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Complications of acute rhinosinusitis in The Netherlands

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Background. Despite the evidence demonstrating that antibiotics are of little benefit in acute rhinosinusitis (ARS), GPs continue to prescribe them, possibly in an attempt to prevent potentially dangerous complications. In this study, we present epidemiological data about the incidence, course and severity of such complications in the Netherlands.

Methods. This retrospective cohort study included all patients hospitalized in The Netherlands in 2004 with a complication of ARS. Records were made of the symptoms of ARS and the complication, demographics, medical history, medical treatment preceding hospitalization, diagnostic techniques, therapeutic management, course and outcome.

Results. Forty-seven patients with 48 complications (16 intracranial and 32 orbital) were included. In the intracranial group (mean age 35.9 years), six patients had been treated with oral antibiotics prior to hospitalization. While hospitalized, all patients were treated with intravenous antibiotics and 15 underwent surgery. Eight patients recovered fully after treatment, three patients had residual symptoms and three patients died (missing data: 2). Of the 31 patients with orbital complications (mean age 17.4 years), 14 received oral antibiotics before admission. While hospitalized, all patients were treated with intravenous antibiotics and 13 underwent surgery. Twenty-seven patients recovered fully and two had residual symptoms (missing data: 2).

Conclusions. Severe ARS complications occur in an otherwise healthy population in an estimated 1:12 000 paediatric and 1:32 000 adult cases in the Netherlands. Our study suggests that antibiotic treatment of ARS in general practice does not play a role in preventing complications.

Keywords. Acute rhinosinusitis, antibiotics, complications.

Introduction

Acute rhinosinusitis (ARS) is one of the commonest diagnoses made in primary care, and its management has significant implications for both public health and costs: multiple meta-analyses[1–3] have shown the limited benefits conferred by routine antibiotic prescription in the general population. Interestingly, despite the evidence of the lack of benefit of blanket antibiotic use in ARS, prescribing patterns vary widely between countries, ranging from 70%[4] to 99%.[5] The Netherlands has one of the lowest (if not the lowest) antibiotic prescription rates in primary care in Europe[6] (and correspondingly, one of the lowest rates of bacterial resistance[7]).

To manage patients with rhinosinusitis, GPs in The Netherlands generally use the guideline from the Dutch College of General Practitioners. The treatment is based on the severity of the symptoms and the risk of developing complications. It advises to start with symptomatic treatment. This guideline states that antibiotics are not indicated for the normal course of ARS.[8] A recent questionnaire-based study showed that 34% of Dutch GPs (consider to) prescribe antibiotics for moderate ARS. In case of severe ARS, this percentage increases to 84%.[9]

However, informed decision about the risk of using antibiotics (or not) must also take into account the potential effect of antibiotics as well as the incidence of rare but potentially serious sequelae of ARS, including orbital and intracranial complications. Box 1 lists early symptoms of complications of ARS justifying immediate referral to specialist care.[10] A balanced cost/benefit analysis requires accurate epidemiological data that documents the incidence, course and severity of these complications. This study presents data of this kind from The Netherlands.

Methods

This retrospective cohort study looked at the medical files of patients hospitalized in Dutch hospitals in 2004

Box 1 Symptoms of complications of ARS justifying immediate referral/hospitalization

- Periorbital oedema
- Displaced globe
- Double vision
- Ophthalmoplegia
- Reduced visual acuity
- Severe unilateral or bilateral frontal headache
- Frontal swelling
- Signs of meningitis or focal neurological signs

with a complication of ARS. We used hospital data from the National Medical Register (Landelijke Medische Registratie, LMR). The Prismant research institute provided all the data. The LMR contains data about admissions in general and academic hospitals in The Netherlands. This information includes medical data such as diagnoses, as well as patient-specific data, including age, gender and date of admission. The LMR is based on the International Classification of Diseases-9 classification and procedures from the Dutch Classification System of Procedures. There were no major changes to these classification systems between 1991 and 2006. Participation in the LMR is voluntary. In 2004, the participation percentage of hospitals in the LMR was 98%. We requested data about all patients admitted to a hospital in 2004 with a possible complication of ARS. To ensure we would not miss certain complications, we selected a wide range of diagnoses that could represent ARS complications (Appendix 1). On the basis of this database, hospitals were visited to handsearch patient files for additional data.

The symptoms of both ARS and the complications were recorded, as well as demographics, medical history, medical treatment preceding hospitalization, diagnostic techniques, therapeutic management, course and outcome.

