Clinical presentation and microbiology of acute salivary gland infections

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ABSTRACT

INTRODUCTION: Acute salivary gland infections (ASI) have been associated with poor outcome in elderly and postoperative patients. Perioperative care and treatment of co-morbidities have improved considerably, but most of our knowledge regarding ASI dates back several decades. The aim of this study was to describe the microbiology and treatment of ASI in a large post-millennial cohort.

METHODS: All patients with ASI admitted to the Department of Otorhinolaryngology – Head and Neck Surgery, Aarhus University Hospital in the period from 2001 to 2017 were included.

RESULTS: In total, 157 patients with ASI were included. The parotid gland (PG) was affected in 89 (57%) cases and the submandibular gland (SMG) in 68 (43%) cases. The most prevalent bacterial findings were viridans streptococci (25 isolates) and Staphylococcus aureus (19 isolates). S. aureus was almost exclusively found in PG (17/19 cases). S. aureus-positive cases showed a significantly higher inflammatory response than other bacteria (C-reactive protein, p = 0.008 and absolute neutrophil count, p = 0.0108).

CONCLUSIONS: S. aureus is a significant pathogen in ASI and especially in PG cases. Other pathogens may play a role in the development of SMG infections. Based on the bacterial findings in this study, we recommend penicillinase-resistant penicillin as first-line treatment in ASI.

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TRIAL REGISTRATION: not relevant. The Danish Data Protection Agency approved the project.

The history of acute salivary gland infections (ASI) dates to the early 19th century and case reports include the US President Garfield (1831-1881) [1]. ASI are mainly promoted by two mechanisms; the gland's connection with the oral cavity can promote retrograde contamination from the oral microbial flora, while blockage of the salivary duct flow caused by stones, stenosis or tumours can lead to acute suppurative infection. Several factors can affect the pathogenesis in the different glands, and the composition of saliva and anatomical location may play a role in the predilection of certain bacteria in either the parotid (PG) or the submandibular gland (SMG) [2]. Among the more than 700 bacterial species found in the oral cavity, *Staphylococcus aureus* is the most commonly recovered bacterium (50-90% of positive cultures), but a pathogenic role for anaerobic bacteria has also been considered [3].

ASI presents as swelling of the affected gland, pain and often trismus, causing an impaired fluid intake and thus worsening of the condition. ASI patients are often referred to an ear-nose and throat (ENT) specialist for management.

A number of risk factors for bacterial sialadenitis have been identified: dehydration, recent surgery and anaesthesia in combination with medical comorbidities, immune suppression and xerostomia inducing drugs [1]. After introduction of the measles, mumps and rubella vaccine in the childhood vaccination programme, a previous frequent cause of ASI, mumps has almost been eradicated in the Western world. In addition to vaccines, increased use of antibiotics [4] in recent decades may have caused changes in the underlying microbiology and clinical presentation. Unfortunately, recent ASI studies are sparse and casuistic, and most of our knowledge about ASI dates back to studies from the 1960s describing mostly nosocomial infections and postoperative parotitis [5]. As antibiotics are included in the management of ASI along with analgesics, fluids, sialagogues and glandular massage, up-to-date knowledge about the involved microbiology is mandatory to eradicate the infection successfully and to avoid bacterial resistance.

The present study was undertaken to describe the clinical presentation and microbiology associated with ASI in a large post-millennial population.

METHODS

All patients admitted to the Department of Otorhinolaryngology, Head & Neck Surgery, Aarhus University Hospital, in the period from 2001 to 2017, with ASI were retrospectively included in the present study. If patients were admitted for ASI more than once in the inclusion period, only the first contact was registered. Readmissions within the first 30 days were classified as treatment failures and were therefore excluded. Juvenile recurrent parotitis was considered an independent disease and such patients were excluded.

