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infectio

ARTÍCULO ORIGINAL

Characterization of pediatric patients with necrotizing pneumonia treated at a quaternary care center in Bogotá, Colombia, 2010-2017

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Abstract

Introduction: The incidence of Necrotizing Pneumonia (NP) as a complication of pneumonia has increased. Between 0.6 and 2% of parapneumonic effusions result in empyema, while up to 20% are complicated by necrosis.

Methodology: A observational, ambispective study was conducted. The retrospective phase included patients treated between 2010 and 2015; the prospective between 2015 and 2017. The clinical records of patients with pneumonia were reviewed. Patients with pneumatoceles in radiography (Rx) or chest tomography (CT), or bronchopleural fistulas diagnosed were included.

Results: 69 patients were collected. Information on immunization was obtained in 67% of patients. Laboratory test results showed leukocytosis > 15,000/mL (65%), thrombocytosis > 450,000/mL (45%), and LDH in pleural fluid > 2500 IU/L (61% of 18 patients). Imaging findings were consolidation (75% vs. 100%) and pneumatocele (33% vs 90%). Microbiological isolates were collected from 27 patients. *Streptococcus pneumoniae* (56%) *and Staphylococcus aureus* (30%) were the most common agents. Twelve (80%) pneumococci were identified: five serotype 3, two serotypes 14 and 19A, one serotypes 6A, 8, and 1.

Conclusions: NP is a complication that should be suspected in children under 5 years of age with torpid evolution, leukocytosis, thrombocytosis, increased LDH levels in pleural fluid, and pneumatoceles in imaging scans.

Keywords: Necrotizing pneumonia, Pediatrics, Pneumococcus

Caracterización de pacientes pediátricos con neumonía necrosante tratados en un hospital de cuarto nivel en Bogotá, Colombia; 2010 - 2017

Resumen

La necrosis pulmonar es una complicación de la neumonía cuya frecuencia se ha incrementado en los últimos años. Entre 0.6 y 2% de los derrames paraneumónicos resultan en empiema y hasta el 20% de los empiemas se complican con necrosis.

Metodología: Estudio descriptivo ambispectivo realizado en un hospital pediátrico de Bogotá, Colombia. Fase retrospectiva 2010-2015 y fase prospectiva 2015-2017. Se revisaron las historias de pacientes con diagnósticos CIE-10 relacionados con neumonía y entre ellos se buscaron pacientes con neumatoceles en radiografía (Rx) o tomografía de tórax (TAC) o con presencia de fístulas broncopleurales diagnosticadas por clínica.

Resultados: Ingresaron 69 pacientes, con edad promedio de 3.7 años, la incidencia de neumonía necrosante (NN) aumentó en el tiempo. Se obtuvo información de vacunación en el 67% de los pacientes, de ellos 25 (54.3%) tenían esquema completo de 3 dosis PCV10. Los hallazgos de laboratorio fueron: leucocitosis > 15.000/ml (65%), trombocitosis > 450.000/ml (45%), LDH en líquido pleural > 2500 UI/l (61% de 18 pacientes). Los hallazgos radiológicos en Rx y TAC fueron: consolidación (75% vs 100%), derrame (50% vs 46%) y neumatocele (33% vs 90%). Se logró aislamiento microbiológico en 27 pacientes; *S. pneumoniae* (56%) y *S. aureus* (30%) fueron los gérmenes más frecuentes. Se tipificaron 12 (80%) neumococos: 5 serotipo 3, 2 serotipo 14 y 19A, 1 serotipo 6A, 8 y 1.

Conclusiones: La neumonía necrosante es una complicación que debe sospecharse en niños menores de 5 años con evolución tórpida, leucocitosis, trombocitosis, LDH aumentada en líquido pleural y neumatoceles en imágenes. El neumococo fue el agente etiológico predominante en esta serie.

Palabras clave: Neumonía necrosante, Pediatría, Neumococo.

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Recibido: 23/11/2021; Aceptado: 28/08/2022

Cómo citar este artículo: M.P. Guerrero, *et al.* Characterization of pediatric patients with necrotizing pneumonia treated at a quaternary care center in Bogotá, Colombia, 2010-2017. Infectio 2023; 27(1): 23-28

Introduction

Pneumonia is a significant cause of morbidity and lethality in children under 5 years of age[1]. In Colombia, the under-five lethality rate from acute respiratory tract infection (ARTI) decreased by 65.67% between 1998 and 2016, going from 36.3 to 13.84 deaths per 100,000 children under the age of 5[1].