Results

The Prismant database provided us with hospitalization data relating to 488 patients with a possible complication of ARS in 2004. After excluding 69 duplicate cases, the number was reduced to 419 cases. In 94 cases, it was not possible to assess the medical file, either because the hospital did not cooperate with this study or because the patient could not be identified due to incorrect identification numbers or for other reasons. As a result, 324 patient files were available and studied.

In 278 of these 324 potential cases, there was no clinical or radiological evidence of ARS in the patient either before or during hospitalization. The most frequently encountered diagnosis in these 278 patients was meningitis (86 cases). The second most common diagnosis was intracerebral abscess with a non-sinogenic focus, for example otitis media. In some patients, an obvious focus of infection was not identified, but these patients had no symptoms of ARS on clinical or radiological examination. These patients were therefore excluded from this study (see Fig. 1 for a flowchart). The reader is referred to Appendix 2 for the characteristics of the excluded patients.

Forty-seven patients were identified, with 48 complications of ARS. The observed complications were divided into two groups: intracranial and orbital (see Table 1). These two groups will be discussed separately in the remainder of this article.

Intracranial complications

Sixteen patients had intracranial complications of ARS: age 5–77 years (mean 35.9 years), 13 of them were males. Five patients were <18 years. Two patients (12%) were diabetic and/or immunocompromized. Six patients had a known ear, nose and throat (ENT) history; two were smokers. Table 2 contains details about the medical histories.

Although all patients were diagnosed with ARS on hospitalization, only eight of them (50%) reported experiencing symptoms of ARS in the days preceding admission. These patients most commonly complained of purulent rhinorrhoea, headache and fever.

Six patients (37%) had been treated with oral antibiotics prior to hospitalization for 4.5 ± 3.3 days (adults: 4.0 ± 0 and children: 5.0 ± 5.7). Five of these patients had complaints of ARS. Three patients with complaints of ARS were not treated with antibiotics. Five different agents were prescribed: amoxicillin (3), doxycyclin (2), azitromycin (2), ciproxin (1) and co-trimoxazol (1).

The most frequently encountered symptoms of intracranial complication upon presentation to the hospital were diminished consciousness and headache. Intracranial and sinus abnormalities were seen on all computed tomography (CT) (15) and magnetic resonance imaging (MRI) scans (6) made. In all of these cases, there was opacification of at least one sinus. A pansinusitis was found at least on one side in nine patients. In 4 (all adults) of 16 patients, dehiscence of the posterior wall of the frontal sinus was seen (due to a mucocele in one case). A defect in the ethmoidal roof was found in one adult patient and a partial thrombosis of the superior sagittal sinus in another.

Sinus aspirate was cultured in seven cases, blood cultures were performed in six cases and cultures of spinal fluid after lumbar puncture were made in seven patients. Table 3 shows the results of these cultures. The results matched in one of the three patients with both cerebrospinal and sinus fluid cultures. Both sinus fluid and blood were cultured in four patients. The results matched in three patients.

All patients were treated with intravenous antibiotics for a mean of 32.2 ± 18.5 days (adults: 28.1 ± 19.2 and children: 46.5 ± 3.5) with 2.9 ± 1.2 different antibiotic agents. In two cases, intravenous treatment

