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REVIEW ARTICLE

Learning from history in the midst of the COVID-19: epidemics/pandemics of antiquity up to the fall of the Western Roman Empire

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Abstract

When humans discovered agriculture and livestock, they ceased to be nomads and began to settle in towns until they created large cities. From the first human settlements in Egypt, Mesopotamia, and the Anatolian Peninsula, populations were exposed and susceptible to new infectious agents, leading to epidemics and pandemics. Great civilizations emerged, such as Egypt, the land of Hatti, Israel, Greece, Carthage, and Rome, among others. Contact between different populations through wars or maritime trade is well documented and has been described as a source of epidemics throughout history. Epidemics described as plagues or pestilences, such as those of Egypt, the Hebrews, or the Hittites, are based on biblical texts or evidence such as tablets or hieroglyphic writings. We also reviewed classical books by authors such as Homer, Aeschylus, Herodotus of Halicarnassus, Thucydides, Diodorus Siculus, Dionysius of Halicarnassus, Titus Livius, Suetonius, and others; and described all epidemics/pandemics chronologically. This article describes the epidemics/pandemics for which there is written evidence from ancient Egypt to the fall of the Roman Empire. We should not be surprised when new epidemics/pandemics appear as causes of political and economic collapse, as this has been common throughout history, decimating, blocking, or even destroying cultures and civilizations repeatedly.

Keywords: *Pandemic. Epidemic. Plague. Pestilence. History. Antonine plague.*

Aprendiendo de la historia en medio del COVID-19: epidemias/pandemias de la antigüedad hasta la caída del Imperio Romano de Occidente

Resumen

Cuando el hombre descubrió la agricultura y la ganadería, dejó de ser nómada y empezó a asentarse en pueblos hasta crear grandes ciudades. Desde los primeros asentamientos humanos en Egipto, Mesopotamia y la península de Anatolia, las poblaciones estuvieron expuestas y susceptibles a nuevos agentes infecciosos, dando lugar a epidemias y pandemias. Aparecieron grandes civilizaciones como Egipto, la Tierra de Hatti, Israel, Grecia, Cartago y Roma, entre otras. El contacto entre las distintas poblaciones a través de las guerras o el comercio marítimo está muy bien establecido y descrito como focos de epidemias a lo largo de la historia. Las epidemias descritas como plagas o pestilencias, como las que ocurrieron a los egipcios, los judíos, o los hititas, se describen con base en textos bíblicos o mediante evidencias como tablillas o escritos jeroglíficos. También revisamos libros clásicos de autores como Homero, Esquilo, Herodoto de Halicarnaso, Tucídides, Diodoro Sículo, Dionisio de

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Halicarnaso, Tito Livio, Suetonio, entre otros. Este artículo describe cronológicamente todas las epidemias/pandemias de las que existe evidencia a través de la escritura desde el antiguo Egipto hasta la caída del Imperio Romano. No debemos sorprendernos cuando aparecen nuevas epidemias/pandemias como causantes del colapso político y económico, ya que ha sido algo común a lo largo de la historia, diezmando, bloqueando o incluso destruyendo culturas y civilizaciones reiteradamente.

Palabras clave: *Pandemia. Epidemia. Plaga. Pestilencia. Historia. Plaga Antonina.*

Introduction

For an infectious disease to cause an epidemic outbreak, the presence or introduction of an infectious agent into a vector such as humans, contact of that agent with enough susceptible individuals in a population not previously exposed to infection, and effective human-to-human contact and transmission is required.

Primitive man ceased to be a nomad when agriculture and animal husbandry appeared, giving rise to the first populations and great civilizations but also to the first epidemics and pandemics. Diseases are as old as humankind. We have had to live with the coronavirus pandemic since the end of 2019 and the beginning of 2020. However, throughout the ages and since man has lived in society, infectious and contagious diseases have also coexisted with us. Pandemics not only mean an infectious disease but also have several characteristics, such as their global distribution in all latitudes and longitudes, with a high spread and contagiousness, and the number of lost human lives, causing the collapse of societies and their systems.

Some of the epidemics/pandemics that have been documented through writing or other traces are described here, from the earliest civilizations to the Cyprian Pandemic, which marked the collapse of the Roman Empire before its split into the Western Roman Empire and the Eastern Roman Empire.

For this review, the following concepts have been considered:

Endemic

From the Greek *endemos*, native, plus *demikos*, relating to people or population. It means present in a community or group of people. It refers to diseases that are prevalent with a high number of cases continuously in a region compared to others. Sanitary phenomenon unlimited in time and limited in space[1].

Epidemic outbreak

Two or more cases epidemiologically linked. The presence of a single case under surveillance in an area where the disease did not exist is also considered an outbreak. An outbreak occurs when there is an unusual increase in the number of cases of a disease above normal; it may be localized in a specific area or extend to several countries. It may last for days, weeks, or years[2].

Epidemic

From the Greek words *epi*, about, *demises*, referring to people or population. A disease affects many people in a community simultaneously, when it is not normally present continuously, or when there is a temporary increase in the number of cases of an endemic disease. The usual rates of the disease must be known to detect a significant increase and determine the occurrence of an epidemic. It occurs in a specific geographical area, and generally implies the occurrence of a large number of new cases in a short period, greater than the expected number[1,2].

Pandemic

From the Greek words *pan*, whole, and *demos*, *demikos*, people. A widespread epidemic covering large groups of countries and several continents. It is the expansion of the territory of the epidemic worldwide. It must meet at least two criteria: the first, as mentioned above, is that it affects several continents, and the second is that the cases in each country are no longer imported but caused by community transmission[1,2].

Plague

We must also mention “pests,” a synonym for pestilence, when discussing epidemics and pandemics. It refers to an epidemic disease, almost always related to the famous plague caused by *Yersinia bacillus*. The terms pests, pestilence, and plague are used in various classical or medieval sources, not always used to refer to a single and specific etiology. Either term refers to the condition of many people with epidemic characteristics and high mortality[3].

Epidemics and pandemics before Christ

The group of people that constituted humanity between the years 10,000 and 5000 B.C. (before Christ) was distinguished into those that progressed to build great archaic and ancient cultures, such as the Sumerian, Assyro-Babylonian, Egyptian, Chinese, Iranian, Indian, Israelite, and pre-Hellenic, among others; and those whose progress was minimal or absent, remaining stagnant, for which they became extinct by themselves or were conquered by human groups stronger than them. Epidemic diseases have occurred in all civilizations. In the ancient cultures, they were approached first with a magical-religious nature and secondly with scientific knowledge through the physicians of that time[4].

A chronological order of the various epidemics/pandemics has been established, beginning in Egypt and almost simultaneously in the Hittite Empire, the Hebrews, and the Philistines, which could be documented as the first major pandemic. Then, the epidemics in Athens, Carthage, and Rome are documented.

The plague of the Egyptians: Egyptian, Hebrew, or Hittite origin

Civilization in North Africa began about 13,000 years ago when the Sahara was a savannah inhabited by gathering and hunting groups. However, the changing climate gave way to desert, and people were forced to settle around the Nile, the region's main water source. The earliest settlements were located in the northernmost part of the country, known as Lower Egypt, and include three major sites: Beni-Salama, Fayum, and Omari (4600-4400 B.C.). During the following periods, sedentarization began, and with the appearance of the desert, agriculture, and livestock became the primary food source. Furthermore, during this period, foreign marketing began with Lebanon, Mesopotamia, and Sumer[5].

Along with the great Egyptian history, the arrival of the Jews in Egypt and their relationship with plagues and pestilence should also be mentioned. Historically, this fact may be related to the Asian migration to the Nile Delta of the Hyksos (foreign rulers from the Middle East). Then, the Egyptians started a war against them until they were driven back to Canaan[6]. This part of the story happened at the time of Amnosis, but it is not known if they were Jews. Regarding the plagues in Egypt, the book of Exodus in the Old Testament of the Bible describes that Moses and his brother Aaron went to Pharaoh's court to warn him that if he did not let his people leave, Yahweh would unleash a terrible plague on Egypt, and so it happened: blood in the waters of the Nile, frogs, mosquitoes, and plague until the Jews were permitted to leave Egypt. According to various film scripts, Ramses II is mentioned as the protagonist pharaoh of this exodus[7]; however, the historical facts point to perhaps a longer period in history.

Some historical facts, such as the Amarna Letters (correspondence between Egypt and foreign countries of the Near East), indicate that some of these facts can be related to the reign of Akhenaten. For example, one of these letters reports a plague that spread from Canaan to the Hittite kingdom and from there to Cyprus and the capital of Egypt. Previously, during the description of the Hittite Empire, an epidemic was mentioned that almost devastated the entire kingdom of the country of Hatti, coming from Egyptian slaves in the years close to the reign of Akhenaten. Therefore, will the first pandemic described in history be this one that encompassed several empires of antiquity? In fact, in 2004, the archaeological discovery of the inhabitants of Akhenaten identified a high frequency of fleas and other fossilized parasites, all containing the bacterium that produces the plague (*Yersinia pestis*)[8].

For centuries in antiquity, the numerous epidemics and pandemics were called "plagues" and caused great mortality. Various ancient sources mention a terrible plague that spread throughout the Mediterranean in the fourteenth century B.C., during the time of Akhenaten. Various medical papyri attest to an epidemic that probably began during the reign of Amenhotep, Akhenaten's father. During his reign, an extraordinary number of statues of Sekhmet, the goddess of plagues, were made to appease the goddess and thus rid Pharaoh and Egypt of disease. In 1344 B.C., it is documented that King Tushratta of Mitanni sent an embassy to Egypt with the statue of the goddess Ishtar, which had healing properties and could fight plagues. It is possible that this plague affected members of Akhenaten's royal family, such as the princesses Maketaton, Neferneferure, and Setepenre, the royal wife Kiya, and Akhenaten himself. The plague spread and persisted during Akhenaten's reign, where archaeological evidence shows the appearance of fleas and bedbugs, vectors that spread parasites and were ideal for epidemic diseases. Simultaneously, in other places outside of Egypt, such as Cyprus, Canaan, Sumur Amurru, and Megiddo, it is mentioned in letters to the Pharaoh that an epidemic and pestilence ruined the cities. Another region also severely affected was Anatolia, previously

mentioned by King Mursili II, in the heart of the Hatti Empire. Other papyri refer to a possible Asian origin of the pandemic (18th Dynasty: 1539-1292 B.C.): "The body is blackened with black spots." They mention plagues spread by rodents, which could be tularemia or "rabbit fever," but others support malaria or bubonic plague[9].

Hittite Empire at the time of Mursili II: the great plague of the Hittites

The region of Anatolia, corresponding to modern Turkey and the northern parts of Syria and Iraq, is an area where various civilizations developed over several millennia, including the Hittite Empire, the Hurrians, and the Mitanni.

In the last quarter of the 3rd millennium B.C., the Anatolian Peninsula was occupied by indigenous population centers confined to small geographical areas. In the center of the plateau, small kingdoms formed a coalition to stop the expansion of the Akkadian King Naram-Sin (2260-2223 B.C.), giving rise to an indigenous group known as the Hattians, for whom the region became known as the "Country of Hatti." Indo-European migrations during the next two centuries mixed with the local population, giving rise to the Hittites. This empire reached its peak during the reign of Suppiluliuma I (1344-1322 B.C.), conquering Assyria, Mitanni, and even Egypt. This King defeated the Pharaoh Amenhotep IV (Akhenaten). This triumph over the Egyptian Empire came with a heavy tribute. According to the Hittite annals written on tablets, an epidemic of plague spread among the thousands of captives the Hittites made in Egypt, and "when the captives entered the land of Hatti, and from that day on, death reigned in the kingdom." Emperor Suppiluliuma I died soon after, and Arnuwanda, his successor, also fell ill (1321 B.C.). He was succeeded by his younger brother Mursili II (1321-1295 B.C.), who took power in a country on the verge of collapse. In the annals of Mursili II, the episode of the plague epidemic is very illustrative of the Hittite mentality. It is known as the "Plague Prayer" and reads as follows: "What is this, oh gods? What are they doing? They have allowed a plague in the land. The land of Hatti, all of it, is dying: so no one prepares the sacrificial loaves and libations for us." The plague was believed to be a divine punishment for the King's sake. The entire population had to observe a series of religious protocols to ensure divine blessing; if any of them were violated, the wrath of the gods would be directed against it, and if the King committed the fault, the gods' punishment was worse, and it fell on all the people. The plague that devastated the empire was considered the result of the fact that Suppiluliuma I, after his victories, stopped making offerings to certain gods, so they sent him the plague that ended his life and that of his son[10].

It is now known that the Hittites attacked the Egyptian frontier at Amka, east of Byblos and Simira. The spoils and prisoners of war left a contaminated trail, as evidenced by the letter RS 4475 from Ugarit, ruled by Nipmaddu II, one of the states of the Hittite Empire. It was a plague that lasted 35-40 years, infecting humans and animals, causing fever, disability, and death, spread by rodents on board ships. This disease points to *Francisella tularensis*, the etiologic agent of tularemia. The description from the Hittite records, such as weak knees and internal burning sensation, is consistent with tularemia. It has been shown that the geographical area has been a reservoir of the etiologic agent since the 2nd millennium B.C. in the Canaan area, later spreading to Egypt in the 18th century B.C. and later with the war on Hittite lands[11].

The Philistines, enemies of the Hebrews: the plague of Azoth

In the Bible, the Philistines are enemies of the Israelites and can be connected to Old Testament stories such as the story of Goliath[12] or Delilah[13]. They were originally a people of the Late Bronze Age, as evidenced by Egyptian, Hebrew, and Assyrian sources. In Egyptian documents, they are referred to as part of the Sea People, who were called the *Peleset*[14]. After their confrontation with the Egyptians, they settled on the coast of Canaan, today's Gaza Strip (Palestine). The Book of Genesis mentions that they were of Egyptian origin, although it is also mentioned that they could have been descendants of the Cretans, the Aegean, or Minor Asia[14]. Recent studies of the DNA of a group of individuals from Ashkelon have provided definitive evidence of the European genetic origin of the Philistines, supporting the theory that they were foreigners who arrived in the Middle East in the 12th century B.C. from Greece, Crete, Sardinia, or even the Iberian Peninsula, as evidenced by ceramics similar to Greek, the use of Aegean rather than Semitic writing, and the consumption of pork[15].

The French Baroque oil painting entitled "The Philistines Struck by the Plague" or "The Miracle of the Ark" shows the Old Testament story of Samuel in which he describes how the Philistines steal the Ark of the Covenant and take it to the Philistine city of Ashdod or

Azoth after defeating the Israelites. They place the Ark in a temple dedicated to the god Dagon, for which Yahweh sends a great plague on the inhabitants of Ashdod and other Philistine cities. "God punished all the inhabitants, from the smallest to the largest, causing them to grow tumors, a disease that lasted until the Ark was returned. There is an atmosphere of desolation, panic, and death in this work, reflecting the fate of those who face God"[16]. According to the descriptions, the Philistines grew tumors or buboes, and according to some translations, the fields were invaded by mice and rats, which could carry flea bites and thus the bubonic plague. However, it is more accurate to consider that the Middle East was free of plague epidemics until the early years of our era. An alternative scenario is that the disease could be dysentery with severe diarrhea, ulcers, and swelling in the perianal area. According to some Hebrew texts, the tumors could be hemorrhoids or dysenteric abscesses, but this is a very weak hypothesis, and anything related to contaminated water or diarrheal diseases is not reported in the biblical text. A new hypothesis has been described, which maintains that the Ark of the Covenant, because of its size, could accommodate more mice than rats and that these animals suffered the disease and transmitted it to humans, forming tumors and, in severe cases, causing death. Tularemia is caused by *F. tularensis* and is a zoonotic disease that presents with glandular ulcers that can be confused with bubonic plague and can have a mortality rate of over 15%. Around 1715 B.C., tularemia was known as the "Asian disease," believed to have originated in Canaan and spread to Egypt through contaminated ships. Tularemia would have occurred more than once in Canaan, and this recurrence suggests that this geographic area was a reservoir for *F. tularensis* in the 2nd millennium B.C[17].

The Bible also mentions in its Old Testament the plague that punished David's sin of ordering a census of his people and killed about 70,000 men out of 1,300,000 people who inhabited Israel and Judah[18]. It also mentions a plague that wounded an Assyrian camp of 185,000 men in one night, causing the Assyrian king Sennacherib to withdraw from Judah without taking Jerusalem[19-22].

Greek polis: the plague of Athens

The particular orography of the Greek territory, consisting of numerous islands, beautiful mountains, valleys, and gorges on the coasts, led to the creation of the first polis in Greece and a new economic and social structure after the disappearance of the Mycenaean culture during the 8th-6th centuries B.C. During the 5th century B.C., the century of Pericles (495-429 B.C.), the great statesman of the polis, Athens reached its maximum splendor, making it a center of innovation and progress, including the various arts, philosophy, historiography, and engineering, among others[23].

The first evidence of an epidemic in Greece is described in the first book of Homer's Iliad: "The Greeks plundered Crise in the Troad and sent Briseis, the daughter of Chryses, Apollo's priest, as a gift to Agamemnon, who made her his concubine and refused to return her to her father. He invoked Apollo, who shot arrows into the midst of the Greeks for 9 days, killing first mules and dogs and later the Greek armies"; the text is interpreted as an epidemic of plague in the Greek camp[24]. According to Williams, it is believed to be related to the depopulation and destruction of Greece around the year 1200 B.C. This author believes that a great epidemic was the cause, and the Dorians, seeing how weak the Greeks were, were able to invade them. Apollodorus, a Greek writer from the 1st century A.D., describes this event as occurring 80 years after the Trojan War[25]. Herodotus also briefly mentions that after the Cretans returned from Troy, a plague struck Crete, affecting both cattle and humans: "...let us return to Crete, where many people, especially the Greeks, came to live as in an inhabited country. In the third age, after the death of Minos, the expedition against Troy took place, in which the Cretans did not appear because of their pain and their neglect to revenge Minos; after returning from Troy, they were attacked by hunger and plague, both men and cattle..."[26]. Herodotus also mentions a plague of dysentery that struck Xerxes on his return to Persia after the First Persian War in 479 B.C. (Xerxes' plague)[27]. Herodotus mentions other plagues: "When a choir of 100 young people was sent to Delphi, only two returned, the other 98 were snatched away by a plague that struck them unexpectedly"[28]. He also described: "...in addition to the plague that broke out in the army, it was decimated along the way. And he left the sick..."[29]. Aeschylus, a Greek tragedian, mentions the plague in the "Supplicants" (never can the plague empty the city of its men) and in the "Persians" referring to the shadow of Darius (did a plague scourge or civil war come?)[30,31].

During the Peloponnesian War, an epidemic is described that changed the war's course. In 430 B.C., Athens was at war with Sparta for control of all of Greece. Athens had conquered the Greek seas and islands with its large navy; however, control of the land was dominated by the

Spartans, who had reached Athens with a large army. Because of this naval dominance, the Athenians could be under siege for years, as they received grain and food by sea. What they did not expect was that one of the ships coming from Egypt would bring a deadly disease that would devastate the city and weaken the army and its fleet for the rest of the war. The plague is said to have started in Ethiopia and spread to Egypt, Libya, and most of Persia before suddenly descending on Athens. Athenian doctors began to document the first cases among sailors and unloaders at the docks, and it was suspected that the Spartans were poisoning the water. The cases multiplied rapidly, and the population began to die of the plague while the healers and priests could do nothing. Thucydides himself, who wrote about the events, fell ill and mentioned that "the disease ended in a few days with all the physicians in the city because, not knowing how to treat it, they fell in droves"[32]. In this way, the infected were neglected, their relatives and friends avoided contact for fear of becoming infected, and the few compassionate souls who came to their aid died of the disease, contributing to its greater and faster spread throughout the city. Symptoms included a burning fever and irritation of the throat and tongue, which, according to Thucydides himself, produced fetid and unnatural breath. This was followed by vomiting and choking, which led to loss of strength and bedriddenness. Later, ulcers appeared all over the body, along with hyperthermia. All these ulcers were very painful, and the patients always had a great thirst, which was never quenched. The end, on the 7th day of the disease, consisted of a stomach ulceration that caused diarrhea, which led to greater weakness and inability to eat[33,34]. Conventionally, this has been called an outbreak of bubonic plague, but based on the symptoms and evolution of the disease, some researchers have concluded that it could have been an epidemic of smallpox or even typhus. The unusual number of corpses overwhelmed the burial services, and many people abandoned their dead in the streets. Even the initiator of the war, Pericles, died during the epidemic[35]. It is estimated that between 70,000 and 100,000 people, a quarter of the population, died in two waves of epidemics between 430 and 427 B.C. The military power of Athens was quite limited, but the war continued until 404 B.C. when the final surrender was given[36].

New methods, such as forensic DNA analysis, have shed new light on the problem of solving the cause of the epidemic in Athens. The highly contagious epidemic presented with a pustular rash, high fever, and diarrhea originated in Ethiopia and spread throughout the Mediterranean. The epidemic broke out in 430 B.C., with further waves in 428 B.C. and 426 B.C., and lasted about 5 years. In 2001, a mass grave was discovered that belonged to the plague years. DNA was extracted from ancient microbial typhoid (*Salmonella enterica* serovar typhi) from three skeletons; however, since typhoid was endemic in the Greek world, it is unlikely to have been the cause of this epidemic (Littman, 2009)[37]. In a recent report analyzing all of Thucydides' clinical descriptions, smallpox or measles are the ones that best explain what could have happened in Athens at the beginning of the Peloponnesian War, and the preponderance of clinical features favors measles as the explanation for this epidemic[38]. In very recent reports, there are those who defend the hypothesis that it could have been an influenza epidemic[39] or even Ebola[40], but the reality is still unknown.