Streptococcus pneumoniae is the etiological agent most associated with pneumonia morbidity and lethality, as it causes one million deaths of children under five in developing countries[2]. In Bogotá, the under-five lethality rate dropped from 21 per 100,000 children in 2008 to 3 per 100,000 in 2017[3].

Despite the decrease in pneumonia cases and lethality, associated complications have been on the rise in recent years. A study conducted in Colombia, which characterized 282 patients diagnosed with pneumococcal pneumonia, reported that 28.7% had complicated pneumonia, increasing from 20.7% between 2008-2011 to 41.6% between 2014-2016[4]. A higher incidence of necrosis translates into longer hospital stays, the need for surgery, and admission to the pediatric intensive care unit (PICU)[5- 8].

Necrotizing Pneumonia (NP) was first reported in the literature in 1994[7]. It is characterized by the destruction of lung parenchyma, tissue liquefaction, cavitation, and subsequent necrosis related to bacteremia and empyema. Patients usually present with fever, poor general condition, pneumatoceles, pleural effusion, and in some cases, bronchopleural fistula (BPF)[9]. Laboratory tests show leukocytosis, neutrophilia, and increased acute phase reactants and lactate dehydrogenase (LDH) in blood and pleura. Respiratory failure and rapid septic shock may occur if these symptoms are not treated properly[8, 10-13].

The objective of the present study is to characterize, from a clinical, epidemiological, and microbiological point of view, patients with Necrotizing Pneumonia who were treated at a quaternary care pediatric hospital in Bogotá, Colombia. This information will allow for a timely diagnosis and initiation of proper antibiotic treatment, reducing the lethality and morbidity associated with the disease.

Methodology

An observational, descriptive, ambispective study was conducted in children under 18 years of age diagnosed with Necrotizing Pneumonia and hospitalized at HOMI, Fundación Hospital Pediátrico la Misericordia between January 2010 and December 2017.

A case of NP was defined as a patient with pneumonia and pneumatoceles on X-ray or chest tomography (CT) or a finding of bronchopleural fistula[11]. Patients with pneumothorax due to barotrauma and chronic lung diseases predisposed to complications (bronchiectasis) were excluded.

The retrospective phase included patients treated between January 2010 and June 2015. To detect NP cases, 7000 clinical records of patients with related ICD 10 (International Classification of Diseases) diagnoses were reviewed (J850, J851, J180, J189, J961, J90, J209, J860, J869). Patients that met the definition were included. Data from patients admitted to the institution with imaging results compatible with pneumatoceles on X-ray or chest CT, or BPF according to the signs and symptoms, was actively collected between June 2015 and December 2017.

Clinical data from each patient were collected. The World Health Organization criteria and the new Colombian charts for anthropometric variables were used to evaluate nutritional status[14,15].

The etiological agent and antimicrobial susceptibility were determined through culture records. The Vitek 2® automated system (BioMérieux, Marcy l`Etoile, France) was used for identification. The pneumococcal serotype reported by the National Institute of Health was considered, where available.

Finally, data were analyzed using the SPSS software. The median for continuous variables and the proportion for discrete variables were used as descriptive statistics.

Results

A total of 69 patients were obtained, 36 during the retrospective phase and 33 in the prospective phase; 61% were males and 39% were females. The prevalence of NP in the study was 5.8 cases per 1000 patients with pneumonia. The incidence of NP increased over time, achieving an incidence of 8/1000 in 2017 (Figure 1 and Table 1). The average age was 3.7 years (11 months - 16 years), and 52% were in the age range of 2 to 5 years (Figure 2).

Patient characteristics, symptoms, signs, and relevant laboratory findings are shown in Table 2.

Associated comorbidities were cerebral palsy (7.7%), immune system disorders (4.6%), asthma (3.2%), ventricular septal defect (3.2%), kidney disease (3.2%), and previous NP diagnosis (1.5%).

