteristics (age in months and sex).
- Clinical data: respiratory rate on admission, presence and characteristics of wheezing, pulmonary score, oxygen saturation ($SatO_2$)/FiO_2 ratio, venous blood gas values on admission (pH, partial pressure of carbon dioxide, HCO_3), pharmacological treatment received (bronchodilators, corticosteroids, antibiotic therapy, magnesium sulfate), type and days of ventilatory support, length of stay in the PICU, and total hospital stay. The attending physician selected pharmacologic treatment based on his or her expertise and the clinical protocols of the PICU.

Statistical analysis

Data analysis was performed with the SPSS® statistical package (version 21.0; IBM Company®, New York, United States). The homogeneity of the demographic variables and other clinical parameters were analyzed at the beginning of the study (having a non-normal distribution) and compared between groups. Descriptions were made using the median and interquartile range, and for the qualitative variables, absolute frequency and relative frequency. The Kruskal–Wallis test for quantitative variables and Fisher's exact test for dichotomous variables were used to analyze the characteristics of the three treatment groups.

Results

Eighty-six children were initially recruited (Fig. 1). Finally, 76 patients were included in the study, of whom 39 were female; the median age of the study population was 25 months (4-160). The median length of hospital stay was 6 days (1-23). On admission to the PICU, the SaO_2/FiO_2 ratio was 195 (90-384), the pulmonary score was 5 (1-8), and the respiratory rate was 40 (20-68). Regarding the gasometer variables, we observed that children had a PCO_2 of 36.15 (15.2-86), a HCO_3- of 21.7 (13.5-40) with a pH of 7.37 (7.13-7.49) on admission to the PICU. Sixty-nine children received intravenous steroids prior to PICU admission. These data are described globally and based on each respiratory support received in table 1. There were no children in the MV group. None of the patients who received HFNC as initial therapy required NIMV. There were no deaths.

Comparisons based on respiratory support

In our series, 52/76 children underwent a chest X-ray. In addition, 33/76 received antibiotics, 13/76 received magnesium sulfate, and 19/76 received a continuous dose of albuterol. Table 2 shows the comparison between the respiratory groups. Children requiring only HFNC required less routine chest radiography, antibiotic therapy, continuous albuterol, and magnesium sulfate.

The median number of PICU days was lower in the only-HFNC group compared to other types of ventilatory support (Table 3, p = 0.025). Furthermore, $SatO_2/FiO_2$ was lower in the only-NIMV group and higher in the only-HFNC group (Table 3, p = 0.026). PCO_2 was higher in the only-NIMV group (Table 3, p = 0.032).

Discussion

In this study, we observed that HFNC was the most frequently used respiratory support in children admitted to the PICU for asthma. Furthermore, children requiring only HFNC had less pharmacological therapy and shorter PICU and hospital stays. The presence of low $SatO_2/FiO_2$ and elevated PCO_2 on admission was associated with using NIMV.

HFNC delivers a warm and humidified airflow with a variable oxygen fraction (between 0.21 and 1) and a flow between 2 L and 60 L[21]. Theoretically, HFNC reduces oropharyngeal dead space, decreases CO_2 rebreathing, improves mucociliary clearance[22], and

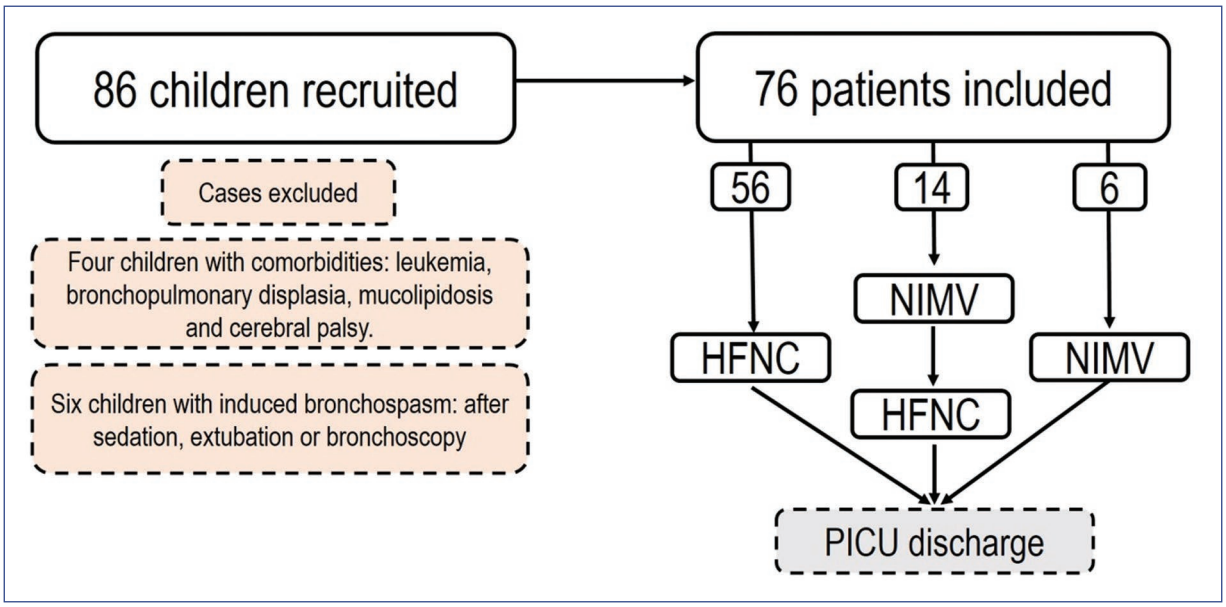

Figure 1. Flowchart of patient inclusion and exclusion.
HFNC: high flow nasal cannula; NIMV: non-invasive mechanical ventilation; PICU: pediatric intensive care unit.

Table 1. Treatments of children admitted to a tertiary PICU due to asthma

Variables analyzed	Total	Only HFNC (n = 56)	HFNC + NIMV (n = 14)	Only NIMV (n = 6)	p-value
Female	39/76 (51%)	26/56 (46%)	9/14 (64%)	4/6 (66%)	0.6
Age (months)	25 (4-160)	29 (4-143)	12.5 (4-164)	14 (5-26)	0.1
Hospital stay (days)	6 (1-24)	5 (2-24)	11 (1-12)	14 (3-22)	0.09
$SatO_2/FiO_2$ ratio	195 (90-384)	204 (97-384)	185 (92-333)	101 (90-271)	0.02
PCO_2	36.15 (15.2-86)	35 (15.7-67)	43.5 (32.8-86)	45.6 (28.1-51)	0.032
Pulmonary score	5 (1-8)	5 (1-7)	5 (3-8)	5 (2-7)	0.53
pH	7.37 (7.13-7.49)	7.37 (7.13-7.49)	7.38 (7.15-7.47)	7.41 (7.29-7.49)	0.6
HCO_3	21.7 (13.5-40)	20.7 (13.5-40)	21.7 (17.9-32.4)	24.6 (21.7-28.9)	0.11
Respiratory rate	40 (20-68)	39 (20-68)	43 (24-68)	52 (29-62)	0.06
Intravenous steroids	69/76 (90%)	50/56 (89%)	14/14 (100%)	5/6 (83%)	0.38

HFNC: high flow nasal cannula; NIMV: non-invasive mechanical ventilation; $SatO_2/FiO_2$: oxygen saturation/fraction of inspired oxygen ratio; PCO_2: partial pressure of carbon dioxide.

generates an airway positive pressure of up to 6 cm H_2O. The interest in using HFNC as respiratory support stems from these properties and increased patient comfort[17,23]. In addition, it does not require breathing synchronization and requires less nursing care (compared to a NIMV device). This constant flow may also facilitate nasopharyngeal air renewal, which would improve CO_2 washout and oxygenation[11].

As mentioned above, asthma is one of the leading causes of PICU admission. In our series, we included a similar number of males and females, with a median age of almost 2 years. This age is younger than that described in other studies and may limit the external validity of our work[14,15]. Although we applied strict exclusion criteria, preschool children inclusion may have introduced a bias. We probably also included

Table 2. Complementary tests according to each type of respiratory support

Respiratory support	Chest X-ray		Empiric antibiotics		Magnesium sulphate		Continuous albuterol	
	Yes	No	Yes	No	Yes	No	Yes	No
Only HFNC	34/56 (60%)	21/56 (40%)	21/56 (37%)	35/56 (63%)	7/56 (12%)	49/56 (88%)	10/56 (18%)	46/56 (82%)
HFNC + NIMV	14 (100%)	0	9/14 (64%)	5/14 (35%)	6/14 (43%)	8/14 (57%)	9/14 (64%)	5/14 (35%)
NIMV	4/6 (66%)	2/6 (33%)	3/6 (50%)	3/6 (50%)	0	6 (100%)	0	6 (100%)
Total	52/76 (68%)	24/76 (30%)	33/76 (44%)	43/76 (56%)	13/76 (17%)	63/76 (83%)	19/76 (25%)	57/76 (75%)
p-value	0.007		0.001		0.02		0.001	

HFNC: high-flow nasal cannula; NIMV: non-invasive mechanical ventilation.

Table 3. Progression and severity variables (median and range)

Respiratory support	PICU days	SaO_2/FiO_2 ratio	pCO_2
HFNC	3 (1-8)	204 (97-384)	35 (15.7-67)
HFNC + NIMV	5 (1-9)	185 (92-333)	43.5 (32.8-86)
NIMV	3.5 (1-10)	101 (90-271)	45.6 (28.1-51)
p-value	0.025	0.026	0.032

HFNC: high flow nasal cannula; NIMV: non-invasive mechanical ventilation; $SatO_2/FiO_2$: oxygen saturation/fraction of inspired oxygen ratio; PICU: pediatric intensive care unit.

cases of bronchospasm, more representative of infectious bronchial hyperreactivity than asthma.