Carthage: epidemics of the Carthaginian army

Born as a colony of Tire toward the end of the 9th century B.C., Carthage inherited the commercial network of its metropolis when the Assyrians and Neo-Babylonians dominated Phenicia. It dominated the former Phoenician colonies in the south of the Iberian Peninsula (Gadir, Abdera, and Malacca), the Maltese archipelago, Western Sicily, Sardinia, and Ibiza. This eventually caused friction with the Magna Graecia, and with Rome, a promising city-state that was expanding southward in Sicily, where Carthaginian colonies were established[41].

According to history, Carthage had to fight not only against Syracuse in Sicily but also against epidemics. The first epidemic is mentioned in 409 B.C.; after a series of victories that brought them to the gates of Syracuse, the Carthaginian army was decimated by an epidemic, and the Carthaginian troops had to abandon the siege[42]. The historian Diodorus Siculus said: "Dionysius the Elder (tyrant of Syracuse), taking advantage of the fact that the epidemic of the Punic army had spread to Africa, established his power and took over practically all of Sicily. However, a new Carthaginian general named Himilcon regained the territory for Carthage at the command of 300,000 men. During this siege, a new epidemic struck his land army, and 150,000 died of disease, prompting Dionysius to attack again and forcing Himilcon to ask for a truce and retreat. Once in Africa, the epidemic spread among the Carthaginians and their allies, greatly reducing the population of Carthage[42,43]. In the years 378 and 368 B.C., two new outbreaks of epidemics spread rapidly and shook Carthage, a situation used by its neighbors Libya and Corsica to revolt[44,45].

Foundation of Rome and its republic: epidemics in the Roman Republic

According to legend, the founder of Rome was Romulus in 751 B.C., a descendant of Aeneas, a hero of Troy who fled the destruction of the city, taking with him dozens of Trojans[46]. During the 4th century B.C., Rome expanded southward, conquering practically the entire peninsula, establishing contact with the Greek cities of Magna Graecia, and spreading along the coasts of the Ionian and Tyrrhenian Seas[41]. Years later, the Romans launched a preventive war called the First Punic War (punicus from the Latin: Phoenician), which conquered Sicily and ended with the defeat of Carthage, which was forced to sign peace in 241 B.C.[47].

The first epidemics in Italy can be dated precisely thanks to the references of Dionysius of Halicarnassus and Livy. Halicarnassus's first reference to an epidemic dates back to the time of Romulus in a war of conquest against Cameria: "The Camerins had attacked the Roman people at a time when the city of Rome suffered an epidemic of plague"[48]. In the year 638 B.C., Marcio Anco was elected king, and he called for a meeting where he mentioned that religious beliefs must be neglected, so the gods punished with many pestilences, causing a large part of the population to die[49]. Livy's first reference to epidemics is in 466 B.C. when Quintus Servilius Priscus (consul) was sent against the Aequi, but his army was infected by an epidemic, forcing him not to attack[50]. In 463 B.C., elections were held, and Lucius Ebucio Helva and Publius Servilius Priscus were elected consuls. Livy mentions that "that year was notable for the great pestilence that swept through both the city and the countryside, affecting both cattle and men. The virulence of the epidemic was aggravated by the overcrowding of the city by rural people and their cattle frightened by enemies. The constant contact between them contributed to the spread of the disease. While Rome was attacked by the Aequi and the Volscians, who ravaged its borders with a huge army, the city of Rome was ravaged by the plague sent by the wrath of the gods. The enemy went to destroy the fields of Rome. However, they were already devastated without having suffered war; the enemies found no one, not even an unarmed peasant, and after touring the country, they abandoned it, as its defenders had already abandoned it. Both consuls died, and most of the leading men were affected, as well as the senators and military men"[51]. In 451 B.C., Dionysius of Halicarnassus reported an epidemic in which almost all the slaves of the city and about half of the Roman citizens died. The plague lasted for a year and was spread by throwing the infected corpses into the sewers and the river, contaminating the drinking water and the air instead of burying them[52]. Livy mentions that in 436 B.C., "the armies were led into the Veientine and Faliscan territory, but there was no enemy in the open field and no reason to fight. Their cities were not attacked because they were suffering from a new epidemic; the following year, the epidemic worsened"[53].

The Romans believed in a divine religious origin and punishment as the cause of these epidemics. This is how Dionysius described it: "The cause of the epidemic was the loss of virginity of a vestal (priestess dedicated to the household goddess Vesta), who was then persecuted so that the gods were pacified and the epidemic could end." To appease the divine punishments of the epidemics, the Romans also established the Lectisternium, a huge banquet to which the deities represented by statues were invited. In 363 B.C., a new epidemic broke out, which spread for several years and caused many deaths. Rome initiated a ritual called "the Dictator of the Nail," which consisted of driving a nail on September 15 to the temple of Jupiter (the main god of Roman mythology), specifically in the wall that faced the temple of Minerva (goddess of wisdom and the arts in Roman mythology), to appease the divine wrath that manifested itself with an epidemic[54]. The Roman chronicles describe two other occasions in which this ritual was used; the first was carried out by the general Gaius Petelio Libo Visolo in 313 B.C. in the face of an epidemic that arose during the war against the Samnites. A second was carried out in 263 B.C. by Fulvio Máximo Centumalo to contain an epidemic during the displacement of the Roman armies to Sicily during the first Punic War[55]. Around 300 B.C., an epidemic was recorded that may be the earliest evidence of the existence of the bubonic plague[56]. In the year 212 B.C., during the Second Punic War, Livy reported an epidemic in the city of Achradina (in Sicily), which was besieged by the Roman general Marcellus: "At first, it was the climate and the location that caused sickness and death, but soon the disease spread by contagion or by caring for the sick. The population could not keep up with the burials, and some chose suicide as a way out. The armies were aware of the contagion. The Carthaginian army dispersed and returned to their cities; the Romans were also affected but to a lesser extent. The Carthaginian general Himilco and the Syracusan rebel Hippocrates died of the plague, which contributed to the successful capture of Syracuse in 211 B.C.[57]. In 205 B.C., and again in 178 and 174 B.C., there was a plague in Italy: "It killed the cattle last year, but now

it began to attack man. Many people died, especially slaves, and the streets were littered with unburied corpses. In 125 B.C., a similar attack occurred in Cyrene[58-60].

Rise of the Western Roman Empire: Antonine plague and Cyprian plague

In 63 B.C., Caesar Octavius, known as Octavian and later as Augustus, was born, establishing the Principality form of government and becoming the first Roman emperor. During the reign of Emperor Nero, Suetonius wrote that there were 30,000 deaths caused by a plague in a single fall[61]. In 69 A.D., a general named Vespasian took power and founded the Flavian dynasty, creating one of the Empire's greatest symbols, the Flavian Amphitheater or Colosseum[62]. During the early reign of Titus, son of Vespasian, there were great disasters such as the eruption of Vesuvius in 79 A.D., which destroyed Pompeii and Herculaneum, a fire in Rome in 80 A.D. and an epidemic of the plague[63]. After these events, the whole Empire was governed with virtue and wisdom, it was called the time of the "Good Emperors" or the "Antonine Dynasty," from Nerva to Commodus[64]. During this dynasty, in 161 A.D., Marcus Aurelius, known as the "wise emperor," came to the throne. During his reign, he triumphed in the Parthian wars between 162 and 166 A.D. This war brought two consequences: a weakening of the Danubian border with the beginning of the Marcomanni war, and a plague that entered the Empire[65].

The first post-Christian pestilence of which we have sufficient information refers to a plague brought by the legions on their return from the East after a military victory against the Parthian Empire (155 A.D.). The magnitude of the disaster is unknown, but it must have affected Rome so severely that in the year 167 A.D., it is described as follows in the Augustan History: "The dead were carried away in carts, the plague killed thousands of people, including aristocrats." It is known that this plague lasted for a long time, claiming victims even 10 years after its initiation[66]. It is considered the first pandemic because it affected all the provinces of the Roman Empire and even caused the death of the Emperor Marcus Aurelius. The emperor requested the intervention of Galen, who cited this plague and compared it to the one described by Thucydides[67]. Roman cities were densely populated and closely interconnected, facilitating the spread of infectious diseases. This first major pandemic to affect the Roman complex was called the "Antonine Plague" (165-180 A.D.) or "Galen's Plague," which occurred in several waves. Claudius Galen described it when he visited the emperor, and today it is considered smallpox. It has been calculated that it had a mortality rate of almost 10% of the population, which means that it claimed the lives of 7 to 7.5 million people in a population of almost 75 million[68]. The symptoms of those infected included vomiting, diarrhea, fever, and ulcers that covered the entire body. Some lost their memory in the final stages of the disease. Galen himself describes it as follows: "Black or dark purple rashes, which dry up and fall off the body after a few days, ulcerative pustules all over the body, diarrhea, fever, loss of voice due to sores on the face; between the 9th and 12th day after the appearance of the rash, the most severe form of the disease occurs, which is the one that causes the highest mortality rate"[69]. A plague with similar symptoms described in China's Han Dynasty supports the possibility that the pandemic originated in China and traveled east through the Silk Road. In Rome, the situation was so critical that it is said that about 2000 people died every day. The crisis hit the economy of the Empire, there were closures of companies, especially those of construction. This situation encouraged the barbarian invasion of the Rhine[67]. During the reign of Emperor Commodus (son of Marcus Aurelius), another epidemic struck Rome and was called the "Second Plague or Epidemic of Commodus" (189-190 A.D.). It is mentioned that there were more than 2000 daily deaths in Rome in 189 A.D. The death of animals is added to the description, a circumstance for which it is thought that it was another epidemic different from the Antonine, perhaps more similar to the one that occurred in 463 B.C., 428 B.C. described by Titus Livy and the one in 451 B.C. described by Dionysius of Halicarnassus. It was reported that Emperor Commodus fled from Rome to Laurento on the advice of his physicians[70].

From 198 to 250 A.D., the Roman world was free of epidemics. At the end of the war with the Goths, a new epidemic was described by the Bishop of Carthage, San Cipriano, known as the "Plague of Cipriano" (251-266 A.D.). It is said to have originated in Ethiopia and to have spread throughout the known world, from Egypt to Scotland, lasting 16 years. The best testimony is given by Cipriano, who describes a disease with diarrhea, vomiting, abdominal pain, generalized decay and fatigue, sore throat, necrosis of the limbs, red eyes, and loss of hearing and vision. For years, attempts have been made to determine the etiology, and it has been proposed that it was a hemorrhagic viral disease similar to Ebola, but this has not been proven. Others mention that it may have been the arrival of childhood

diseases such as measles or smallpox in Mediterranean countries. Ancient accounts agree on a high mortality rate. For example, in Alexandria, a city that had about 500,000 thousand inhabitants, almost 60% of the population could have died (300,000 people), while in Rome, Emperor Claudio Gotico died because of this pandemic. Many stories from the time mention that the plague was so great that it threatened the survival of the Empire. The Augustan History mentions that the epidemic was so great in Rome that up to 5000 people died in a single day and that entire cities were left empty for fear of contact, for which distancing was then understood as a measure to avoid catching the disease. After the pandemic, the Empire would never regain its glorious past, and the decline of Rome began[70].

During the third century A.D., the first instability of the Roman Empire began. Based on a military anarchy, the Godians, the soldiers called soldier emperors, and the Illyrian emperors rose to the throne. Faced with military weakness, the Empire began to suffer border breaches, mainly by the Ostrogoths and Visigoths on the Rhine and Danube and the Sassanid Persians in Syria and Mesopotamia. In 284, Diocletian won a military victory and was proclaimed emperor; he restored the governability of the Empire by establishing what he called the Tetrarchy. This system of government was based on the division of the Empire into four sectors, two of which were ruled by the Augustans and the other two by the Caesars, who were considered their legitimate successors and later became the Western and Eastern Roman Empires[71].

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.

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Conflicts of interest

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RESEARCH ARTICLE

Antibiotics in the end-of-life phase in pediatric oncological patients with a diagnosis of terminal illness: a dilemma

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Abstract

Background: *Pediatric cancer patients in the final phase of life receive antibiotics empirically. The decision to start, maintain, or stop the antibiotic administration as part of care at this stage is a dilemma.* **Methods:** *We conducted a retrospective, descriptive, cross-sectional study including cancer patients in the final phase of life, hospitalized during the last 5 to 7 days of life. We included demographic variables, diagnoses, days of hospitalization, cultures, antibiotics used, prevalent symptoms in the last week of life, and principal diagnosis at the time of death, and performed descriptive statistics and a chord diagram.* **Results:** *Twenty-two patients were included; 18 (81.81%) received antibiotic treatment. The mean age was 8.75 years. The predominant pathologies were central nervous system tumors in seven patients (31.81%). Of the total, 18 (81.81%) had an infectious diagnosis reported as bloodstream infection, followed by pneumonia in three (13.63%). The main cause of death was respiratory failure (40.9%). Of the 18 patients with an infectious diagnosis, 16 (88.88%) received empiric therapy. Predominant factors for antibiotic use were more than 7 days of hospitalization (75%), ICU admission (100%), invasive devices (88.8%), and aminergic support (100%). The predominant symptoms were dyspnea (68.18%), pain (50%), and fever (40.9%), which persisted in nine (60%), two (18.18%), and five (55.5%) patients, respectively.* **Conclusions:** *The lack of guidelines for antibiotic administration leads to excessive and potentially unnecessary use, which can lead to discomfort, prolonged hospitalization, bacterial resistance, excessive cost, and suffering without symptom control.*

Keywords: *Antibiotics. Terminal illness. Pediatric oncology.*

Uso de antibióticos en niños con patología oncológica en la fase final de vida: el dilema

Resumen

Introducción: *Los pacientes pediátricos oncológicos en la fase final de vida reciben antibióticos de forma empírica. La decisión de iniciar, mantener o suspender la administración del antibiótico como parte del cuidado en esta etapa es un dilema.* **Métodos:** *Se llevó a cabo un estudio retrospectivo, descriptivo y transversal que incluyó pacientes oncológicos en fase final de vida, hospitalizados durante los últimos 5 a 7 días de vida. Se incluyeron variables demográficas, diagnósticos, días de estancia hospitalaria, cultivos, antibióticos utilizados, síntomas prevalentes en la última semana de vida y diagnóstico principal al momento de fallecer. Se realizó estadística descriptiva y un gráfico de cuerdas.* **Resultados:** *Se incluyeron 22 pacientes: 18 (81.81%) recibieron manejo antibiótico. La media de edad fue de 8.75 años. Las patologías predominantes*

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fueron tumores de sistema nervioso central en siete pacientes (31.81%). Del total, 18 (81.81%) pacientes presentaron infección del torrente sanguíneo; tres (13.63%) presentaron neumonía. La principal causa de muerte fue insuficiencia respiratoria (40.9%). De los 18 pacientes con diagnóstico infeccioso, 16 (88.88%) recibieron terapia empírica. Los factores prevalentes para el uso antibiótico fueron una estancia hospitalaria mayor a 7 días (75%), hospitalización en Unidad de Cuidados Intensivos (100%), dispositivos invasivos (88.8%) y apoyo aminérgico (100%). El síntoma prevalente fue disnea (68.18%), dolor (50%) y fiebre (40.9%), mismos que persistieron en nueve (60%), dos (18.18%) y cinco pacientes (55.5%), respectivamente.
Conclusiones: *La falta de pautas respecto a la administración de antibióticos conlleva a su uso excesivo y potencialmente innecesario, lo cual puede ocasionar incomodidad, prolongar la hospitalización, resistencia bacteriana, costos excesivos y sufrimiento, sin control de los síntomas.*

Palabras clave: *Antibióticos. Enfermedad terminal. Oncología pediátrica.*

Introduction

Palliative care (PC) is a specialty that has grown in recent years due to the need to provide comprehensive and interdisciplinary care to patients diagnosed with life-threatening illnesses, usually chronic, degenerative, incurable diseases with a profound impact on the quality of life of patients and their families. In these cases, the physician has to initiate comprehensive management focused on symptom control, suffering reduction, and appropriate treatment from the time of diagnosis until the end of life or eventual cure.

Pediatric palliative care undoubtedly differs from adult palliative care[1,2]. The treatment plan in palliative care should always be individualized and focused on the patient and the family to achieve better outcomes, always keeping in mind that "*the goal is to add life to the child's years, not just years to life*"; thus, the quality of life, not survival, becomes the priority[3]. However, barriers still exist at the cultural, educational, economic, and regulatory levels, even within the medical field.

One of the most frequent complications in terminally ill patients is infection, including respiratory tract infections, urinary tract infections, gastrointestinal tract infections, wound infections, and bacteremia. Urinary antibiotics reduce dysuria, in contrast to respiratory infections, for which opioids are preferred because they provide better symptom control (dyspnea or sensation of suffocation)[4]. Up to 90% of hospitalized patients with advanced cancer are treated with antibiotics during the last week before death[4-10]. These infections are frequent due to their immunocompromised status, and the symptoms of sepsis can be similar to those seen at the end of life. However, research has shown that antibiotics are often used in these patients in the absence of clinical signs consistent with bacterial infection, often due to lack of judgment in end-of-life medical decision-making[6].

In the advanced stages of oncologic disease, healthcare professionals and patients (and their families) are faced with difficult decisions regarding treatment and general medical care. However, in palliative care, the use of antibiotics always presents an ethical dilemma. Deciding whether to initiate or withdraw treatment for an infection can be difficult at this stage of the disease in the face of a poor short-term prognosis. Although the administration of antibiotics may lead to adverse outcomes, two benefits (increased survival and symptom relief) are the main reason why their use is indicated and justified[10]. Therefore, the medical actions within the doctor-patient relationship should be defined as follows:

- Mandatory. Those that cannot be denied to any patient. For example, hydration and nutrition.
- Permitted. Those that may be beneficial to the patient. For example, the administration of antibiotics and mechanical ventilation.
- Ethical. Those that should be given to all terminally ill patients. For example, control of pain and other terminal symptoms.
- Unethical. Those that should not be given to any patient. For example, repeated resuscitation and malicious procedures.

Terminal oncologic disease is defined as advanced, irreversible, and progressive oncologic pathology with no reasonable chance of cure and failure of established treatment, with changing evolution of symptoms over time, multiple complications, loss of independence, emotional impact on the patient, family, and healthcare team, and a short survival time (in children it is not limited to 6 months as in adults). Some treatments are considered exceptional in a patient with terminal cancer and their administration should be individualized because of their doubtful benefits, such as dialysis, mechanical ventilation, use of amines, cardiopulmonary resuscitation maneuvers, transfusions, and broad-spectrum antimicrobials.

Although these are permissible interventions, they can become unethical because of the potential harm they could cause to the patient since they are not curative treatments and would only be permissible if they improved comfort and well-being during the remainder of life.

Thus, the debate continues as to whether these drugs are effective in reducing uncomfortable symptoms, improving the quality of life, and prolonging survival, or on the contrary, they only prolong the process of death and add more sources of suffering. Additional problems with the use of antibiotics include the need to ensure intravenous access, increasing the risk of adverse effects, pharmacologic interactions, *Clostridium difficile* infection, the risk of acquiring or generating multidrug-resistant microorganisms, in addition to causing significant costs to health and family resources, financially and emotionally.

Healthcare resources are always scarce and must be allocated equally and fairly to all patients, but most importantly, to benefit the patient without causing avoidable harm. There is a financial burden when resources are not allocated appropriately, but this pales in comparison to the emotional burden on the patient, family, and healthcare team.

Expenses of the family accompanying the hospitalized child also increase (eating out, transportation, paying for showers for personal hygiene, abandoned siblings, absenteeism from work, and funeral expenses, which are higher when they come from the province). This becomes irrelevant when hospitalization is aimed at improving the vital and functional prognosis but becomes more difficult in the case of terminally ill children, when death is inevitable and expected. These treatments are known as potentially inadequate treatments: although they have an effect, they do not offer a benefit because they do not improve vital function or prognosis.

The above can be clarified by the following example: Consider the case of a 13-year-old male patient with Ewing's sarcoma and a history of hip disarticulation two years prior. At present, the patient has a recurrence in the lumbar spine and unresectable pulmonary metastases affecting approximately 60% of the lung. He is also diagnosed with pulmonary aspergillosis and is currently receiving palliative radiation therapy. The patient is admitted to the hospital due to respiratory failure and fever and diagnosed with septic shock due to pneumonia, given that he is an immunocompromised patient. Mechanical ventilation and amines are required, and an antimicrobial regimen is initiated. However, after 72 hours with no response and positive blood cultures, the therapeutic approach was changed. In this example, it is important to note that the use of antibiotics will not change the prognosis, which is unfavorable in the short term (no apparent benefit). In addition, escalation of the antimicrobial regimen in response to a pneumonic process is considered ineffective, given the high risk of mortality even with all available antimicrobial therapies.

On the one hand, the physician has to decide to continue or discontinue treatment. However, this decision impacts the patient and his family because of the hope that the treatment will be effective, but has no legal or ethical justification and is known as therapeutic obstinacy.

On the other hand, the physician finds himself in the situation of having to make decisions at the end of the patient's life. In this context, it is essential to have more solid guidelines or criteria to help them in their decision-making process. In addition, it would be highly advisable for physicians to seek the advice and collaboration of the hospital's bioethics committee to address and deliberate on the therapeutic dilemma they are facing.

The use of antibiotics is supported and documented as one of the last therapeutic approaches to be withdrawn from terminally ill patients with advanced cancer, in contrast to other interventions, such as artificial nutrition, invasive mechanical ventilation, hemodialysis, and blood transfusions, which are considered extraordinary in this context[5]. Although the reason for this trend is not well understood, the use of antibiotics is probably perceived as a procedure that only requires the availability of the drug and adequate access for its administration (whether intravenous, intramuscular, or oral). This may give the impression of being a less invasive approach and, at the same time, give physicians some moral comfort in feeling that they are doing something to prevent the death of a terminally ill patient.

