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Manuel Pedro Azevedo Brandão Paiva Martins

Diagnóstico e tratamento de complicações pós-septais de rinossinusite aguda em crianças: Uma experiência de 14 anos num hospital terciário/Management of post-septal complications of acute rhinosinusitis in children: A 14-year experience in a tertiary hospital

MARÇO, 2021

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DESIGNAÇÃO DA ÁREA DO PROJECTO

Medicina Clínica (Otorrinolaringologia)

TÍTULO DISSERTAÇÃO/~~MONOGRAFIA~~ (riscar o que não interessa)

Management of post-nasal complications of acute rhinosinusitis in the paediatric population: A 14-year experience in a tertiary hospital.

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Faculdade de Medicina da Universidade do Porto, 25/03/2021

Assinatura conforme cartão de identificação: Manuel Pedro Azevedo Brandão Paiva Martins

Management of post-septal complications of acute rhinosinusitis in children: A 14-year experience in a tertiary hospital

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Abstract

Introduction: Acute rhinosinusitis accounts for the majority of all cases of orbital infections and is the most common cause of periorbital oedema in children. Up to 10% of patients with orbital complications of acute rhinosinusitis may experience vision loss and other complications such as meningitis, intracranial abscess or even death. Therefore, these patients require prompt diagnosis and proper treatment.

Objectives: This study aims to report the clinical presentation and management of post-septal orbital complications of acute rhinosinusitis in the paediatric population.

Materials and Methods: A retrospective medical chart review of all children aged under 18 years old who were diagnosed with post-septal orbital complications of acute rhinosinusitis at a tertiary academic hospital, between 01/2007 and 12/2020. Patients were grouped according to the Chandler Classification (groups 2-5).

Results: Fifty-five children (mean age of 6.91 $\pm$ 4.61 years) fulfilled the entry criteria for post-septal orbital complications of acute rhinosinusitis, based on clinical evaluation by an otorhinolaryngologist and CT-scan findings. Forty (72.72%) patients were also evaluated by an ophthalmologist. The majority of patients were male (76.36%). Twenty-four patients had post-septal cellulitis (43.63%), 21 patients had a subperiosteal abscess (38.18%) and 10 patients had an orbital abscess (18.18%). Eyelid swelling was the most frequent sign, followed by fever. Microbiology varied considerably and gram-positive agents were clearly predominant. Eighteen (32.73%) patients had been treated with oral antibiotics prior to hospital admission, exhibiting a significantly higher risk of recurrence of orbital infection ($p = 0.020$). Ethmoid and maxillary sinuses were the most involved paranasal sinuses (90.91%). Ceftriaxone was the most frequently used antibiotic and adjuvant therapies consisted mostly of systemic corticotherapy, nasal decongestants and nasal saline irrigations. Thirty-three patients (60%) were successfully treated medically, and 22 patients (40%) required surgical drainage. Seven patients (12.73%) developed further complications and six recovered without sequelae. Eighteen (32.73%) patients were taking oral antibiotics prior to hospital admission, and this group showed a significantly higher risk of recurrence of orbital infection ($p = 0.02$). The mean length of hospital stay was 8.0 $\pm$ 5.0 days and recurrence of orbital infection occurred in six patients (10.91%). The absolute neutrophil blood count was significantly different amongst Chandler groups ($p = 0.021$), with higher counts in patients with subperiosteal abscess. The duration of hospitalization was significantly higher in patients submitted to surgery ($p < 0.001$).

Conclusion: Post-septal orbital complications of acute rhinosinusitis are infrequent but dangerous events in the paediatric population. Close collaboration with Ophtalmology is paramount, as the child's vision is at risk. Eyelid swelling and proptosis are early signs. CT-scan imaging plays an invaluable role in the diagnosis and decision-making. Predictive indicators for surgery were not found. However, emergent endoscopic nasal surgery with abscess drainage should be considered whenever vision is at risk, there is no improvement after aggressive medical treatment or in cases impending intracranial complications.

Keywords: Acute rhinosinusitis; ethmoiditis; children; orbital complications; subperiosteal abscess; orbital cellulitis.

1. Introduction

Acute rhinosinusitis accounts for 66-75% of all cases of orbital infections [1–4]. Up to 10% of patients with orbital complications of acute rhinosinusitis experience some degree of vision loss and possible extra-orbital extension includes cavernous sinus thrombosis, meningitis, intracranial abscess and subcutaneous abscess [5–10]. Therefore, these patients require prompt diagnosis and appropriate treatment [11].

Since the pioneer study in 1970 by Chandler et al. [12], the Chandler Classification has prevailed as the standard grading score for describing the spectrum of clinical presentations encountered in orbital complications of acute rhinosinusitis [11–14]. This classification describes the signs and symptoms of the disease [11] and comprises 5 stages of infection, each with increasing risk of vision loss and other comorbidities [5]. The diagnosis and staging of the disease are usually made with the Chandler Classification in conjunction with computed tomography (CT) findings [14].

Interestingly, the literature shows that the microbiology of acute rhinosinusitis has changed considerably over time [15,16], partly due to alterations in the vaccination programs worldwide, with the introduction of the Hib and PCV7/13 vaccines [1,8]. Thus, the proportion of cultures positive for *Haemophilus influenzae* and *Streptococcus pneumoniae* has decreased significantly [1,8,17–19], whereas the current challenge of antibiotic resistance has resulted in a concerning increase in infections by methicillin-resistant *Staphylococcus aureus* (MRSA) and *Streptococcus anginosus* [10,15,17,20–24].

Over the last 20 years, several authors identified multiple risk factors and characteristics associated with orbital complications of acute rhinosinusitis [8]. Nevertheless, there is not a consensus on the best cut-off values for these criteria in order to guide the selection of the best treatment [15]. Likewise, there are some algorithms for the management of orbital complications secondary to acute rhinosinusitis [11,25,26]. However, all systematic reviews highlight the lack of large case series, the heterogeneity between study designs and the many significant gaps in the literature, which preclude the achievement of any solid conclusions [11,15,27]. Indeed, there is limited information in the literature regarding population-based bacterial and viral microbiota involved in upper respiratory tract infections, which interferes with the best empiric antibiotic therapy choice. Also, the role of adjuvant medical therapies (corticotherapy, nasal decongestants and other) and factors that predict surgery have yet to be clarified.

This study aimed to analyse the clinical presentation and management in a series of 55 children with post-septal orbital complications of acute rhinosinusitis, at a tertiary academic hospital. Among several other variables, the use of adjuvant therapies, the length of hospitalization, the data collected from all complementary means of diagnosis (imaging, blood analysis and other), the preferred antibiotic therapy and the final outcomes were studied to find correlations between clinical characteristics, diagnosis, treatment and prognosis.