As it is known, the evidence on the utility of HFNC as an optimal respiratory support in severe asthma is scarce[1,13,20]. Ramnarayan et al. conducted a pilot study to evaluate it through a multicenter and randomized clinical trial. They found that switching from HFNC to NIMV was frequent[15]. Similarly, an observational study of 42 asthmatic children by Pilar et al. concluded that initial support with HFNC was not optimal and that NIMV support was delayed. As mentioned above, HFNC was the most frequently used respiratory support[14]. In addition, we did not observe any treatment failures or increased PICU or hospital admission days in those who received HFNC as first respiratory support. These findings are in contrast to what has been published previously and should be considered with caution[15].

Given the design of our study, it is difficult to define objective data to understand and explain why the transition from HFNC to NIMV was unnecessary. We observed that patients receiving HFNC showed higher $SatO_2/FiO_2$ values and lower CO_2 levels, probably indicating a better situation on admission to the PICU for these children[20]. Furthermore, the decision to initiate one type of ventilatory support over another was not randomized but left to the clinician's judgment. It appears that $SatO_2/FiO_2$ and CO_2 levels significantly influenced the choice of NIMV as treatment. In addition, children receiving NIMV required more chest X-rays, empirical antibiotic therapy, magnesium sulfate, and continuous nebulized albuterol. Overall, these aspects would provide insight into the higher clinical severity in the NIMV group[1].

Finally, as noted above, the use of HFNC remains controversial because it is still being determined whether it can prolong hospital stays and delay other types of assistance while being cost-effective for the healthcare system. In our series, there was no delay in other types of care. In addition, we observed that patients who received HFNC had a shorter PICU stay and a significantly shorter hospital stay. Although these observations cannot be considered a direct effect of HFNC use, they are of interest because they objectively demonstrate that, at least in our center, patients requiring HFNC for severe asthma are discharged promptly without excessive impact on resource utilization.

This study has several limitations. As mentioned above, physician expertise led to selecting children who could be treated with HFNC with a low risk of treatment failure. Therefore, our results may be difficult to generalize. In addition, we included children < 2 years of age. We tried to exclude cases of acute bronchiolitis, but we assume this cohort may not represent critical asthma patients. Finally, the different pharmacological treatments used were not evaluated; their indications and impact on clinical evolution and respiratory support effectiveness should be evaluated in future studies.

In conclusion, HFNC was a safe approach for children admitted to the PICU for asthma. Those patients who received HFNC as primary respiratory support did not require escalation to NIMV. The absence of blood gas changes on admission to the PICU and the absence of high oxygen requirements may help to select good responders to HFNC. However, external validation of our results is complex. Data from other centers are needed to verify our observations.

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 of lung ultrasound in the evaluation of children with lower respiratory tract infection in the emergency room

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Abstract

Background: *Lung ultrasound is a bedside tool that allows the evaluation of pulmonary parenchymal involvement in pediatric patients through the lung ultrasound score (LUS). We aimed to evaluate a group of patients under 3 years of age with lower respiratory tract infections using LUS at the Hospital Infantil del Estado de Sonora.* **Methods:** *We included patients younger than 3 years admitted to the emergency department with lower respiratory tract infections. A lung ultrasound was performed within the first 24 h of admission to the emergency department and evaluated using LUS. We analyzed age, sex, etiology of infection, days of stay, use of mechanical ventilation, Downes scale, failure of mechanical ventilation on admission, and mortality. Descriptive analysis was performed with frequencies and percentages for qualitative variables and medians and interquartile intervals for quantitative variables. Differences in the distribution of LUS variables were evaluated with the Fishers' exact test and Student's t-test.* **Results:** *We included a total of 19 patients with lower respiratory tract infections, 73.7% with bronchiolitis. Fifty percent of the cases scored 7 on the LUS, 91.7% were admitted to the pediatric intensive care unit, and 53.8% required invasive mechanical ventilation.* **Conclusions:** *The use of LUS in lower respiratory tract infections can predict the need for PICU admission, the use of invasive ventilatory support, and prolonged hospital stay.*

Keywords: *Ultrasonography. Child. Bronchiolitis. Critical care*

Utilidad de ecografía pulmonar en la valoración de niños con infección respiratoria baja en urgencias

Resumen

Introducción: *El ultrasonido pulmonar es una herramienta a pie de cama que permite evaluar la afectación del parénquima pulmonar en pacientes pediátricos por medio de la escala de LUS (lung ultrasound score, por sus siglas en inglés). El objetivo del estudio fue evaluar a niños menores de 3 años con infección respiratoria baja mediante la escala de LUS, en el Hospital Infantil del Estado de Sonora.* **Métodos:** *Se incluyeron pacientes menores de 3 años que ingresaron al Servicio de Urgencias con infección respiratoria baja. Se realizó ecografía pulmonar en las primeras 24 horas de ingreso a urgencias y se evaluó mediante la escala de LUS. Se analizó, edad, sexo, etiología de la infección, días de estancia, uso de terapia ventilatoria, escala de Downes, fracaso a la terapia ventilatoria de ingreso y mortalidad. Se realizó un análisis descriptivo por medio de frecuencia y porcentaje para las variables cualitativas y para las cuantitativas con mediana e intervalo intercuartil.*

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Las diferencias en la distribución de las variables por la escala de LUS con la prueba exacta de Fisher y la t de Student.
Resultados: *Se identificaron 19 pacientes con infección pulmonar aguda, de los cuales el 73.7% presentó bronquiolitis. El 50% de los casos obtuvo 7 puntos de la escala de LUS, el 91.7% ingresó a UCIP y el 53.8% requirió ventilación mecánica asistida.*
Conclusiones: *El uso de la escala LUS en infección respiratoria baja puede predecir la necesidad de ingreso a Unidad de Cuidados Intensivos Pediátricos, así como la utilización de soporte ventilatorio invasivo y una estancia hospitalaria prolongada.*

Palabras clave: *Ultrasonido. Niños. Bronquiolitis. Cuidados intensivos.*

Introduction

Bronchiolitis is the most common viral respiratory infection in children under 2 years of age, followed by community-acquired pneumonia[1]; up to 30% of children with bronchiolitis have superimposed pneumonia[2]. The COVID-19 pandemic radically changed the epidemiology of other viral respiratory infections in children. In 2023, Guerrero del Cueto et al. described the incidence of bronchiolitis in the last 12 years and its epidemiologic changes[3]. These authors observed 2,138 admissions with a diagnosis of bronchiolitis during the 2010-2019 period[3]. In 2020, hospitalization reduced in 94.4%; however, in the summer of 2021, cases increased for 6 months, reaching a total of 171 cases, with a torpid evolution and requiring admission to the pediatric intensive care unit (PICU), similar to what had been reported by Moreno et al., where admission to the PICU was 9.4%[4,5]. Another study found that 33.4% of children with bronchiolitis were admitted to the PICU, 44.6% required supplemental oxygen with a conventional nasal cannula, and 10.6% required assisted mechanical ventilation (AMV) but with a low mortality rate[6]. Therefore, risk stratification of each patient is essential to intensify monitoring and tailor early initiation of ventilatory support. Lung ultrasound is a bedside tool that has proven helpful in early detection of the adverse course of these conditions. Several clinical scales assess these types of conditions, but none of them is accurate[7].

Manzur-Sandoval et al. (2021) used the lung ultrasound score (LUS) in adults to predict in-hospital mortality in patients diagnosed with COVID-19; they found that the median score was 19 points, the overall mortality rate was 39.4%, and in cases above 19 points, mortality increased to 50%[8].

The LUSBRO scale has been used in children with bronchiolitis. The investigators defined 6 points as a cut-off to indicate greater severity and to predict PICU admission, need for mechanical ventilation, duration of mechanical ventilation, and hospital stay; they reported that 55% of patients were admitted to the PICU, and 6.3% required invasive mechanical ventilation[9].

In 2022, the LUS was used to assess 85 pediatric patients with acute respiratory infection (ARI): 5.4% were admitted to the PICU. Moreover, the association between the pediatric early warning score and days of hospital stay and oxygen use was not statistically significant[10]. However, there is limited literature on this scale in pediatric patients.

This study aimed to evaluate children under 3 years of age with pulmonary pathology of infectious origin using the LUS at the Hospital Infantil del Estado de Sonora (HIES).

Methods

We conducted a descriptive observational study of a consecutive case series of patients under 3 years of age with lower respiratory tract infection. This study was approved by the Research Ethics Committee of the HIES. The study group consisted of patients diagnosed with community-acquired pneumonia and bronchiolitis who were admitted to the Emergency Department of the HIES from January to February 2023.

All patients under 3 years of age admitted to the Emergency Department with a lower respiratory tract infection diagnosed with bronchiolitis and community-acquired pneumonia, according to the American Association of Pediatrics, were included. Bronchiolitis was defined as the first episode of wheezing in a child under 24 months of age, of viral etiology, with expiratory dyspnea and the presence of a catarrhal prodrome[11]. Community-acquired pneumonia was defined as an acute infection of the pulmonary parenchyma with systemic manifestations, causing acute respiratory symptoms, accompanied by an infiltrate on chest radiography, who had not been hospitalized for at least 1 week or whose symptoms appeared more than 48 h after hospital discharge[12].

Neonates with < 37 weeks of gestational age, patients with chronic lung disease (bronchopulmonary dysplasia), bronchial asthma, and congenital heart disease were excluded.

Data were collected within the first 24 h after admission to the emergency department. The clinical score was defined by the Wood-Downes scale modified by Ferres, which was calculated considering the presence of wheezing and subcostal, intercostal, supraclavicular, suprasternal retractions; respiratory frequency and heart rate; symmetric, regular symmetric, or decreased ventilation; and the presence of cyanosis. Patients were graded as follows: mild, with the presence of 1-3 points; moderate, 4-7 points; and severe, 8-14 points[13]. Oxygen saturation was determined by pulse oximetry.