To date, studies of antibiotic use in patients with terminal illnesses have focused primarily on adults. However, the results of these studies are limited and do not provide a solid basis for determining whether the use of antibiotics in this stage of life is beneficial in reducing symptoms, improving quality of life, or prolonging survival. Moreover, it is not possible to say with certainty whether using antibiotics in this setting could lead to further complications.

This study aimed to analyze the characteristics of pediatric patients with terminal cancer who were

hospitalized shortly before their death. The purpose of this research is to encourage future studies that can provide guidelines and recommendations for the management and prescription of antibiotics in the last stage of life of these patients. In addition, we sought to describe the characteristics of children and adolescents with terminal oncologic diseases who received antibiotics during their hospitalization at the Palliative Care Program of the Hospital Infantil de México Federico Gómez between 2018 and 2020. This analysis aims to facilitate shared decision-making between health professionals and patients' families under these circumstances.

Methods

We conducted a descriptive, retrospective, cross-sectional study that included patients aged 0 to 18 years with terminal oncologic diseases. These patients were admitted to the palliative care program of the tertiary level hospital (Hospital Infantil de México Federico Gómez) and were hospitalized during their last 5 to 7 days of life. The study period was from January 2018 to January 2020.

Data collected included demographic variables, primary and secondary diagnoses, total days of hospitalization, cultures obtained, antibiotics used in the last 5 to 7 days of life, symptoms presented in the last week of life, do-not-resuscitate (DNR) order signatures, and principal diagnosis at the time of death.

Drug data were collected from medical progress notes and nursing notes, categorized by therapeutic class using the NCHS (National Center for Health Statistics) Multum Lexicon database. Category 2 and 3 antibiotics were identified and grouped based on their chemical structure.

Descriptive statistics were performed using frequencies and percentages and a chord diagram with the program Chordial Version 1.2 for MAC.

Quantitative variables were expressed as medians and interquartile ranges and compared according to the baseline oncologic disease.

This research study followed the ethical norms of our institution and the *Ley General de Salud* (General Health Law) of 2016, in its eighth title bis, "palliative care for the terminally ill", as well as the Nuremberg Declaration of 1947, which establishes the ethical conditions for research on human beings. This declaration was amended in 1964 during the World Assembly in Helsinki and updated for the last time in 2000 in Edinburgh.

Results

During the study period, from January 2018 to January 2020, 90 children with cancer died. These children were part of the palliative care program, and not all children with cancer admitted at the hospital were enrolled. From the total number of deaths, we excluded 16 patients who were in the agonal phase, less than 7 days before death, and 48 children who died at home. These 48 children who died at home did not receive antimicrobials in the last 7 days before death. This left us with a group of 26 patients who died in the hospital, of whom we could obtain complete information from 22 files.

Twenty-two patients were included, of whom 18 (81%) received antibiotic treatment. The mean age of the patients was 8.75 years (interquartile range: 6 months to 18 years), with no sex predominance (1:1 ratio). As for the underlying oncologic pathologies, 19 (86.3%) were found to be solid tumors. Of these, central nervous system tumors were found in seven patients (31.81%), followed by neuroectodermal tumors in four patients (18.18%). Hematologic malignancies in three patients (13.6%), mainly leukemia in two patients (9.09%); 16 patients (72.72%) had metastases.

In our study population, 18 patients (81.81%) had an infection documented in their medical records, including bloodstream infection identified as septic shock, septicemia, or nosocomial sepsis in 11 cases (49.98%), followed by pneumonia in three patients (13.63%). Of these 18 patients, empiric therapy was initiated in 16 (88.88%), while two patients (11.1%) without an infectious diagnosis received treatment. A total of 18 patients (81.8%) were treated with antimicrobial therapy (Table 1 and Fig. 1).

The most common factors found for increased antibiotic use were ICU admission (100%) and association with amine use (100%).

The most frequent symptom that led to the initiation of antimicrobial therapy was shortness of breath (15 patients, 68.18%), followed by pain (11 patients, 50%) and fever (nine patients, 40.9%). Despite the initiation of antibiotic treatment, these symptoms persisted in nine (60%), two (18.18%), and five patients (55.5%), respectively (Table 2). The most frequent cause of death was respiratory failure (nine patients, 40.9%), followed by endocranial hypertension (four patients, 18.18%). Of all patients included, 19 (86%) signed a DNR order, 11 (50%) in the last week of life, and 8 (36.3%) more than one week before death.

Table 1. Patient characteristics and the use of antibiotics (n = 22)

Characteristic	Total	%	Use of antibiotics	%	Non-use of antibiotics	%
Age	22	100	18	81.81	4	18.18
< 6 months	1	4.54	1	4.54	0	0
6 months -1 year	1	4.54	0	0	1	4.54
2-5 years	5	22.7	5	22.7	0	0
6-10 years	4	18.18	3	13.6	2	9.09
> 11 years	11	50	9	40.90	1	4.54
Sex						
Female	11	50	8	36.36	3	13.6
Male	11	50	10	45.45	1	4.54
Primary oncological diagnosis						
Solid tumors	19	86.3	15	68.18	4	18.18
Nervous system	7	31.81	4	18.18	3	13.6
Neuroectodermal tumor	4	18.18	4	18.18	0	0
Osteosarcoma	2	9.09	2	9.09	0	0
Ewing's sarcoma	2	9.09	2	9.09	0	0
Carcinoma of the cecum	1	4.54	1	4.54	0	0
Retinoblastoma	1	4.54	1	4.54	0	0
Rhabdomyosarcoma	1	4.54	1	4.54	0	0
Renal tumor	1	4.54	0	0	1	4.54
Hematological	3	13.6	3	13.6	0	0
Leukemia	2	9.09	2	9.09	0	0
Lymphoma	1	4.54	1	4.54	0	0
Metastasis	16	72.72	13	59.09	3	13.6
Infectious diagnosis						
Septic shock	5	22.72	3	13.63	2	9.09
No infectious diagnosis	4	18.18	2	9.09	2	9.09
Pneumonia	3	13.63	3	13.63	0	0
Septicemia	3	13.63	3	13.63	0	0
Nosocomial sepsis	3	13.63	3	13.63	0	0
Encephalitis	1	4.54	1	4.54	0	0
Urinary tract infection	1	4.54	1	4.54	0	0
Intussusception	1	4.54	1	4.54	0	0
Cervical abscess	1	4.54	1	4.54	0	0
Cause of death						
Respiratory failure	9	40.9	8	36.36	1	4.54
Endocranial hypertension	4	18.18	3	13.63	1	4.54
Pulmonary hemorrhage	3	13.63	3	13.63	0	0
Septic shock	2	9.09	1	4.54	1	4.54
Pleural effusion	1	4.54	1	4.54	0	0
Acute pulmonary edema	1	4.54	1	4.54	0	0
Multiorgan failure	1	4.54	0	0	1	4.54
Spontaneous tension pneumothorax	1	4.54	1	4.54	0	0
Total days of hospital stay						
8-30 days	9	40.90	8	36.36	1	4.54
> 30 days	7	31.81	4	18.18	3	13.63
< 7 days	6	27.27	6	27.27	0	0
Hospitalization Service						
Oncology	13	59.09	12	54.54	1	4.54
Neurosurgery	5	22.72	2	9.09	3	13.63
Intensive Care Unit	4	18.18	4	18.18	0	0
Positive cultures	9	40.90	8	36.36	1	4.54

(Continues)

Table 1. Patient characteristics and the use of antibiotics (n = 22) *(continued)*

Characteristic	Total	%	Use of antibiotics	%	Non-use of antibiotics	%
Use of invasive devices						
None	8	36.36	6	27.27	2	9.09
1	4	18.18	3	13.63	1	4.54
2	4	18.18	3	13.63	1	4.54
3	5	22.72	5	22.72	0	0
4	1	4.54	1	4.54	0	0
Use of amines	7	31.81	7	31.81	0	0
Infectious diseases assessment	11	50	7	31.81	4	18.18

Table 2. Symptoms and signs during the last 5 to 7 days of life and 24 h before death (n = 22)

Symptoms 5 to 7 days before death	n	%	AB use of total patients who had the symptom	n	%	Persistence of the symptom 24 hours before death	n	%	Yes	%	No	%
Tachycardia	18	81.81	Yes	14	77.7	→	18	100	14	77.7	0	0
			No	4	22.22		0	0	4	22.2	0	0
Breathing difficulty	15	68.18	Yes	12	80	→	10	66.6	9	60	3	20
			No	3	20				1	6.66	2	13.33
Pain	11	50	Yes	9	81.81	→	2	18.18	2	18.18	7	63.63
			No	2	18.18				0		2	18.18
Fever	9	40.9	Yes	8	88.8	→	6	66.6	5	55.5	3	33.3
			No	1	11.11		0		1	11.1	0	0
Purulent discharge	2	9.09	Yes	2	100	→	2	100	2	100	0	0
			No	0	0		0	-	-	-	-	-
Cough	2	9.09	Yes	1	50	→	0	0	0	0	1	50
			No	1	50		0	0	0	0	1	50
Wound dehiscence	1	4.54	Yes	1	100	→	1	100	1	100	0	0
			No	0	0		0	-	-	-	-	-

AB: antibiotic.

Discussion

Several studies in adult oncology patients show that antibiotics are frequently prescribed at the end of life[4,11] and that the most common infections are respiratory tract infections, urinary tract infections, gastrointestinal infections, wound infections, and bloodstream infections. In contrast, our results showed that the most frequent cause was sepsis without focus, followed by pneumonia. Additionally, opioids have been described as a more convenient option than antibiotics for treating dyspnea and pain, providing better symptom control and more comfort[10,12]. Although there are several publications on antibiotic management in patients nearing the end of life, these are small observational studies highlighting the lack of symptom control despite initiating an antimicrobial regimen in the final phase of life. These findings motivate healthcare professionals to escalate the therapeutic approach[13-16]. Other retrospective pilot studies have attempted to evaluate the potential benefit of broad-spectrum antibiotics in hospitalized patients during the last week of life in the terminal phase of the disease.

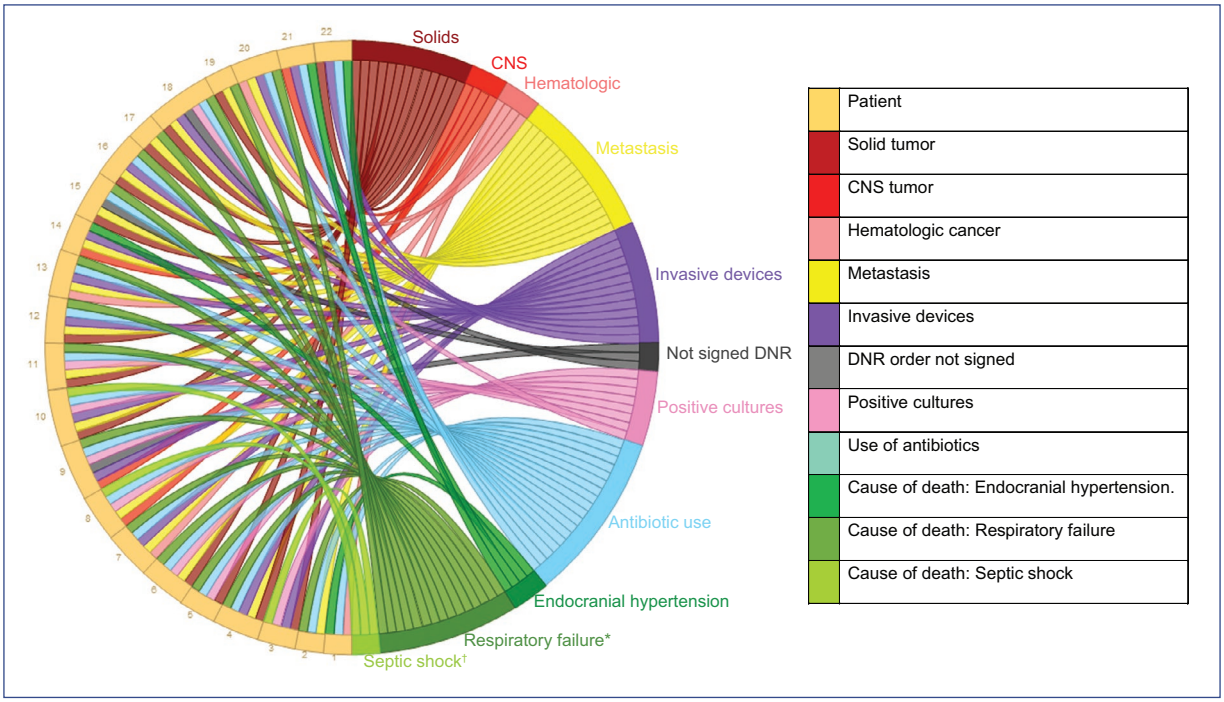

Figure 1. Chord diagram. The left side of the graph refers to the n = 22 patients analyzed. On the right side, the colors represent their characteristics.
*In respiratory failure, other causes such as pleural effusion, acute pulmonary edema, spontaneous tension pneumothorax, pulmonary hemorrhage were included.
†In septic shock, multi-organ failure was included.
CNS: central nervous system; DNR: do not resuscitate.

These studies found a significant empirical use of broad-spectrum antibiotic therapy in these patients. Although treatment modalities at the time of consultation may reflect the medical team's efforts to manage potentially reversible complications, including possible infections, a high rate of empiric treatment predominates. This difference is hard to identify[14,17], especially in patients with persistent symptoms such as fever or dyspnea. The decision to escalate antibiotic treatment is often based on a critical pathway rather than clear evidence of an infectious process. Therefore, this treatment sometimes fails to completely control the symptoms that led to the patient's admission, as observed in our study. However, microbiological evidence of infection was found in almost half of the patients studied justifying, at least in part, the initiation or escalation of antibiotic treatment. This approach should be accompanied by comfort measures and appropriate tailoring of the therapeutic effort to facilitate decision-making.

It is ethically unacceptable for patients to receive treatments not indicated according to their clinical situation. Therefore, it is essential to adapt the diagnostic, therapeutic, and monitoring strategies to each patient's specific clinical condition and needs at each moment of their evolution, defining the objectives of their care and acting accordingly. For the analysis of the patient's clinical history, it is essential to involve all the specialists and professionals of different disciplines who participate significantly in the child's care (oncologist, palliative pediatrician, infectious disease specialist, among others). Each specialist's particular and specific perspective adds depth to the analysis and avoids omitting aspects that could be important for decision-making[18-21]. Thus, in this study, 19 of the patients had signed DNRs, which indicates that the attending physician, together with the family, was aware of the expected fatal outcome of the disease and the risk of death in a short period; however, it gives the impression that the signing of the DNR order did not influence the decision to initiate antimicrobial therapy. The chord diagram shows that only three patients did not sign the DNR.

Multiple complications can accompany the disease and its end, such as infections, which are the most frequent.

Although survival was not evaluated in this study because, unfortunately, all patients died, the study by Reinbolt et al.[22] found no significant differences in survival between patients with or with no diagnosed infection nor between those who received antimicrobials and those who did not.

The patients analyzed in our study had an underlying pathology with no reasonable cure options and were expected to die within a limited period, were enrolled in the palliative care program, and had signed advance directives that included the DNR order. This population is very specific and cannot be compared to patients with life-threatening oncologic pathology who may still have options for cure and may die from complications of the disease or treatment. In terminally ill patients, infectious complications may occur even as part of the natural history of the disease and the end of life, and their aggressive management may not change the outcome, which is death. This is not because of the infectious process but because of the underlying pathology. For example, consider a patient diagnosed with extensive brainstem glioma admitted for apnea and respiratory failure. If this patient is diagnosed with pneumonia, antibiotic treatment may be initiated because of the clear presence of infection. However, the benefit of this treatment is questionable. The main cause of respiratory failure comes from the central nervous system and is intractable. In this context, antibiotics become a futile treatment to address the primary cause of hospitalization. Such situations pose an ethical dilemma of a utilitarian and deontological nature. For example, antibiotic treatment could improve symptoms related to infection[15]. In this series, fever and dyspnea improved only 33.3% and 20%, respectively, in those who received antimicrobials, which aligns with palliative care goals. However, these symptoms may improve with other non-antibiotic therapies such as sedatives, anxiolytics, antipyretics, and opioids, considering that even specific symptoms of infection, such as purulent discharge or wound dehiscence, did not improve in the study. In these patients, the goal is to control or attenuate the uncomfortable symptom. Although care must be taken to treat the cause of the symptomatology, it may not be treatable due to the advanced nature of the underlying disease, making it necessary to redirect the goals of therapy to improve the comfort and quality of life of patients and their family. The real challenge is to distinguish between patients who will benefit from vigorous antimicrobial therapy and improve their quality of life and those who will not benefit and whose death is inevitable and even the initiation of antibiotic therapy may be harmful, prolonging life with pain and greater suffering[19-21].

The Hippocratic tradition becomes the starting point of ethical rules in the practice of Western medicine. It is important to emphasize the principle of not doing harm, which can be done in different ways, either through action (imprudence, ignorance, and inexperience), omission (negligence), or inadequate risk management due to failure to foresee the possibility of occurrence of these events in advance. Healthcare professionals should actively seek continuous communication with the family and the patient throughout the course of the disease, especially in the final stages, to inform about the existence of viable therapeutic alternatives according to the diagnosis, evolution, symptoms, and prognosis, in an individualized manner, without attempting to standardize management for patients with specific characteristics[20-23]. The lack of clear guidelines regarding the use of antibiotics in terminally ill oncology patients leads to unnecessary overuse of antibiotics, with the possibility of delaying death and perpetuating poor quality of life, discomfort, and dysthanasia. In cases of serious medical doubt regarding prognosis, a time trial with well-defined objectives and specific goals of antibiotic use should be performed, which may reduce the anxiety of medical staff and family.

This study has a limited population sample. Its main aim is to draw attention to the importance of further research into medical decision-making at the end of life in pediatric patients with oncological diseases. It is important to identify who may benefit from using antimicrobials and thus prevent serious harm associated with their administration.

To address this dilemma, we should conduct further research focused on comparative analyses of treatment burden versus cost/benefit regarding antibiotics. It is also important to identify predictive variables that can tell us which patients might benefit from these treatments and to what extent. Importantly, each decision must be made from an individual perspective, considering the circumstances and preferences of the patient and family. It is essential to maintain constant communication and to ensure that medication is part of a comprehensive therapeutic approach in which the goals of care are transparent and defined.

This study has some limitations, including the small sample size and the presence of incomplete records that do not include the symptoms or antibiogram reports needed to determine the susceptibility of the isolated organisms. The lack of clear guidelines on the use of antibiotics in children with terminal oncological diseases may lead to unwarranted prescriptions. This may

result in increased patient discomfort due to hospitalization, the need for intravenous access, and additional tests, among others. These interventions may unnecessarily prolong the patient's life, and delay an inevitable death, which may lead to dysthanasia.

The medical team should not underestimate DNR order by the family and the physician responsible for the patient in a palliative care setting. It warns against potentially inappropriate medical therapies for little or no expected benefit to the patient. The possible lack of antimicrobial efficacy in reducing symptoms, the increased burden on the patient, family, and healthcare system must be considered on an individual basis.

Respiratory failure as the main symptom triggering the initiation of antimicrobial therapy and as the first cause of death does not necessarily reflect an underlying infectious process and could even be considered the first symptom of the onset of agony.

Admission to an intensive care unit requires intensive use of all available medical and human resources. Therefore, the admission of patients with terminal oncological pathology who are already part of a palliative care program and who have signed a DNR order is not recommended. However, if admission is considered, it should be carefully weighed against the objective risks and benefits, considering the prognosis associated with the primary disease. An alternative could be to subject these patients to therapeutic trials with defined timelines for the use of antimicrobial therapies. The clinical results of these trials will guide the decision to adjust or maintain previously established treatment.