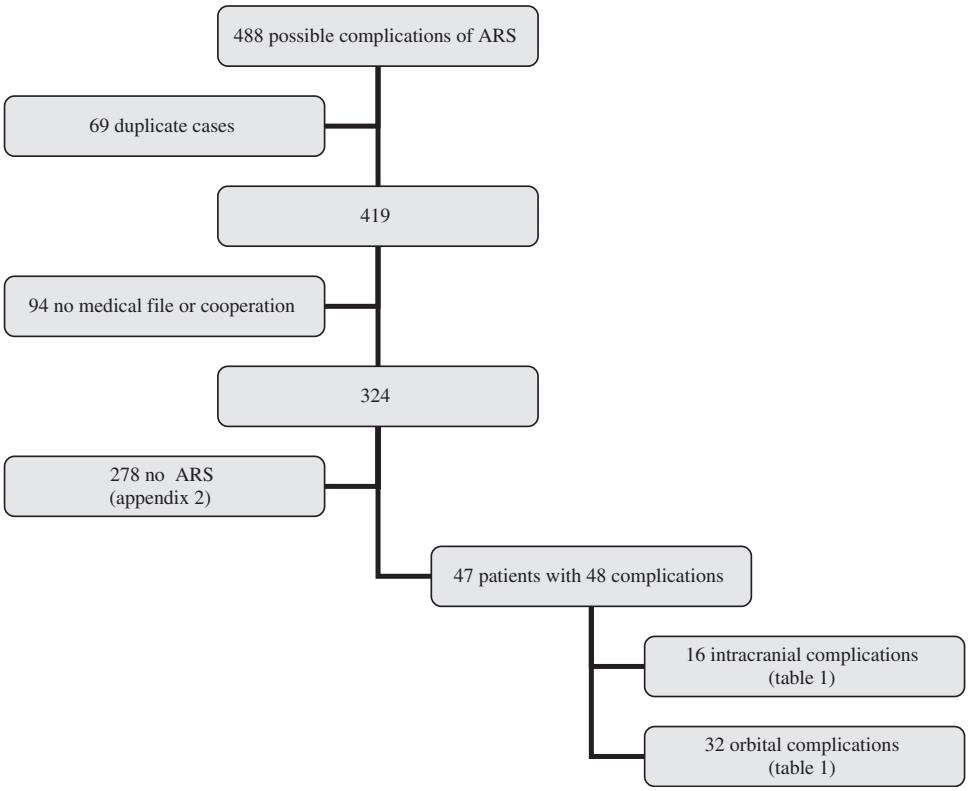

FIGURE 1 *Case selection flowchart*

TABLE 1 *Complications of ARS*

Diagnosis	Total number of patients	Children	Total (in percentage)
Intracranial	16	5	100
Subdural empyema	9	4	56
Meningitis	3	0	19
Intracerebral abscess	2	1	13
Epidural empyema	1	0	6
Encephalitis	1	0	6
Orbital	32	21 (22 complications)	100
Orbital cellulitis	14	13	47
Pre-septal cellulitis	12	6	34
Subperiostal abscess	4	2	13
Intra-orbital abscess	2	1	6

TABLE 2 *Medical history*

	Intracranial complications			Orbital complications		
	Yes	No	Unknown	Yes	No	Unknown
Diabetes mellitus	2	11	3	0	19	12
Immunocompromized	1	11	4	0	19	12
Smoking	1	9	6	2	23	6
CRS with/without nasal polyps	3	13	16	5	19	38
Recurrent ARS	3	4	9	9	6	16
Facial trauma	2	4	10	0	13	18
Nasal/paranasal surgery	1	6	9	5	8	18

consisted of one single antibiotic: benzylpenicillin in one case, an unknown antibiotic in the other. Five patients were treated with two antibiotic agents. Nine patients were treated with three or four different antibiotics simultaneously. Metronidazole was used in all but one of these cases. In addition to antibiotic therapy, 11 patients received systemic corticosteroids, 9 patients were given anti-epileptic medication, 8 patients (4 children) were treated locally with saline nasal douches and/or xylometazolin nose drops and all but 1 patient (an adult who had encephalitis without abscess) underwent surgery. Tables 4 and 5 list the diagnoses, together with the associated neurosurgical and rhinological management.

Eight patients (50%) recovered fully after treatment and three patients (19%) had residual symptoms after dismissal from the hospital. Two of these three patients were children with pansinusitis complicated by subdural empyema. The third patient was an adult with meningitis secondary to maxillary sinusitis and herpes. All were treated with intravenous antibiotics, antiepileptic medication and neurosurgical surgery. One child did not undergo ENT surgery. The two children had mild dysphasia after dismissal; the adult patient suffered from polyneuropathy. In two cases,

the outcome is unknown and three patients (19%) (all males and aged 18, 62 and 77 years) died. The youngest patient, a previously healthy man, died of a massive pulmonary embolus 6 days after the sinuses and subdural empyema were surgically drained. The oldest patient had significant comorbidity, including Kahler's disease, for which he was undergoing chemotherapy, as well as diabetes and hypertension. He was admitted with encephalitis against a background of uncontrolled diabetes and immunosuppresion. Despite antibiotic therapy, he went into a coma and died 8 days after admission. The third patient (male and aged 62 years) was admitted with epileptic seizures and was subsequently diagnosed with an intracerebral abscess, which ruptured into the cerebral ventricles after remaining undiagnosed for 18 days. Despite repeated surgery (placement of ventricular and intracranial drain and drainage of the abscess), he fell into a coma and mechanical ventilation was discontinued after 6 weeks.