The etiologic agent was determined by real-time polymerase chain reaction for influenza A (H1N1) PDM09, seasonal influenza A/H3, influenza B, respiratory syncytial virus (RSV), metapneumovirus, adenovirus, and enterovirus. Blood tests and chest radiographs were obtained as part of the routine clinical practice. Respiratory support included invasive and noninvasive ventilation, such as low-flow nasal prongs, continuous positive airway pressure (CPAP), and high-flow nasal cannula. PICU admission was defined as patients requiring invasive mechanical ventilation.

Subsequently, lung ultrasound was performed by a pediatric resident trained in lung ultrasound and supervised by a pediatric intensivist and critical care sonographer during the first 24 h after admission to ED. A Sonoscape S2 portable color Doppler ultrasound unit with a 12 MHz linear probe was used. The lung ultrasound score was assessed using the LUS. Six areas of each lung were examined: anterior (superior and inferior), lateral (superior and inferior), and posterolateral (superior and inferior). Scoring for each area was 0-3 points: 0 points pleural sliding with A-lines and < 2 isolated B-lines per intercostal space; 1 point ≥ 3 isolated B-lines (not coalescing); 2 points: coalescing B-lines ("white lung") with or without small subpleural consolidations; 3 points: extensive lung consolidation pattern (small subpleural consolidations are excluded); X lung zone not evaluated (patient could not be mobilized). The total score was the sum of the 12 lung zones assessed. The minimum score was 0 and was considered normal, with a maximum of 36 points[14].

Statistycal analysis

Statistical analysis was performed using medians and interquartile ranges for quantitative variables and frequencies and percentages for qualitative variables. In addition, differences in distribution were evaluated using the Student's t-test and Fisher's exact test. All p-values ≤ 0.05 were considered statistically significant. The analysis was performed with the Statistical Package for Social Sciences version 22 for personal computers.

Results

During the study period, 19 patients with pulmonary pathology of infectious origin were identified, of whom 12 (63.1%) were young infants, four (21.1%) were old infants, and three (15.7%) were preschool children. Ten (52.6%) were males. Bronchiolitis was diagnosed in 14 (73.7%) patients and community-acquired pneumonia in five (26.3%) patients. The median hospital stay was 9 (1-37) days. The Wood–Downes scale was moderate in 18 (94.7%) cases. Of the patients, 89.5% were admitted with intercostal retraction; 52.6% had chest radiographs with interstitial infiltrate, 15.8% had unilateral consolidation, and 31.6% had bilateral consolidation. Laboratory tests revealed the presence of RSV in 14 (73.6%) cases, HADV in one case (5.2%), and negative results in four (21%); 12 (63.1%) patients had a positive procalcitonin. The type of ventilatory support on admission to the emergency department was as follows: nine (47.36%) cases with low-flow nasal prongs, seven (36.84%) with invasive mechanical ventilation, two (10.5%) with a high-flow nasal cannula, and one (5.3%) with CPAP; 12 (63.2%) cases required admission to the PICU (Table 1).

All patients underwent lung ultrasound and were scored according to the LUS. The median LUS was 7 points, the IOR 25% received a value of 5, the IOR 75% of 8 (range 4-11). According to the analysis, scores ≥ 7 points were considered less severe, and scores of 7 or more points were considered more severe. Of the 19 hospitalized patients, six (31.6%) had a score of 6 or less, of which five (83.3%) received nasal prongs and one (16.7%) required a high-flow nasal cannula (Table 2).

Thirteen (53.8%) patients scored ≥ 7 LUS points and required AMV; however, in seven (36.8%) cases, ventilation therapy failed on admission (Fig. 1). In contrast, only one patient (8.3%) required invasive mechanical ventilation on admission with an LUS score of 6 or less, compared to 91.7% with invasive mechanical ventilation and LUS scores > 7 (Fishers' exact test; p = 0.010). When we analyzed LUS and days of hospital stay of patients, we found that those with ≤ 6 points had a mean length of stay of 5.3 (± 2.3) days, compared to patients with LUS > 7 points in which the mean was 20 (± 13.3) days (p = 0.017).

Of the patients admitted to the PICU, 91.7% had a score > 7 points, and 71.4% of the cases not admitted

Table 1. Clinical characteristics of patients with lower respiratory tract infections in children under 3 years of age, Hospital Infantil del Estado de Sonora

Variable	n = 19	%
Age		
Young infants	12	63.1
Old infants	4	21.1
Preschoolers	3	15.78
Sex		
Male	10	52.6
Female	9	47.4
Disease		
Bronchiolitis	14	73.7
Community-acquired pneumonia	5	26.3
Type of ventilatory support		
Nasal prongs	5	26.3
High flow	1	5.3
CPAP	1	5.3
AMV	12	63.2
PICU		
Yes	12	63.2
No	7	36.8
Chest X-ray		
Interstitial infiltrate	10	52.6
Unilateral consolidation	3	15.8
Bilateral consolidation	6	31.6
Wood-Downes scale		
4-7	18	94.7
8-14	1	5.3
Intercostal retraction		
Yes	17	89.5
No	2	10.5

AMV: assisted mechanical ventilation; CPAP: continuous positive airway pressure; PICU: pediatric intensive care unit.

Table 2. Evolution of ventilatory therapy evaluated by LUS in patients under 3 years of age with lower respiratory tract infection, Hospital Infantil del Estado de Sonora

Patient	Ventilatory therapy on admission	LUS	Days for failure	Rescue ventilatory therapy
1	Nasal prongs	9	1	AMV
2	Nasal prongs	7	1	AMV
3	Nasal prongs	6	2	High flow
4	Nasal prongs	5	1	CPAP
5	High flow	5	1	AMV
6	High flow	8	3	AMV
7	CPAP	8	3	AMV

AMV: assisted mechanical ventilation; CPAP: continuous positive airway pressure; LUS: lung ultrasound score.

Table 3. LUS according to score by severity variables in children with lower respiratory tract infection

Variable	LUS				p
	≤ 6 points		≥ 7 points		
	n	%	n	%	
Assisted mechanical ventilation					0.010*
Yes	1	16.7	11	84.7	
No	5	83.3	2	15.3	
PICU admission					0.010*
Yes	1	16.7	11	84.7	
No	5	83.3	2	15.3	
IHDS average	5.3	± 2.3	20	± 13.3	0.017†

*Fisher's exact test.
†Student's t-test.
IHDS: in-hospital days of stay; LUS: lung ultrasound score; PICU: pediatric intensive care unit.

to the PICU had a score of ≤ 6 points, with a statistically significant difference (Fisher's exact test; p = 0.010) (Table 3). Mortality occurred in one patient (5.3%) who required mechanical ventilation since admission, with a LUS of 11 points.

Discussion

In this study, LUS was found to identify patients with an unfavorable course who required early ventilatory support. Various clinical scales have been proposed to determine the severity of the disease, such as the Downes scale modified by Ferres. However, none of them has shown to identify those patients with an unfavorable outcome[7].

The performance of lung ultrasound in these patients represents a diagnostic and staging tool for predicting early ventilatory support and admission to the PICU; performing early interventions by noninvasive ventilatory therapy could improve the patient outcome. Several lung ultrasound scales have been described, such as the LUS for adult patients hospitalized with a diagnosis of COVID-19, the LUSBRO scale for patients with bronchiolitis, and in neonatology, lung ultrasound has been used for the administration of surfactant in premature infants, among other scales in different age groups[8,15].

The scale used in this study to analyze pediatric patients with ARI was LUS. The median of the scale was 7 points; it was observed that 91.7% of the patients were admitted to the ICU, similar to what has been reported in other studies. In the study by Bobillo et al. in 2021,

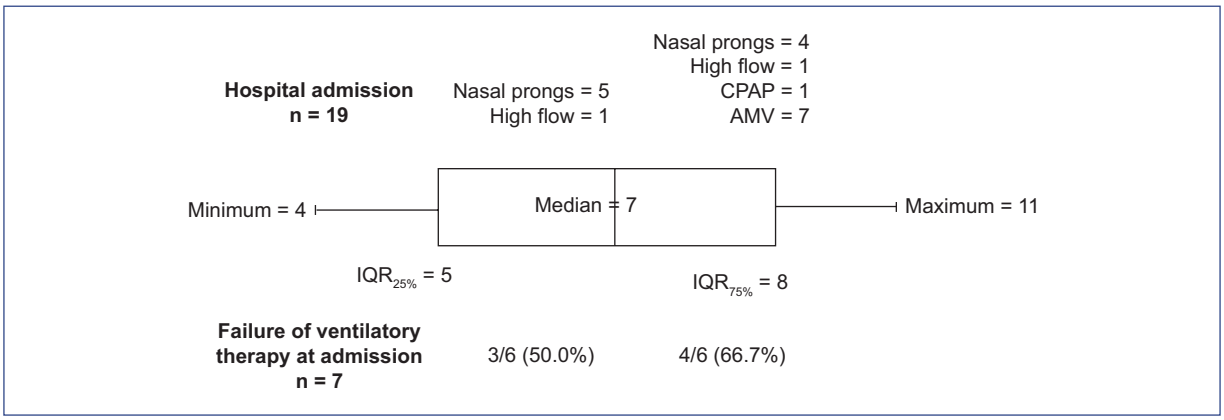

Figure 1. LUS values in 19 children with lower respiratory tract infection and ventilatory management on admission to the Hospital Infantil del Estado de Sonora.
AMV: invasive mechanical ventilation; CPAP: continuous positive airway pressure; LUS: lung ultrasound score.

they used the LUSBRO scale and found that 55% of the cases admitted to the PICU received ≥ 6 points[9].

In this study, high LUS values were significantly associated with the use of invasive ventilatory support; more than half of the cases with ≥ 7 points required this therapy. Bueno et al., in 2019, observed that 2/3 of the patients eventually required AMV; in addition, they presented anteroposterior consolidation in the lung and more than 3 confluent B-lines bilaterally[16]. In 2021, 59% of adult patients with COVID-19 with LUS ≥ 19 required mechanical ventilation[8].