What is really important is the clinical-ethical analysis of whether the initiation or withdrawal of antibiotic therapy is an appropriate treatment at this stage of life, a difficult task that involves not only the medical perspective in terms of knowledge but also the ethical and moral perspective of the responsible physician.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Diagnosis of urinary tract infection in infants under 3 months with fever without a source: reliability of urinalysis and urine culture

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Abstract

Background: *Urinary tract infection (UTI) is infants' most common serious bacterial infection. This study aimed to investigate the reliability of urianalysis (UA) to predict UTI, to specify the colony forming units (CFU)/ml threshold for diagnosis, and to identify variables that help suspect bacteremia in infants under 3 months with UTI.* **Methods:** *We reviewed clinical records of children under 3 months hospitalized for a fever without source and recorded age, sex, days of fever pre-consultation, temperature and severity at admission, discharge diagnoses, laboratory tests, and treatments. According to the discharge diagnosis, we divided them into UTIs (-) and (+) with or without bacteremia.* **Results:** *A total of 467 infants were admitted: 334 with UTI and 133 without UTI. In UTIs (+), the pyuria had a sensitivity of 95.8% and bacteria (+) 88.3%; specificity was high, especially for nitrites (96.2%) and bacteria (+) (92.5%). Positive predictive value (PPV) for nitrites was 95.9%, for bacteria 96.7%, and oyuria 92.5%. Escherichia coli was present in 83.8% of urine and 87% of blood cultures. UTIs with bacteremia had inflammatory urinalysis, urine culture > 100,000 CFU/ml, and higher percentage of C reactive protein (CRP) > 50 mg (p= 0.002); 94.6% of the urine culture had > 50,000 CFU.* **Conclusions:** *The pyuria and bacteria (+) in urine obtained by catheterization predict UTI. The cut-off point for diagnosis was ≥ 50,000 CFU/ml. No variables to suspect bacteremia were identified in this study.*

Keywords: *Urinary tract infection in infants. Fever. Severe bacterial infection. Febrile infants.*

Diagnóstico de infección del tracto urinario en lactantes menores de 3 meses con fiebre sin foco identificado: fiabilidad del análisis de orina y urocultivo

Resumen

Introducción: *La infección del tracto urinario (ITU) es una infección bacteriana grave frecuente en lactantes. El objetivo de este trabajo fue investigar la fiabilidad del análisis de orina (AO) para predecirla, precisar el umbral de unidades formadoras de colonias (UFC)/ml para el diagnóstico y buscar variables que ayuden a sospechar de bacteriemia en lactantes menores de 3 meses con ITU.* **Métodos:** *Se revisaron fichas clínicas de lactantes menores de 3 meses hospitalizados por fiebre sin foco evidente, registrando edad, sexo, días de fiebre preconsulta, temperatura y gravedad al ingreso, diagnósticos de egreso, exámenes de laboratorio y tratamientos. Según diagnóstico de egreso, se separaron en ITU (-) y (+), con o sin bacteriemia.*

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Resultados: *Ingresaron 467 lactantes: 334 con ITU y 133 sin ITU. En ITU (+), la sensibilidad de la piuria fue de 95.8% y bacterias (+) 88.3%; la especificidad fue alta para nitritos (96.2%) y bacterias (+) (92.5%). El valor predictivo positivo (VPP) fue de 95.9% para nitritos, 96.7% para bacterias y 92.5% para piuria. Escherichia coli se encontró en el 83.8% de los urocultivos (UC) (+) y en el 87% de los hemocultivos (+). Las ITU con bacteriemia presentaron elementos inflamatorios, UC con ≥ 100,000 UFC/ml y mayor porcentaje de proteína C reactiva (PCR) > 50 mg/l (p= 0.002); el 94.6% de los UC (+) tuvo ≥ 50,000 UFC/ml.* **Conclusiones:** *La piuria y bacterias (+) en el AO son excelentes para pronosticar ITU en orina obtenida con sonda vesical y el punto de corte para el diagnóstico debe ser ≥ 50,000 UFC/ml. No encontramos señales que ayudaran a sospechar ITU con bacteriemia.*

Palabras clave: *Infección urinaria en lactantes. Fiebre. Infección bacteriana grave. Lactantes febriles.*

Introduction

Urinary tract infection (UTI) is common in childhood; its prevalence in infants under 3 months presenting with fever without a source (FWS) is 5-20%[1-4], with a predominance in males, especially in uncircumcised children[2,4-5].

National studies showed a prevalence of UTI of 16.4% in 550 infants under 3 months hospitalized for FWS and 18.4% in 468 newborns (NB) < 29 days. In both groups, as in other publications, UTI was the most common severe bacterial infection (SBI) (~70%)[1,2,4].

For infants under 3 months presenting to the Emergency Department (ED) with FWS, it is imperative to request a complete urinalysis (UA) and urine culture (UC)[6,7] because initiation of antibiotic treatment in cases of UTI within the first 48 to 72 hours of fever can significantly reduce the risk of renal scarring, hypertension, and chronic renal failure.

Although the diagnosis of this infection is confirmed with significant bacteriuria in the UC, UA is available within a few hours. If UA contains inflammatory elements (UAI) such as nitrites, pyuria, or bacteria, the probability of infection is high[6-17].

There is controversy in the available literature regarding the usefulness of UA for predicting UTI, with reported sensitivities of 48-99% and specificities of 88-98%[1,18-21]. In addition, there is no consensus on the threshold of colony forming units (CFU)/ml required to confirm the diagnosis in urine obtained by bladder catheterization (BCC). For the American Academy of Pediatrics (AAP) (2011 and 2016) and others[8-11,13,15] it is > 50,000 CFU/ml, but in other publications > 10,000 CFU/ml is accepted[8,22-24], accompanied by UAI. If UA is normal (UAN) and UC (+), contamination or asymptomatic bacteriuria should be suspected, and only in exceptional cases of incipient UTI[9,10].

Although UC (+) of urine obtained from a collection bag (B) is unreliable due to frequent contamination[9-11,24-27], some recommend this method for the initial screening of UTI in infants who, because of their good general condition and mild severity, do not require immediate antibiotic treatment[9,10,26]. If the UA of this sample shows inflammatory elements, the UA and UC are repeated in urine obtained by BCC or BP (bladder puncture). This strategy significantly reduces the need for these invasive methods, from 63% to less than 30% in one published study[26].

Because of the controversies on the usefulness of UA to predict UTI[2] and the CFU/ml threshold to confirm the diagnosis of UTI, we decided to conduct this analysis in a group of infants under 3 months discharged with this diagnosis from the Pediatric Service of the Hospital Clínico Roberto del Río and, secondarily, to look for general and laboratory variables that could predict the presence of bacteremia at an early stage.

Methods

For mainly descriptive purposes, a cohort of infants under 3 months consecutively admitted to the Pediatrics Service of the Hospital Clínico Roberto del Río with a diagnosis of FWS (ICD 10 R50) between 2/1/2010 and 2/28/2020 was randomly selected after approval by the Institutional Ethics Committee.

Patients were identified from the daily report of pediatric hospitalizations. The inclusion criteria were age under 3 months, fever without source > 38°C of ≤ 4 days of evolution, no history of UTI, hospitalizations, bladder catheterization, chronic diseases or antibiotic treatment in the last 10 days, and complete blood count (CBC), UA-UC in samples obtained with BCC or collector and blood culture (BC). Other tests such as C-reactive protein (CRP), ultrasound and renal scintigraphy, indirect viral immunofluorescence (IF), stool culture, and cerebrospinal fluid (CSF) were not required. The analysis was retrospective and descriptive, without a prior hypothesis. According to the discharge diagnosis, two groups were formed: UTI (+) and UTI (-).

Table 1. Infants under 3 months hospitalized for FWS, general characteristics and urinalysis

Variables n° (%)	Without UTI (n = 133)	With UTI (n = 334)	Value p*
Age (days), median (IQR)	25 (11-44)	40 (21-65)	< 0.001
Age group			
< 29 days	79 (59.4%)	129 (38.6%)	0.001
29-59 days	36 (27.1%)	102 (30.5%)	
60-89 days	18 (13.5%)	103 (30.8%)	
Sex			
Female	64 (48.1%)	78 (23.4%)	< 0.001
Male	69 (59.9%)	256 (76.7%)	
Severity at admission			
Mild	109 (94.8%)	288 (86.2%)	0.029
Moderate	6 (5.2%)	46 (13.2%)	
Temperature at admission			
< 38ºC	16 (13.8%)	29 (9.0%)	0.011
38-38.9ºC	94 (81.0%)	243 (75.5%)	
39-39.9ºC	5 (4.3%)	46 (14.3%)	
≥ 40ºC	1 (0.9%)	4 (1.2%)	
Days of hospitalization			
< 3	35 (26.3%)	11 (3.3%)	0.001
3 to 5	87 (65.4%)	153 (45.8%)	
6 to 8	8 (6.0%)	116 (34.7%)	
> 8	3 (2.3%)	54 (16.2%)	
Urine sample			
Collector	45 (33.83%)	0	0.001
Catheter	58 (43.61%)	88 (26.4%)	
Collector/catheter	30 (22.6%)	246 (73.7%)	
Nitrites			
(+)	5 (3.8%)	117 (35.0%)	0.001
(-)	128 (96.2%)	217 (65.0%)	
Bacteria			
(-)	123 (92.5%)	39 (11.7%)	0.001
(+)	7 (5.3%)	109 (30.2%)	
(++)	3 (2.30%)	101 (32.6%)	
(+++)	0	85 (25.4%)	
Leukocytes			
< 10	107 (80.5%)	13 (3.9%)	0.001
10 a 49	20 (15.0%)	26 (7.8%)	
50 a 99	3 (2.3%)	17 (5.1%)	
100 a 150	1 (0.8%)	21 (6.3%)	
151 a 200	1 (0.8%)	12 (3.6%)	
201 a 300	1 (0.8%)	22 (6.6%)	
≥ 300	0	223 (66.8%)	

p* Fisher's exact test for categorical variables. Wilcoxon-Mann-Whitney test for quantitative variables.
FWS: fever without source; IQR: interquartile range; UTI: urinary tract infection.

Table 2. Laboratory studies and cultures of infants under 3 months hospitalized for FWS

Variables n (%)	Without UTI (n = 133)	With UTI (n = 334)	PPV (95%CI)
Colony count (-)	133 (100%)	0 (0.0%)	NA
10,000	-	4 (1.2%)	
10,001 a 49,000	-	14 (4.2%)	
50,000 a 99,999	-	23 (6.9%)	
>100,000	-	293 (87.7%)	
Urine culture (-)	133 (100%)		
Urine culture (+)	0	334 (100%)	NA
Escherichia coli	-	280 (84.0%)	
Klebsiella pneumoniae	-	18 (5.4%)	
Klebsiella oxytoca	-	9 (2.7%)	
Enterococcus faecalis.	-	12 (3.6%)	
Enterobacter cloacae	-	11 (3.3%)	
Proteus mirabilis	-	4 (1.2%)	
Blood culture: (+)	0	54 (16.2%)	NA
Escherichia coli	-	47 (87.0%)	
Enterococcus faecalis.	-	3 (5.6%)	
Klebsiella pneumoniae	-	2 (3.7%)	
Klebsiella oxytoca	-	1 (1.9%)	
Enterobacter cloacae	-	1 (1.9%)	
CRP in blood (mg/l)			
<50	113 (92.60%)	173 (53.2%)	94.4 (90-97)
≥ 50	9 (7.40%)	152 (46.8%)	
Leukocytes in blood (mm^3)			
< 18,000	119 (93.00%)	233 (69.8%)	91.8 (85-96)
> 18,500	9 (7.00%)	101 (30.2%)	
Neutrophils in blood (mm^3)			
< 9,500	118 (92.20%)	223 (66.7%)	91.7 (86-95)
> 9,500	10 (7.80%)	111 (33.2%)	
Kidney US			
Normal	0	185 (56.2%)	
Altered	0	144 (43.8%)	NA

95%CI: confidence interval; CRP: C-reactive protein; FWS: fever without source; NA: not applicable; PPV: positive predictive value (+); US: ultrasound; UTI: urinary tract infect.

Table 3. Variables of 334 infants under 3 months hospitalized for FWS and discharged with a diagnosis of UTI. Comparative analysis between cases of UTI with blood culture (+) and (-)

Variables n (%)*	Blood culture		Value	PPV
	(-)	(+)	p†	(95%CI)
Nitrites				
(+)	93 (33.2)	24 (44.4)	0.121	NA
(-)	187 (66.8)	30 (55.6)		
Bacteria				
(-)	33 (11.8)	6 (11.1)	0.213	NA
(+)	89 (31.8)	12 (22.2)		
(++)	84 (30.0)	25 (46.3)		
(+++)	74 (26.4)	11 (20.5)		
Leukocytes				
< 10	11 (3.9)	2 (3.7)	0.644	NA
10 to 49	25 (8.9)	1 (1.9)		
50 to 99	14 (5.0)	3 (5.6)		
100 to 150	17 (6.1)	4 (7.4)		
151 to 200	11 (3.9)	1 (1.9)		
201 to 300	19 (6.8)	3 (5.6)		
> 300	183 (65.4)	40 (74.1)		
Nº of colonies				
10,000	4 (1.4)	0	0.021	NA
10,001 to 49,999	14 (5.0)	0		
50,000 to 99,999	23 (8.2)	0		
≥ 100,000	239 (85.4)	54 (100.0)		
Urine culture (+)	280	54	0.974	NA
Escherichia coli	233 (83.2)	47 (87.0)		
Klebsiella pneumoniae	16 (5.7)	2 (3.7)		
Klebsiella oxytoca	8 (2.9)	1 (1.9)		
Enterococcus faecalis.	9 (3.2)	3 (5.6)		
Enterobacter cloacae	10 (3.6)	1 (1.9)		
Proteus mirabilis	4 (1.4)	0 (0.0)		
CRP/blood				
< 50	156 (56.9)	17 (33.3)	0.002	22.4
≥ 50	118 (43.1)	34 (66.7)		(18.5-26.8)
Leukocytes/blood				
< 18,000	197 (70.4)	36 (66.7)	0.628	17.8
≥ 18,000	83 (29.6)	18 (33.3)		(12.5-24.8)
Neutrophils/blood				
< 9,500	187 (66.8)	36 (66.7)	1	16.2
≥ 9,500	93 (33.2)	18 (33.3)		(11.5-22.6)
Kidney US				
Normal	160 (58.2)	25 (46.3)	0.133	20.14
Abnormal	115 (41.8)	29 (53.7)		(15.9-25.1)

*Percentage of each category.
†Fisher's exact test.
95%CI: confidence interval; CRP: C-reactive protein; FWS: fever without source; NA: not applicable; PPV: positive predictive value; US: ultrasound; UTI: urinary tract infection.

We divided the children with UTI into those with BC (+) and BC (-) to compare them and identify general and laboratory variables that could help predict the presence of bacteremia early. The clinical records of the patients were reviewed, recording age, sex, days of fever before consultation, temperature, severity (estimated according to level of consciousness, environmental awareness, hydration, and type of breathing) on

Table 4. Correlation between urinary inflammatory variables and urine culture colony counts in infants under 3 months with UTI

			Colony counts			
Variables*	0 (n = 133)	10,000 (n = 4)	10,001-49,000 (n = 14)	50,000-99,000 (n = 23)	> 100,000 (n = 293)	p value†
Nitrites						< 0.001
-	96.20%	75%	100%	69.60%	63.00%	
+	3.80%	25%	0%	30.40%	37.00%	
Bacteria						< 0.001
-	92.50%	25%	42.90%	26.10%	9.20%	
+	5.30%	75%	42.90%	34.80%	28.50%	
++	2.30%	(-)	7.10%	17.40%	35.60%	
+++	(-)	(-)	7.10%	21.70%	26.80%	
Leukocytes						0.001
< 10	80.50%	0.00%	21.40%	4.30%	3.10%	
≥ 10	19.50%	100%	78.60%	95.70%	96.90%	

*Percentages of each category.
†Fisher's exact test.
UTI: urinary infection.

Table 5. Usefulness of some urinalysis and blood test variables to predict the diagnosis of UTI in infants under 3 months hospitalized for FWS

Variables*	Sensitivity	Specificity	PPV (+)	NVP (-)
Urine				
Nitrites (+)	35.03	96.24	95.9	37.1
95%CI	29.9 2-40.41	91.44-98.77	90.73-98.25	35.13-39.12
Bacteria (+)	88.32	92.48	96.72	75.93
95%CI	84.38-91.57	86.61-96.34	94.2-98.2	70.05-80.96
Leukocytes ≥ 10	96.1	80.5	92.6	89.2
95%CI	93.4-98.0	72.68-86.82	89.7-94.56	82.7--93.4
Blood				
CRP > 50mg/l	46.7	92.6	94.4	39.5
95%CI	41.2-52.4	86.5-96.6	89.9-97.0	36.8-42.3
Leukocytes ≥ 18,000	30.2	93	91.8	33.8
95%CI	25.4-35.5	87.1-96.7	85.4-95.6	31.9-35.7
Neutrophils ≥ 9,500	33.2	92.2	91.7	34.6
95%CI	28.2-38.6	86.1-96.2	85.7-95.4	32.6-36.7

*Percentage of each category.
95%CI: confidence interval; CRP: C-reactive protein; FWS: fever without source; NVP: negative predicitive value; PPV: positive predictive value; UTI: urinary tract infection.

admission to the ED and hospital, laboratory tests, procedures used to obtain urine, treatments indicated, and days of hospitalization. The information obtained was recorded in a specially designed database in an Excel spreadsheet.

For microscopic examination, we used non-centrifuged urine and leukocyte count in a Neubauer chamber, while the rest of the elements were measured with a reagent strip. We considered UAI when in the UA the following were identified: > 10 leukocytes/mm^3 (pyuria), or positive nitrites (+/+++), or positive bacteria (+/+++), and UAN when these elements were absent. We considered UC (+) when there was growth of > 10,000 CFU/ml of a uropathogenic microorganism and UC (-) when there was no bacterial growth, the count was below the pre-determined threshold, or when contaminants such as skin or genitourinary flora as coagulase-negative *Staphylococcus*, *Lactobacillus*, and *Corynebacterium* were isolated. We considered UC to be contaminated when two or more pathogens were isolated.

Table 6. Usefulness of blood tests to predict bacteremia in 344 infants under 3 months discharged from the hospital with a diagnosis of UTI

Variables	Sensitivity	Specificity	PPV	NVP
CRP > 50 mg/l	66.67	56.9	22.4	90.2
95%CI	52.1-79.2	50.8-62.9	18.5-26.8	86.0-93.3
Leukocytes > 18,000/mm^3	33.3	70.4	17.8	84.5
95%CI	21.1-47.5	64.6-75.6	12.5-24.8	81.7-87.0
Neutrophils > 9,500/mm^3	33.3	66.8	16.2	83.9
95%CI	21.1-47.5	60.9-72.3	11.4-22.6	80.9-86.5

95%CI: confidence interval; CRP: C-reactive protein; NPV: negative predictive value; PPV: positive predictive value; UTI: urinary infection.

The gold standard to confirm the diagnosis of UTI is UC (+) in urine obtained with BCC or any colony count with BP. UTI with bacteremia was identified with BC (+) to the same microorganism isolated in the UC, while it was considered without bacteremia when the BC was (-). For the statistical analysis, we used median (range) and Wilcoxon-Mann-Whitney test for quantitative variables; n (%) and Fisher's exact test for categorical variables or χ^2. Univariate and multivariate logistic regression was used to search for laboratory variables predictive of bacteremia.

Results

One thousand two hundred fifty infants with FWS under three months met the inclusion criteria. The sample included the 334 infants discharged with a diagnosis of UTI and 133 infants randomly selected without UTI as controls. From the group of infants with UTI, 54/334 (16.2%) had bacteremia and 129/334 (38.6%) were less than 29 days old; of these, 5.4% were between 4 and 6 days old.

Table 1 shows the general characteristics of infants with UTI and controls, all with UA and UC. In comparison, infants in the UTI group were found to be significantly ($p < 0.001$) older than controls, and there was a higher proportion of males. Also, more infants with UTI of moderate severity, temperature > 39°C, and frequency of nitrites (+), pyuria, or bacteria (+) were detected in the UA. In the control group, 3.8% had nitrite (+), 7.5% had bacteria (+), and 19.5% had pyuria, but this frequency decreased to 4.5% as the leukocyte threshold increased to > 50/mm^3. All children with UAI in specimens collected with the collector required another UA and UC in urine collected with BCC.

Table 2 shows the comparison of laboratory variables such as US, CRP, leukocytes, and neutrophils in febrile patients with and without UTI; the differences between groups are significant ($p < 0.001$). In the group with UTI, we observed a higher percentage of CRP > 50 mg/l: 152/161, positive predictive value (PPV): 94.4% (confidence interval [CI] 95%:90-97), negative predictive value (NPV): 39.5 (95%CI 36.8-42.3); leukocytes > 18,000 mm^3 in 101/110, PPV 91.8% (CI95% 85.4-95.6), NPV 33.8 (CI95% 31.9-35.7) and neutrophils > 9500 mm^3 in 111/121, PPV 91.7% (CI95%: 85.7-95.4), NPV 34.6 (CI95% 32.6-36.7). In addition, 94.6% of UC (+) had > 50,000 CFU/ml and 1.2% had 10,000 CFU/ml; *Escherichia coli* was isolated in 83.8% of UC (+) and 87.04% of BC (+).

Table 3 shows laboratory results in infants with and without bacteremia. In the latter, the frequency of blood CRP > 50 mg/l is higher ($p < 0.002$). When evaluating the proportion of infants with blood variables (+) who had bacteremia, we found that 34/152 had CRP > 50 mg/l, PPV 22.4% (95%CI 18.52-26.75), NPV 90.2 (95%CI 86-93.2); 18/101 with leukocytes > 18,000/mm^3, PPV 17.8 (95%CI 12.5-24.8), NPV 84.6 (95%CI 81.7-87) and 18/111 with neutrophils > 9500/mm^3, PPV 16.2 (95%CI 11.36-22.62), NPV 83.9 (95%CI 80.9-86.5). In 87.03% of UTIs with bacteremia, *E. coli* was the etiologic agent, and 100% of these were associated with UAI; in UTIs without bacteremia, *E. coli* was isolated in 83.2% of UC (+) and 96.7% of these were associated with UAI. Other etiologic agents were observed in 16.2% of UC, and 11.2% were associated with UAI. Bacteremia was present in 17% of UTIs in infants under 29 days and in 15.5% of UTIs in older infants.

Table 4 shows that the percentage of UAI (nitrites (+) or pyocytes or bacteria (+) in infants with UTI) increases

significantly ($p < 0.001$) in direct relation to the increase of CFU/ml in UC.

Considering positive those discharged with a diagnosis of UTI, we can see the diagnostic usefulness of some UA and blood variables (Table 5). The sensitivity of 95.81% (95%CI 93.07-97.69) for pyuria and 88.32% (95%CI 84.38-91.57) for bacteria (+) stand out; the specificity for the three variables is > 80%, with nitrites standing out with 96.24% (95%CI: 91.4-98.8) and bacteria (+): 92.48% (95%CI 86.6% -96.3%); PPV > 90% and NPV is low for nitrites, but improves > 70% for bacteria and leukocytes. In blood, all three variables have a PPV > 90%.

In Table 6, the multivariate logistic regression was adjusted by including in the model only those variables with $p < 0.25$ in the univariate analysis (Hosmer-Lemeshow criterion) for predicting BC (+). Therefore, we conclude that only the variable CRP > 50 mg/l has a significant effect on the variable blood culture (+).