2. Materials and Methods

This study was performed at a tertiary university hospital centre, under the approval of the Institutional Board of Medical Ethics (#373/2020).

A retrospective medical chart review was performed on all children aged under 18 years who were diagnosed from the period of 01/2007 to 12/2020 with post-septal orbital complications of acute rhinosinusitis. Patients were grouped according to the Chandler Classification. One hundred and thirty-two cases were initially identified through a database search of medical records using the International Classification of Diseases Ninth (ICD-9) and Tenth (ICD-10) Revision codes for orbital cellulitis/orbital abscess (376.01; H05.0), periorbital cellulitis (682.0; L03.213) and acute ethmoidal sinusitis (461.2; J01.20). Subsequently, close analysis of these medical records identified a total of 55 paediatric patients with a definitive diagnosis of post-septal complications corresponding to Chandler groups 2 to 5. [14]

The analysed data included year of admission, patient age and gender, diagnosis, laterality, clinical presentation (signs and symptoms), ophthalmologic evaluation, laboratory parameters (white blood cell count, absolute neutrophil count and C-reactive protein levels), microbiology results, previous health conditions, drugs used before admission, imaging results, size and location of the abscess, extent of sinus involvement, treatment options (medical treatment alone or in combination with surgical treatment), choice of antibiotic regimen, use of adjuvant therapies, type of surgical approach, possible complications, recurrence, length of hospital stay and final outcome. Recurrence was defined as a further episode of orbital complications of rhinosinusitis occurring after medical discharge from the previous episode.

Statistical analysis was performed using SPSS Statistics version 23.0 for Windows (IBM Corp, Armonk, NY, USA), with $P<0.05$ considered to be statistically significant. The Student's T-test was used to evaluate associations between continuous variables with a normal distribution, whereas variables without normal distribution were analysed with the Mann-Whitney U Test or the One-way ANOVA, followed by the Tukey's Test for Post-Hoc Analysis. Data normality was defined by measuring the distribution's skewness and kurtosis (maximum tolerated value = 1). Chi-square Test was used to compare categorical data, but in some groups there was an insufficient "n" for this analysis, so Fisher's Exact Test was used instead.

3. Results

3.1. Clinical and demographic results

Fifty-five children were admitted to our Institution via the Emergency Room with the diagnosis of post-septal orbital complications of acute rhinosinusitis, corresponding to Chandler groups 2 to 5 [12]. The diagnosis was based on clinical evaluation by the attending otorhinolaryngologist and radiologic findings on CT-scan. Forty (72.72%) patients were also evaluated by an ophthalmologist to assess visual acuity, pupillary reactivity and extraocular movements; neurological observation was requested whenever neurological symptoms were present or findings suggested potential intracranial complications; two cases required neurosurgical consultation.

Patient's age ranged between 1 and 17 years (mean age of 6.91 ± 4.61 years) and 42 patients were male (76.36%). Of all cases, 24 had post-septal cellulitis (43.63%),

21 had a subperiosteal abscess (38.18%) and 10 had an orbital abscess (18.18%). There were no cases of cavernous sinus thrombosis (Chandler Group V) at admission. All cases presented with unilateral involvement. Twenty-seven (49.09%) patients had right eye involvement and 28 (50.91%) patients had left eye involvement. The median number of cases was 4 per year (IQR = 2.25) and the highest number of admissions occurred in 2012 (n = 13 cases).

3.2. Patient Presentation

In this series, eyelid swelling (96.36%) was the most frequent sign, followed by fever (43.63%). There was a high incidence of reported loss of visual acuity (29.09%), eye pain (23.64%), purulent rhinorrhoea (23.64%) and proptosis (21.82%). Neurological symptoms (vomiting, altered state of consciousness, prostration, neck stiffness, photophobia and headache) were more frequent in patients with orbital abscess (40%). Chemosis (3.63%), diplopia and ophthalmoplegia (18.18%) were less frequently reported among all groups. Symptom's intensity and duration were also highly variable between patients and, despite the tendencies described, no significant correlations were observed between patient presentation and the final diagnosis.

3.3. Prior Health Conditions and Comorbidities

Twenty-nine (52.73%) of the 55 patients included in this study had at least one previous medical condition and 20 (36.36%) of these had been formerly diagnosed with some type of otorhinolaryngological disorder. Allergy was the most common underlying medical condition, including 10 (18.18%) patients with confirmed positivity for inhaled

allergens. Eight patients (14.55%) reported current oropharyngeal infections, such as tonsillitis, adenoiditis and dental infection. However, statistical analysis did not reveal any significant correlations between patient's previous health conditions and their diagnosis, treatment and risk of complications.

Eighteen (32.73%) patients were under oral antibiotics prior to referral to our hospital. The most prescribed antibiotic was oral amoxicillin with clavulanate. A significant statistical difference was found between the previous use of antibiotics and the risk of recurrence ($p = 0.020$, Fisher's Exact Test). No other significant differences were observed between the previous use of antibiotic therapy and the course of the disease.

3.3. Microbiology

Only 19 patients (34.55%) had reports for bacteriologic/mycologic culturing and eight of these cultures were negative. Specimens were obtained from either nasal swabs or intraoperatively by aspiration of the abscess (orbital or subperiosteal) and/or sinus exudate. All positive results were tested for antimicrobial susceptibility. Three cases of *Streptococcus pneumoniae*, two cases of *MRSA*, two cases of *Haemophilus influenzae*, two cases of *Streptococcus mitis/oralis*, one case of *Streptococcus pyogenes* and one case of both *Streptococcus anginosus* and *Streptococcus gordanii* were detected. One of the MRSA displayed intermediate resistance to rifampicin, while one of the *Streptococcus mitis/oralis* was resistant to ampicillin. Additionally, one case of the *Haemophilus influenzae* showed resistance to trimethoprim/sulfamethoxazole.

Fourteen (25.45%) patients had blood cultures performed during hospital stay and only two cases were positive for *Streptococcus anginosus* and *Corynebacterium afermentans*, respectively.