Concerning hospital stay, this study found a correlation between greater lung parenchymal involvement (as observed on lung ultrasound) and more days of hospital stay, as reported in the literature. A study published in 2018 found that for every 5-point increase in the global lung ultrasound score, there was a 1.2-day increase in hospital length of stay, which was statistically significant[17].

More than half of the patients with ventilatory failure on admission had a LUS score ≥ 7. Krishna et al., in 2022[18], found an association between high values of the lung ultrasound USS scale and the type of ventilatory support. The authors observed that 13.2% of patients with posterior subpleural consolidation presented failure of noninvasive ventilatory support (low-flow nasal prongs) and required upper respiratory support, CPAP in 71.4% and 14.2% other methods with a high-flow nasal cannula.

In adult patients with COVID-19, in-hospital mortality was observed to be 50% in patients with LUS score ≥ 19. However, in our study, only one patient obtained the highest score. Mortality correlated with greater parenchymal involvement documented on the LUS, suggesting the need for more aggressive ventilatory therapy upon admission to the ED[8].

One situation that needs to be reviewed is the comparison between LUS and chest computed axial tomography (CT), as the results are contradictory in adults. On the one hand, Tung-Chen et al. (2019) described a significant correlation between the results, highlighting a similar accuracy in detecting lung abnormalities[19]. On the other hand, Colombi et al. (2020) showed that CT performed better than LUS in patients with COVID-19 and that LUS was highly sensitive but not specific[20].

Furthermore, studies in pediatric patients have shown that LUS is highly sensitive for detecting normal lung tissue and highly reliable for detecting consolidations. At the same time, CT has a high specificity for excluding pleural effusion and interstitial disease[21]. Carrard et al. (2022) reported that LUS was superior in diagnosing pneumonia in children with pleural effusion and allowed adequate differentiation of consolidations. However, CT showed better visualization of hydroaerial cavities and atelectasis[22]. The study by Musolino et al. in 2022 showed that lung ultrasound was better to CT in detecting small subpleural parenchymal consolidations[23]. However, another study compared the diagnostic performance of LUS and chest CT, and the results were similar. Lung ultrasound was better than chest radiography in identifying consolidations[24]. However, an important consideration is that chest radiography involves radiation, which increases the risk of developing cancer in children[25].

Strengths of the study include the homogeneity of the population studied, which allows for objective ultrasound evaluation in previously healthy lungs. An intensive care physician performed the ultrasound examination. An analysis of the lung regions was performed, allowing a broader assessment of the parenchyma compared to chest radiography. In addition, the portable ultrasound device provided a tool for bedside patient assessment.

Limitations of the study include the sample size, the fact that the interpretation of lung ultrasound is operator-dependent, and that the patients studied were those requiring supplemental oxygen support. Further studies with larger sample sizes and patients with mild respiratory pathology are needed.

In conclusion, this study demonstrated that the use of the LUS in lower respiratory tract infections predicts the need for invasive ventilatory support, PICU admission, and prolonged hospital stay.

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.

Use of artificial intelligence for generating text. The authors declare that they have not used any type of generative artificial intelligence for the writing of this manuscript, nor for the creation of images, graphics, tables, or their corresponding captions.

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Effect of school reopening on pediatric morbidity and mortality during the third epidemiological wave of COVID-19 in a Mexican state

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Abstract

Background: *Determining the effect of reopening schools on pediatric SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection rates increased the need to share the experience of governments in many geographic regions for better future decision-making in similar health emergencies.* **Methods:** *Through a prospective study based on a population-based cohort, students from 18,988 schools in the State of Mexico who began returning to school were followed. Daily sanitation filters were implemented in each school and district liaisons were informed on a daily basis through a negative network. Identified cases were confirmed by reverse transcriptase-polymerase chain reaction. Simple case frequencies, percentages, and incidences of COVID-19 were estimated. State incidences were compared with the national incidence.* **Results:** *A total of 3,586 cases were confirmed; 2,048 (57.1%) were children. Twenty-four (0.6%) were hospitalized for moderate to severe COVID-19; nine (37.5%) died, and only one was a schoolchild. From week 36, an average infection rate of 0.36 was observed. The highest infection rate in schoolchildren was observed in epidemiologic week 40 (1.01); from this week on, a decrease in the number of cases was observed until week 50.* **Conclusions:** *The use of non-pharmaceutical interventions has more advantages than limitations, as long as the strategies are homogeneous and properly implemented to ensure adequate control of infections.*

Keywords: *COVID-19. Schoolchildren. Pandemic. Epidemiological surveillance.*

Efecto de la reapertura de escuelas en la morbimortalidad pediátrica durante la tercera ola epidemiológica por COVID-19 en un estado mexicano

Resumen

Introducción: *La determinación del efecto de reabrir las escuelas sobre las tasas de infección pediátrica por SARS-CoV-2 (síndrome respiratorio agudo grave coronavirus 2) incrementó la necesidad de trasmitir la experiencia de los gobiernos de muchas regiones geográficas para mejores decisiones futuras en emergencias sanitarias similares.* **Métodos:** *Mediante un estudio prospectivo basado en una cohorte poblacional se dio seguimiento a los alumnos de 18,988 escuelas del Estado de México que iniciaron con el regreso a clases. Se implementaron filtros sanitarios diarios en cada escuela y cotidianamente se informaban a los enlaces jurisdiccionales a través de una red negativa. Los casos identificados eran confirmados a través*

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de RT-PCR (reacción en cadena de la polimerasa con transcriptasa inversa). Se estimaron frecuencias simples de casos, porcentajes e incidencias de COVID-19. Las incidencias del estado se compararon con la incidencia nacional. **Resultados:** *Un total de 3,586 casos fueron confirmados; 2,048 (57.1%) correspondieron a niños. Veinticuatro (0.6%) fueron hospitalizados por COVID-19 moderado a grave; nueve (37.5%) fallecieron, y solamente una correspondió a un escolar. A partir de la semana 36 se observó una tasa promedio de infecciones de 0.36. En la semana epidemiológica 40 se observó la mayor tasa de infección en escolares (1.01); a partir de esta semana se observa un declive de los casos hasta la semana 50.* **Conclusiones:** *La implementación de intervenciones no farmacéuticas tiene más ventajas que limitaciones, siempre y cuando las estrategias sean homogéneas y correctamente ejecutadas, lo que asegurará un adecuado control en los contagios.*

Palabras clave: *COVID-19. Escolares. Pandemia. Vigilancia epidemiológica.*

Introduction

In December 2019, the emergence of a new coronavirus, SARS-CoV-2, responsible for causing severe pneumonia in China, was confirmed[1,2]. Subsequently, on March 11, 2020, the World Health Organization declared the resulting disease, named COVID-19, a pandemic[3]. Although initial data indicated that adults and older adults were the most affected population, within weeks, cases were reported in children under 18 with symptoms of acute respiratory infection. In addition, an unusual increase in cases of Kawasaki disease associated with COVID-19 was observed[4].

In Mexico, the first case of COVID-19 was reported in February 2020. As of August 30, 2022, the Dirección General de Epidemiología del Gobierno de México had confirmed 7,329,493 cases of SARS-CoV-2 infection. Of these, 594,420 (8.1%) were patients under 19 years[5] (Fig. 1).

Worldwide reports indicate low rates of moderate and severe disease in the pediatric population, in contrast to mild disease, characterized primarily by symptoms of fever and cough, followed by rhinorrhea, vomiting, diarrhea, headache, and myalgias[1,6-12]. Although this age group generally has a favorable prognosis, severe cases have been documented with severe respiratory compromise requiring ventilatory support and, in some cases, resulting in death, especially in individuals with risk factors for developing complications[13].

For this reason, the role of children as potential spreaders of infection in the community and schools became one of the most debated issues during the COVID-19 pandemic[14,15]. This is because the transmission of respiratory pathogens such as SARS-CoV-2 depends on contact patterns and interactions between populations. Therefore, understanding these dynamics in closed environments is critical to ensure the effectiveness of efforts to avoid mass infections[16]. Contagion in the school environment has been a topic of debate with mixed opinions, largely due to the limited evidence available[17]. As a result, the decision to reopen schools has been left to governments in various geographical regions and to parents, despite the limited evidence of the spread of SARS-CoV-2 among the student population[18].

In Mexico, this issue became relevant in August 2021, during the fourth week of the third wave of SARS-CoV-2 infections when the resumption of classes was announced after several months of suspension of classroom activities. The main concern was the risk of contagion in the exposed group, which intensified the debate on the need to vaccinate this age group[19].

The State of Mexico has a population density of more than 15 million inhabitants, the highest in the country. Of these, about 5 million are children. In 2021, a total of 103,023 cases of COVID-19 in children aged 5-14 years were registered in Mexico, of which 7,079 (6.8%) were reported in the State of Mexico[20].

In order to evaluate the impact of the reopening of schools in our country, the "*Programa Regreso Seguro a Clases para el control de contagios de la COVID-19*" ("Safe Return to School Program for the Control of COVID-19 Contagions") has followed the student population. In this program, a continuous analysis was made on the fluctuations in the number of cases reported in the school environment.

Methods

Through a prospective study based on a population-based cohort, students from 18,988 public and private primary and secondary schools in the 19 health jurisdictions of the State of Mexico were followed. This follow-up was carried out for a period of 20 weeks, corresponding to epidemiological weeks 31 to 50 of the year 2021, when these students started the mixed educational modality, combining online and face-to-face classes. In the school year 2021-2022, the total enrollment in the State of Mexico reached 4,251,599 students, 2,149,984 (50.6%) female and 2,101,615 (49.4%) male.