Discussion

Although the signs and symptoms of UTI in infants under 3 months are not specific, UAI is an excellent tool for predicting the diagnosis and even justifying early initiation of antibiotics, which, as is well known, can significantly reduce the risk of renal scarring, hypertension, and chronic renal failure[5,9,10,14].

Our results, in agreement with other publications[6-16], show the high percentage of UAI in infants with UTI: sensitivity for pyuria was 95.8% (95%CI 93.7-97.7) and 88.3% for bacteria (+) (95%CI 84.4-91. 6); the specificity for the three inflammatory variables studied was also high, especially for nitrites 96.2% (95%CI 91.4-98.8) and bacteria (+) 92.5 (95%CI 86.6-96.3), showing that the percentage of UAN in children without UTI is also high. Similarly, the PPV > 90% confirms the good ability of UAI to predict UTI in infants younger than three months with FWS. The absence of nitrite does not satisfactorily predict the absence of infection, in contrast to bacteria (+) and pyuria, which have NPVs of 75.9% (95%CI 70.5-81) and 89.2% (95%CI 82.8-93.4), respectively.

In contrast to other publications[8,15], we found that 100% of UTIs with bacteremia were associated with UAI. In those without bacteremia, although somewhat less, UAI was also detected in 97.8% of those caused by *E. coli* and 93.6% of those caused by other microorganisms, consistent with what has been described in the literature[8,12].

Our results confirm that in infants with FWS, UA is a valuable tool in routine clinical practice for pediatricians to suspect the diagnosis of UTI and initiate the appropriate treatment empirically. At the same time, it is important to consider that UA and UC should always be requested simultaneously[12,18].

The low sensitivity and specificity of UA described in some publications could be due to the method used for urine collection, false positives, the etiologic agent, or the lower threshold of CFU/ml required to confirm the diagnosis[8,18-21]; the latter is consistent with what was observed in this study, where the frequency of UAI was significantly higher as the number of CFU/ml in the UC increased ($p < 0.001$).

As in other reports[19,22,23], our threshold of CFU/ml to confirm the diagnosis of UTI was 10,000; however, only 1.2% of UC (+) reached this value. Eighty-seven percent of all UTIs and 100% of UTIs with bacteremia had > 100,000 CFU/ml. When considering all UTIs, 94.6% had > 50,000 CFU/ml, which allows us to conclude that in samples obtained with BCC, the confirmatory threshold for UTI in infants under 3 months with FWS is > 50,000 CFU/ml, in agreement with the AAP and other authors[8-11,13,15,24]. However, counts of 10,000 to 49,900 CFU/ml are equally confirmatory in infants with FWS and UTI, but if the UA is normal, the test should be repeated.

The multivariate logistic regression analysis did not identify variables that could help predict the presence of UTI with bacteremia, consistent with the observations of other authors[28-31]. The frequency of BC (+) in patients younger than 29 days (17%) was not significantly different ($p > 0.05$) from those of older age (15.6%).

Despite the limitations inherent in retrospective studies and the lack of renal scintigraphy, we have satisfactorily met our objectives. In additon, our results may be useful in daily clinical practice and for future prospective studies.

In conclusion, we verified that UA is a valuable predictor of UTI in infants < 3 months with FWS, with good sensitivity, specificity, and PPV. *E. coli* is the main etiologic agent, present in 83.8% of UC (+) and in 87% of BC (+). In urine samples obtained with BCC, 94.6% of BC (+) have > 50,000 CFU/ml and 87.7% > 100,000 CFU/ml. Of the variables studied, CRP > 50 mg/l is the only one significantly associated with BC (+) ($p < 0.02$). However, it is not an acceptable indicator for an early prediction of bacteremia.

Ethical disclosures

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

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

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

Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Effectiveness of pancreatic stent placement in pediatric patients with acute recurrent and chronic pancreatitis

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Abstract

Background: *The use of pancreatic prostheses in children with acute recurrent pancreatitis (ARP) and chronic pancreatitis (CP) has evolved. The main established indication is the treatment of persistent abdominal pain. This study aimed to evaluate the efficacy of pancreatic stenting for refractory abdominal pain in pediatric patients with ARP and CP.* **Methods:** *We conducted a retrospective case series study. We included patients under 16 years of age diagnosed with ARP and CP in the study. Endoscopic retrograde cholangiopancreatography (ERCP) was performed with the insertion of one and later two pancreatic stents. We evaluated abdominal symptoms before and after treatment, number of changes, duration of treatment, and complications with follow-up at 24 months and after withdrawal.* **Results:** *Nine patients with ARP and CP were included in the study: six with undetermined etiology and three with pancreas divisum. The mean age was 12.4 years. Prosthesis placement relieved abdominal pain in 100% of cases, with 3.2 replacement sessions every 6.2 months for 27.4 months, and mild complications (15.7%). One patient experienced pain on removal of the prosthesis and required bypass surgery.* **Conclusion:** *Pancreatic stent placement in patients with refractory abdominal pain with ARP and CP proved to be effective and safe, providing medium-term symptom relief and minimal complications.*

Keywords: *Pancreas divisum. Chronic pancreatitis. Pediatrics. Pancreatic prosthesis.*

Eficacia de la prótesis pancreática en pacientes pediátricos con pancreatitis aguda recurrente y crónica

Resumen

Introducción: *El uso de prótesis pancreáticas en niños con pancreatitis aguda recurrente (PAR) y crónica (PC) ha evolucionado. La principal indicación establecida es el tratamiento del dolor abdominal persistente. El objetivo de este estudio fue evaluar la eficacia del uso prótesis pancreática para el dolor abdominal refractario en pacientes pediátricos con PAR y PC, sin respuesta a manejo conservador.* **Métodos:** *Se llevó a cabo un estudio retrospectivo de serie de casos. Se incluyeron pacientes menores de 16 años con diagnóstico de PAR y PC. Se realizó una colangio pancreatografía retrograda endoscópica (CPRE) para introducir inicialmente una y posteriormente dos prótesis pancreáticas. Se evaluaron síntomas*

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abdominales antes y después del tratamiento, número de recambios, duración del tratamiento y complicaciones con seguimiento a 24 meses y posterior a su retiro. **Resultados:** *Se incluyeron 9 pacientes con PAR y PC: seis de etiología no determinada y tres con páncreas divisum. La edad promedio fue de 12.4 años. La colocación de prótesis alivió el dolor abdominal en el 100%, con 3.2 sesiones de recambio cada 6.2 meses en 27.4 meses, y complicaciones leves (15.7%). Un paciente presentó dolor al retirar las prótesis y requirió cirugía derivativa.* **Conclusiones:** *El uso de prótesis pancreática en pacientes con dolor abdominal refractario con PAR y PC demostró ser eficaz y seguro al aliviar los síntomas a mediano plazo con mínimas complicaciones.*

Palabras clave: *Pancreatitis crónica. Páncreas divisum. Pediatría. Prótesis pancreática.*

Introduction

Pancreatitis has been classified as acute pancreatitis (AP), acute recurrent pancreatitis (ARP), and chronic pancreatitis (CP). ARP is defined as at least two distinct episodes of AP with complete resolution of pain or complete normalization of serum pancreatic enzyme levels before a new episode of AP is diagnosed, regardless of the specific time interval between episodes of AP. CP is defined as abdominal pain typical of pancreatitis plus characteristic imaging findings, exocrine insufficiency plus imaging findings, or endocrine insufficiency plus imaging findings[1-3]. The causes may be obstructive or non-obstructive. The former include common bile duct cysts, pancreas divisum, annular pancreas, duodenal diverticulum, duodenal duplication, parasitic infection, and anomalies of the pancreaticobiliary junction. Non-obstructive causes include hereditary factors, autoimmune factors, cystic fibrosis, hyperlipidemia, trauma, medications, and hypercalcemia[4-6]. Endoscopic treatment aims to improve abdominal pain and prevent damage of the pancreatic parenchyma and duct, which can lead to exocrine and endocrine pancreatic complications[7].

In recent years, endoscopic therapy has become a widely used primary treatment option for patients with abdominal pain due to a variety of pancreatic disorders, including ARP, CP, pancreatic duct leakage or disruption (pancreas divisum), pseudocyst drainage, and prevention of pancreatitis after endoscopic retrograde cholangiopancreatography (ERCP)[7,8]. One of the most common forms of pancreatic endotherapy is sphincterotomy and pancreatic stent placement. These are placed in the main pancreatic duct to relieve ductal obstruction, often in refractory abdominal pain due to strictures, stones, or papillary stricture. They have also been used in the minor papilla to treat symptomatic pancreas divisum secondary to a stenotic minor papilla[8].

The purpose of this study was to evaluate the efficacy of using a pancreatic prosthesis to reduce pain in pediatric patients with ARP and CP.

Methods

We conducted a retrospective case series study from July 2013 to December 2021. The study was descriptive and observational. We included consecutive cases of children aged 6-16 years diagnosed with ARP and CP confirmed by clinical presentation and imaging studies, who persisted with abdominal pain despite medical treatment and whose clinical records had complete information. Medical treatment included a diet without cholecystokinetics, analgesics, and proton pump inhibitors.

Of the 14 patients who met the inclusion criteria, five were excluded due to incomplete records, loss of follow-up, or failure to achieve 24 months of follow-up from baseline.

We evaluated variables such as age, sex, number of episodes of pancreatitis before the endoscopic intervention, indication for pancreatic prosthesis placement, prosthesis replacement time, number of replacements, pancreatic duct diameter at baseline and at removal, complications, and clinical evolution after prosthesis removal. As part of the medical management, patients were prescribed a diet without cholecystokinetics and analgesic treatment for pain.

Before prosthesis placement, magnetic resonance cholangiopancreatography was performed to evaluate the presence of anatomical abnormalities, stenosis, stones, and pancreatic duct caliber. Subsequently, ERCP was performed to cannulate the pancreatic duct with a triple lumen sphincterotome; after the passage of the hydrophilic guide, a 3 mm sphincterotomy was performed, and a pancreatic prosthesis of 5 or 7 French of diameter by 5 or 7 cm length was placed, depending on the characteristics of the duct.

After placing this prosthesis, patients were followed up after 1 month to observe the clinical evolution, then every 6 months for prosthesis replacement, and after 24 months to evaluate the diameter of the pancreatic duct. Two prostheses were placed according to the diameter of the duct for better drainage.

The procedure was performed by a team of experienced pediatric endoscopists using adult duodenoscopes (TJF TYPE 160VF Olympus Tokyo Japan and ED530XT Fujifilm Corporation Japan), a triple lumen sphincterotome (Wilson-Cook Medical Inc., Winston-Salem, N.C.), hydrophilic guidewire (Wilson-Cook Medical Inc., Winston-Salem, N.C.), and pancreatic prosthesis (Wilson-Cook Medical Inc., Winston-Salem, N.C.).

All procedures were performed under general anesthesia by an experienced pediatric anesthesiologist. Procedures were performed in the radiology department, limiting fluoroscopy time with minimal radiation exposure and covering the patients' genital organs. Ultravist 300 (Bayer AG Germany) 50% contrast was used to visualize the diameter of the affected duct; pancreatic duct measurements were obtained at the beginning and end of the study.

Ethical aspects

Following the Declaration of Helsinki, the study was approved by the hospital's Health Research and Ethics Committee under number HIM-SR-2021-022.

Statistical analysis

A descriptive analysis was performed. The Shapiro–Wilk test was performed for quantitative variables, a non-parametric distribution was shown, and values were described as medians, minimums, and maximums. Frequencies and percentages were used for qualitative variables. STATA version 11 was used.

Results

Nine patients were included in the study: five females (56%) and four males (44%). The median age was 12.4 years, ranging from 9 to 16 years. Cholangiopancreatography showed pancreatic duct dilatation of 3 mm in two, 4 mm in three, and 5 mm in four patients. In six cases (67%), no etiology was found, so they were considered idiopathic after the studies. In three cases (33%), an anatomical alteration (pancreas divisum) was found (Table 1). The main symptom in all cases was pain associated with elevated serum levels of pancreatic enzymes. Before study entry, patients had a median of 4.5 pancreatitis events (minimum 3 and maximum 7). The median follow-up period was 28 months (minimum 24 and maximum 40 months). Some patients had prolonged follow-up due to conditions that delayed prosthesis replacement: two patients were delayed because scheduled surgical procedures were suspended during the COVID-19 pandemic, and one adolescent became pregnant during follow-up and underwent postpartum replacement.

A total of 43 procedures were performed, with a median of five per patient (range 4-6), including placement, replacement, and removal of the prosthesis. The replacement frequency was every 6.2 months (range 1-8 months); there was only one case where replacement had to be performed after 1 month due to obstruction of the prosthesis with pancreatitis, requiring the placement of a double prosthesis. The replacements performed between 7 and 8 months were due to the inactivity of the institution on the scheduled date due to the COVID-19 pandemic.

After 2 years of treatment or more than three exchanges, all nine patients had their prostheses removed. Eight patients (88.8%) remained asymptomatic 6 months after prosthesis removal. Three of them (33%) reached 18 years of age and were referred asymptomatic to an adult hospital for further follow-up. The remaining five patients (56%) are still under clinical follow-up; four have been asymptomatic for 12, 26, 27, and 32 months. The last patient required surgical treatment for pain relief 5 months after removal and was referred to an adult hospital for follow-up at age 18, remaining asymptomatic to date.

When the prostheses were removed, the diameter of the ducts increased (5 mm in one, 6 mm in two, 7 mm in one, and 8 mm in five). During the first year of the study, two patients had mild pancreatitis, one had two episodes, and the rest had no pain.

Complications reported after ERCP, sphincterotomy, prosthesis placement, prosthesis replacement, or removal were mild AP in seven patients (15.7%) after 43 procedures; one patient had migration of the intraductal prosthesis (2%), which was successfully removed and repositioned with an endoscopic balloon.

Discussion

Pain caused by pancreatitis (mainly ARP and PC) is a prominent and often debilitating symptom that usually does not disappear in the natural course of the disease; its mechanism may be because intraductal hypertension due to its obstruction. Initially, these conditions had to be treated by a specialist, but if the patient did not respond, or got complicated, surgery was necessary.

Table 1. Description of the nine patients after pancreatic prosthesis placement

Case	Age/sex	ERCP/ prosthesis used	Months of treatment	Complications	Post-removal follow-up (months)	Type of pancreatitis	Clinical manifestations	Previous pancreatitis	PD start body/tail	PD final body/tail	Therapeutic success
1	Female 11 years	5/5	26	Pancreatitis post-ERCP and pain	5	ARP pancreas divisum	Pain Surgery Age-related discharge	4	3 mm/2 mm	8 mm/4 mm	No
2	Female 11 years	6/8	40	Pancreatitis post-ERCP Intraductal migration	36	CP idiopathic	Asymptomatic	7	4 mm/2 mm	8 mm/3 mm	Yes
3	Male 16 years	4/4	24	Pancreatitis post-ERCP	6	CP idiopathic	Asymptomatic Age-related discharge	5	5 mm/3 mm	6 mm/4 mm	Yes
4	Female 16 years	4/4	31	Pancreatitis post-ERCP	6	CP idiopathic	Asymptomatic Age-related discharge	4	5 mm/3 mm	8 mm/5 mm	Yes
5	Male 13 years	5/6	34	No	4	CP idiopathic	Asymptomatic	5	5 mm/3 mm	8 mm/3 mm	Yes
6	Male 11 years	4/4	27	Pancreatitis post-ERCP	26	ARP pancreas divisum	Asymptomatic	3	4 mm/2 mm	5 mm/2 mm	Yes
7	Male 16 years	5/6	24	No	2	ARP idiopathic	Asymptomatic Age-related discharge	4	4 mm/2 mm	6 mm/3 mm	Yes
8	Female 9 years	5/6	24	No	12	ARP idiopathic	Asymptomatic	6	3 mm/2 mm	8 mm/3 mm	Yes
9	Female 9 years	5/7	26	Pancreatitis post-ERCP	27	CP pancreas divisum	Asymptomatic	3	5 mm/3 mm	7 mm/4 mm	Yes

ARP: acute recurrent pancreatitis; CP: chronic pancreatitis; ERCP: endoscopic retrograde cholangiopancreatography; PD: pancreatic duct.

Currently, with the advent of therapeutic ERCP, we have an intermediate treatment[9,10].

Endoscopic therapy has become a widely used primary treatment option for patients with abdominal pain secondary to pancreatic changes in adults[11-13]. However, its detractors mention that the prosthesis produces a reaction with increased duct volume and fibrosis, especially when applied to a duct of normal caliber[14,15]. Some studies suggest that abdominal pain does not usually go away with this treatment[15]; in contrast, several reports in children suggest that this therapeutic approach can be performed safely and provide short-term relief of symptoms[16-18].

In a 12-year study, Güitrón-Cantu et al.[19] included 20 pediatric patients with ARP treated with sphincterotomy (70%), placement of a 7 French caliber pancreatic prosthesis (90%), and replacement with a 10 French prosthesis (50%) every 4-6 weeks, for a total of 35 procedures (average 1.7 sessions) at 24 months follow-up. A non-serious complication rate of 5.7% was reported, with a reduction in the severity and frequency of pain after the procedure; only one patient required bypass surgery. In contrast, we had less cases in a longer period, and we performed sphincterotomy, placement, and replacement with smaller caliber prostheses (5-7 French each), for a longer time and number of replacement sessions. Regarding complications, although we reported a higher percentage (15.7%) without mortality, pain relief and lack of response to treatment were similar.

Lans et al.[20] reported prosthesis replacement every 3 or 4 months, with retention for 1 year and clinical improvement in 90%. Thus, a good clinical response was observed in these three studies (89-94%) despite having different prostheses caliber, distinct replacement times, and duration of treatment. This response was related to adequate drainage of the pancreatic duct. In addition, a low rate of non-serious complications was observed here (5.7% vs. 15%), consistent with Johanson et al.,[21] who reported intraductal migration of the prosthesis as a complication in 5.2% vs. 1.7% in our study. Finally, Kohoutova et al.[18] performed therapeutic ERCP with prosthesis placement in children with CP with a complication rate of 3%.

Regarding the persistence of symptoms after endoscopic treatment, Güitrón-Cantu et al.[19] reported 5% (compared to 11.1% in our series) that ended up in derivative surgery with subsequent improvement, showing that both endoscopic and surgical procedures allow for clinical improvement[5].

Therefore, we consider that pancreatic prosthesis placement by ERCP is a reproducible technique. It has the advantage of being an advanced and minimally invasive endoscopic procedure with a low percentage of complications, promoting a reduction in hospital stay and faster recovery. This technique contributes palliatively to the improvement of abdominal pain in appropriately selected children and as a bridge to surgery in those who do not improve. Due to the small sample size of our study, however, the results presented should be taken with caution.

In pediatric patients with ARP and CP and refractory abdominal pain, pancreatic prosthesis placement is effective and safe in relieving symptoms in the medium term (24 months) with minimal complications.

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.

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Conflicts of interest

The authors declare no conflicts of interest.

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RESEARCH ARTICLE

Ten years of pediatric surgery in a secondary level perinatal hospital in Mexico

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Abstract

Background: *Neonatal surgery is one of the most specialized and demanding areas of pediatric surgery due to the specific anatomical and physiological characteristics of this vulnerable group of patients. This study aimed to present the experience of 10 years of neonatal surgical management in a secondary care perinatal hospital in Mexico.* **Methods:** *We conducted a descriptive, observational, cross-sectional, and retrospective study in a perinatal hospital in Toluca, Mexico, from August 01, 2012, to July 31, 2022. We included patients who underwent surgery within the hospital facilities by the Service of Pediatric Surgery. We studied demographic, clinical, and surgical variables and performed descriptive and inferential statistics.* **Results:** *A total of 551 patients underwent surgery during this period with a prevalence of 0.5%. The number of patients operated in the neonatal period was 497 (90.1%). Forty-eight pathologies were recorded, with a predominance of congenital malformations in 64.6% and prenatal diagnosis in 40.5% of cases. The survival rate was 89.7%. In the bivariate analysis of mortality, we found an inverse relationship between weight and gestational age ($p < 0.05$).* **Conclusion:** *Although not a local or national reference center, the hospital where the study was conducted treats various congenital and acquired diseases, with a mortality rate that tends to decrease, close to the international average, and lower than national reports.*

Keywords: *Pediatrics. Surgery. Newborn. Congenital abnormalities.*

Diez años de cirugía pediátrica en un hospital perinatal de segundo nivel en México

Resumen

Introducción: *La cirugía pediátrica en la atención del recién nacido es una de las ramas más especializadas y demandantes debido a las particulares características anatómicas y fisiológicas de este vulnerable grupo de pacientes. El objetivo de este estudio fue presentar la experiencia de diez años de manejo quirúrgico neonatal en un hospital perinatal de segundo nivel de atención en México.* **Métodos:** *Se llevó a cabo un estudio descriptivo, observacional, transversal y retrospectivo, en un hospital perinatal de Toluca, México, del 01 de agosto de 2012 al 31 de julio de 2022. Se incluyeron los pacientes sometidos a cirugía dentro de las instalaciones del hospital por parte del servicio de Cirugía Pediátrica. Se estudiaron variables demográficas, clínicas y quirúrgicas, realizando estadística descriptiva e inferencial.* **Resultados:** *Un total de 551 pacientes fueron intervenidos quirúrgicamente en este periodo, con una prevalencia de 0.5%. La cantidad de pacientes operados en*

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el periodo neonatal fue de 497 (90.1%). Se presentaron 48 patologías con predominio de las congénitas en el 64.6% y diagnóstico prenatal en el 40.5% de los casos. La supervivencia de los pacientes fue del 89.7%. En el análisis bivariado de mortalidad se encontró una relación inversa con el peso y edad gestacional (p < 0.05). **Conclusiones:** *En el hospital donde se realizó el estudio, a pesar de no ser un centro de referencia local o nacional, se atiende una amplia diversidad de padecimientos congénitos y adquiridos, con una mortalidad con tendencia a disminuir cercana a la media internacional y menor que los reportes nacionales.*

Palabras clave: *Pediatría. Cirugía. Recién nacido. Anomalías congénitas.*

Introduction

Pediatric surgery in America began in the early 20th century, when the surgical diseases of newborns forced a group of surgeons to devote themselves exclusively to the care of children. However, neonatal surgery really started when the first neonatal surgical unit was established in Liverpool in 1953[1-4]. Neonatal surgery is the most demanding and specialized field of pediatric surgery due to these patients' unique physiological, anatomical, and biochemical characteristics[5].