In cases with purulent secretion, swabs were obtained from the glandular ducts or pus material was obtained from surgical incision or aspiration. Culturing and identifying bacteria was part of the routine diagnostic

ORIGINAL ARTICLE

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procedure. Briefly, blood agar, chocolate agar, anaerobic plates and thioglycolate broth were used to culture the specimens. The media were incubated at 35 °C in a carbon-dioxide enriched atmosphere and anaerobically for up to three days. Identification of microorganisms was performed by standard methods [6] (2001-2009) or matrix-assisted laser desorption ionisation-time of flight mass spectrometry (2009-2017).

Information regarding smoking habits was drawn from the Danish Health Authority [7].

Statistical methods

Statistical analyses were performed using Fisher's exact test, Student's t-test for parametric data and the Kruskal-Wallis test for non-parametric data. Assessments of normal distribution of the data were performed using quantile-quantile plots. Statistical significance was set to a $p < 0.05$.

Ethical considerations

The study was approved by the Danish Data Protection Agency. In accordance with Danish law, the study was not reported to the local ethical committee.

Trial registration: not relevant.

RESULTS

In total, 157 (78 males) consecutive cases of ASI were eligible for the study (**Figure 1**). Thus, the mean annual incidence was 1.4/100,000/year whereof 14/157 were children (under the age of 18 years). PG was affected in 89 (57%) cases and SMG in 68 (43%) cases. The median age was 53 years (range: 3-93 years), the median duration of symptoms was four days (range: 1-30 days), and the median duration of admission was three days (range: 1-12 days). The duration of admission was significantly longer in PG cases than in SMG cases ($p = 0.039$, Kruskal-Wallis test). No statistically significant difference was found between the two glands concerning C-reactive protein ($p = 0.09$, Kruskal-Wallis test) or absolute neutrophil count ($p = 0.28$, Student's t-test) (**Table 1**). None of the patients had undergone surgery prior to admission. Thirteen patients (8%) had active acute medical diseases such as pneumonia or erysipelas at the time of admission.

Information about the patients' smoking habits and medical history was available in 131/157 (83%) and 132/157 (84%) of patients, respectively. In total, 44/131 (34%) had a daily use of tobacco and 19/132 (15%) received antidepressants or antipsychotics drugs daily, whereas 15/132 (11%) received diuretics (Table 1**)**.

Sialolithiasis was found in 33 (21%) patients. Statistically significantly more stones were found in Warthon's duct (27/68, 40%) than in Stensen's duct (6/89, 7%) ($p < 0.0001$, Fisher's exact test). Surgical interventions were performed in 55 (35%) patients. Classification of interventions and glands are shown in Table 1. Abscess was found in 24 (28%) patients with PG infection and in 12 (17%) patients with SMG infection ($p = 0.185$, Fisher's exact test).

Antibiotic therapy

Prior to admission, antibiotics were prescribed to 66% of patients. In 48% of cases, phenoxymethyl-penicillin was the drug of choice. During hospitalisation and upon discharge, 99% and 95% of the patients received antibiotics, respectively. During hospitalisation, the most frequently used antibiotics were benzyl-penicillin (19%), benzyl-penicillin + metronidazole (19%), dicloxacillin (15%), cefuroxime + metronidazole (12%) and cefuroxime (6%). Upon discharge, phenoxymethyl-penicillin (24%), dicloxacillin (21%) and amoxicillin (16%) were the most frequently prescribed antibiotics.

FIGURE 1 / Number of acute salivary gland infection patients admitted to the Department of Otorhinolaryngology – Head and Neck Surgery, Aarhus University Hospital in the study period.