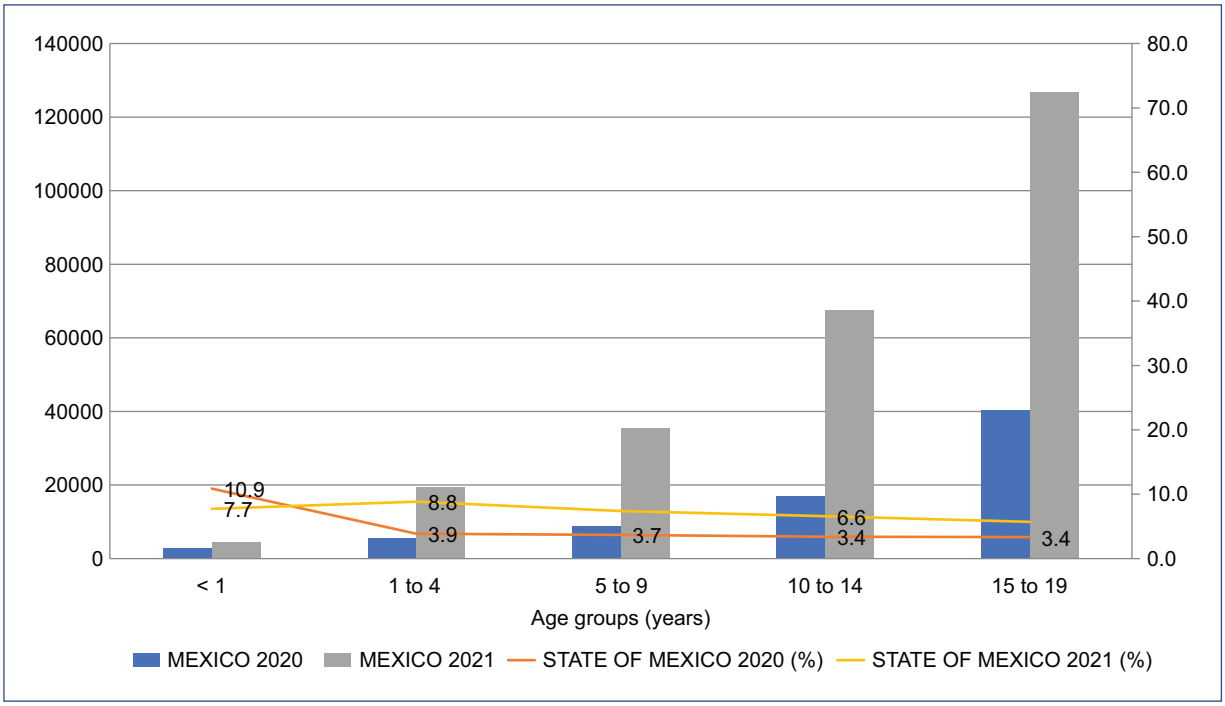

Figure 1. Cases of COVID-19 in children under 18 years in Mexico and the State of Mexico. From March 2020 to December 2021, cases of COVID-19 occurred in children under 19 years, with the highest frequency in the 15-19 age group, followed by the 10-14 age group at the national and state levels. In addition, an increase in the number of cases is observed in 2021 compared to 2020, although there was stability in infection rates at the state level. Source: *Dirección General de Epidemiología del Gobierno de México.*

Procedures performed in the Safe Return to School Program

Intersectoral coordination was first established between the Secretariats of Health and Education of the Government of the State of Mexico to conduct epidemiologic surveillance in schools. This was achieved through the regional coordinators of the education system and the jurisdictional directors of the health system, with the objective of keeping a daily record of suspected cases identified in schools or reported to the educational institution by parents or guardians.

For this purpose, daily sanitary filters were established in each school. These filters included the presence of trained teachers responsible for monitoring the temperature and detecting suspicious symptoms such as rhinorrhea, fever, cough, headache, or general malaise at the school entrance for the student population and the teaching and administrative staff.

Daily, the education liaisons sent the health liaisons a negative network format (a method of tracking and maintaining continuous surveillance to help identify suspect cases by notifying units, in this case, schools, of the absence of cases), which was reinforced with active surveillance when cases occurred. Identified cases were referred to health units for confirmation or exclusion by RT-PCR (reverse transcriptase-polymerase chain reaction) and for advice on hygiene measures in the affected homes, classrooms, and schools to break the chain of transmission.

Jurisdictional health personnel followed up with each reported patient by telephone and maintained daily contact until discharge to monitor progress.

Operational definitions

This study included subjects using the following operational definitions as inclusion or exclusion criteria:

– Laboratory-confirmed case of COVID-19: Refers to a person who meets the operational definition of a suspected case and has received a confirmed diagnosis by RT-PCR testing at the ISEM Molecular Biology Laboratory. This laboratory is part of the National Network of Public Health Laboratories recognized by the Instituto de Diagnóstico y Referencia Epidemiológicos “Dr. Manuel Martínez Báez” (InDRE).

– Laboratory-confirmed COVID-19 death: Refers to a deceased person who met the operational definition of a suspected case and received a diagnosis confirmed by the Molecular Biology Laboratory of our institution. This laboratory is a member of the National Network of Public Health Laboratories recognized by the Institute of Epidemiological Diagnosis and Reference "Dr. Manuel Martínez Báez" (InDRE, for its Spanish acronym).

Sources of information

A review of epidemiologic reports was performed to compare the epidemiologic behavior of COVID-19 in the student population of the State of Mexico with that reported at the national level. These reports were obtained through the negative/active network registered by the Subdirección de Epidemiología del Instituto de Salud del Estado de México (ISEM) and were compared with the data published in the Epidemiological Bulletin of the Dirección General de Epidemiología de la Secretaria de Salud (SSA), specifically regarding the weekly report of cases of COVID-19.

Statistical analysis

For statistical analysis, frequencies, percentages, and incidences of COVID-19 per 100 monthly school discharges were calculated. State incidences were compared with the national incidence, with 95% confidence intervals. Microsoft Excel was used for the preparation of tables and graphs and for data analysis.

Results

Demographic characteristics

A total of 3,586 cases were detected and confirmed in schools in the State of Mexico. Of these, 2,048 (57.1%) were children, 1,312 (36.5%) were teachers and 226 (6.3%) came from the administrative staff.

The mean age of the students was 12 ± 3 years, the mean age of the teachers was 52 ± 6 years, and the mean age of the administrators was 43 ± 8 years. 1,115 (48%) of the students were female, 961 (67%) of the teachers were female, and 155 (62%) of the administrators were female. Of the 3,586 individuals who tested positive for SARS-CoV-2, 24 (0.6%) required hospitalization due to clinical data of moderate to severe COVID-19, of whom nine (37.5%) died. Additional details on demographic characteristics are shown in Table 1.

Epidemiological behavior

The Safe Return to School Program began in 31st epidemiological week of 2021, with a national infection rate of 5.0 and a state rate of 3.79, a difference of 1.21 between the two rates. An increase in the number of cases was observed in both curves for week 33, with a national rate of 10.1 and a state rate of 6.87, a difference of 3.27. However, no school detection cases were reported during weeks 31 to 36.

From epidemiological week 36, school detection cases began to be reported, with an average rate of 0.36 during follow-up until epidemiological week 51. In epidemiological week 40, the highest rate in schoolchildren was recorded, reaching 1.01. From this week on, a decrease in cases was observed, which was maintained until week 50 (Fig. 2). During the surveillance period, 32 schools were closed, representing 0.16% of the total number of schools.

Mortality

Before returning to school, during the first 30 epidemiological weeks, 8,921 deaths due to COVID-19 were recorded in the state population, with a weekly average of 53.5 deaths. After the return to school, 1,607 deaths were recorded, with a weekly average of 76.5. This resulted in a change in the mortality rate from 52.4 to 9.4 deaths per 100,000 inhabitants in the State of Mexico.

In the cohort studied, of the 3,586 persons with positive SARS-CoV-2 test results, 0.6% (24 persons) required hospitalization due to moderate to severe clinical symptoms of COVID-19. Of these hospitalized patients, nine (37.5%) died, and only one of the deaths was a student (11%). This translates to a mortality rate of 0.02 deaths per 100,000 students in the state during this period, compared to 0.021 deaths in the pre-return to school period ($p > 0.5$).

A similar pattern was observed for hospitalizations, with a pre-return to school rate of 0.30 per 100,000 students compared to 0.27 after the return to school surveillance period ($p > 0.05$).

The highest number of cases was recorded during epidemiological week 40, after which a decrease was observed until week 45. When comparing the national and state rates with school rates, the latter was always less than 1, with a linear pattern and a brief plateau during the weeks with the highest number of cases. When the maximum number of cases occurred at both the national and state levels (the outbreak's peak), the negative

Table 1. Characteristics of individuals testing positive for SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) during epidemiologic surveillance

Variable	Students, n = 2,048 (%)	Teachers, n = 1,312 (%)	Administrative staff, n = 226 (%)
Mean age of hospitalized patients	12	52	52
Type of school Public Private	 1211 (59.1) 837 (40.8)	 700 (79,7) 267 (20.3)	 116 (51.3) 110 (48.6)
Clinical picture Mild Moderate Severe	 2023 (98.7) 15 (1.1) 10 (0.09)	 1005 (76.6) 285 (21.7) 22 (1.6)	 162 (71.0) 60 (26.3) 4 (1.7)
Deaths	1 (0.04)	7 (0.5)	1 (0.44)
Hospital admissions	4 (0.19)	17 (1.2)	3 (1.3)
Hospitalized with vaccination scheme	0 (0)	11 (64)	2 (66)
Vaccination	0 (0)	967(73.7)	138 (61.0)

network strategy proved effective as part of the subsequent containment measures in schools. Comparatively, the behavior of the curves were different. During the monitoring period, 32 (0.16%) schools were closed.

Discussion

The pandemic SARS-CoV-2 infection has had a predominant impact on the adult population[14], although it has also affected the pediatric population. One of the main concerns regarding reopening schools was the possibility of an increase in cases in children, with consequent complications, including death[21]. Schools play a critical role in the functioning of society, and their closure during the SARS-CoV-2 pandemic sparked a global debate. Therefore, the development of strategies that would allow the safe reopening of these institutions became a matter of great urgency at international level. Monitoring by the ISEM shows that implementing timely containment and detection measures and adequate epidemiologic surveillance helps limit the spread of COVID-19 in educational settings.