Over the years, with advances in neonatal intensive care, we have seen an improvement in the survival of neonates with smaller gestational ages and more challenging and complex clinical conditions[6,7]. It is well known that pediatric patients are not little adults, and this is especially true for neonates, who require facilities designed specifically for them[8].

In 1967, the "Hospital de la Mujer" was inaugurated, which later became the Hospital de Ginecología y Obstetricia (HGyO) of the Instituto Materno Infantil del Estado de México (IMIEM), the first hospital in Toluca to provide specialized care for the mother-child binomial. Since 2011, this hospital has had a pediatric surgery service[9], joining the maternity hospitals that provide surgical management within their facilities, being a pioneer in the State of Mexico. It currently has 75 beds, divided into the neonatal intensive care unit (NICU), Infectious Diseases, Metabolic Disorders, Transitional Care, Growth and Development, and the Surgical Unit. In terms of human resources, it has a staff of 27 specialists in neonatology and a pediatric surgeon. It has the peculiarity of not accepting outpatients, so all the newborns that undergo surgery are those born in the same facilities.

Neonatal surgery is divided into surgery for congenital malformations and surgery for acquired conditions secondary to complications of prematurity or prolonged hospitalization[10]. It is important to know the casuistry of neonatal surgical diseases in one of the oldest perinatal hospitals in the most populated state of Mexico. This study aimed to describe the 10-year experience of surgical management of patients treated at the Neonatal Service of the HGyO of the IMIEM.

Methods

Study design

We conducted a descriptive, observational, cross-sectional, and retrospective study in the Neonatal Service of the HGyO of IMIEM, Toluca, State of Mexico.

Population

Patients who underwent surgery at the HGyO by the Pediatric Surgery Service between August 01, 2012, and July 31, 2022, were included in the study. Patients who underwent surgery outside the hospital facilities were excluded. Patients with incomplete information in their records were eliminated. Procedures such as circumcision, catheter placement, paracentesis, peritoneal or chest tube placement were not included in the study.

Variables

The following variables were analyzed: age and weight at the time of surgery, sex, gestational age in weeks (wg), prenatal diagnosis, surgical diagnosis, procedure performed, anatomic region intervened, type of surgery (emergency or planned, time elapsed from diagnosis to surgery, and NICU stay), type of pathology (congenital or acquired) and mortality.

Emergency surgery was considered as a procedure performed immediately because the neonate's life or organ function was at risk. Programmed surgery was considered a procedure performed when, despite the nosologic process, the neonate's hemodynamic, respiratory, and target organ conditions remained stable according to the disease, allowing the optimal moment for surgical intervention to be sought. Data were obtained from the Pediatric Surgery Service database and the patient's clinical records.

Statistical analysis

Descriptive statistics were reported as frequency, central tendency, or dispersion measures, depending

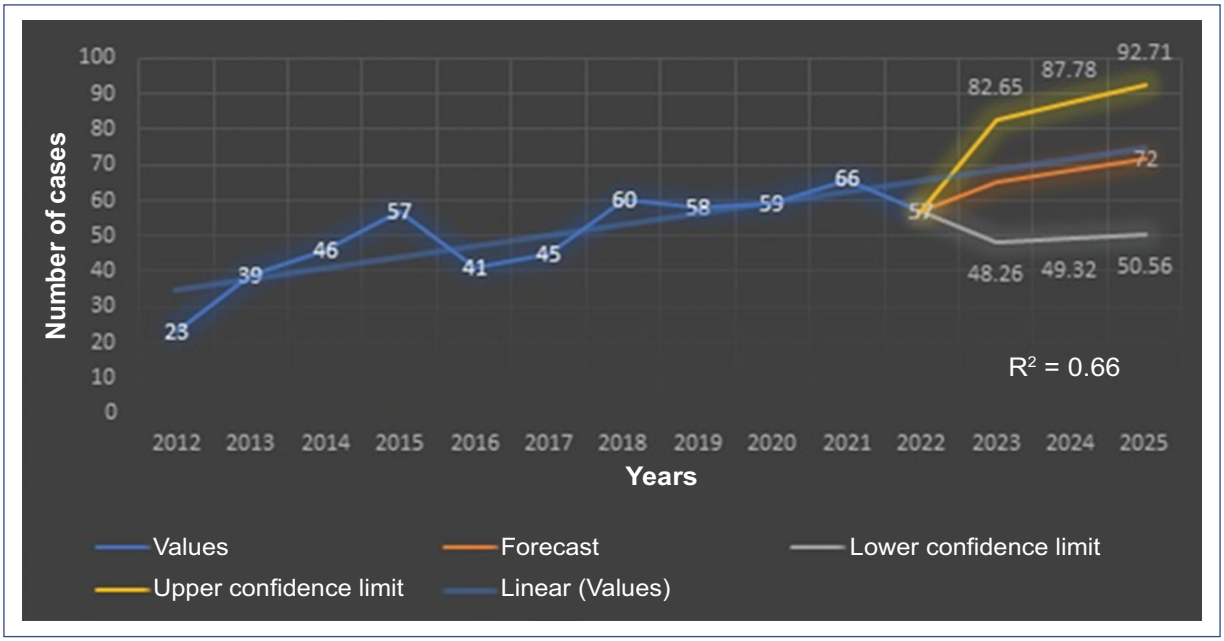

Figure 1. Distribution of surgeries during 2012-2022 and its projection for 2025.

on the variable type. For inferential statistics, comparisons were made using the χ^2 test or Fisher's exact test for qualitative variables and Student's t-test and ANOVA for quantitative variables. Data were processed using SPSS software version 25 and Excel version 1811. The study was approved by the Bioethics and Teaching and Research Committee of the HGyO of the IMIEM.

Results

Prevalence and patient characteristics

Over a 10-year period, from 2012 to 2022, the mean number of births in the HGyO was 99,946. A total of 551 patients underwent surgery during this period, with a prevalence of 0.5%. The distribution of the number of surgeries per year is shown in figure 1. There is an upward trend of 2.7 cases per year in the number of cases treated during the study period and projected growth of 72 cases per year in 2025, with a model $r^2 = 0.66$ and $p = 0.02$. Demographic and clinical characteristics of the neonates who underwent surgery are shown in table 1. Overall, the mean gestational age was 36 weeks (range 26-42.3 wg), with only 47.2% term neonates; the mean weight was 2370 g (range 580-4800 g), with the patients divided as follows: 24 neonates (4.4%) < 1000 g, 64 (11.6%) between 1000 and 1500 g, 226 (41%) between 1500 and 2500 g, 203 children (36.8%) between 2500 and 3500 g, and 34 (6.2%) > 3500 g.

The mean age of the neonates at the time of surgery was 15.6 days, and 438 (79.5%) of the patients underwent surgery within the first month of life. Adjusting for gestational weeks in preterm infants, 497 (90.1%) patients had surgery in the neonatal period.

Identified diseases and prenatal diagnosis

A total of 48 conditions were identified in patients who underwent surgery, classified as congenital and acquired (Figs. 2 and 3 show the number of cases for each diagnosis, and table 2 shows their prevalence). During the 10-year period covered by the study, there was an increase in the presentation of omphalocele, annular pancreas, esophageal atresia, and necrotizing enterocolitis (NEC), with a marked decrease in the number of cases of intestinal atresia.

Of the surgical procedures performed, 195 (35.3%) were for acquired pathologies, and 356 (64.6%) were for congenital conditions; of the latter, only 144 (40.5%) had a prenatal diagnosis. Duodenal obstruction was the most common diagnosis in more than 70% of cases, followed by diaphragmatic hernia and abdominal wall defects. Percentages are shown in figure 2.

Table 1. Demographic and clinical characteristics of patients according to gestational age

Variable	Weeks of gestation			Total	p
	≤ 28	29-36.6	≥ 37		
Number of cases, n (%)	20 (3.6)	271 (49.2)	260 (47.2)	551 (100)	< 0.001
Age at the time of surgery (days), mean (SD)	29 (23.9)	17 (16)	13 (14.6)	15.6 (16)	< 0.001
Weight at the time of surgery (g), mean (SD)	1672 (721)	2025 (652)	2784 (644)	2370 (761)	< 0.001
Female, n (%)	9 (45)	136 (50.2)	113 (43.5)	258 (46.8)	0.304
Prenatal diagnosis, n (%)	0 (0)	48 (17.7)	64 (24.6)	112 (20.3)	< 0.001
Surgical emergency, n (%)	6 (30)	106 (39.1)	83 (31.9)	195 (35.4)	0.200
Congenital pathology, n (%)	10 (50)	177 (65.3)	187 (71.9)	374 (67.9)	0.069
Region operated, n (%) Gastrointestinal Genitourinary Thoracic Cervical	 12 (60) 4 (20) 3 (15) 1 (5)	 196 (72.3) 42 (15.5) 29 (10.7) 4 (1.5)	 190 (73.1) 24 (9.2) 38 (14.6) 8 (3.1)	 398 (72.2) 70 (12.7) 70 (12.7) 13 (2.4)	0.188
Mortality, n (%)	4 (20)	40 (14.8)	13 (5)	57 (10.3)	0.001

SD: standard deviation.

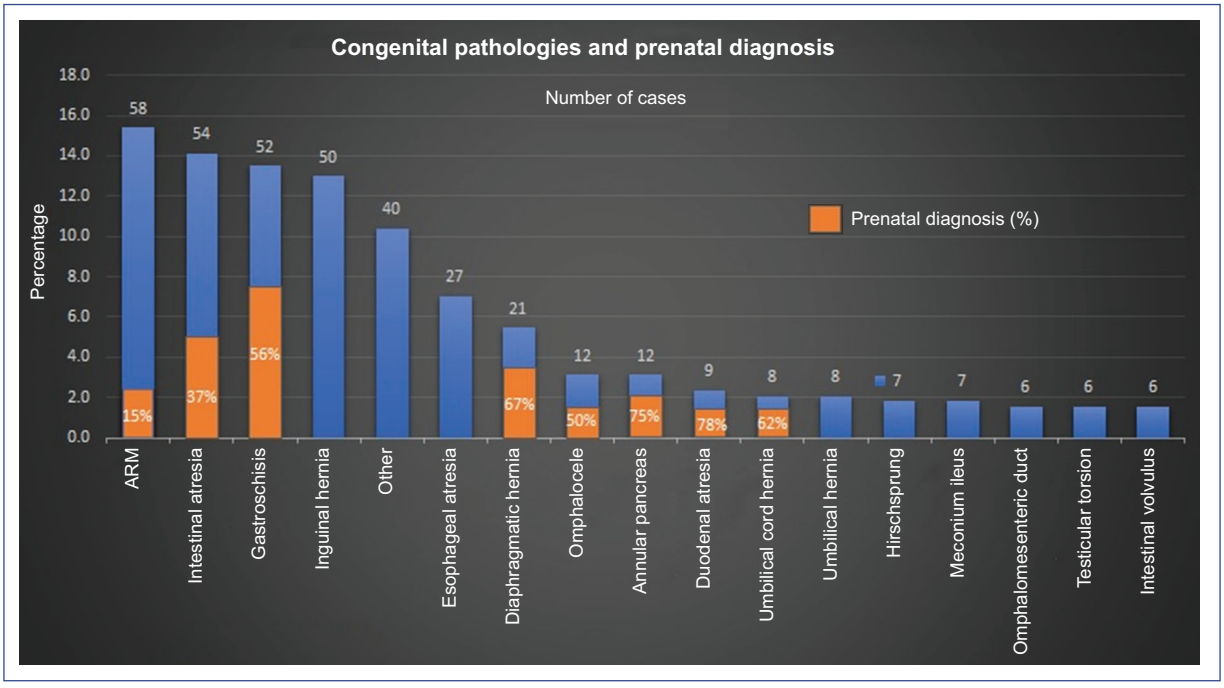

Figure 2. Congenital pathologies and prenatal diagnosis. ARM: anorectal malformation. Other: includes 17 pathologies with low presentation: cloacal malformation, adenomatoid cystic disease, diaphragmatic eventration, ovarian cyst, ductus arteriosus, hiatal hernia, lymphatic malformation, biliary tract atresia, pulmonary sequestration, renal cystic disease, phimosis, hepatic hemangioma, hydronephrosis, laryngomalacia, bronchogenic cyst, common bile duct cyst and mesentery cyst.

Surgical care and NICU stay

In congenital pathologies with prenatal diagnosis, the mean time elapsed from birth to the time of surgery was 3 days, and with no prenatal diagnosis, 3.6 days (p = 0.07). In the case of acquired pathologies, the mean time from diagnosis to surgery was 5.1 days. For programmed surgeries, the mean time was 5.4 days.

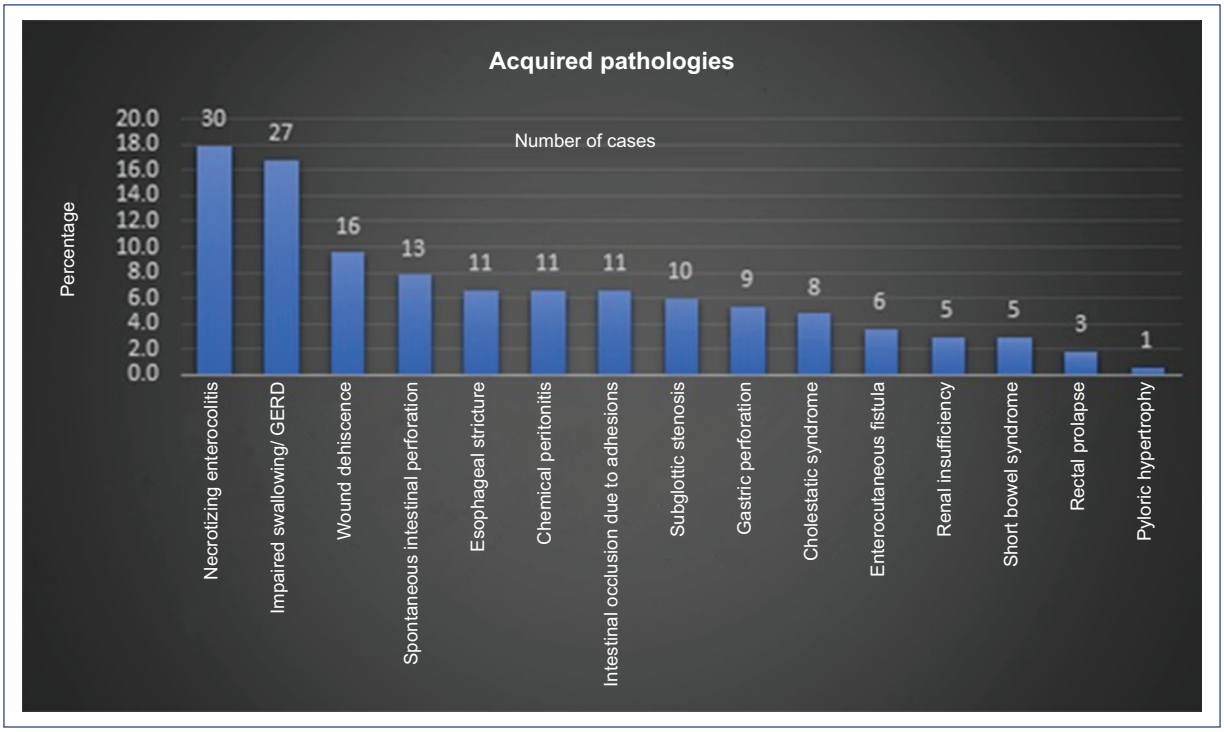

Figure 3. Acquired pathologies. GERD: gastroesophageal reflux disease.

In terms of length of stay in the NICU, the mean was 18.9 days for all pathologies. When differentiating between planned and emergency surgery, the mean was 18.4 and 19.7 days, respectively ($p = 0.376$). Regarding the difference between congenital and acquired pathologies, we found a mean NICU stay of 14.9 days for the former and 27.3 days for the latter ($p < 0.05$). We found no statistically significant differences between NICU stay and gestational age of the patients, with a mean of 21.5 days for those < 28 wg, 18.2 for neonates between 29 and 36.6 wg, and 19.4 for those > 37 wg. However, diagnosis-to-surgery time and NICU stay had highly variable results depending on the pathology involved (Table 3).

Surgeries performed

Most of the surgeries were performed on the gastrointestinal tract, with 398 cases (72.2%), followed by the genitourinary tract and the thoracic region, with 70 patients each (12.7%), and finally the cervical region with 13 patients (2.4%) (Fig. 4).

Survival

In-hospital survival of neonatal surgical patients was 89.7%. Among the 57 patients who died (10.3%), there was a steady decrease in mortality with increasing weight at the time of surgery, with those over 2500 g having the best survival. Seventy-seven percent of deaths occurred in preterm patients (< 37 wg). About 57.9% of mortality occurred in patients with congenital malformations and 72% in neonates requiring emergency surgery. In the bivariate analysis between mortality and associated factors, we found statistical significance for weeks of gestation, weight, type of surgery, time from birth or diagnosis to surgery, and days of stay in the NICU (Table 4).

Concerning mortality and its distribution according to the disease, the pathologies that did not present mortality were diaphragmatic eventration, pulmonary sequestration, bronchogenic cyst, cystic adenomatoid malformation, duodenal atresia, annular pancreas, and intestinal volvulus. Mortality was distributed as follows: NEC, intestinal atresia, esophageal atresia, and gastroschisis with 14% each, spontaneous intestinal perforation with 5.3%, anorectal malformation with 5%, and omphalocele with 3.5%; the remaining 30% was distributed among 13 different diseases.

Patients who died spent an average of 24.3 days in the NICU, compared to 18.2 days for survivors, showing a statistically significant difference ($p = 0.007$).

Table 2. Frequency and prevalence of main pathologies

Number	ICD-11	Diagnosis	Frequency (%)	Prevalence
1	LB17.0	Anorectal malformation	58 (10.5)	5.8
2	LB15.1	Intestinal atresia	54 (9.8)	5.4
3	LB02	Gastroschisis	52 (9.4)	5.2
4	DD51	Inguinal hernia	50 (9)	4.9
5	KB88	Necrotizing enterocolitis	30 (5.4)	2.7
6	KB80	Swallowing impairment/GERD	28 (5.1)	2.7
7	LB12.1	Esophageal atresia	27 (5)	2.7
9	DD50	Diaphragmatic hernia	21 (3.8)	2.1
10	KB86.Y	Spontaneous intestinal perforation	13 (2.3)	1.3
11	LB21.0	Annular pancreas	12 (2.1)	1.1
12	LB01	Omphalocele	12 (2.1)	1.1
13	LB12.3	Esophageal stricture	11 (1.9)	1
14	KB2Y	Subglottic stenosis	10 (1.8)	1

Total births: 99465. Source: SINAC/SINBA.
GERD: gastroesophageal reflux disease; ICD: international classification of diseases.

Table 3. Evolution and mortality of the main pathologies

Diagnosis	Diagnosis - surgery time (days)	NICU stay (days)	Mortality n (%)
Anorectal malformation	2.5	14	3 (5.1)
Intestinal atresia	2.3	18.6	8 (14.8)
Gastroschisis	1.7	22.6	8 (15.4)
Inguinal hernia	6.4	0.6	0 (0)
Necrotizing enterocolitis	1.8	24.2	8 (26.7)
Swallowing impairment/GERD	8.9	49.8	1 (3.6)
Esophageal atresia	5.9	24.2	8 (29.6)
Diaphragmatic hernia	7.1	20.1	3 (14.2)
SIP	1.7	23.9	3 (23.1)
Annular pancreas	2.8	16	0 (0)
Omphalocele	4.5	25.5	2 (16.7)
Esophageal stricture	4.3	41.1	1 (9.1)
Subglottic stenosis	10.1	64.9	1 (10)

GERD: gastroesophageal reflux disease; NICU: neonatal intensive care unit; SIP: spontaneous intestinal perforation.

The total annual mortality is shown in figure 5, with a decreasing trend of 0.7% per year from 2012 to 2022; we can also see the mortality projection for 2025, which will be 5% if the same trends continue, with an r^2 of the linear regression model of 0.51 and $p = 0.013$.

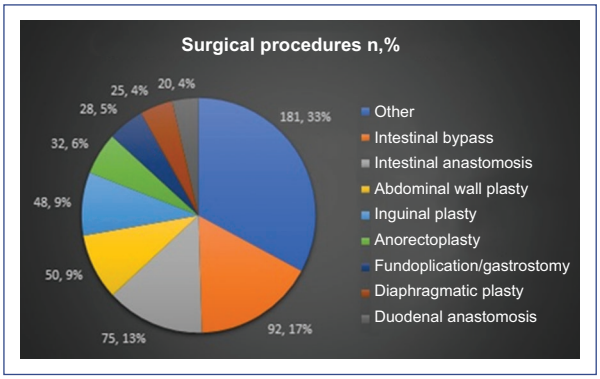

Figure 4. Surgical procedures performed. Others: include 36 more procedures, which were grouped due to their low frequency, as follows: esophageal plasty, silo placement, tracheostomy, umbilical plasty, peritoneal dialysis catheter placement, esophageal elongation, ligation of ductus arteriosus, nephrectomy, lobectomy, pneumonectomy, pyloromyotomy, among others.