3.4. Laboratory Studies

Laboratory tests included white blood cell (WBC) and absolute neutrophil (ANC) count in the peripheral blood and serum levels of C-reactive protein (CRP). Upon admission, blood chemistry showed that 25 patients (45.45%) had elevated white blood cell count, 29 patients (52.73%) had elevated absolute neutrophil counts and 36 patients (65.45%) had elevated CRP levels. No significant differences were observed between CRP levels and the patient age, the Chandler Classification group, and the length of hospitalisation. However, a significant difference was found between the WBC counts and the patient Chandler's group classification ($F(2.42) = 3.721$, $p = 0.033$, One-way ANOVA). Tukey's Test for Post-Hoc Analysis ($p = 0.05$) revealed that WBC counts for patients with subperiosteal abscess ($17.14 \pm 4.79 \times 10^9$/L) were usually higher than WBC counts for patients with orbital abscess ($12.70 \pm 4.10 \times 10^9$/L). A significant difference was also observed between the ANC and the patient Chandler's group classification ($F(2.41) = 4.272$, $p = 0.021$, One-way ANOVA). Tukey's Test for Post-Hoc Analysis ($p = 0.021$) revealed that ANC counts for patients with subperiosteal abscess ($12.27 \pm 4.29 \times 10^9$/L) were usually higher than ANC counts for patients with post-septal cellulitis ($8.5 \pm 3.91 \times 10^9$/L).

3.5. Imaging Studies

All children underwent a CT-scan and a magnetic resonance imaging (MRI) with gadolinium enhancement was performed if intracranial complications were suspected.

Images of 83 CT scans (Figure 1) from 55 patients and eight MRIs from five patients were available for review. One patient also did an orthopantomography, because a dental infection was suspected to be the primary source of sinus contamination. No patients had plain sinus radiographies.

Regarding the rhinosinusitis location, ethmoid sinusitis (90.91%) and maxillary sinusitis (90.91%) were found to be the most prevalent. Isolated inflammation of one paranasal sinus was rare (7.27%) and a large proportion of patients suffered from pansinusitis (41.80%). More detailed information on paranasal sinus involvement is available in Table 1. We did not find any significant association between the pattern of sinus involvement and the type of treatment or the risk of intracranial complications.

CT scans revealed 21 children (38.18%) with subperiosteal abscesses, with a median diameter of 4.5 mm (IQR = 5 mm). There were 10 cases (18.18%) of intraorbital abscesses, but their dimensions were only measured in two reports (9 mm and 3 mm, respectively).

Of the 31 abscesses (subperiosteal and orbital), 22 (70.97%) were pure medial in location, one (3.23%) was superolateral, two (6.45%) were superomedial, two (6.45%) were inferomedial and four (12.90%) had a more diffuse location. No significant differences were observed between abscess location and the treatment choice.

3.5. Treatment

Ceftriaxone was the most frequently used antibiotic (50 patients), commonly in combination with other intravenous antibiotics, such as clindamycin, metronidazole or vancomycin. Other less used antibiotics were meropenem, ertapenem, teicoplanin, ceftazidime and flucloxacillin. Inpatient adjuvant therapies were employed in 51 cases (92.73%), consisting mostly of oral/IV corticotherapy (49 patients), nasal vasoconstricting decongestants (33 patients), non-steroidal anti-inflammatory drugs (14 patients), paracetamol (10 patients), antihistamine drugs (five patients) and nasal saline irrigations (21 patients).

Thirty-three patients (60%) were successfully treated medically, and 22 patients (40%) required a combination of medical treatment and surgical intervention (Table 2). There was a significant association between the need for surgical treatment and the Chandler Classification, as patients with orbital abscess were more likely to require surgery than the others (p = .003, χ^2 test). No surgical complications were reported in this series. Functional endoscopic sinus surgery (FESS) alone was performed on 16 patients (72.73%), while it was associated with an external approach in the remaining six cases (27.27%). Moreover, eight patients required more than one surgical intervention and two of the latter underwent craniotomy by Neurosurgery for epidural abscess drainage (Table 3).

The time frame between hospital admission and surgery diverged from a few hours to 5 days, according to the clinical severity upon presentation.

Statistical analysis showed no significant association between the type of treatment (combined vs. pharmacological only) and patient's age, gender, perinasal

sinus involvement, abscess location, previous antibiotic therapy, laboratory parameters and risk of recurrence.

After hospital discharge, 27 children (49.09%) continued treatment with oral antibiotics. The most common outpatient antibiotic regimen was oral amoxicillin/clavulanate (n = 21), followed by oral cefuroxime (n = 4). Other less used antibiotics were flucloxacillin (n = 1), clindamycin (n = 1) and gentamycin (n = 1).

Finally, two cases of orbital abscess complicated with intracranial venous thrombosis also required hypocoagulation with intravenous enoxaparin, which was changed in both patients to oral warfarin after hospital discharge.

3.6. Complications

During the hospital stay, seven patients (12.73%) developed further complications, from which six recovered without sequelae. There were no casualties. Morbidities arose in one patient with an orbital abscess, as the infection spread intracranially, producing two epidural abscesses with mass effect, requiring anterior craniotomy and abscess drainage. Post-operative CT scan revealed a thrombosis of the superior longitudinal sinus and hypocoagulation with IV enoxaparin was promptly initiated. After a 40-day hospitalization stay, the patient was discharged, maintaining hypocoagulation with oral warfarin; the patient was also referred for Ophthalmology, Otorhinolaryngology, Neurosurgery and Physical and Rehabilitation Medicine external consultations.

Besides the previously described case, three more patients with orbital abscess developed intracranial complications: one patient developed a cavernous sinus

thrombosis (Chandler group V complication); one patient presented with bilateral extradural empyema and subcutaneous frontal abscess (Pott's Puffy tumour); a third patient developed a subdural empyema and a frontal extradural abscess, which were surgically treated by ORL and Neurosurgery.

One patient with subperiosteal abscess presented with an unfavourable clinical evolution, exhibiting ocular pain, increasing palpebral oedema and neurological signs, such as headache, vomiting and prostration. This patient required a revision FESS at the 5^{th} post-operative day, as the CT scan showed a relapsing subperiosteal abscess.

Two patients with post-septal cellulitis also developed complications during hospital stay. One showed erosion of the lamina papyracea consistent with osteomyelitis and therefore required FESS and surgical debridement of the necrotic material. The other underwent nasal endoscopy revealing polypoid degeneration of the unciform process associated with infectious bulging of the right maxillary sinus, which motivated a revision FESS.

Statistical analysis showed a significant difference between the risk of intracranial complications and both the Chandler Classification ($p < .001$, χ^2 test) and the type of treatment ($p = 0.025$, Fisher's Exact Test).

3.7. Outcomes and Recurrence

All but one patient were discharged from hospital symptom-free, without neurological or visual sequelae. Two patients were also referred to Ophthalmology and Neurosurgery outpatient consultations.