Our analysis showed an increase in cases in the sixth week after reopening, but these cases did not exceed the increase observed in the community. These findings are consistent with those observed in Canada, where a 0.13 percentage point (95% CI: -0.15, 0.41) increase in COVID-19 cases was also reported in the 30 days following the resumption of face-to-face classes[22]. This pattern suggests that the increase in positive cases is more pronounced in adult staff than in the student population despite implementing non-pharmacological prevention measures. However, this increase is not considered significant, which is consistent with findings from schools in China[23]. Through epidemiological surveillance and proper implementation of measures, we are helping to make schools a low-risk environment for disease transmission. A study conducted in Greece suggests that the young population did not contribute significantly to the spreading of the SARS-CoV-2 virus because they tend to have milder symptoms[24]. However, this conclusion must be treated with caution because children may have risk factors that complicate the disease.

Theoretically, we expected to find more cases in the student population due to their greater interaction with each other compared to teachers and administrative staff. This assumption was confirmed when we observed that the percentage of positive cases among students was up to 20% higher than among teachers and 50% higher than among administrators. A similar situation has been observed in the United States and other countries that have opted to resume face-to-face classes. The researchers found an incidence of 16.1 (95% CI: 14.4 to 17.9) on the first day after schools reopened. However, these cases should be considered community-acquired because of the incubation period. In addition, a 1.3-fold higher incidence of 20.5 (95% CI: 18.5 to 22.5) cases was observed in the 14- to 17-year-old age group on the 20th day after school reopening. In contrast, a lower transmission rate was observed in the group of teachers and administrative staff.

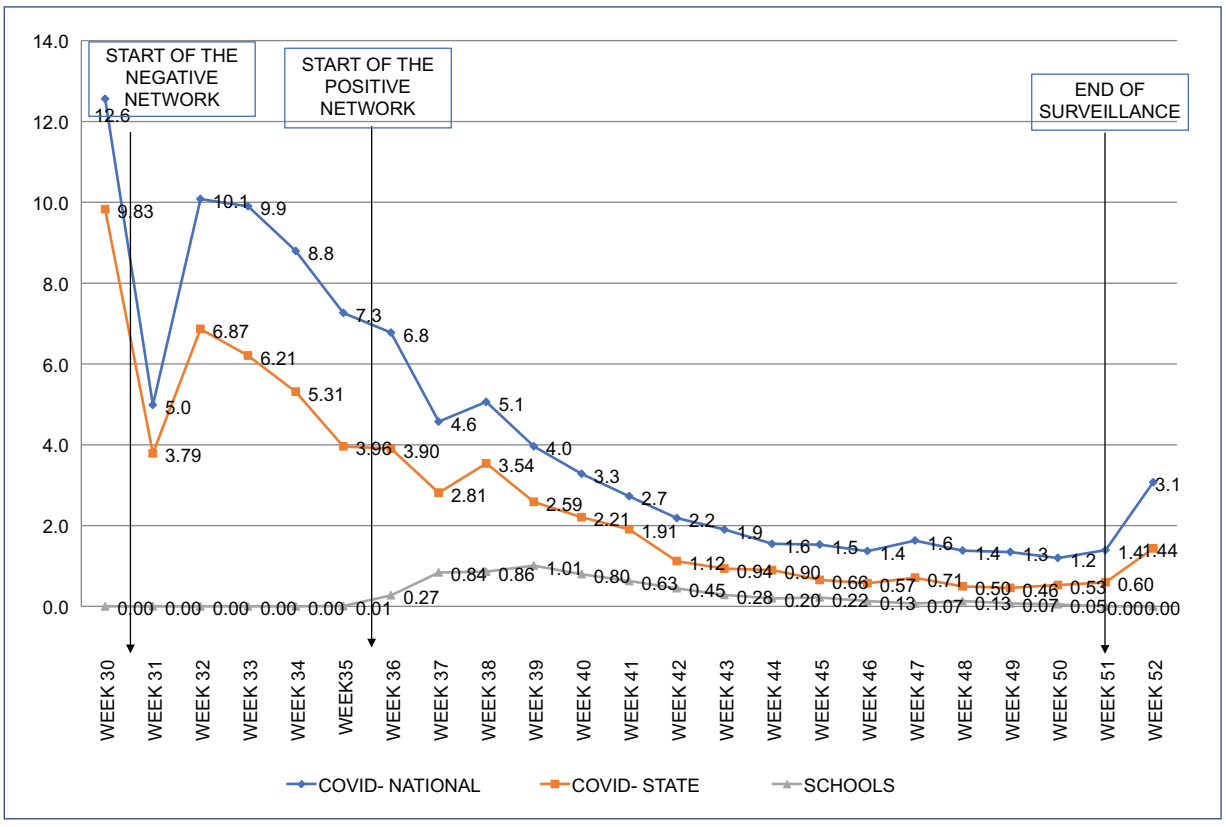

Figure 2. Cases of COVID-19 in children under 18 years in Mexico and the State of Mexico. A comparison of COVID-19 infection rates during epidemiological weeks 31 to 52 is presented. It is important to note that the behavior of the follow-up curve in schools was different from that observed at the national and state levels. The increases did not exceed rate 1.

In a study conducted in Israel, conflicting data were observed as a significant school outbreak was recorded only ten days after the resumption of face-to-face activities in educational institutions. This study reported an infection rate of 13.2% in students and 16.6% in staff. In this country, the distancing of students and staff could not be effectively implemented due to a heat wave that coincided with the reopening of schools[6]. These findings clearly highlight the essential role of community interventions and epidemiologic surveillance in reducing SARS-CoV-2 transmission. They also confirm what we postulated in our study: schools can reopen without a significant increase in community spread if appropriate preventive measures are implemented.

The low case mortality rate among schoolchildren, even in a period when they had not yet received the vaccine, is consistent with that reported in European Union countries and the United Kingdom, where the proportion of hospitalized cases was lower in the age groups of 5 to 11 years and 12 to 18 years (3% and 4%, respectively)[25]. The situation was different in prisons, orphanages, and nursing homes in the United States, where up to 25% of positive cases were detected within the same community. This underscores the urgency of implementing timely epidemiologic surveillance programs[26,27].

Consistent with these findings, low SARS-CoV-2 transmission has been observed in other settings, such as the resumption of social events, as long as disease prevalence remains low and risk reduction strategies are implemented[28]. The implementation of non-pharmaceutical interventions offers more advantages than disadvantages as long as the strategies are applied consistently and appropriately, ensuring effective infection control. In the case of school reopening, there was no increase in the rate of COVID-19 infection or mortality in the pediatric population.

Finally, although there are uncertainties in our epidemiologic projections, our results are consistent with previous studies that conclude that the implementation of non-pharmaceutical interventions offers more

advantages than disadvantages as long as the strategies are applied uniformly and appropriately[29]. Some questions remain to be evaluated, such as the behavior of prolonged COVID-19 in identified pediatric patients and the impact of vaccination on school dynamics[30].

Limitations

Diagnostic testing of the entire school population was not feasible due to the high costs associated with this procedure. Therefore, this study focused only on confirmed cases, which may have resulted in a potential underestimation of the prevalence of SARS-CoV-2, especially in the pediatric population, due to the presence of milder symptoms.

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 declare that no patient data appear in this article.

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Determination of surgical intervention in pre-term infants with necrotizing enterocolitis

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Abstract

Background: *Necrotizing enterocolitis (NEC) is the most common surgical disease in the neonatal period with a high mortality rate. To date, there is no consensus on the indications for surgery in the absence of pneumoperitoneum. This study aimed to determine the indications for surgery in pre-term infants with NEC and their mortality.* **Methods:** *We conducted a descriptive, observational, cross-sectional, and retrospective study including pre-term infants with NEC from two perinatal hospitals in Toluca, Mexico, between 2017 and 2022. Descriptive and inferential statistics and group comparisons were performed using Fisher and Kruskal–Wallis tests.* **Results:** *Of 236 patients with NEC, 52 (22%) required surgery; we analyzed 42 cases with complete clinical records. The indications for surgery were divided into (a) clinical deterioration (33.3%); (b) radiographic findings (31%); (c) laboratory alterations (19%); and (d) positive paracentesis (16.7%). The group of radiographic findings underwent surgery later, up to 2 days after the other groups. The mortality rate of surgical NEC was 42.9%.* **Conclusions:** *The most common indication for surgery in pre-term infants with NEC was clinical worsening despite optimal medical management; radiographic findings were the indication associated with the highest mortality. Laboratory abnormalities and positive paracentesis were the indications with the best outcomes but the least used.*

Keywords: *Necrotizing enterocolitis. Surgery. Newborn. Pediatrics.*

Determinación de intervención quirúrgica en pacientes pretérmino con enterocolitis necrosante

Resumen

Introducción: *La enterocolitis necrosante (ECN) es la enfermedad quirúrgica más frecuente en la etapa neonatal con una alta mortalidad. A la fecha, no existe consenso en las indicaciones quirúrgicas en ausencia de neumoperitoneo. El objetivo del estudio fue conocer las indicaciones de cirugía en neonatos pretérmino con ECN y la mortalidad.* **Métodos:** *Se llevó a cabo un estudio descriptivo, observacional, transversal y retrospectivo, incluyendo a neonatos pretérmino con ECN de dos hospitales perinatales de Toluca, México, entre 2017 a 2022. Se realizó estadística descriptiva e inferencial y comparación de grupos con prueba de Fisher y Kruskal - Wallis.* **Resultados:** *De 236 pacientes con ECN, 52 (22%) requirieron cirugía; se presenta el análisis de 42 casos con su expediente clínico completo. Las indicaciones para intervención se dividieron en los siguientes grupos: a) deterioro clínico (33.3%); b) hallazgos radiográficos (31%); c) alteraciones de laboratorio (19%) y d) paracentesis positiva (16.7%). El grupo de hallazgos radiográficos se operó más tardíamente, hasta dos días después de los*

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demás grupos. La mortalidad en ECN quirúrgica fue del 42.9%. **Conclusiones:** *La indicación más utilizada para determinar cirugía en neonatos pretérmino con ECN fue el deterioro clínico a pesar de terapéutica médica máxima; los hallazgos radiográficos fueron la indicación que se relacionó con mayor mortalidad. Las alteraciones de laboratorio y paracentesis positiva fueron las de mejores resultados, pero las menos empleadas.*

Palabras clave: *Enterocolitis necrosante. Cirugía. Recién nacido. Pediatría.*

Introduction

Necrotizing enterocolitis (NEC) is the most common acquired inflammatory bowel disease in pre-term and low-birth-weight infants. Although its incidence is 7-12% the exact figure varies depending on the gestational age, the definition used to determine the disease, and whether some other pathologies, such as spontaneous intestinal perforation, are included. NEC has an estimated rate of one newborn per 1000 live births[1-3].