Table 4. Mortality analysis

Variable	Mortality n (%)	p
Weeks of gestation		0.001
≤ 28	4 (20)	
29-36.6	40 (14.7)	
≥ 37	13 (5)	
Sex		0.78
Female	28 (12.1)	
Male	29 (9.8)	
Weight (g)		< 0.001
≤ 1500	23 (26.1)	
1500-2500	20 (8.8)	
≥ 2500	14 (5.9)	
Prenatal diagnosis		0.21
Yes	9 (8)	
No	21 (12.8)	
Type of surgery		< 0.001
Urgent	41 (21)	
Scheduled	16 (4.5)	
Type of pathology		0.062
Congenital	33 (8.8)	
Acquired	24 (13.5)	

Discussion

Neonatal surgical practice is a specialized area of pediatric surgery due to the complexity of patients during this critical period of life. Care after these high-risk surgeries requires a qualified hospital where the number of procedures and the care team are essential for optimizing outcomes, maintaining the quality of care, and conducting research[11,12]. Our NICU has a technical infrastructure that has allowed neonatal surgical management for more than 10 years. In our hospital, we have found that six out of 1000 patients require surgical management, similar to the classic reports of Rickham (1:200 neonates) and much higher than the results of Riquel et al. (1:600) in their 10-year study[13]. Our prevalence of 0.5% of surgical cases is relevant because this is not a referral center, treats only patients born in its facilities, and has only one specialist in pediatric surgery. Even under these conditions, an average of one neonatal surgical case per week has been performed over the past 10 years, in addition to minor procedures such as thoracentesis, pleurostomy, peritoneal drains, paracentesis, circumcisions, and placement of central venous access, among others, which are not included in the study.

In our casuistry, we found that patients with < 37 wg represented 52.8% of the cases and those weighing < 2500 g represented 57%, so our patients had lower weight and gestational age compared to the average of other international reports[14-16]. This increases the need for pre-operative, intraoperative, and post-operative care and indirectly indicates our unit's high level of neonatal care.

Surgical interventions in the early stages of life can be due to congenital or acquired pathologies; 32.1% of our cases were acquired pathologies, consistent with other reports[17,18] that establish that the main causes of surgical interventions in the neonatal stage are congenital diseases. In Mexico, approximately one in 50 live births have a major malformation that limits functionality and threatens life[12]. In IMIEM's HGyO, we found four cases of major congenital malformations per 1000 live births, lower than the national reports, which are between 7 and 8.4: 1000 live births[19,20]. This finding could be influenced by the fact that we are not a referral hospital and that we only report in the casuistry the malformations that are of interest and that have been addressed by the pediatric surgeon.

Diagnosing congenital pathologies before the patient's birth is an advantage for postnatal care, so it should be the norm. In the 20-year study by Yagi et al., prenatal diagnosis was reported in 34.9% of cases[16]; in comparison, we obtained prenatal diagnosis in 40.5% of cases. We still consider this percentage to be low because not having this diagnosis increases the patient's risks, making it difficult to plan their care and provide prenatal counseling to the family member. Therefore, in our environment, it is a priority to improve prenatal control, and ideally, as mentioned by Benachi and Sarnacki, there should be an active collaboration between obstetrician-gynecologists and pediatric surgeons[21].

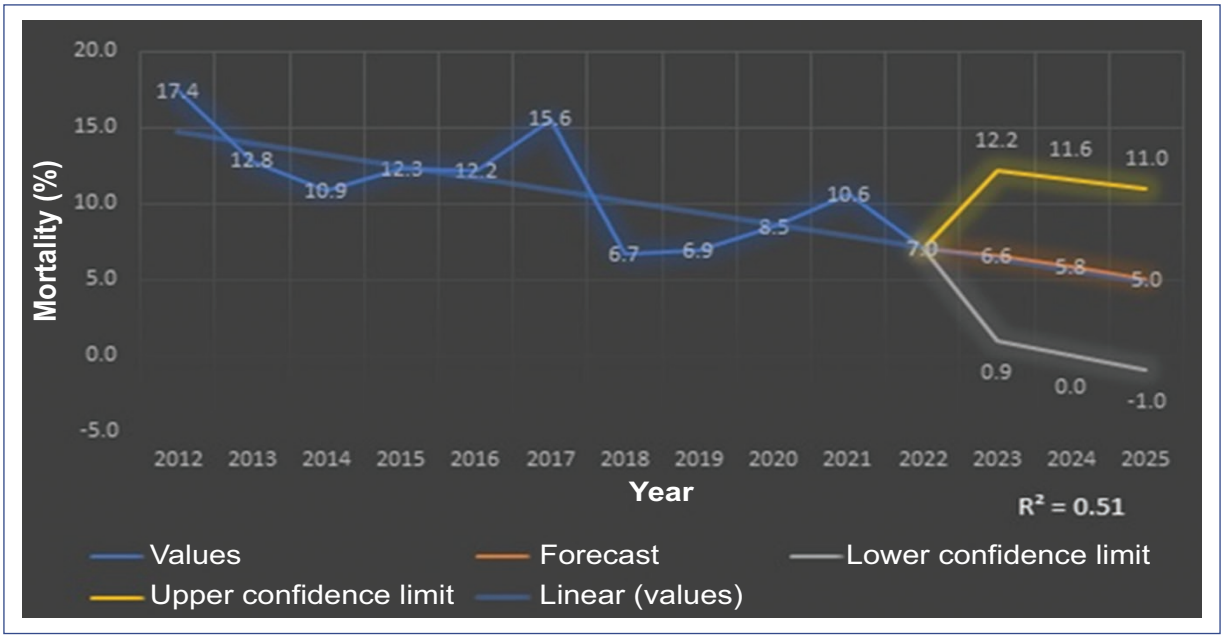

Figure 5. Mortality per year and its projection for 2025.

The diversity of pathologies found in our study is relevant since, in general, it almost duplicates that found in other national and international reports[13,15-18,20,22,23]. This diversity allows to maintain an adequate practice in the medical and surgical care of all these diseases, having in this aspect a considerable strength in our hospital. For example, we coincide in six of the first seven most common diagnoses found in the Latin American Collaborative Study of Congenital Malformations (ECLAMC, by its Spanish acronym)[24].

Concerning the time elapsed from diagnosis to surgery, there was a wide variation according to the emergency status and surgical diagnosis, as shown in table 3. In general, few procedures require immediate intervention, and in most cases, the first hour of life is used to perform the study protocol and stabilize the patient. This was the case even in congenital pathologies already diagnosed prenatally, where the average intervention time was 3 days. We found an enormous variation according to the pathology; for example, in gastroschisis, the intervention was performed in the first minute of life, and diaphragmatic hernia, where we waited several days for the hemodynamic and ventilatory stabilization of the neonate. The pathologies that were operated on most quickly were intestinal volvulus, gastric perforation, gastroschisis, spontaneous intestinal perforation, and NEC, with an average of 1.5 days. This period, rarely mentioned in studies, has a direct impact on the evolution of the patient, indicating the quality of the pre-operative preparation and the prompt availability of surgical care. In our case, by not receiving transfer patients, we were able to provide timely care to the newborn, and positive impact on the results.

Few reports have analyzed the length of stay in the NICU for surgical patients. Siddharth et al. reported a mean of 13.8 days[15] and Saggers et al. 13 days[18], durations significantly lower than those in our study (18.9). However, in our hospital, the NICU stay is not only related to the surgical diagnosis and the health status of the patient but also to external causes, such as the availability of places in intermediate therapy. Therefore, the figure we obtained may not be a reliable parameter of the patient's evolution. There was a significant difference in the length of stay in the NICU between congenital and acquired pathologies, which could be because these diseases occur as a consequence of prematurity and prolonged hospitalization, such as NEC, swallowing, and suckling disorders, esophageal stenosis, chemical peritonitis due to umbilical catheter dysfunction, subglottic stenosis, and renal failure, among others.

One indicator of the quality of care in a NICU is the neonatal surgical mortality rate, which is closely related to a country's economic development, being seven times higher in low socioeconomic countries than in developed countries[25]. Our overall mortality rate was 10.3%, which is within the international average but higher than

that reported in developed countries such as the United States (4%), Japan (6.6%), and South Korea (6.7%) and lower than countries such as India (35%) and Nigeria (45%)[16,26]; in terms of previous national studies, our results are lower than the 33% reported by Rodriguez et al.[20]

The percentage of neonatal deaths attributable to congenital anomalies, many of which are correctable by surgery, is increasing. They also represent a significant financial burden and public health problem[27,28]. Our mortality rate for surgical congenital anomalies was 0.3/1000 live births, which is lower than the mortality rate reported in Mexico for patients with these anomalies (whether or not they have undergone surgery), which is 2:1000[29]. Similarly, reports from the Instituto Mexicano del Seguro Social and the Instituto Nacional de Perinatología describe congenital anomalies as one of the top five causes of neonatal death[30,31].

Mortality in our study varied widely, as shown in table 3, but for most diseases, the proportions were similar to those reported internationally[16-18,32,33]. In addition, there was a general downward trend over the 10 years of the study. This decrease was mainly observed in NEC, which reached a peak mortality of 28% and decreased from 2018 when we started early surgical intervention protocols for this disease. The only pathologies with a higher mortality in our hospital were esophageal atresia and gastroschisis, which is a call to review our care protocols for these diseases.

Within our bivariate analysis of mortality, we found an inverse relationship between mortality – weeks of gestation and patient weight, consistent with international reports[16,28]. However, unlike countries with high resources, our mortality in neonates under 30 wg and 1500 g who required surgery was almost 6% higher. Thus, it is essential to maintain multidisciplinary management, constant development, and technological updating of the NICU, to have better viability in the premature patient. Another variable with significant relationship with patient mortality was the emergency surgery, which presented almost five times more deaths than scheduled surgery. Therefore, our priority is to conduct prospective studies to determine whether this is due to the conditions of the critically ill patients or whether there is an extrinsic part that could be improved in the perioperative multidisciplinary care. Concerning the time patients remained in the NICU, we found a progressive increase in mortality as the surgical neonates remained longer in the NICU, with 63.2% of the total mortality in patients who remained longer than 21 days, suggesting that the critical condition of a neonate warranting a stay in the NICU is a determining factor of survival. Conversely, we did not find statistical significance in the difference in mortality between patients with or with no prenatal diagnosis, either in general or specifically by pathology, even though the neonates who had prenatal diagnosis had earlier surgery.

Among the factors that influence the survival of our patients, it is important to emphasize that we only care for patients born in our unit. This avoids transfers that could destabilize the high-risk neonate, reduces the time of care, and limits the pathogenic organisms that could enter our unit, reducing sepsis events. There are studies suggesting that the surgeon's experience impacts mortality, which is 12% higher when the procedure is performed by a physician with less experience, with a relative risk of 1.5[34,35]. In our study, the fact that all surgical care is provided by a single pediatric surgeon with more than 10 years of experience in neonatal surgical care and that there are no residents may be an advantage. All of the above undoubtedly contribute to improving the outcome of neonatal surgical patients. However, one aspect that could be improved in our hospital would be the availability of a pediatric surgical service on all shifts, which would further reduce the time of surgical care.

It is well known that technological advances in neonatology, surgery, and anesthesia have reduced the mortality rate in neonatal surgery from 72% six decades ago to < 10% today in developed countries[22,25,36]. During the decade described here, we observed a steady decrease in mortality. One of our goals is to continue this trend, and continue to provide safe care, not only to improve survival but contribute to the quality of life of the surgical neonate and his or her family, remembering that the provision of adequate surgical care to all newborns will allow more children to develop their full potential by preventing death or treating disability[37,38].

Among the limitations of this study, we find the reduced number of variables included, which does not allow us a better view of the behavior of surgical diseases in the neonatal stage.

In recent decades, the incidence of neonatal surgical pathology has increased; the care of these patients requires multidisciplinary management and represents a challenge within pediatric surgery. Although we are not a local or national reference center we have many congenital and acquired diseases, with a decreased mortality trend, close to the international average, and lower than national reports.

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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CASO CLÍNICO

Bronquiolitis obliterante postinfecciosa en niños: serie de casos en un hospital pediátrico de Perú

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Resumen

Introducción: *La bronquiolitis obliterante postinfecciosa es una enfermedad pulmonar poco frecuente; existen limitados reportes en Sudamérica.* **Caso clínico:** *En esta serie se reportan 10 pacientes con esta enfermedad diagnosticados en el Instituto Nacional de Salud del Niño-Breña (Lima-Perú). La mediana de edad al diagnóstico fue de 19 meses. Todos los pacientes presentaron el antecedente de infección respiratoria aguda grave. Los síntomas más frecuentes fueron tos, dificultad respiratoria, sibilancias e hipoxemia; el patrón de atenuación en mosaico fue la característica más frecuente en la tomografía. Todos tenían serología positiva para adenovirus. Se administró tratamiento con pulsos de metilprednisolona, azitromicina, hidroxicloroquina y corticoides inhalados. Ningún paciente falleció durante el seguimiento.* **Conclusiones:** *En los niños previamente sanos con antecedente de infección respiratoria aguda grave y sintomatología obstructivo bronquial persistente se debe considerar el diagnóstico de bronquiolitis obliterante postinfecciosa. Este es el primer reporte en Perú con un régimen terapéutico adaptado a nuestra institución.*

Palabras clave: *Bronquiolitis obliterante. Adenovirus. Humanos. Bronquiectasia. Niños. Perú.*

Postinfectious bronchiolitis obliterans in children: case series at a pediatric hospital in Peru

Abstract

Background: *Postinfectious bronchiolitis obliterans is a rare lung disease; there are limited reports in South America.* **Case report:** *We report 10 patients with this disease diagnosed at the Instituto Nacional de Salud del Niño-Breña (Lima-Peru). The median age at diagnosis was 19 months and all patients had a history of severe acute respiratory infection. The most frequent symptoms were cough, respiratory distress, wheezing, and hypoxemia. The mosaic attenuation pattern was the most frequent on the tomography. All the patients had positive serology for adenovirus. The treatment received was methylprednisolone pulses, azithromycin, hydroxychloroquine, and inhaled corticosteroids. No patient died during the follow-up.* **Conclusions:** *In previously healthy children with a history of severe acute respiratory infection and persistent bronchial obstructive symptoms, the diagnosis of postinfectious bronchiolitis obliterans should be considered. This is the first report in Peru with a therapeutic regimen adapted to our institution.*

Keywords: *Bronchiolitis obliterans. Human. Adenoviruses. Bronchiectasis. Children. Peru.*

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Introducción

La bronquiolitis obliterante es una enfermedad pulmonar obstructiva crónica poco frecuente debida a un daño de la vía aérea que puede ser secundaria a un trasplante de médula ósea, trasplante pulmonar o como consecuencia de una infección respiratoria viral, denominándose en este caso, bronquiolitis obliterante postinfecciosa (BOPI)[1].

La incidencia y la prevalencia de esta enfermedad son desconocidas a escala mundial. Los reportes se limitan a series de casos en algunos países; sin embargo, se ha descrito una mayor casuística en Sudamérica debido a su asociación con virus respiratorios, como el adenovirus[2]. La BOPI se presenta en menores de 2 años, iniciando el cuadro clínico con sintomatología similar a la bronquiolitis aguda viral; sin embargo, la evolución tórpida caracterizada por dificultad respiratoria marcada, sibilancias, crepitantes e hipoxemia persistente provoca que estos pacientes requieran oxigeno suplementario o, incluso, ventilación mecánica[3,4].

En comparación de otros países sudamericanos, no se han descrito estudios sobre esta enfermedad en el Perú[2]. El objetivo de este estudio fue describir la experiencia en el diagnóstico y tratamiento de los pacientes con BOPI en un hospital pediátrico peruano.

Caso clínico

En este trabajo se reportan 10 pacientes con BOPI diagnosticados en el Instituto Nacional de Salud del Niño-Breña (INSN-B) de Lima, Perú, de enero del 2010 a diciembre del 2020. El estudio fue aprobado por el comité de ética e investigación del INSN-B (N° 006-2021-CIEI-INSN).

La mediana de edad al diagnóstico fue de 19 meses, con un rango intercuartílico (RIC) de 12 a 26 meses; seis pacientes fueron de sexo masculino. Un paciente contaba con historia familiar de asma (caso 5) y otro presentaba síndrome de Down (caso 7). Tres pacientes se manejaron como aspiración pulmonar secundaria a enfermedad por reflujo gastroesofágico (ERGE) antes del diagnóstico de BOPI (casos 1, 3 y 9). Ningún paciente reportó antecedente de dificultad respiratoria al nacimiento, diarrea crónica o cirugías previas. Todos los pacientes iniciaron la enfermedad con un episodio de infección respiratoria aguda grave (IRAG).

Posterior a la IRAG, los pacientes presentaron obstrucción bronquial persistente asociada con hipoxemia, tos húmeda, retracciones subcostales/intercostales y crépitos. Cuatro pacientes requirieron ingreso a la unidad de cuidados intensivos y uso de ventilación mecánica. Cuatro pacientes presentaban desnutrición aguda al momento del diagnóstico (Tabla 1).

En la tomografía de tórax, el patrón de atenuación en mosaico fue la característica más frecuente al diagnóstico (Fig. 1) y seguimiento (Fig. 2). No se registró aislamiento viral en ningún paciente con la técnica de reacción en cadena de la polimerasa (PCR); sin embargo, la serología fue positiva para adenovirus (presencia de inmunoglobulina G (IgG) anti-adenovirus) en todos los pacientes.

Las inmunoglobulinas (IgA, IgM, IgG) fueron normales en todos los pacientes, con lo que se descartaron inmunodeficiencias. La prueba de cloro en sudor por sospecha de fibrosis quística se realizó en el caso 8, y fue negativa. En siete pacientes se realizó endoscopia digestiva alta ante la sospecha de ERGE, encontrándose esofagitis no erosiva.

El esquema de tratamiento consistió en pulsos de metilprednisolona a dosis de 30 mg/kg/día por tres días consecutivos al mes por seis meses, y luego bimestralmente por otros seis meses. Luego del primer año de tratamiento, la frecuencia de los pulsos de metilprednisolona se decidió según la severidad de los síntomas que requirieron atención por emergencia. Aunado a los pulsos de metilprednisolona, se indicó hidroxicloroquina (10 mg/kg/día, en dos dosis) y azitromicina (10 mg/kg/día, tres veces por semana). Además, se indicaron corticoides inhalados a dosis altas (budesonida 1600 μg o fluticasona 1000 μg), salbutamol (inhalado o nebulizado) y nebulizaciones con solución salina hipertónica al 3% en todos los pacientes. En el caso 1 se usó también montelukast y vitamina D, porque el paciente presentaba exacerbaciones frecuentes de los síntomas respiratorios (Tabla 1).

En todos los pacientes que recibieron hidroxicloroquina, se realizó fondo de ojo antes del inicio de su administración y después cada seis meses, con resultado normal. En la ecocardiografía anual y se encontró hipertensión pulmonar en cinco pacientes al diagnóstico. Los casos 6, 7, 9 y 10 no acudieron periódicamente a sus controles después del alta.

En el seguimiento, la mayoría presentaron exacerbaciones, pero en ningún paciente se registraron pruebas de función pulmonar. Los casos 3 y 8 aún son dependientes de oxígeno; los demás se encontraban estables con adecuado estado nutricional hasta el último control registrado.

Discusión

La bronquiolitis obliterante postinfecciosa es una enfermedad pulmonar crónica con pocos reportes en Sudamérica y posiblemente subdiagnosticada[2].