Table 6 provides an overview of the total number of complications and management, including the numbers for children.

Orbital complications

Thirty-two orbital complications were found in 31 patients, 22 of whom were male and 21 children (one child had two complications). The age range was 6 months to 74 years (mean 17.4 years). No patients were diabetic or immunocompromized, three had known allergies and two patients were smokers. Eleven patients had an ENT history. Table 2 lists details about the medical history.

Twenty patients (65%) reported experiencing typical symptoms of ARS in the days preceding admission. Another three children had complaints of headache, fever and malaize without purulent rhinorrhoea. In eight cases, it is unknown whether ARS symptoms were present or absent.

Fourteen patients (43%) had been treated with oral antibiotics for 5.2 ± 5.7 days (adults: 6.33 ± 7.1 and children: 5.5 ± 6.4) prior to hospitalization: amoxicillin (4), amoxicillin/clavulanic acid (4), claritromycin (2), flucloxacillin (1), doxycyclin (1) or unknown(2). Seven of these patients did have symptoms of ARS. Thirteen patients with complaints of ARS were not treated with antibiotics prior to hospitalization. Orbital involvement manifested with swelling (29) and redness (12) of the eyelids, pain in the eye (13), proptosis (8), limitation of eye movement (6) and/or impaired vision (4).

Abnormalities of the sinus and orbit were seen on all CT (23) and MRI scans (7) made. Opacification of one or more sinuses was seen in all patients. Orbital wall defects were found in three adult patients, and a maxillary sinus cyst was seen in two others (one child).

Three cultures of sinus aspirate were performed and a blood culture was performed in 11 children. Table 3 lists the results of these cultures. There were no cases in which a sinus aspirate and a blood culture were taken from the same patient.

After admission to hospital, all patients were treated with intravenous antibiotics. The mean duration of intravenous antibiotic therapy in this group was 6.6 ± 7.6 days (adults: 5.1 ± 1.9, children: 5.3 ± 2.2) with 1.2 ± 0.6 different antibiotic agents. In 29 cases, intravenous

TABLE 3 *Cultures*

	N
Intracranial complication	
Sinus culture	7
Streptococcus intermedius	2
Streptococcus milleri	1
Streptococcus pneumoniae	1
Peptostreptococcus micros	1
Corynebacterium xerosis	1
Coagulase-negative *Staphylococcus*	1
Anaerobes	1
Fusobacterium varium	1
Blood culture	6
Streptococcus *pneumoniae*	1
Peptostreptococcus micros	1
Fusobacterium varium	1
Coagulase-negative *Staphylococcus*	1
No bacteria	2
Lumbar puncture	7
Streptococcus pneumoniae	3
Streptococcus milleri + *Heamophilus parainfluenza*	1
Unknown microorganism	2
No bacteria	1
Orbital complication	
Sinus culture	3
Streptococcus intermedius	1
Streptococcus aureus	1
No bacteria	1
Blood culture	10
Coagulase-negative *Staphylococcus*	1
No bacteria	9

TABLE 4 *Surgical management of intracranial complications of ARS*

Diagnosis (*n*)	Rhinological surgical treatment (*n*)	Neurosurgical treatment (*n*)	Other surgical treatment (*n*)
Subdural empyema (9)	Sinus drainage (6)	Drainage empyema (8)	
Meningitis (3)	Sinus drainage (3)	Ventricle drain (1)	Tracheotomy (1)
Intracerebral abscess (2)	Sinus drainage (1)	Drainage empyema (2) Ventricle drain (1)	
Epidural empyema (1)	Sinus drainage (1)	Drainage empyema (1)	
Encephalitis (1)	No surgery	No surgery	

TABLE 5 *Surgical management of orbital complications of ARS*

Diagnosis (*n*)	Rhinological surgical treatment (*n*)	Orbitosurgical treatment (*n*)
Orbital cellulitis (13)	Sinus drainage (5)	Orbital decompression (1)
Pre-septal cellulitis (12)	Sinus drainage (2)	Orbital decompression (1)
Subperiostal abscess (3)	Sinus drainage (2)	Orbital decompression (1) Drainage abscess (1)
Intra-orbital abscess (3)	Sinus drainage (2)	Drainage abscess (2)