Reports about immunization were obtained for 46 of the 69 patients (67%): 25 (54.3%) had complete immunization course of 3 doses of PCV10, 11 (23.9%) had an incomplete course, and 10 (21.7%) patients had not received any dose. Eight of the 25 patients with a complete PCV10 schedule had a pneumococcal infection caused by the following serotypes: serotype 3 in 4 patients; serotype 19A in 2 patients; and serotypes 14 and 8 in 1 patient each. The remaining 7 pneumococci were found in the group of patients with incomplete scheme.

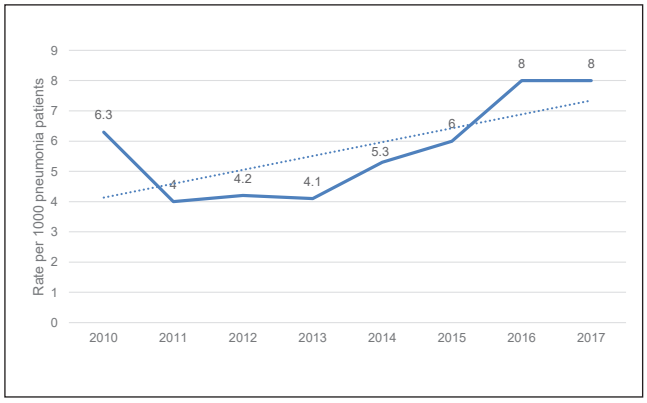

Figure 1. Annual incidence of necrotizing pneumonia 2010-2017

Table 1. Number of cases of necrotizing pneumonia per year

Year	2010	2011	2012	2013	2014	2015	2016	2017
Necrotizing Pneumonia	9	5	6	6	8	9	13	13
Total pneumonia cases	1410	1268	1427	1469	1485	1548	1624	1718

All patients were taken to chest X-ray examination and given the evidence of pneumatoceles in the initial scan and their favorable clinical evolution, no additional radiological studies were performed in 4 patients. The reminder patients (65/69) underwent a chest CT scan, which allowed for the definition of NP findings based on clinical suspicion. Regarding the imaging findings, 65 (94.2%) patients presented with consolidation, 35 (50.7%) with effusion, and 59 (85.5%) with pneumatocele (Table 3).

On the other hand, blood cultures were taken from 69 patients (100%), with positive results in 25 (36.2%). Pleural fluid was cultured in 53 patients (77%) with positive results in 13 cultures (25%). In total, microbiological isolation was obtained in 27 patients (39%), of which 16 came from blood cultures, 6 from pleural fluid, and 5 from both samples.

The most frequently bacterium was *Streptococcus pneumoniae*, and 12 (80%) of the 15 pneumococci isolated were identified, finding 5 serotypes 3, 2 serotypes 19A, 2 serotypes 14, 1 serotype 6A, 1 serotype 8, and 1 serotype 1. Two (60%) of the serotypes 6A and 19A isolates presented decreased susceptibility to penicillin. In total, 8 isolates of *Staphylococcus aureus* were obtained (5 in blood, 2 in blood and pleural fluid, and 1 in pleural fluid), of which 87.5% were resistant to oxacillin. There was no resistance to clindamycin.

Two gram-negative bacteria: *Pseudomonas aeruginosa* and *Escherichia coli* were also isolated. The only fungus reported was *Aspergillus flavus*, which was isolated in pleural fluid in a patient with chronic granulomatous disease.
The median hospital stay was 26 days (range 1 to 84 days), ranging from 20 to 30 days in 52% of cases. Patients presenting with pleural effusion associated with necrosis had a longer stay (27.2 days). Two patients from the retrospective group and three from the prospective group died. Lethality was 7.2%. Table 4 summarizes the outcomes.

Discussion

The study was performed in a quaternary care center in Bogotá D.C., Colombia. An increase in NP incidence in recent years was identified, which may be explained by the emergence of *Streptococcus pneumoniae* serotype 3 and methicillin-resistant *Staphylococcus aureus*[16,17]. NP predominated in children under 5 years of age (81%), a higher percentage than that found by Machado, who reported a figure of 64% in children of this age[11]. The average age was similar to that found by Hacimustafaoglu, with an average of 45.6 ± 39.6 months[18].

On admission, the most frequent symptoms were fever >5 days (68%), cough (98%), and general malaise (85%). Agudelo[16] reported that persistent fever, despite proper management, allowed for the suspicion of pneumonia complication. In turn, Jin *et al.*[20] found that most patients were in poor general condition and had a cough and high fever. Tsai *et al.*[21,22], like Martin *et al.*, described dyspnea, chest pain, fever, and cough; in fact, Tsai noted that these symptoms are sometimes associated with purulent expectoration. Most patients were previously healthy and well-nourished, which agrees with other studies[11].