Tabla 1. Características clínicas, estudios complementarios y tratamiento en niños con bronquiolitis obliterante postinfecciosa

Característica	Caso 1	Caso 2	Caso 3	Caso 4	Caso 5	Caso 6	Caso 7	Caso 8	Caso 9	Caso 10
Edad al diagnóstico (meses)	48	26	34	18	16	20	12	10	20	6
Edad actual	7a	4a	6a	2a 11m	4a	--	16m	8a	-	-
Sexo	M	F	M	M	F	F	M	M	F	M
Comorbilidades	Rinitis, ERGE probable	Ninguno	ERGE probable	Ninguno	Ninguno	Ninguno	Síndrome Down	Ninguno	ERGE probable	Ninguno
Edad IRAG (meses)*	4	20	2	1	2	1	2	2	15	3
Episodios de obstrucción bronquial†	2	1	2	10	8	4	2	1	2	3
Ingreso a UCI‡	No	No	No	Sí (14 días) VM: 7 días	No	No	No	Sí (20 días) VM: 10 días	Sí (45 días) VM: 15 días.	Sí (19 días) VM: 15 días
Estancia hospitalaria al diagnóstico	36 días	6 días	13 dias	25 días	10 días	24 días	36 días	39 días	51 dias	21 dias
Estado nutricional al diagnóstico (puntaje Z)	P/T -4.9 P/E -1.6 T/E -3.0	P/T 1.21 P/E 0.65 T/E -0.48	P/T 0.49 P/E 1.07 T/E 1.39	P/T -1.15 P/E -2.05 T/E -2.59	P/T -0.35 P/E -0.54 T/E -0.57	P/T -2.40 P/E -1.63 T/E 0.18	P/T 1.46 P/E -1.35 T/E -4.4	P/T -2.56 P/E -2.43 T/E -1.09	P/T -2.83 P/E -3.24 T/E -2.59	P/T -0.01 P/E -0.80 T/E -1.26
Estado nutricional último control (percentil/ puntaje Z)	IMC/E (p54)	P/T 0.77 P/E 0.99 T/E 0.88	IMC/E (p74)	P/T 2.02 P/E -1.68 T/E -5.4	P/T 0.20 P/E 0.44 T/E 0.55	-	P/T -0.96 P/E 0.07 T/E 1.71	IMC (p32)	-	-
Estudios complementarios										
Serología viral	Adenovirus (IgG)	Adenovirus (IgG), Chlamidea pneumoniae (IgM)	Adenovirus (IgG), Chlamidea pneumoniae (IgM)	Adenovirus (IgG)	Adenovirus (IgG)	Adenovirus (IgG)	Adenovirus (IgG)	Adenovirus (IgG)	Adenovirus (IgG)	Adenovirus (IgG)
Endoscopia digestiva alta	Esofagitis no erosiva	No se realizó	Esofagitis no erosiva, hernia hiatal	Esofagitis no erosiva	Esofagitis no erosiva	No se realizó	Esofagitis no erosiva	Esofagitis no erosiva	Esofagitis no erosiva	No se realizó

(Continúa)

Tabla 1. Características clínicas, estudios complementarios y tratamiento en niños con bronquiolitis obliterante postinfecciosa *(continuación)*

Característica	Caso 1	Caso 2	Caso 3	Caso 4	Caso 5	Caso 6	Caso 7	Caso 8	Caso 9	Caso 10
Ecocardiografía	Sin alteraciones	Sin alteraciones	Hipertensión pulmonar	Sin alteraciones	Sin alteraciones	Hipertensión pulmonar	Sin alteraciones	Hipertensión pulmonar	Hipertensión pulmonar, insuficiencia tricúspidea moderada	Hipertensión pulmonar, insuficiencia tricúspidea
Tomografía de tórax	Patrón de atenuación en mosaico, atrapamiento aéreo	Patrón de atenuación en mosaico, atrapamiento aéreo, engrosamiento bronquial	Patrón de atenuación en mosaico, bronquiectasias cilíndricas	Patrón de atenuación en mosaico, atrapamiento aéreo	Patrón de atenuación en mosaico, atrapamiento aéreo	Patrón de atenuación en mosaico, atrapamiento aéreo, atelectasias segmentarias	Patrón de atenuación en mosaico, atrapamiento aéreo	Patrón de atenuación en mosaico y bronquiectasias	Patrón de atenuación en mosaico y bronquiectasias	Patrón de atenuación en mosaico, atrapamiento aéreo
Tratamiento	MTP (6 mensuales y 6 bimensuales), hidroxicloroquina, azitromicina, fluticasona, budesonida, montelukast, vitamina D, NBZ	MTP (3 mensuales y uno después de 18 meses), hidroxicloroquina, azitromicina, fluticasona, budesonida, NBZ	MTP (6 mensuales, descontinuó el seguimiento por 2 años y reinició con 2 mensuales), hidroxicloroquina, azitromicina, fluticasona, NBZ	MTP (3 mensuales), hidroxicloroquina, azitromicina, fluticasona, NBZ	MTP (6 mensuales, descanso 2 meses, luego recibió 2 mensuales, descanso 2 meses, luego recibió otro pulso, luego no acudió a controles por un año, regresó y recibió un pulso más), hidroxicloroquina, azitromicina, fluticasona, budesonida, NBZ	MTP (1 vez), hidroxicloroquina, azitromicina, fluticasona, NBZ	MTP (3 mensuales), hidroxicloroquina, azitromicina, fluticasona, NBZ	MTP (5 descontinuados), hidroxicloroquina, fluticasona, sildenafilo, NBZ	MTP (2 mensuales), azitromicina, hidroxicloroquina, fluticasona, NBZ, sildefanilo, domperidona, omeprazol	MTP (2 mensuales), hidroxicloroquina, azitromicina, fluticasona, NBZ
Exacerbaciones en el seguimiento	Cuatro	Una	Dos	Ninguna	Tres	Se desconoce	Se desconoce	Múltiples	Se desconoce	Se desconoce

*Bronquiolitis/neumonía viral.
†Posterior a IRAG.
‡En el último episodio de obstrucción bronquial.
a: años; m: meses; ERGE: enfermedad de reflujo gastroesofágico; F: femenino; IMC: índice de masa corporal; IRAG: infección respiratoria aguda grave; M: masculino; MTP: pulso de MTP (30mg/kg/día por 3 días); NBZ: nebulizaciones con solución salina hipertónica/salbutamol; P/E: peso para la edad; P/T: peso para la talla; T/E: talla para la edad; UCI: Unidad de cuidados intensivos; VM: ventilación mecánica.

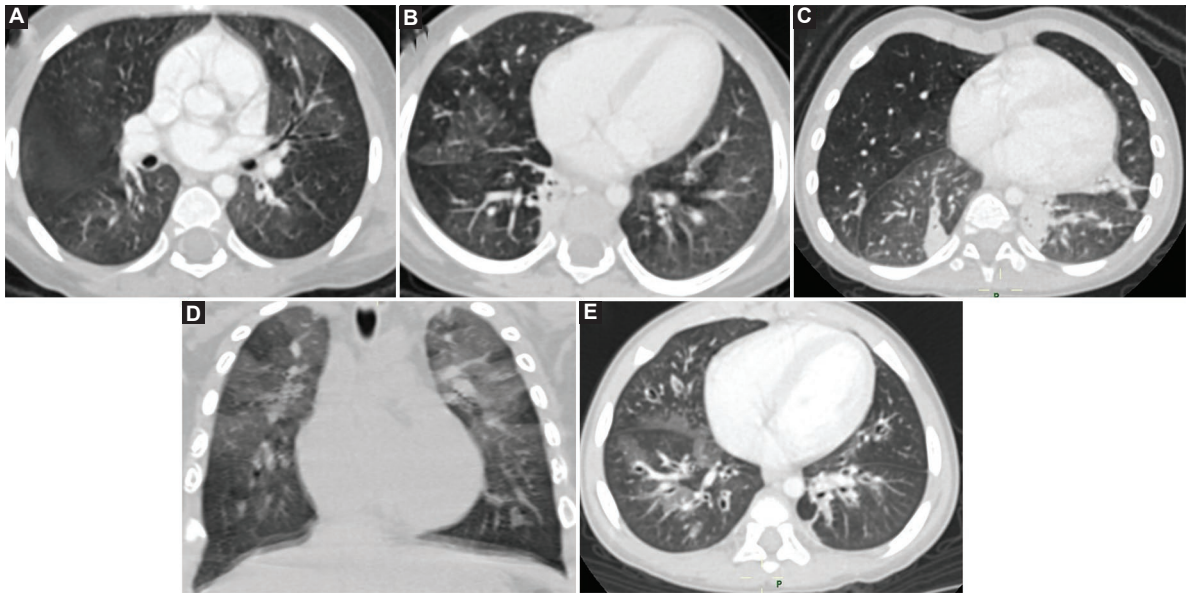

Figura 1. Tomografía de tórax con contraste en niños con bronquiolitis obliterante postinfecciosa al diagnóstico. **A:** caso 2 (26 meses): Corte axial. Se observan opacidades intersticiales en vidrio deslustrado en parches con patrón de atenuación en mosaico alternados con áreas de atrapamiento aéreo y engrosamiento bronquial. **B:** caso 5 (16 meses): Corte axial. Se observan opacidades intersticiales en vidrio deslustrado en parches con patrón de atenuación en mosaico alternados con áreas de atrapamiento aéreo. **C:** caso 6 (20 meses): Corte axial. Se observan opacidades intersticiales en vidrio deslustrado en parches con patrón de atenuación en mosaico alternados con áreas de atrapamiento aéreo y atelectasias segmentarias. **D:** caso 7 (1 año): Corte coronal. Se observan opacidades intersticiales en vidrio deslustrado en parches con patrón de atenuación en mosaico alternados con áreas de atrapamiento aéreo. **E:** caso 9 (20 meses): Corte axial. Se observan opacidades intersticiales en vidrio deslustrado en parches con patrón de atenuación en mosaico alternados con áreas de atrapamiento aéreo y bronquiectasias.

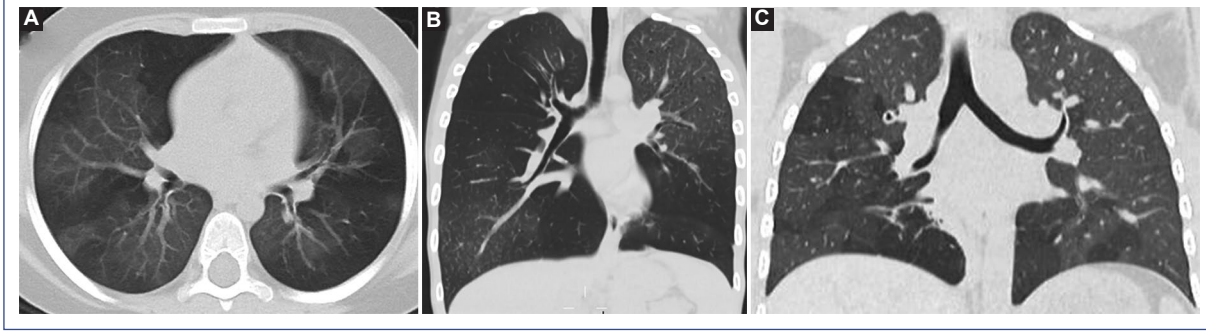

Figura 2. Tomografía de tórax con contraste en niños con bronquiolitis obliterante postinfecciosa en el seguimiento. **A:** caso 2 (4 años): Corte axial. Se observan opacidades intersticiales en vidrio deslustrado en parches con patrón de atenuación en mosaico alternados con áreas de atrapamiento aéreo. **B:** caso 3 (6 años): Corte coronal. Se observan opacidades intersticiales en vidrio deslustrado en parches con patrón de atenuación en mosaico alternados con áreas de atrapamiento aéreo, así como múltiples nódulos centrolobulillares (árbol en brote en lóbulo inferior derecho y lóbulo superior izquierdo). **C:** caso 5 (4 años): Corte coronal. Se observan opacidades intersticiales en vidrio deslustrado en parches con patrón de atenuación en mosaico alternados con áreas de atrapamiento aéreo.

En este estudio, la mediana de edad al diagnóstico fue de 19 meses, menor en comparación con países asiáticos. En Turquía, un estudio de 64 pacientes con BOPI de cuatro centros pediátricos pulmonares registró una edad al diagnóstico de 3.7 años[5]; en China, otro estudio de 42 pacientes de un hospital universitario

reportó una edad al diagnóstico de 2.3 años[6]. Sin embargo, la mediana de edad al diagnóstico que detectamos fue similar en comparación con países latinoamericanos. Colom et al.[7] reportaron una edad de diagnóstico de 14 meses en 46 pacientes de un hospital en Argentina, y Gómez-Viracacha et al.[8] reportaron una edad al diagnóstico de 18 meses en 19 pacientes en un hospital de Colombia. Esta diferencia podría explicarse porque en Sudamérica se registran más casos y un mayor riesgo de padecer esta enfermedad que otras regiones de Europa y América[9].

La serología viral durante la hospitalización fue positiva para adenovirus en todos los pacientes. En Colombia, un estudio realizado entre 2015 y 2016 identificó 21 niños con BOPI, de los cuales tres tuvieron aislamiento para el virus sincitial respiratorio (VSR), dos para adenovirus y dos con coinfección de VSR-adenovirus[10]. Otro estudio colombiano en 19 pacientes pediátricos con BOPI registró VSR en dos de estos pacientes y coinfección VSR-adenovirus en uno de ellos[8].

El adenovirus es el microorganismo más reportado en esta enfermedad[9]; algunos serotipos como el 7h han sido detectados en infecciones respiratorias graves en algunos países de Sudamérica[11]. El adenovirus utiliza el receptor CAR (coxsackie-adenovirus receptor) para unirse a la célula hospedera. La afectación sistémica se explicaría por genes inmunomodulatorios que inhiben la lisis de las citocinas y el factor de necrosis tumoral alfa (TNF-α), produciendo una mayor replicación viral dentro de los linfocitos y una infección latente[12]. Posteriormente se internalizan en los macrófagos y liberan TNF-α con inflamación neutrofílica, activando citocinas proinflamatorias e interleucinas[13] que producen la neumonía severa y compromiso sistémico. Debido a una regeneración del parénquima pulmonar en una etapa inflamatoria persistente, existe alteración de los fibroblastos, miofibroblastos, células basales y neumocitos tipo 2, produciendo elevada fibrinogénesis con alteración de los bronquiolos que puede conducir a la aparición de bronquiectasias[14]. En este estudio se encontró el registro de la serología viral, pues no se dispone permanentemente de otros métodos diagnósticos como la PCR, lo cual sería ideal para el aislamiento oportuno y que se eviten contagios intrahospitalarios[15].

Las manifestaciones clínicas más frecuentes fueron la tos, dificultad respiratoria y sibilancias; sin embargo, son poco específicas, pues comparten similitud con otras enfermedades pulmonares crónicas . Por esto, el diagnóstico de BOPI puede ser erróneo por confusión con patologías más comunes como el síndrome obstructivo bronquial agudo o asma. En estos casos, la poca respuesta al tratamiento y la recurrencia orienta a buscar otros diagnósticos como fibrosis quística, inmunodeficiencias, discinesia ciliar primaria, entre otros[5]. En todos estos pacientes se habían descartado inmunodeficiencias; solo en uno, fibrosis quística por tener bronquiectasias en la tomografía y una evolución estacionaria.

La tomografía de tórax se ha convertido en una herramienta importante en el diagnóstico de BOPI. El patrón en mosaico, atenuación vascular y bronquiectasia centrales son características diagnósticas de BOPI[4]. En los pacientes de este estudio, la característica más frecuente fue el patrón en mosaico, similar a otros reportes[5,8]. Esta característica tomográfica se debe al atrapamiento aéreo y cortocircuito vascular de las zonas hipoventiladas a zonas normales o sobreventiladas; además, la perfusión está disminuida en áreas de atenuación del parénquima debido a la vasoconstricción por hipoxia tisular[9].

La biopsia pulmonar es el estándar de oro para el diagnóstico; sin embargo, no se realiza rutinariamente por el estado clínico del paciente y por las complicaciones de este procedimiento, reservándose para aquellos en quienes haya duda diagnóstica[1,9].

Aún no existe un consenso en el tratamiento, pues son limitados los estudios aleatorizados y controlados por la poca casuística de esta enfermedad. El tratamiento busca disminuir la respuesta inflamatoria y debe ser personalizado según la presentación clínica-radiológica, con el objetivo corregir la hipoxemia, brindar un adecuado soporte nutricional, evitar sobreinfecciones y terapia física. Los corticosteroides se utilizan con frecuencia; sin embargo, su eficacia para mejorar los resultados de los pacientes con BOPI y la elección de la mejor vía de administración es controvertida. En este estudio se utilizaron pulsos de corticoides, similar a lo realizado en un estudio de Brasil, donde se reportó que este tratamiento disminuía los episodios de sibilancias y hospitalizaciones y mejoraba la saturación[16]. El esquema que utilizamos consistió en pulsos de metilprednisolona (30 mg/kg/día por tres días) distribuidos cada mes o cada dos meses según la necesidad de requerimiento de oxígeno y episodios de sibilancias. Entre los pulsos, se brindaban, además, corticoides inhalados según la disponibilidad del medicamento en el hospital. Los corticoides inhalados podrían formar parte del tratamiento antiinflamatorio[4]. En China, en un estudio de 54 pacientes con BOPI, utilizaron la terapia BAMA (budesonida, azitromicina, montelukast y acetilcisteína) y reportaron mejoría clínica y de la función pulmonar[17]; en otro estudio realizado en menores de 5 años con BOPI, los autores detectaron que la terapia con budesonida, montelukast

y azitromicina mejoraba los síntomas respiratorios y la función pulmonar[18]. El uso de la fluticasona como parte de la terapia FAM (fluticasona, azitromicina y montelukast) también se ha descrito en pacientes con bronquiolitis obliterante post trasplante de médula ósea, y ha reportado buena adherencia y disminución del deterioro pulmonar en estos pacientes[19].

El uso de los macrólidos como la azitromicina tres veces por semana se ha utilizado en pacientes con bronquiectasias no fibrosis quística; sin embargo, su uso en BOPI es controvertido. Se ha reportado un posible beneficio debido a sus efectos antiinflamatorios e inmunomoduladores[6]; sin embargo, un estudio argentino no encontró diferencias significativas en la función pulmonar o el número de exacerbaciones pulmonares entre azitromicina y placebo a los seis meses de seguimiento[20].

La hidroxicloroquina es utilizada en algunos centros hospitalarios como antiinflamatorio y inmunomodulador[21,22] debido a su utilidad en las enfermedades pulmonares parenquimatosas difusas[23]. Sin embargo, por su elevada concentración en la retina y corazón, es recomendable la evaluación anual y ajuste de dosis según se requiera para evitar algún efecto adverso[23]. Se requieren más estudios para demostrar el beneficio de la hidroxicloroquina en BOPI[3]; sin embargo, los reportes que han descrito alguna complicación de su uso en enfermedades pulmonares en niños[23], y exclusivamente en BOPI, son limitados[21]. En nuestra institución se decidió usar este medicamento por la experiencia previa en otras enfermedades intersticiales pulmonares[24,25], y por una iniciativa de adaptar a nuestro contexto el esquema (pulso de corticoide, corticoide inhalado, azitromicina e hidroxicloroquina), en el cual evidenciamos subjetivamente una adecuada adherencia y mejoramiento clínico en los controles, a pesar de la limitada evidencia.

El pronóstico de los pacientes con BOPI depende de la gravedad de la neumonía y el requerimiento de oxígeno; los pacientes pueden llegar a la adolescencia y adultez sin problemas en sus actividades cotidianas, incluso en la maternidad[3]. Durante el seguimiento, es importante la medición de la función pulmonar[3]. En los pacientes evaluados en este estudio no había registro de este examen por la edad, pues en nuestra institución se realiza espirometría a partir de los 6 años.

Las complicaciones que los pacientes pueden presentar al diagnóstico y en el seguimiento son la alteración de la función pulmonar, reingresos por infecciones recurrentes, deformaciones torácicas, hipertensión pulmonar, hipoxemia o desnutrición, que pueden disminuir tras un diagnóstico oportuno y un tratamiento multidisciplinario eficaz[1,3].

En conclusión, en nuestra institución la BOPI fue más frecuente en pacientes de sexo masculino con antecedente de IRAG; en la tomografía, el patrón de atenuación en mosaico fue la característica más frecuente. La terapia con pulsos de metilprednisolona, azitromicina, hidroxicloroquina, corticoides inhalados y la terapia respiratoria mejoraron la condición clínica de los pacientes. Este es el primer reporte peruano de BOPI que aportaría a la casuística publicada.

Responsabilidades éticas

Protección de personas y animales. Los autores declaran que para esta investigación no se han realizado experimentos en seres humanos ni en animales.

Confidencialidad de los datos. Los autores declaran que han seguido los protocolos de su centro de trabajo sobre la publicación de datos de pacientes.

Derecho a la privacidad y consentimiento informado. Este estudio incluyó una revisión retrospectiva de historias clínicas, para lo cual se obtuvo la aprobación de una junta de revisión formalmente constituida (Junta de Revisión o Comité de Ética Institucional).

Conflicto de intereses

Los autores declaran no tener ningún conflicto de intereses.

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LETTER TO THE EDITOR

Mass psychogenic illness: an entity poorly studied in Mexico

Enfermedad psicógena masiva: entidad poco estudiada en México

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Outbreaks of mass psychogenic illness (MPI) or mass hysteria are common social phenomena worldwide, and Mexico has been no exception. This pathology has been defined as a group of physical signs and symptoms that suggest the presence of an organic disease but no clinical evidence or support in specific laboratory studies[1]. In our setting, it is known only through the written press or through dissemination in social networks; in the Mexican medical literature, there is a striking lack of reports or formal research, which has led to a deficiency of epidemiological, clinical and psychological-psychiatric knowledge of these crises.

MPI is characterized by the rapid spread of signs and symptoms of illness within a cohesive group, such as schools and workplaces; it predominantly affects females, and its transmission is thought to be purely visual[2]. Headache, dizziness, nausea, and abdominal pain are the most common symptoms reported in the literature[3].

In 2006, after playing with a Ouija board, a group of teenage students in a town in southern Sonora presented with fainting, nausea, headaches, and laughing for no apparent reason. Hypotheses of stress, divine punishment, infection, or food poisoning soon followed. The crisis assessment by Gregorio Katz, a child psychiatry pioneer in Mexico, concluded that it was a "collective hysteria of conversive type" caused by emotional factors in those adolescents[4].

More recently, in October 2022, slightly more than 100 adolescents from three high schools in two cities in Chiapas presented with mysterious symptoms diagnosed by the authorities as secondary to cocaine intoxication. However, this condition was not confirmed during the hospitalization and examination of several dozen of those affected[5]. To this day, the outbreak's characterization, evolution, and outcome have been forgotten.

Admittedly, the root cause of MPI is still unknown. However, a recent study identified some predisposing factors, including cleanliness and safety at school, and previous psychological trauma[6]. In contrast to other authors[7], this study did not find an association with depression and anxiety scores in the studied school population. However, these circumstances should be kept in mind in the face of the confinement and social distancing for the control of the COVID-19 pandemic.

Doubts about the etiology of MPI usually lead to great concern among families, and educational and health authorities. In this regard, personal factors have been associated with this entity, such as personal demotivation, emotional maladjustment, and loss of cultural values.

The first step in controlling MPI falls to the epidemiological authorities and local medical services; early identification of social conditions and psychological stress in adolescents, symptomatic or not, are part of the multidisciplinary study to guide a rapid therapy to prevent further audiovisual spread. In addition, the diagnosis and management of outbreaks provide reassurance to the families of those affected and to the general population. On the contrary, withholding information and

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not adequately disclosing the results of the study of these events leads to greater social unrest.

Finally, a proper documentation and scientific dissemination of the investigation of each case of MPI is the duty and obligation of health authorities. This research would undoubtedly contribute to the epidemiological and medical knowledge and, above all, to identifying the socio-psychological and psychiatric precipitating factors of our young people[3].

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