The mean length of hospital stay was 8.0 $\pm$ 5.0 days, ranging from 1 to 43 days. The hospitalization period was found to be significantly longer in patients submitted to surgery ($p < 0.001$, Mann-Whitney U Test), as displayed in Graph 1.

Recurrence of orbital infection occurred in six patients (10.91%); table 4 summarizes the clinical profile of these cases. Recurrence risk did not result in any significant association with Chandler Classification or choice of treatment.

4. Discussion

Acute rhinosinusitis is esteemed to account for at least three fourths of orbital infections [23,28] and may also evolve to other severe complications, including cavernous sinus thrombosis, amaurosis, septicaemia, meningitis and intracranial abscesses [29–33]. These complications can occur at any age, but are more common in the paediatric population, with an overall incidence of 3-4% of children diagnosed with acute rhinosinusitis [29,33,34].

The present retrospective study examined a series of 55 consecutive children with post-septal complications of acute rhinosinusitis, focusing mainly on clinical presentation, complementary means of diagnosis and treatment. To our knowledge, the current series is one of the largest published by one single institution in recent years.

The distribution and mean age of our sample (6.91 $\pm$ 4.61 years) were in line with results reported by other studies [1,5,35–38]. Nonetheless, we found a male predominance of 76.36%, which is considerably superior to previous reports of a male:female ratio of 2:1 [5,36]. Most studies describe milder disease and thereby less

need for surgical intervention in younger children [39–42]. Patients younger than 9 years appear to be more prone to improve without surgery and have less severe infections than older patients [15,27,43,44]. However, this tendency was not observed in our study, in which no significant differences were found between patient age and Chandler Classification or type of treatment, respectively.

Eyelid swelling (95.24%), fever (42.86%) and loss of visual acuity (38.10%) were the most frequent clinical findings upon admission in the group of individuals with subperiosteal abscess, whereas proptosis (23.81%), restricted ocular motility (14.29%) and chemosis (4.76%) were more scarcely reported. This data differs from the results of a recent major systematic review [15], in which the most frequent symptom at admission was ophthalmoplegia (45.9%), followed by proptosis (44.0%), fever (35.4%), eyelid oedema (25.4%), chemosis (21.6%) and decreased visual acuity (9.4%). These disparities may have resulted from the retrospective nature of our study and the inherent diversity in reporting clinical findings by the different attending physicians on admission. Also, in our study most children with subperiosteal abscess were restless with painful ocular symptoms and headache, leading to suboptimal collaboration during physical examination. Moreover, this group showed a high incidence of exuberant eyelid oedema with inability to open the affected eye, making it difficult to perform a thorough ocular examination.

Most authors also consider patient's signs and symptoms as predictors for diagnosis and treatment [5,10,27,35,36,38,41,45–47]. Such symptoms are frequently referred as indications for surgical intervention and usually include loss of visual acuity, proptosis, ophthalmoplegia and high fever. In our study, no significant associations were

observed between patient presentation and both the final diagnosis and the type of treatment. This lack of association might also be explained by the atypical distribution of signs and symptoms reported, as previously discussed.

A substantial proportion of our patients (18.18%) had a background of atopy to inhaled allergens, consistent with results reported in recent case series [48]. Moreover, our investigation showed an increased risk of recurrence in patients treated with antibiotics prior to hospital admission, which is an unprecedented association. Antimicrobial resistance may play a role in the rate of recurrence, an hypothesis that needs to be explored in future research.

Despite the availability of conjugated vaccines against *Streptococcus pneumoniae* since 2001 and its introduction in our national vaccination plan in 2015, *Streptococcus pneumoniae* was still the most isolated pathogen in our study. In contrast to the anticipated decline in cases with the use of these vaccines, the number of admissions for post-septal complications of acute rhinosinusitis after 2015 (median of 4.0$\pm$2.0 cases/year) was similar to the number of cases reported in the previous period (median of 4.0$\pm$3.0 cases/year), even though the peak of infection occurred in 2012 (13 cases). Interestingly, and all three cases of *Streptococcus pneumoniae* infection occurred in 2012.

On the other hand, antibiotics with activity against MRSA were used in 13 different children (23.64%). In fact, methicillin-resistant *Staphylococcus aureus* is currently a prevalent causative organism in paediatric orbital complications of acute rhinosinusitis and should therefore be considered when prescribing the initial empirical treatment. Furthermore, 65.45% of patients did not undergo sampling for

bacteriologic/mycologic cultures and even among those who did a significant proportion did not provide any identifiable results (42.11%), a common drawback in many other papers [26,48,49]. Thus, prompt initiation of an effective empirical antibiotic therapy is of paramount importance. Only two blood cultures (14.29%) were found to be positive, whereas the other 12 cases had no positive result. These data may imply that, in our patient population, blood cultures played a small role in diagnosis and treatment. Although a high proportion of patients presented with fever at admission (43.63%), the low incidence of positive haemocultures may have been related to the use of antibiotics prior to hospital admission. This is particularly common, since our institution receives patients from several other hospitals in the northern region of the country, where antibiotic treatment had already been initiated.

Most patients presenting with post-septal complications of acute rhinosinusitis in our study were found to have increased blood CRP levels and elevated WBC and ANC counts. In fact, we found a positive association between both WBC and ANC counts and the disease severity. WBC counts of patients with subperiosteal abscess were significantly higher than those of the patients with orbital abscess, and ANC counts of patients with subperiosteal abscess were significantly higher than those of the patients with post-septal cellulitis. These unparalleled associations suggest the possibility of an aggravated inflammatory response in subperiosteal abscess, offering a new hypothesis for a diagnosis criterion based on laboratory findings. Indeed, experimental studies have demonstrated that neutrophil mediated abscess formation is a relevant component of the innate immune response, which aids in host defence against skin infections, inhibiting the dissemination of pathogenic agents to deeper tissues [50–53].

Several authors have attempted to find an association between laboratory inflammation markers and the need for surgical intervention [15,41,42,54,55], but, similarly to our study, no associations were found. Exceptionally, Hongguang et al. [29] found a significant association between the length of hospitalization and both the average CRP levels and the number of days necessary for CRP to return to normal values after treatment. However, this relationship was not observed in any other case series, including ours.

Keeping with the most recent recommendations [11,45,56], all children in our study underwent a sinus CT-scan within 24 hours of presentation. This imaging procedure is recommended whenever post-septal complications cannot be excluded in the physical examination and allows diagnosis of orbital cellulitis and subperiosteal abscess with reported accuracies ranging from 91 to 100% [11,57–59]. CT scans were repeated in 24 to 48 hours if the patient's clinical condition deteriorated despite the employed medical therapy. MRI was usually reserved for cases in which there was either clinical or CT-scan imaging suspicion of intracranial complications or cavernous sinus thrombosis, such as progressive neurologic changes and persistent fever regardless of aggressive medical treatment [11,16,60,61].