Regarding laboratory findings, leukocytosis (63.7%) was significantly related to necrosis due to the release of inflammatory substances. Krenke *et al.*, in their case study analysis, found a median number of leukocytes of 21,300/mL, as well as an increased PCR value with a range of 18.2 mg/dL (normal value <1 mg/dL). Moreover, Machado *et al.* reported that half of the patients studied had leukocytosis greater than 25,000/mL, with PCR >120 mg/L in 24% of them[11]. Hacimustafaoglu compared groups of children with necrotizing pneumonia, pneumonia with effusion, and severe pneumonia without necrosis, finding a higher elevation of leukocytes and erythrocyte sedimentation rate (ESR) in the necrosis group[18]. These

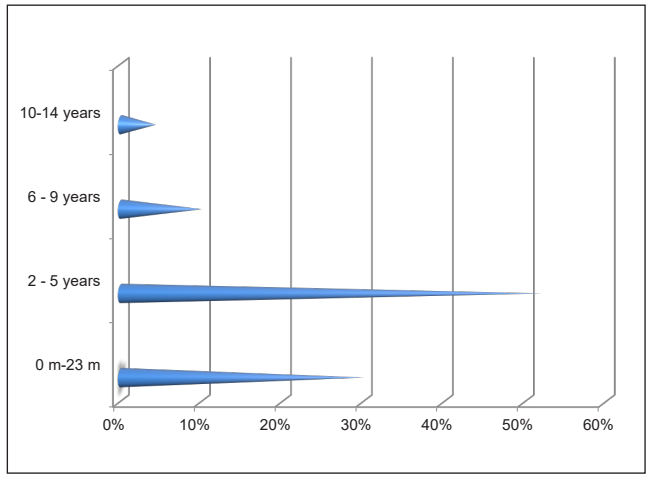

Figure 2. Age distribution of NP and/or fistula (%) N:69

Table 2. Clinical and laboratory findings on admission. N=69 (%)

Clinical features	
Age on admission (years): Median (range)	3.7 (11 months - 16 years)
Previous days with fever: Median (range)	9 (1-60)
Respiratory rate (breath/min): Median (range)	40.5 (23-62)
Cough n (%)	67 (97)
Fever n (%)	67 (97)
Chest pain n (%)	16 (23)
Alteration during auscultation n (%)	64 (93)
Laboratory values	
Leukocytes/mL: Median (range)	19.367 (1920-84.000)
Platelets/mL: Median (range)	501.627 (56.000-1.500.000)
C-reactive protein mg/dL: Median (range)	183.9 (6-425)
Procalcitonin ng/mL: Median (range)*	6.25 (0.01-14.2)
Serum lactate dehydrogenase: Median (range)*	285 (180-1184)
>250 (UI/L) n (%)	11/14 (78)
Pleural lactate dehydrogenase: Median (range)*	2207 (300-68813)
>2500 (UI/L) n (%)	11/18 (61)

* Laboratory tests not performed on all patients. Serum LDH:14, pleural LDH: 18, Procalcitonin:22.

markers may be predictors of necrosis and would help suspect this complication early. Also, Khanafer found a relationship between severe *S. aureus* infection and leukopenia, with values of 4,700 leukocytes/mL at 48h of hospitalization and leukocyte count ≤3,000 leukocytes/mL in 41.9%[26]. In the present study, only one of the 8 patients with *S. aureus* isolation presented with leukopenia.

Thrombocytosis has also been reported. It is caused by fibrin production and tissue remodeling, with greater platelet adherence and proliferation. 46% of patients had platelet counts >450,000/mL and 11.5% of >800,000/mL. In the Krenke *et al.* study, thrombocytosis was also identified, with a mean of 818.510 cell/mm^3 [13].

Serum LDH values were >250 IU/L in 17% of the patients and >2500 IU/L in pleural fluid in 61% of them (of 18 who underwent the measurement); elevated LDH levels were more frequent in proximity to the necrosis process (Liu Shuai *et al.*) (24). Machado *et al.* found an LDH value greater than 2500 IU/L in pleural liquid[11], Jing Rong *et al.* found an increase in pleural LDH >5475 IU/L[20], while T. Tan *et al.* found increased pleural LDH >7500 IU/L in patients with decortication requirement[25].