TABLE 6 *Complications and management*

	Intracranial		Orbital	
	Total	Children	Total	Children
Number of complications	16	5	32	21
Before hospitalization				
ENT history	6	1	11	6
ARS symptoms	8	3	20	12
Antibiotics given by GP	6	3	14	5
Diagnostics during hospitalization				
Sinus aspirate	7	2	3	2
Blood cultures	6	1	0	11
Lumbar punction	7	1	0	0
Therapy during hospitalization				
Intravenous antibiotics	16	5	32	21
Systemic corticosteroids	11	2	4	3
Anti-epileptics	9	3	0	0
Local treatment (nose drops etc.)	8	4	21	14
Surgery	15	5	13	5
Outcome				
Full recovery	8	1	27	17
Residual symptoms	3	2	2	1
Unknown outcome	2	2	2	2
Death	3	0	0	0

treatment consisted of a single antibiotic: amoxicillin/clavulanic acid (27), co-trimoxazol (2), cefuroxim (1) or clindamycine (1). One child with orbital cellulitis and ethmoiditis was treated with two antibiotic agents: amoxicillin/clavulanic acid in combination with clindamycine. In addition to antibiotic therapy, 4 patients also received systemic corticosteroids, 21 patients were treated locally with saline nasal douches and/or xylometazolin nose drops and 13 patients underwent surgery (see Table 5). Twenty-seven patients (87%) recovered fully after treatment. Two patients (6.5%) had persistent proptosis after dismissal from the hospital. In two cases, the outcome is unknown. No patients in this group died. Table 6 provides an overview of the total number of complications and management, including the numbers for children.

Discussion

This study tried to establish the incidence, course and severity of complications of ARS in The Netherlands. We wanted to know whether the low use of antibiotics in The Netherlands led to more ARS complications. Our interest was triggered by the paucity of data on this subject. The paper from Stoll from France showed a very high level of antibiotic use and the paper from van Zuijlen *et al.* showed that the incidence of acute mastoiditis in the Netherlands is higher than in countries with higher antibiotic prescription rates.[11,12]

This analysis confirms the preponderance of youthful and male patients: 65% of patients with orbital complications and 31% of those with intracranial complications were under 18[13–16] and the male/female ratio was 2.6:1.[11,13,17–21] The higher prevalence in males is still unexplained.

It is estimated that Dutch children have 7–10 common colds each year. The estimated frequency for adults is 2–5 episodes/year.[10] As mentioned elsewhere, 0.5–2% of these common colds result in acute bacterial rhinosinusitis (ABRS). In 2004, the Dutch population consisted of 3.6 million children (<18 years) and 12.7 million adults. This results in an estimate of 300 000 (between 126 000 and 720 000) paediatric and 700 000 (127 000–127 million) adult cases of ABRS during this year. We found complications in 25 children and 22 adults, which results in an estimated incidence of complications in 1:12 000 cases a year of ABRS in children and 1:32 000 cases a year of ABRS in adults. Stoll *et al.* found 43 complications of ARS in a period of 17 months, resulting in an estimated incidence of 30 complications/year. The population served by the hospitals participating in the study by Stoll *et al.* consists of an estimated 12 million people. If the incidence of ABRS in this French population is the same as in our Dutch adult population, the estimated incidence of complications in this French population would then be 30 complications/year mainly in adults in a population of 12 million. This is comparable to the Dutch situation.

The numbers of cases in which symptoms of ARS preceded the complication in our series are comparable to that reported by Stoll *et al.*: 60% and 63%, respectively. In our sample, the first symptoms of an intracranial complication were headache and diminished consciousness. This is in accordance with the early symptoms justifying immediate referral as listed in Box 1. In the group with orbital complications, the most frequently found symptoms were swelling of the eye, redness of the eye and pain in the eye. Interestingly enough, this last symptom is not mentioned in the European position paper on rhinosinusitis and nasal polyps as an alarm symptom requiring instant referral.[10] Our data suggest perhaps it should be.

In Stoll's French series, 95% of patients with proven bacterial ARS and 44% of the total patient group were treated with antibiotics before hospital admission. This percentage is comparable with the 42% we

found. This relatively low percentage might be caused by the fact that a significant percentage of patients (60%) did not have symptoms of ARS before they were admitted into hospital with the complication. However, in our series, having symptoms of ARS or not did not influence the prescribing of antibiotics by the GPs significantly. In a British study by Babar-Craig *et al.*[22], 59% of the patients were treated with antibiotics prior to admission and similar complication rates were seen in patients who were treated with prior antibiotics and those who were not.