Despite the close proximity of the orbit to all the paranasal sinuses, the ethmoid sinus is usually referred as the main source of infection, because of the fragility of the lamina papyracea, the paper-thin bony plate that separates the orbit from the ethmoid cells [10,15,62]. Moreover, the anterior and posterior ethmoidal foramina, along with the valveless orbital veins may allow hematogenous propagation of infection in both anterograde and retrograde directions [29]. In some patients, congenital dehiscence can

provide an additional route of transmission [1]. Nevertheless, our results show a similar prevalence of ethmoid and maxillary sinuses involvement in all Chandler categories, with an overall high prevalence of pansinusitis. Similar results have been reported by Chandler et al. [12], Williams [63] and Hongguang et al, [29]. These observations suggest that the ethmoid sinuses act as important routes for infection that spreads to the orbit, but they may not be the primary source of infection, as it may have arisen in any of the other paranasal sinuses, then spreading into the orbital cavity through either venous dissemination or bony destruction.

According to an early publication by Remmler and Boles [64], if an abscess originates from the frontal sinus, the diploic system of the frontal bone is more likely to be compromised by the infection, with increasing risk for intracranial dissemination through retrograde thrombophlebitis via the valveless veins of Breschet. For this reason, some authors consider frontal sinusitis as an indication for urgent drainage of subperiosteal/orbital abscess, regardless of the abscess location [27,43,44,65–67]. However, we did not find a significant association between frontal sinus involvement and the need for more urgent surgical treatment nor the risk of intracranial complications. Moreover, for 30 patients with frontal sinusitis, medical management was effective in 18 cases (60%). Similar findings were reported by Taubenslag et al, [68] and Todman et al, [69]. Therefore, we believe that frontal sinusitis shouldn't be judged independently as an absolute indication for surgical treatment, since this may lead to overtreatment and unnecessary surgery.

Several papers point out the abscess location as a major determinant for the choice of treatment, as non-medial abscesses tend to be more aggressive, often

requiring surgical treatment [15,27,39,49]. However, we did not find a significant association between abscess location and the type of treatment. This difference might be explained by the fact that only two of our cases presented with non-medial involvement (both had superolateral location), therefore underestimating this group of patients. Both cases required an external approach, so we tend to agree with previous studies [48,49,70] on the necessity to accomplish an external approach on superiorly based abscesses.

On the other hand, many authors have identified abscess dimensions and volume on CT imaging as one of the key predictive features for the need of surgical intervention [11]. Cut-off subperiosteal abscess volume sizes of 500-3800 mm^3, a length greater than 10-17 mm and a width greater than 4.5 mm have been previously cited [11,41,46,54,55,69,71–74]. Unfortunately, for 8 of our 21 cases of subperiosteal abscess there was no information regarding abscess dimensions and volume and the remaining 13 cases were insufficient to draw any associations between abscess size and the need for surgical treatment. Larger studies need to be undertaken to determine a specific volume threshold that would equate with surgical management.

Guidelines from the Infectious Diseases Society of America (IDSA) [75] state that high-dose amoxicillin-clavulanate is the first-line therapy for children with acute rhinosinusitis [76], but there is no established algorithm for the pharmacological management of post-septal orbital complications. In our institution patients were usually treated with ceftriaxone, frequently in association with clindamycin, metronidazole and/or vancomycin. This antibiotic regimen follows the recommendations from the American Academy of Pediatrics [77], which advocates

vancomycin, metronidazole and either ceftriaxone, ampicillin-sulbactam, or piperacillin-tazobactam for the treatment of orbital complications of acute rhinosinusitis [22]. This organization also advises prompt surgical intervention and abscess drainage when a patient fails to improve within 24 to 48 hours of antibiotic therapy [46], a practice endorsed by several other authors [11,42,48,54,58,78]. In our study the period between hospital admission and surgical intervention varied from a few hours to 5 days. Nevertheless, we did not find any statistically significant association between this time period and the risk of further complications, so we cannot make any formal recommendation on the most appropriate watchful-waiting time before surgery. In our view, this period should be carefully assessed on an individual-basis, according to the patient's clinical evolution. Therefore, surgery can never be completely disregarded, and surgical teams should be readily available to intervene whenever a patient's clinical condition deteriorates despite aggressive medical treatment.

Inpatient adjuvant therapies were employed in most of our patients, in order to reduce inflammatory symptoms and facilitate clearance of secretions [14,48]. Controlling excessive intraorbital oedema can also prevent further complications, such as optic nerve compression, secondary glaucoma and orbital compartment syndrome [5,79]. Furthermore, Chen et al. conducted a prospective study in 2017, showing that the concomitant use of IV steroids and IV antibiotics is harmless and reduces the length of hospitalization [80]. Unfortunately, the widespread use of these therapies in our study hinders a fair evaluation of their actual role in reducing symptoms and promoting a faster recovery.

The decision to use endoscopic (FESS) or combined procedures to decompress the orbit was based on clinical evaluation, CT findings and abscess size/location. The extent of the intervention (anterior/posterior ethmoidectomy, antrostomy, meatotomy, etc.) also depended on the location of the disease. External approaches were mainly reserved for superiorly and laterally based abscesses (external orbitotomy), frontal/subcutaneous abscesses and intracranial complications (craniotomy). No differences in outcome based on surgical approach were observed in this study, but there is an obvious trend towards the preference for endoscopic treatment, since no patient was exclusively submitted to an open approach. This tendency correlates with the general belief that FESS is usually the best approach for the surgical management of this pathology, because of the lack of an external incision, inferior morbidity and shorter hospital stay [49,70,81–85].

In our case series, patients who underwent surgical intervention had a significantly longer hospital stay than those treated only medically. These data is also supported by other manuscripts [41,42,46,86] and highlights the importance of a proper medical treatment, in order to avoid potentially unnecessary surgical interventions. Surgery and a higher Chandler Classification were also related to increased risk of recurrence in our study. This is an interesting finding, as we did not find any previous reports of these relationships, even though recurrence itself is considered by some authors as a surgical criteria [27].

Finally, our findings also support the state of art's concept [5] that increased risk of intracranial complications is associated with both higher Chandler Classification categories and the need for surgery. In fact, all the cases that evolved into intracranial

complications belonged to Chandler Group IV (orbital abscess) and all required surgical treatment. Therefore, patients with post-septal complications of rhinosinusitis must be carefully monitored, since rapid surgical intervention may be required at any time during hospitalization.