Regarding imaging, most patients underwent a CT scan (94%) because this diagnostic tool is one of the most effective for characterizing necrotizing pneumonia, findings. Consolidation, effusion, pneumatocele, and pneumatocele + effusion were the most common findings, all of which were directly related to necrosis and the presence of pneumothorax. Concomitance of pleural effusion and necrosis was associated with a longer hospital stay, similar findings were reported by Fletcher[17].
A large number of patients required surgery, the most frequent being thoracostomy in 54 (78.2%). The presence of clinical bronchopleural fistula was identified in only 17% of the operated patients, who also required new surgeries, more days of thoracostomy tube, and more days of hospitalization[26].

Microbiological agents were collected by blood culture or pleural fluid samples obtained during thoracostomy from 27 of the 69 cases (32%), a higher number of patients than reported in previous studies. The most frequently isolated bacterium was pneumococcus serotype 3, mainly resistant to penicillin, similar to Machado's findings[11]. Hacimustafaoglu et al.[18] also identified pneumococcus as a causal microorganism in 30% of patients and found *S. pyogenes* in one patient and serologic IgM positivity for *M. pneumoniae* in 3. A lower number of microbiological isolates was identified in pleural fluid culture compared with blood cultures, which can be attributed to a longer antimicrobial management time prior to the surgical procedure to obtain the pleural fluid versus a shorter time for blood cultures.

A determining factor for necrosis is the virulence of the pneumococcal serotype; the serotypes most commonly associated with necrosis are 1, 3, 14, 19A, and 33, due to the greater invasiveness of the microorganism and an important inflammatory response by the host[17,22]. In Bogotá, Colombia the national surveillance program for invasive pneumococcal diseases found a significant increase in the frequency of Complicated Pneumonia (CP) cases from 14.1% in the pre-vaccination period vs 31.8% in post-vaccination period[27]. This finding is related to the replacement of serotypes, previously in the PCV10 pre-vaccination period the PCV10 serotypes explained 44% of CP cases; but in the postvaccination period PCV10 serotypes explained 8.2% of CP and PCV10 serotypes without coverage (PCV13 serotypes) explained 60.6% of CP. In this study by Gutierrez et al[27] most cases of CP were related to serotypes 19A and 3. On the other hand the serotypes 1, 3 and 19A show more pathogenic behavior related with greater number of pneumococcal complications[27].

It has been identified that serotype 3 is associated with severe complications and BPF since it contains higher capsular density, protecting it from the immune system; the present study shows that this was indeed the most frequently isolated serotype[20]. It is also associated with an increased need for surgical procedures, higher lethality, like other serotypes (6A, 6B, 9N, and 19F)[28]. In Gutierrez et al study patients with serotype 3 represented the highest proportion of PICU admission[27].

It should be noted that, in this study NP was not associated with drug-resistant *S. pneumoniae* since 87% of the isolates were susceptible to penicillin. However, in the study of the national surveillance program for invasive pneumococcal diseases[27], they found an increase in resistance that was related to an increased use of broad-spectrum antibiotics such as ce-

ftriaxone and clindamycin therapy. Also, the progressive increase and predominance of serotype 19A in pneumococcal infections in the pediatric population of Bogotá D.C. explain part of the increase in resistance to most of the antibiotics used to treat this kind of infection[27].

Concerning the suspicion of *S. aureus* as an etiological agent of pulmonary infection, personal or family history of carbuncle or recurrent skin abscesses should be considered[29]. Several factors may be associated with methicillin-resistant *S. aureus* (MRSA) infection such as previous surgeries, hospital stay in the previous year, prolonged hospital stays, parenteral nutrition, previous management with macrolides or fluoroquinolones (levofloxacin)—, pleural effusion, history of MRSA infection, nasopharyngeal MRSA colonization, history of chronic lung disease, being younger than 12 months, or recent joint infection[30]. Another study also identified being younger than 12 months and recent joint infection as risk factors for MRSA infection[5,31,32]. A study conducted at HOMI, Fundación Hospital Pediátrico la Misericordia evaluated the risk factors for infection with community-acquired methicillin-resistant *S. aureus*, finding an important association with the presence of leukocytosis, neutrophilia, and previous antibiotic use in the last 3 months[32].