At present, NEC is one of the most common surgical emergencies in the neonatal period, with nearly half of the diagnosed patients requiring surgery. Surgical NEC has worse outcomes compared to the variety that has exclusively medical resolution, with a reported mortality of up to 95% for the total NEC variety[1,4]. Deciding when a patient requires surgical management is still controversial among pediatric surgeons, although it is a determining factor in the patient's prognosis. Pneumoperitoneum remains the only absolute indication for surgery; unfortunately, it is present in < 50% of cases. Relative indications for surgery include the presence of clinical deterioration despite optimal medical management, portal venous gas, ascites, positive paracentesis, fixed bowel loops, abdominal distension with erythema, and thrombocytopenia. Patient survival and quality of life depend not only on the severity of the disease but also on the timing of surgical intervention[5-7].

This study aimed to determine the indications for surgical management in pre-term infants with NEC and their mortality.

Methods

Study design

We conducted an observational, descriptive, retrospective, cross-sectional, and descriptive study.

Setting and participants

Neonates ≤ 36.6 weeks of gestation (WG) with a diagnosis of NEC Stage IIa or greater (according to Bell criteria), admitted to the neonatal intensive care unit (NICU) of two perinatal hospitals in the city of Toluca: Hospital de Ginecología y Obstetricia del Instituto Materno Infantil del Estado de México and Hospital Materno Perinatal Mónica Pretelini Sáenz del Instituto de Salud del Estado de México, between January 2017 and June 2022, were included in the study. Patients with incomplete information in their records were eliminated from the study.

Variables

We analyzed post-natal age, sex, gestational age, weight, primary indication for surgery, procedure performed, radiographic and laboratory findings, Bell staging, time from diagnosis to surgery, days of fasting and parenteral nutrition (TPN), development of short bowel syndrome, and mortality. Data were collected from the medical records of the two participating hospitals.

Definitions

NEC was diagnosed according to modified Bell's clinical, radiographic, and laboratory criteria[8].

Indications for surgery were categorized as (a) clinical worsening despite optimal medical management, (b) radiographic findings, (c) positive paracentesis, and (d) laboratory alterations.

Clinical deterioration was defined as the clinically poor evolution of patients characterized by the presence of hypotension, oliguria, bradycardia, increased abdominal circumference with tension (> 2 cm from the basal circumference), changes in skin color at the abdominal level, and the presence of a palpable abdominal tumor. This clinical picture was present despite the fact that the neonate had maximum intensive management, consisting of fasting, orogastric tube, parenteral feeding, aminergic support, mechanical ventilation, and broad-spectrum antibiotics.

Total NEC was defined when > 80% of the small bowel was ischemic-necrotic.

Paracentesis was considered positive according to Kosloske's criteria if a sample is ≥ 0.5 ml of fluid with a cloudy or clear appearance but with a positive Gram stain was obtained[9].

Extensive pneumatosis was defined as being present in four quadrants on abdominal radiographs.

Statistical analysis

Descriptive statistics were performed using measures of frequency, central tendency, and dispersion. For group comparisons, χ^2 or Fisher's exact test was used for qualitative variables and Kruskal–Wallis for quantitative variables. Data processing was performed using the SPSS V.25 statistical package.

Approval was obtained from the ethics and research committees of the two hospitals.

Results

During the study period, 7550 pre-term infants were born in both hospitals, of whom 236 were diagnosed with NEC Stage IIa or higher according to Bell's staging, with a prevalence of 3%. One hundred and eighty-four neonates (78%) did not require surgery, and the remaining 52 (22%) underwent surgery; of these, 10 were excluded because of incomplete records. Finally, 42 patients with NEC requiring surgery were analyzed.

The median gestational age of the pre-term neonates who underwent surgery was 33 WG, the median age at the time of surgery was 12 days, and the median weight was 1400 g. Of the total number of patients, 17 (40.5%) were treated with vasoactive amines up to 72 h before surgery. Neonates were grouped according to comorbidities into infectious (sepsis was the main one found in 17 neonates, 40.5%), respiratory (respiratory distress syndrome in five, 11.9%), cardiopathies (patent ductus arteriosus in six patients, 14.3%; other cardiopathies including atrial septal defect, ventricular septal defect, and Ebstein's anomaly in four, 9.5%), and others (intrauterine growth retardation and perinatal asphyxia in five, 11.9%). The median of time from the diagnosis of NEC to surgical intervention was 56 h (interquartile range [IQR]: 37.7-86.7).

Once the surgical management was decided, 23 patients (54.8%) underwent exploratory laparotomy (EX LAP), four (9.5%) underwent exclusive peritoneal drainage (PD), and 15 (35.7%) underwent PD followed by EX LAP. The procedures performed during EX LAP were intestinal diversion in 17 neonates (40.5%), intestinal anastomosis in 10 (23.8%), and diversion with intestinal anastomosis in 11 (26.2%) of the cases.

We grouped the indications for surgery according to the main criteria used by the different surgeons as follows: (a) clinical deterioration despite optimal medical management (33.3%); (b) based on radiographic changes (31%); (c) due to changes in laboratory tests (19%); and (d) positive paracentesis (16.7%). The demographic and clinical characteristics of the patients according to each of these groups are shown in table 1.

Radiographic findings were pneumoperitoneum in eight neonates (19%), extensive pneumatosis in three (7.1%), and portal venous gas in two (4.8%) neonates.

Predominant laboratory findings were thrombocytopenia in four neonates (9.5%), hyponatremia in three (7.1%), and neutropenia in one (2.4%) neonate.

Total enetrocolitis was present in 16 cases (38%), of which five patients (31.2%) belonged to the clinical deterioration group, eight (50%) to the radiographic findings group, two (12.5%) to the laboratory changes group, and one neonate (6.3%) to the paracentesis group (p = 0.18). Of these patients, three underwent a second-look surgical reintervention 24-48 h after the initial event, with no improvement in bowel ischemic conditions.

The median number of fasting days in the operated neonates was 13 (IQR: 9.7-19), and the median number of days on TPN was 16 (IQR: 12.7-22).

One of the most frequent and worst prognostic complications of surgical NEC is the development of short bowel syndrome, which occurred in 10 (23.8%) of our patients.

According to Bell's staging, 13 neonates (31%) were in Stage IIa/b at the time of surgery, and 29 (69%) were in Stage IIIa/b; of the latter, 45% belonged to the group with radiographic findings, which were the patients taken to the operating room at the latest. Other significant findings in the neonates who were Bell Stage III were that they accounted for 64% of all those who used amines, 76% of those who required an intestinal diversion, and 100% of those with short bowel syndrome.

The overall mortality of NEC in our study group was 42.9%, corresponding to 18 patients; 12 (66.7%) had total NEC. Of the neonates with Bell Stage III, 72.2% died. There was no difference in mortality between neonates who underwent first-intention intestinal anastomosis and those who underwent intestinal diversion. The analysis between different factors and mortality is shown in table 2.

Discussion

Recent technological advances have allowed more pre-term infants to survive, leading to an increase in the presentation of pre-term conditions, including NEC, whose incidence in most reports is higher than our results[6,10]. This may be secondary to the fact that our study only included patients diagnosed with NEC Bell

Table 1. Demographic and clinical characteristics of patients with surgical NEC according to the indication for surgery

Variable	Clinical deterioration (n = 14)	Radiographic findings (n = 13)	Laboratory alterations (n = 8)	Positive paracentesis (n = 7)	p-value
Females, n (%)	7 (50)	6 (46.2)	3 (37.5)	6 (85.7)	0.26
Gestational age in weeks, median/(IQR)	32.2/(30.3-34.1)	34.1/(31.4-35.3)	34/(32.4-35)	33.5/(31.5-35.2)	0.30
Age in days at the time of surgery, median/(IQR)	9/(7-12)	12/(9-13)	12.5/(8.8-14.5)	12/(10.7-14.3)	0.38
Weight in kilograms, median/(IQR)	1.3/(1.2-1.4)	1.4/(1.4-1.8)	1.3/(1.2-1.6)	1.5/(1.1-1.6)	0.35
Use of amines * n (%)	5/35.7	6/46.2	2/25	4/57.1	0.63
Comorbidities n (%)					0.64
RDS	2 (14.3)	0	1 (12.5)	2 (28.6)	
Sepsis	7 (50)	4 (30.8)	3 (37.5)	3 (42.9)	
PDA	1 (7.1)	3 (23.1)	1 (12.5)	1 (14.3)	
Other cardiopathy	2 (14.3)	1 (7.7)	0	1 (14.3)	
Perinatal asphyxia	2 (14.3)	1 (7.7)	0	0	
Diaphragmatic hernia	0	2 (15.4)	0	0	
IUGR	0	1 (7.7)	1 (12.5)	0	
Time in hours from diagnosis to surgery, median/(IQR)	61.5 (44-81)	89 (77-96)	43 (45-52)	27 (26-37)	0.01
Bell's stage at the time of surgery, n (%)					0.01
Bell IIa	2 (14.3)	0	0	1 (14.3)	
Bell IIb	6 (42.9)	0	1 (12.5)	3 (42.9)	
Bell IIIa	6 (42.9)	5 (38.5)	7 (87.5)	3 (42.9)	
Bell IIIb	0	8 (61.5)	0	0	
Surgical intervention, n (%)					
EX LAP	7 (50)	9 (69.2)	3 (37.5)	4 (57.1)	0.25
Exclusive peritoneal drainage	2 (14.3)	0	0	2 (28.6)	
Peritoneal drainage+EX LAP	5 (35.7)	4 (30.8)	5 (62.5)	1 (14.3)	
Procedure, n (%)					0.11
Intestinal diversion	5 (35.7)	8 (61.5)	3 (37.5)	1 (14.3)	
Intestinal anastomosis	2 (14.3)	2 (15.4)	2 (25)	4 (57.1)	
Diversion + intestinal anastomosis	5 (35.7)	3 (23.1)	3 (37.5)	0	
Fasting days, median/(IQR)	16 (10-18)	14 (12-20)	11.5 (8-13)	9 (8-17)	0.13
Days with TPN, median/(IQR)	21 (16-23)	18 (14-29)	14 (11.5-16)	13 (11-20)	0.06
Short bowel syndrome, n (%)	2 (14.3)	7 (53.8)	0	1 (14.3)	0.02
Mortality, n (%)	6 (42.9)	8 (61.5)	2 (25)	2 (28.6)	0.37