Limitations of this study include its retrospective design and sporadic lack of information in clinical charts. In addition, we only had a modest sample size for some specific groups of patients and there was a low incidence of positive microbiology results. Furthermore, our study included several different practitioners and surgeons, which might have influenced disease reporting and management approaches.

5. Conclusions

This study aimed to address patient-centred clinical management of post-septal orbital complications of acute rhinosinusitis in the paediatric population. The differential diagnosis and treatment of these complications can often be challenging and thereby close cooperation and multidisciplinary input between parents, paediatricians, otorhinolaryngologists, ophthalmologists and neurosurgeons is of utmost importance.

Orbital complications of acute rhinosinusitis remain a common pathology in the paediatric population. Eyelid swelling is almost always present, but a great variety of symptoms may occur and the exclusion or neurological involvement at the time of the first evaluation is paramount for treatment's success, patient survival and avoidance of long-term sequelae.

Our findings support the crucial role of pharmacological therapy in the treatment of post-septal orbital complications, reducing hospitalization length and recurrence risk. However, we also believe that surgical teams should be readily available to intervene whenever a patient's clinical condition deteriorates.

Predictive factors for the need of surgery were not found in this study. Abscess drainage should be considered when there is no clear improvement with medical therapy, whenever vision is at risk and in cases with abscesses or intracranial complications. FESS is the main surgical technique in this patient population, providing safe and effective results.

Future research regarding paediatric post-septal complications of acute rhinosinusitis is needed to create more comprehensive and objective management protocols.

6. Conflicts of interest

No conflicts of interest.

7. Financial disclosure statements

No financial relationships exist for any authors.

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Tables and Figures

Table 1: Paranasal sinus involvement distribution for the 55 patients with paediatric orbital complications of acute rhinosinusitis (2007 to 2020).

Paranasal Sinus Involvement	N (%)
All	23 (41.80%)
Ethmoid	4 (7.30%)
Ethmoid + Maxillary	13 (23.60%)
Ethmoid + Maxillary + Frontal	8 (14.50%)
Ethmoid + Maxillary + Sphenoidal	6 (10.90%)
Total Reported	54 (98.20%)
Unknown	1 (1.80%)
Total	55 (100.00%)

Figure 1: Computed tomography (CT) axial view of three patients with post-septal complications of acute rhinosinusitis. Picture A: Post-septal cellulitis on the right in an eight years old boy. Picture B: Subperiosteal abscess on the left in a five years old girl. Picture C: Orbital abscess on the left in a five years old girl. Please note the adjacent signs of ethmoidal sinusitis in all patients.

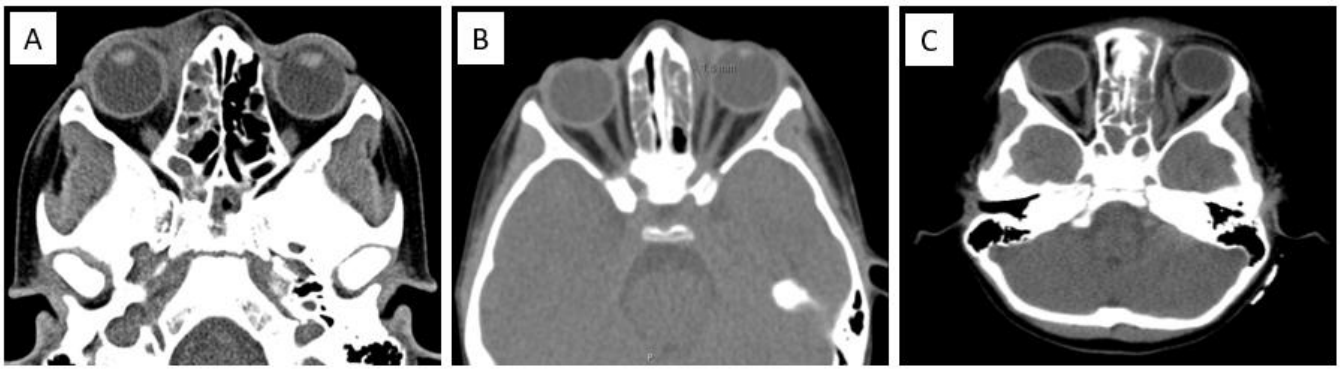

Table 2: Type of treatment in paediatric orbital complications of acute rhinosinusitis.

Chandler Group	Medical Treatment Only	Medical Treatment + Surgical Treatment
II	20	4
III	11	10
IV	2	8
Total	33	22

Table 3: Type of surgical intervention for patients with paediatric orbital complications of acute rhinosinusitis.

Chandler Group	FESS[1] Only	FESS + External Approach	Adenoidectomy	Craniotomy
II	4	0	1	0
III	8	2	2	0
IV	4	4	1	2
Total	16	6	4	2

1. Functional endoscopic sinus surgery.

Graph 1: Mean length of hospital stay for patients receiving medical treatment or a combination of medical and surgical treatment.

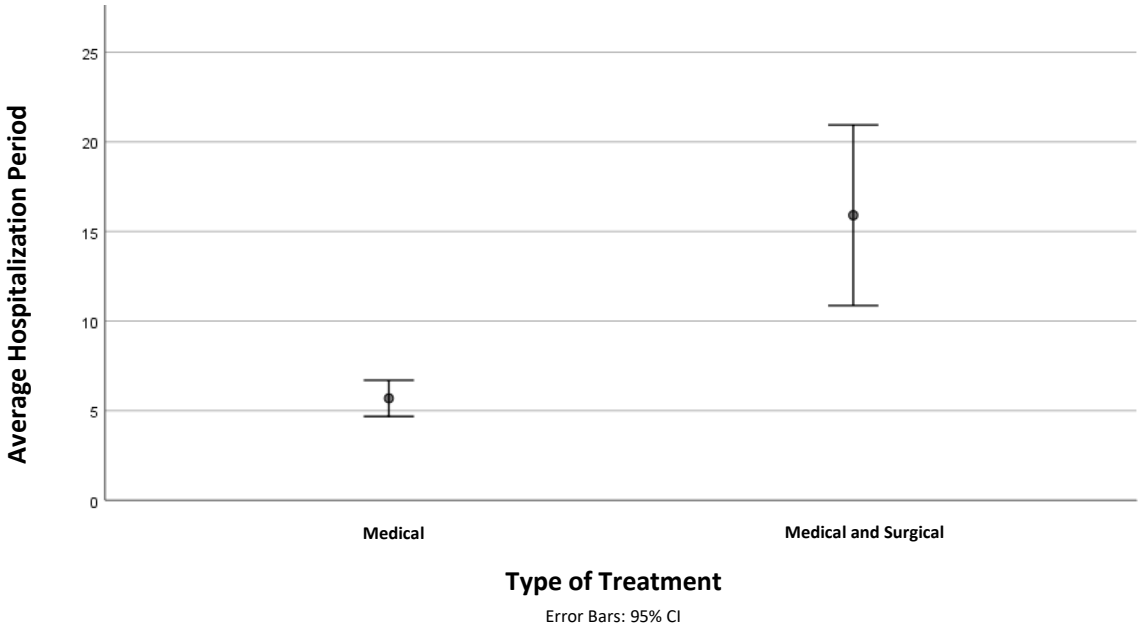

Table 4: Summary of clinical cases with recurrence of orbital infection.