S. aureus resistance in cases of necrotizing pneumonia in the present study (87.5%) was higher than that observed in the community (38%). This leads to infer that the infection is possibly related to a larger proportion of Panton-Valentine leukocidin (PVL) producers[33], a finding that should be confirmed using molecular methods. As for treatment for this isolate, it is recommended to start clindamycin, vancomycin, linezolid, or ceftaroline depending on the patient's clinical stability and the presence of bacteremia[22,34].

Timely suspicion of pneumonia complications is essential to make an early clinical diagnosis and initiate a proper therapeutic approach, thus avoiding deterioration of the quality of life and subsequent impairment of pulmonary function. In general, pulmonary function is restored between 6 months and 12 months with adequate rehabilitation.

One of the limitations of this study is that it is possible that not all patients were included in the retrospective phase because their diagnoses were miscoded. Attempts were made to correct this bias by reviewing a large number of medical records, but registration bias could have occurred during this same phase, which implies that data on pneumococcal vaccination and serotyping of *S. pneumoniae* isolates were not available for all patients. In addition, no procalcitonin or LDH levels were measured in all the patients. Finally, no molecular diagnostic techniques were available in the institution at the time of the study, limiting the ability to collect a larger number of isolates.

In conclusion, the incidence of necrotizing pneumonia has increased over time. NP should be suspected in previously healthy, well-nourished patients under 5 years of age, with inadequate immunization schedule against *S. pneumoniae*, presenting a torpid clinical course, with elevated acute phase reactants, thrombocytosis, and elevated pleural LDH, with imaging findings of pneumatoceles or clinical findings of bronchopleural fistula.

If NP is suspected, it should be confirmed using imaging diagnostic tools such as CT scan or chest ultrasound for a better diagnostic approach. Many patients will require surgery for the resolution of the condition, especially if there is associated empyema.

Table 3. Imaging findings related to necrotizing pneumonia N=69 (%)

Finding	Chest X-ray (n:69) n (%)	Chest CT (n:65) n (%)
Effusion	35 (50)	**
Consolidation + effusion	32 (46,3)	28 (43)
Consolidation + pneumatocele	11 (15,9)	28 (43)
Pneumatocele	8 (11,6)	**
Consolidation	8 (11,5)	**
Pneumothorax	6 (8,6)	6 (9,2)
Consolidation + effusion + pneumatocele	3 (4,3)	3 (4,6)
Pneumatocele + effusion	2 (2,8)	**

** Not observed as a single imaging finding.
CT: Computed tomography

Table 4. Outcomes. N=69 (%),

Outcomes n(%)	
Surgery n (%)	61 (88.4)
Days of hospital stay: Median (range)	26.1 (1-84)
PICU Admission n (%)*	43 (62.3)
Empyema n (%)	38 (55)
BPF n (%) **	16 (23)
Lethality n (%)	5 (7.2)

*PICU: Pediatric Intensive Care Unit, ** BPF: Bronchopleural fistula.

Ethical considerations

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this investigation. All participants gave signed informed consent to participate in the study.

Right to privacy and informed consent. The authors declare that no data that enables identification of the patients appears in this article.

Funding. This study was financed by the Department for Science, Technology & Innovation in Colombia (COLCIENCIAS, Official call #567), the Iberoamerican Association for Postgraduate Universities (AUIP), and the Colombian Professional Council of Biology (CPBiol).

Author's contribution. Conception and design of the work: CC and MCP. Collecting data: JACG and LS. ELISA analysis: JACG and FMU. Statistical method: JACG and AD. Interpretation of data for the work: JACG, FMU, MCP, LS, AD and CC.

Drafting the work and revising it critically for important intellectual content: JACG, FMU, AD and CC.

Conflict of interest. The authors declare that the revision was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest. Authors declare absence of conflicts of interest in the planning and development of the study.

The hospital ethics committee approved the study with the record #CIE 27-15 of 13/05/2015. The patients included in the prospective phase were informed about the study and signed the informed consent. The retrospective phase did not require informed consent because the data was taken from a review of medical records.

Author contributions statements:
Statistical analysis: MPG, GC, KM.
Data collection: MPG, GC, KM.
Writing of the final manuscript, editing, review and approval: MPG, GC, KM

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