*Use of amines up to 72 h before surgery.
$p < 0.05$: statistical significance.
EX LAP: exploratory laparotomy; IQR: interquartile range; IUGR: intrauterine growth retardation; PDA: persistent ductus arteriosus with hemodynamic repercussions; RDS: respiratory distress syndrome; TPN: parenteral nutrition.

Stage IIa or higher. Similarly, our proportion of patients with NEC requiring surgery was 22%, which is lower than the 25-50% considered internationally[2,11].

At present, there are no definitive guidelines for surgical intervention in patients with NEC without clear evidence of perforation. Thus, surgeons are constantly faced with the difficult situation of choosing between early surgery that benefits the patient or unnecessary late surgery, and in the worst-case scenario, wrongly deciding that a newborn does not need surgery. Therefore, alternatives should be sought to make this decision in a correct and timely manner. Recently, the usefulness of different biomarkers, ultrasound, and technologies such as infrared spectroscopy have been mentioned[1,12,13]. However, they have the disadvantage of not being available in all places, as is the case of the hospitals where this research was conducted. Therefore, it is important to know the indications that are considered when deciding to intervene in a patient since, in most of the world, this decision is made according to the severity of the disease as defined by the modified Bell's criteria[14].

Table 2. Bivariate analysis of mortality in patients with surgical NEC

Variable	Mortality, n (%)	p
Gestational age		
≤ 33 WG	12 (50)	0.35
34-36.6 WG	6 (33.3)	
Weight in grams		
≤ 1500	13 (46.4)	0.37
≥ 1501	5 (35.7)	
Use of amines	9 (52.9)	0.22
Comorbidity		
Sepsis	8 (47.1)	0.01
PDA	3 (50)	
Other cardiopathy	4 (100)	
Diaphragmatic hernia	1 (50)	
IUGR	2 (100)	
Bell's stage at the time of surgery:		
IIa	1 (33.3)	0.71
IIb	4 (40)	
IIIa	8 (38.1)	
IIIb	5 (62.5)	
Indication for surgery		
Clinical deterioration	6 (42.9)	0.37
Radiographic findings	8 (61.5)	
Laboratory alterations	2 (25)	
Paracentesis	2 (28.6)	
Diagnostic time surgery		
≤ 36 h	3 (33.3)	0.22
36.1-72 h	4 (28.6)	
≥ 72 h	11 (57.9)	
Surgical intervention		
EX LAP	9 (39.1)	0.58
PD	1 (25)	
PD + EX LAP	8 (53.3)	
Procedure:		
Intestinal diversion	7 (41.2)	0.76
Intestinal anastomosis	4 (40)	
Diversion and intestinal anastomosis	6 (54.5)	
Radiographic finding		0.17
Pneumoperitoneum	5 (62.5)	
Gas in the portal vein	2 (100)	
Pneumatosis	1 (33.3)	
Laboratory findings		0.42
Thrombocytopenia	2 (50)	
Leukopenia	0	
Hyponatremia	0	
Total NEC	12 (75)	0.01
Short bowel syndrome	5 (50)	0.43

$p < 0.05$: statistical significance.
EX LAP: exploratory laparotomy; IUGR: intrauterine growth retardation; NEC: necrotizing enterocolitis; PD: peritoneal drainage; PDA: persistent ductus arteriosus with hemodynamic repercussion; WG: weeks of gestation.

According to our results, the main indication used by surgeons to perform surgery for a premature patient with NEC was having a poor evolution with deterioration of their clinical condition despite optimal medical management. In the report by Bethell et al., this failure of medical management was the second most common indication, the main one being the diagnosis of intestinal perforation[11]. However, radiographic evidence of perforation is rare, being present at best in 50% of cases[15]. Hence, many patients with bowel perforation will not have pneumoperitoneum. Only 19% of our patients had peritoneal free air, and in general, radiographic findings were the second most common criterion for deciding to operate.

In this work, we found that other criteria used for surgery were laboratory findings and paracentesis. Regarding the former, there are reports that support it as an adequate guide for determining surgery, as in the case of the seven indicators of metabolic deterioration described by Tepas et al.[16,17], whose advantage is their easy availability in most hospital units. Accordingly, we found that thrombocytopenia, hyponatremia, and neutropenia were the most common changes in these indicators and were the reason for the surgical decision in 19% of our patients. Regarding paracentesis, it remains a current recommendation in neonates with suspected NEC complicated by necrosis and intestinal perforation; this surgical indicator has the advantage of high sensitivity and specificity (87/100%)[9,18]. However, it was infrequently performed in the NICUs where we conducted this study. It was the least common indication used by surgeons (16.7% of cases), perhaps due to concerns about adverse effects secondary to abdominal puncture.

It is noteworthy that 69% of our surgical population was in Bell Stage III, which is described as a phase of complications of the disease. In our report, we confirmed that these patients presented an advanced stage of NEC, as more than half of them were supported by vasoactive amines before and at the time of surgery. In addition, most of the patients required intestinal diversion for the resolution of the disease, meaning that the patients will require at least one more surgery to restore intestinal transit. This stage showed the highest mortality. We also found that all neonates who developed short bowel syndrome corresponded to Bell's group III. These are undoubtedly important findings that highlight the need for early intervention to improve outcomes in surgical NEC.

Yanowitz et al. reported that EX LAP was the most frequent initial surgical procedure (68% of their cases), followed by PD in 32%[19]; our data also showed a predominance of EX LAP but a lower proportion of PD as the only treatment since although it was used in 45.2% of cases, it was maintained as definitive therapy in only 9.5%.

Therefore, we observed PD as a temporary measure to stabilize the patient with lower weight and gestational age before surgery, which occurred in 36% of our patients.

Patient hemodynamic status, comorbidities, weight, surgical findings, surgeon preference, and available resources, among others, are the main factors that influence the type of surgery performed in neonates[2]. Appropriately designed studies are needed to determine the superiority of primary anastomosis over intestinal diversion in cases of NEC[20]. According to what we reported, we had a 2:1 ratio in the number of neonates with intestinal diversion and anastomosis, with no difference in mortality (41.2% vs. 40%), median fasting days (12 days for both), and median TPN days (16 vs. 17) between the two procedures.

The key to improved survival and quality of life for patients with NEC depends largely on early surgery. Despite technological improvements in neonatal care, including advances in monitoring, medications, parenteral nutrition, and surgical and anesthesia techniques, high morbidity and mortality persist in these neonates[5,21]. In the present study, the median of time from the diagnosis of NEC to the indication for surgery by the surgeon was 56 h. According to the studied groups, we observed that neonates in the group with radiographic findings underwent surgery later, with a difference of > 2 days compared with the neonates who underwent surgery earlier in the paracentesis group ($p = 0.01$). Similarly, we observed that patients who developed short bowel syndrome had a median of time from diagnosis to surgery of 88.5 h compared to patients who did not develop this complication, with a median of time of 49.5 h ($p = 0.02$). We suggest that this could be because patients who received earlier surgical care had better bowel conditions—less duration of ischemia and necrosis—which allowed the preservation of a greater amount of viable bowel. Therefore, preventing one of the main complications that alter the quality of life, increase costs for family members and the health system, and put the patient's life at risk, such as short bowel syndrome followed by intestinal insufficiency. Regarding survival, we found no statistical significance in the time between patients who died and those who did not (75 vs. 49.5 h, $p = 0.5$).

We reported a mortality of 42.9%, higher than the average of 34.5% in international reports[22]. However, our 38% prevalence of total NEC was much higher than the 9.3% reported by Murthy et al.[23]. This high prevalence contributed to the increased mortality we found since this type of NEC is the one with the worst prognosis, with mortality between 68.8-95%[4], consistent with the 75% we reported.

Although no statistically significant differences in demographics and comorbidities were found between the groups, the group with radiographic findings had the highest mortality (61.5%). This may be due to the late presentation of signs, such as pneumatosis and gas in the portal vein, as well as pneumoperitoneum, also absent in most cases of bowel perforation. The frequency of pneumoperitoneum in our results was even lower than that reported in previous literature. In addition, neonates who underwent surgery later likely had a more compromised physiological state, which may have contributed to the poor outcome. Moreover, the groups with lower mortality were those who underwent surgery for clinical NEC and laboratory changes, and those with positive paracentesis. Exploring these surgical indications in prospective studies may lead us to perform timely surgery and improve outcomes.

The main limitation of the study is its retrospective nature, which prevents us from exploring important associations for the evaluation of patients with surgical NEC.

Based on our findings, we conclude that the most common indication for surgery in pre-term neonates with NEC was clinical deterioration despite optimal medical management; radiographic findings were the indication associated with the highest mortality. Laboratory changes and positive paracentesis had the best results but were the least used.

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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