Post-septal Cellulitis	1 year	Pre-septal Cellulitis	Unknown	Unknown	Unknown
Previous Diagnosis	Time of onset in relation to former hospital discharge	Recurrence Diagnosis	Treatment	Complications	Outcome
Orbital Abscess	1 month	Orbital cellulitis	Unknown	Unknown	Unknown
Subperiosteal Abscess	3 months	Subperiosteal Abscess	Pharmacological treatment associated with surgery[1]	Unfavourable clinical evolution with late hypersensitivity reaction to vancomycin and ceftriaxone	Discharged symptomless
Subperiosteal Abscess	2 days	Subperiosteal Abscess	Pharmacological treatment associated with surgery[2]	None	Discharged symptomless
Subperiosteal Abscess	1 month	Post-septal Cellulitis	Pharmacological treatment associated with surgery[3]	None	Discharged symptomless
Post-septal Cellulitis	1 month	Pre-septal Cellulitis	Pharmacological treatment only[4]	None	Discharged symptomless
Post-septal Cellulitis	1 year	Pre-septal Cellulitis	Unknown	Unknown	Unknown

1. Inpatient initial treatment with ceftriaxone and vancomycin, later replaced by ertapenem and teicoplanin. Patient also required adenoidectomy and 2 FESS procedures. **2.** Pharmacological treatment with ceftazidime and vancomycin. Patient required 3 surgical interventions: 1 maxillary sinus aspiration, associated with antrostomy, anterior ethmoid polyp removal and posterior ethmoidectomy; 1 revision FESS with orbitotomy; another revision FESS with adenoidectomy and left middle nasal conchae biopsy. **3.** Inpatient pharmacological treatment with vancomycin and ceftriaxone. Outpatient pharmacological treatment with amoxicillin/clavulanate. Patient also underwent adenoidectomy and turbinectomy. **4.** Inpatient treatment with oral methylprednisolone and IV paracetamol.

ANEXOS

INTERNATIONAL JOURNAL OF PEDIATRIC OTORHINOLARYNGOLOGY

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The purpose of the *International Journal of Pediatric Otorhinolaryngology* is to concentrate and disseminate information concerning prevention, cure and care of **otorhinolaryngological disorders** in **infants** and **children** due to developmental, degenerative, infectious, neoplastic, traumatic, social, psychiatric and economic causes. The Journal provides a medium for clinical and basic contributions in all of the areas of **pediatric otorhinolaryngology**. This includes medical and surgical otology, bronchoesophagology, laryngology, rhinology, diseases of the head and neck, and disorders of communication, including voice, speech and language disorders.

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Reference to a journal publication with an article number:

[2] J. van der Geer, J.A.J. Hanraads, R.A. Lupton, 2018. The art of writing a scientific article. Heliyon. 19, e00205. https://doi.org/10.1016/j.heliyon.2018.e00205.
Reference to a book:
[3] W. Strunk Jr., E.B. White, The Elements of Style, fourth ed., Longman, New York, 2000.
Reference to a chapter in an edited book:
[4] G.R. Mettam, L.B. Adams, How to prepare an electronic version of your article, in: B.S. Jones, R.Z. Smith (Eds.), Introduction to the Electronic Age, E-Publishing Inc., New York, 2009, pp. 281–304.
Reference to a website:
[5] Cancer Research UK, Cancer statistics reports for the UK. http://www.cancerresearchuk.org/aboutcancer/statistics/cancerstatsreport/, 2003 (accessed 13 March 2003).
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PROCESS 2020 Checklist			
Topic	**Item**	**Checklist Item Description**	**Page Number**
Title	**1**	- The phrase 'case series' and the area of focus should appear in the title (e.g. patient population, diagnosis, intervention or outcome).	No
Key Words	**2**	- Include three to six keywords that identify what is covered in the case series (e.g. patient population, diagnosis, intervention or outcome). - Include 'case series' as one of the keywords.	3
Abstract	**3a**	Introduction and Importance - Describe what is unique or educational. - What is the overarching theme of the case series?	2
	3b	Methods - Describe what was done, how and when was it done and by whom.	2
	3c	Outcomes - Describe the outcomes of the intervention and management strategy.	2
	3d	Conclusion - Describe the take home message(s), including what has been learnt? - How will this impact future clinical practice?	2
Introduction	**4**	- Describe the background of the case series and specify the overarching theme (e.g. common disease, intervention, or outcome). - The introduction should explain what is unique or educational about the case series. - Relevant scientific literature should be referenced. - Introduction should be 1-2 paragraphs in length.	3 and 4

Methods	**5a**	Registration - State the research registry number in accordance with the Declaration of Helsinki - "Every research study involving human subjects must be registered in a publicly accessible database". This can be obtained from, for example, ResearchRegistry.com, ClinicalTrials.gov, or ISRCTN. - If a protocol already exists, state the corresponding registration number and access directions (e.g. website or journal, and include a hyperlink that is publicly accessible). It must be written in the English language.	5
	5b	Study Design - State that the study is a case series. - State whether the case series is: (1) prospective/ retrospective, (2) single/multi-centre, and if (3) cases are consecutive/non-consecutive.	5
	5c	Settings and Time-Frames - Describe the setting(s) in which the patient was managed (e.g. research institution, teaching/district general hospital, community, or private practice). - Document any relevant dates (e.g. recruitment, intervention, follow-up, and data collection time-frames).	5
	5d	Participants - Describe the relevant characteristics (e.g. demographics, comorbidities, tumour staging, smoking status) and if relevant, exposure(s) of the participants. - Describe the method of participant recruitment, if relevant. - State any subsequent inclusion or exclusion criteria, and how the participants were selected. - Methods used to ensure the de-identification of patient information.	5