Most of the patients with complications of ARS were healthy and often young: only two patients were immunocompromized, showing that complications of ARS mainly occur in healthy patients. However, one of the immunocompromized patients died of the complication so there is a risk of serious consequences and therefore a need to start early with antibiotics when a complication has developed.

An intriguing finding is the fact that the common pathogens causing ARS, like *Haemophilus influenzae* and *Moraxella catharralis*, are underrepresented in our sample. Is this due to the fact that cultures are more often taken in case of fulminant or persistent infection not responding to antibiotic treatment? Or are patients with infections caused by more exotic pathogens truly more prone to developing complications? Or could it be that these common pathogens are already eliminated before the culture is taken? These questions cannot be answered by our data.

Thirty-six percent of patients had a history of nasal or sinus disorder, mainly previous episodes of ARS (26%), nasal/paranasal surgery (13%) and chronic rhinosinusitis (CRS) with nasal polyps (11%). A French study by Stoll *et al.*[11] of patients aged ⩾13 years found an ENT history in almost 50% of cases. They found previous nasal surgery (19%) and facial trauma (16%) to be the most common antecedents, whereas we found the latter in only 4% of patients. This is a finding that raises more questions than it answers: it is clear that patients with previous ENT surgery and CRS are overrepresented in our series. It could be that these patients are at a higher risk of both intracranial and orbital complications, perhaps through minor bony dehiscences created either during the surgery (even though this was not seen, except in one patient with mucocoele) or through the subclinical erosion of the bony plates by the disease. Confirmation of this new finding by other studies could perhaps lead to different prevention strategies, including a lower threshold for intervention in these patients when they develop ARS.

In this article, we presented a retrospective case series. This study design has its limitations like confounding and information bias. The fact that hospital notes are sometimes minimal has resulted in missing data. Because of these limitations, strong conclusions cannot be drawn from our data. However, the above-mentioned findings are quite interesting and might stimulate further (prospective) research on the subject. However, groups of subjects in these studies will need to be extremely large because of the low incidence of complications of ARS.

Conclusions

Severe ARS complications are rare, but they do occur in an otherwise healthy population in an estimated 1:12 000 paediatric and 1:32 000 adult cases in The Netherlands. Severe complications do not seem to be more frequent in this country with very low antibiotic use compared to countries with high antibiotic prescription rates. Our study suggests that antibiotic treatment of ARS in general practice does not play a role in preventing complications.

Declaration

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Appendix 1.

Search terms National Medical Register

- Intracranial diagnoses
  - Bacterial meningitis
  - Intracranial and intraspinal abscess
  - Phlebitis and thrombophlebitis of intracranial venous sinuses
  - Other encephalitis due to infection classified elsewhere
- Nasal diagnoses
  - Acute nasopharyngitis (common cold)
  - Acute sinusitis
- Orbital diagnoses
  - Oedema of eyelid
  - Acute inflammation of the orbit, unspecified
  - Orbital cellulitis/abscess of orbit
  - Orbital periostitis
  - Orbital osteomyelitis
  - Exophtalmus unspecified
  - Orbital oedema or congestion
  - Lateral displacement of the globe

Appendix 2.

Diagnoses in subjects without ARS

Diagnosis	*N*	%
Intracranial diagnoses		
Meningitis, non-sinogenic focus	86	30.9
Intracerebral abscess, non-sinogenic focus	41	14.7
Tumour	8	2.9
Sinus thrombosis, non-sinogenic focus	7	2.5
Epidural empyema, non-sinogenic focus	7	2.5
Subdural empyema, non-sinogenic focus	9	3.2
Hemiplegia, non-sinogenic cause	4	1.4
Subdural haematoma	2	0.7
Cerebellar abscess, dental focus	2	0.7
Commotio cerebri	1	0.4
Orbital diagnoses		
Orbital cellulitis, non-sinogenic focus	19	6.8
Orbital abscess, non-sinogenic cause	4	1.4
Periorbital cellulitis	2	0.7
Evisceratio bulbi due to trauma	2	0.7
Other		
Uncomplicated sinusitis	6	2.2
Otitis media	4	1.4
Ulcerative skin lesions	2	0.7
Mucocele	1	0.4
Furunkel nasi	1	0.4
Sinus cyst	1	0.4
Trigeminal nerve neuralgia	1	0.4
Sepsis	1	0.4
Tracheo-/bronchomalacia	1	0.4
Unknown	66	23.7
Total	278	100