	5e	Pre-Intervention Patient Optimisation - Lifestyle (e.g. weight loss). - Medication review (e.g. anticoagulation, oral hypoglycemics/insulin). - Pre-surgical stabilisation/preparation (e.g. treating hypothermia/hypovolemia/hypotension, ICU care for sepsis, nil by mouth, or enema). - Other (e.g. psychological support).	Not applicable
	5f	Interventions - Describe the type(s) of intervention(s) used (e.g. pharmacological, surgical, physiotherapy, psychological, preventative). - Describe any concurrent treatments (e.g. antibiotics, analgesia, antiemetics, venous thromboembolism prophylaxis).	Not applicable
	5g	Intervention Details - Describe the rationale behind the treatment offered, how it was performed and time to intervention. - For pharmacological therapies, include information on the formulation, dosage, strength, route, and duration. - For surgery, include details such as anaesthesia, patient position, preparation used, use of other relevant equipment, sutures, devices, and surgical stage. - The degree of novelty for a surgical technique/device should be mentioned (e.g. 'first in human' or 'first in this context'). - Medical devices should have manufacturer and model specifically mentioned.	Not applicable
	5h	Operator Details - Where applicable, include operator experience and position on the learning curve, any relevant training, and specialisation (e.g. 'junior trainee with three years of surgical specialty training in Plastic Surgery and seven similar cases completed previously under direct supervision').	Not applicable

	5i	Quality Control - What measures were taken to reduce inter- or intra-operator/operation variation, to ensure quality, and to maintain consistency between cases (e.g. independent observers, lymph node counts, standard surgical technique). - State any specific disparities between cases.	Not applicable
	5j	Follow-Up - When (e.g. how long after discharge, frequency, maximum follow-up length at the time of submission). - Where (e.g. home via video consultation, primary care, secondary care). - How (e.g. telephone consultation, clinical examination, blood tests, imaging). - Any specific long-term surveillance requirements (e.g. imaging surveillance of endovascular aneurysm repair or clinical exam/ultrasound of regional lymph nodes for skin cancer). - Any specific post-operative instructions (e.g. post-operative medications, targeted physiotherapy, psychological therapy). - State if any participants were lost to follow-up and why.	Not applicable
Results	6a	Participants - Please state the number of patients involved, the patient characteristics (e.g. demographics, comorbidities, smoking status, and if applicable, tumour staging (e.g. TNM)).	6
	6b	Deviation from the Initial Management Plan - State if there were any changes in the planned intervention(s) (e.g. what was changed and why). - Please include a suitable schematic diagram if appropriate.	Not applicable

	6c	Outcomes and Follow-Up - Expected versus attained clinical outcome as assessed by the clinician. Reference literature used to inform expected outcomes. - When appropriate, include patient-reported measures (e.g. questionnaires including quality-of-life scales). - Describe and explain the percentage of patients lost to follow-up.	12, 13 and 14
	6d	Intervention Adherence and Compliance - Where relevant, detail how well the patient adhered to and tolerated the advice provided (e.g. avoiding heavy lifting for abdominal surgery, or tolerance of chemotherapy and pharmacological agents). - Explain how adherence and tolerance were measured.	Not applicable
	6e	Complications and Adverse Events - Precautionary measures taken to prevent complications (e.g. antibiotic or venous thromboembolism prophylaxis). - All complications and adverse or unanticipated events should be described in detail and ideally categorised in accordance with the Clavien-Dindo Classification (e.g. blood loss, length of operative time, wound complications, re-exploration or revision surgery, impact on length of stay). - If relevant, was the complication reported to the relevant national agency or pharmaceutical company. - Specify the duration of time between completion of the intervention and discharge, and whether this was within the expected timeframe (if not, why not). - Where applicable, the 30-day post-operative and long-term morbidity/mortality may need to be specified. - State if there were no complications or adverse outcomes.	12 and 13
Discussion	**7a**	- Summarise the key results.	14-23
	7b	Relevant Literature and Placing the Results in Context	14-23

		- Include a discussion of the relevant literature and, if appropriate, similar published studies. - Describe the implications for clinical practice guidelines (e.g. NICE) and any relevant hypotheses generated.	14-23
	7c	Strengths - Describe the relevant strengths of the study. - Detail any multidisciplinary or cross-speciality relevance. Weaknesses and Limitations - Describe the relevant weaknesses or limitations of the study. - For novel techniques or devices, outline any contraindications and alternatives, potential risks and possible complications if applied to a larger population.	14 and 23
	7d	Directions for Future Research - State how the methodology and findings discussed can impact future research and clinical practice. Describe the questions that have arisen as a result of this study. - State the alternative study design(s) best suited to address these questions.	16
Conclusions	**8a**	Key Conclusions - Outline the key conclusions from this study.	23 and 24
	8b	Rationale - Ensure that any of the conclusions made are supported by a strong rationale.	23 and 24
	8c	Future Work - Briefly discuss any questions arisen from this study and any differences in approach to patient diagnosis or management which the authors might adopt in future similar studies.	23 and 24
Patient Perspective	**9**	- Where appropriate, the patients should be given the opportunity to share their perspective on the intervention(s) they received (e.g. sharing quotes from a consented, anonymised interview, or questionnaire).	Not applicable

Informed Consent	**10**	- The authors must provide evidence of consent, where applicable, and if requested by the journal. - State the method of consent at the end of the article (e.g. verbal or written). - If not provided by the patients, explain why (e.g. death of patient and consent provided by next of kin). If the patients or family members were untraceable then document the tracing efforts undertaken.	Not applicable
Additional Information	**11a**	- State any conflicts of interest.	24
	11b	- State any sources of funding.	25
	11c	Other Relevant Disclosures - Please state any author contributions, acknowledgments, and where required, institutional review board and ethical committee approval. - Disclose whether the case has been presented at a conference or regional meeting.	24
Clinical Images and Videos	**12**	- Where relevant and available, include clinical images to help demonstrate the cases pre-, peri-, and post-intervention (e.g. radiological, histopathological, patient photographs, intraoperative images). - Where relevant and available, include a link (e.g. Google Drive, YouTube) to the narrated operative video to highlight specific techniques or operative findings. - Ensure all media files are appropriately captioned and indicate points of interest to allow for easy interpretation.	29
Referencing the Checklist	**13**	- Include reference to the PROCESS 2020 publication by stating: 'This case series has been reported in line with the PROCESS Guideline' at the end of the methods section (and include citation in the references section).	No