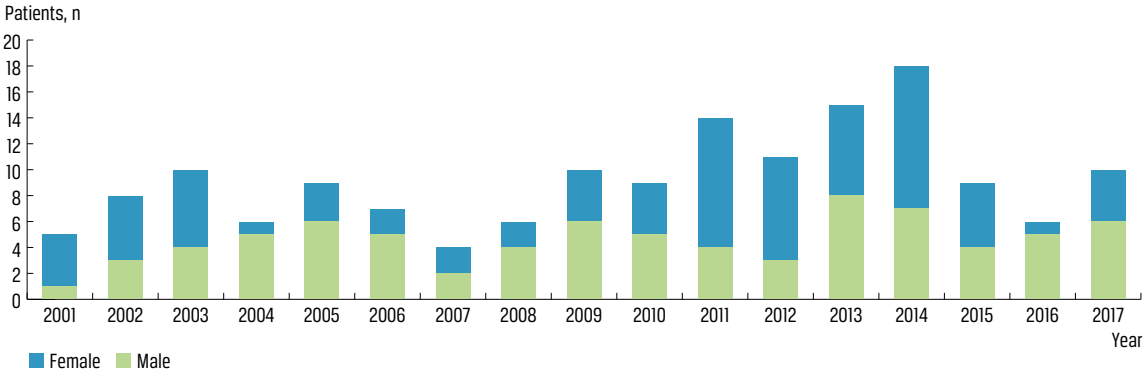

TABLE 1 / Demographic, antimicrobial therapy, biochemical data and surgical interventions in 157 patients with sialadenitis stratified by gland and type of infection.

	Parotid gland		Submandibular gland		
	abscess (n = 24)	inflammation (n = 65)	abscess (n = 12)	inflammation (n = 56)	Total
Males, n (%)	14 (58)	31 (48)	9 (75)	24 (43)	78 (50)
Age, yrs, median (range)	64.5 (37-91)	48 (3-93)	56 (32-82)	47.5 (7-93)	53 (3-93)
Duration of symptoms, days, median (range)	6.5 (2-30)	3 (1-12)	6.5 (1-21)	4 (1-28)	4 (1-30)
Antibiotics, %					
Prior admission	71	71	58	59	66
During admission	100	98	100	96	99
Upon discharge	96	91	100	88	95
Duration of admission, days, median (range)	4.5 (2-12)	3 (1-9)	3.5 (2-8)	3 (2-8)	3 (1-12)
CRP concentration, mg/l, mean (± SD)	133 (± 112)	95 (± 79)	96 (± 76)	79 (± 77)	95 (± 85)
Absolute neutrophil count, × 10^9/l, mean (± SD)	9.5 (± 4.8)	9.5 (± 5.3)	10.0 (± 3.0)	8.4 (± 4.3)	9.1 (± 4.7)
Smoker, %	45	31	55	26	34
Sialolithiasis, n (%)	4 (17)	2 (3)	3 (25)	24 (43)	33 (21)
Medicine, %					
Antidepressants and antipsychotics	5	15	17	18	14
Diuretics	14	13	17	7	11
Surgical intervention, n					
Transoral duct opening	1	1	4	16	22
External incision	15	1	5	1	22
Gland resection	0	0	3	1	4
Fine needle aspiration only	7	0	0	0	7

CRP = C-reactive protein; SD = standard deviation.

Microbial findings

Samples were collected in 90 (57%) cases. More than one pathogen was found in 24% of the cultures. The most common pathogens were viridans streptococci (25 isolates) and *S. aureus* (19 isolates) (**Table 2**). *S. aureus* was almost exclusively found in PG (17/19 cases), whereas isolates with viridans streptococci were more equally distributed between the glands (PG: 14 isolates and SMG: 11 isolates).

A statistically significantly longer duration of admission was seen in *S. aureus*-positive cases than in cases with infections caused by other bacteria (p = 0.0015, Kruskal-Wallis), and a statistically significantly higher inflammatory response was observed for the two groups: C-reactive protein (p = 0.008 Kruskal-Wallis) and absolute neutrophil count (p = 0.0108, Student's t-test) (**Table 3**).

DISCUSSION

The purpose of this study was to describe the clinical presentation and microbiology of ASI in a post-millennial population treated at a tertiary university clinic.

Previously, patients with ASI have been described as being either young (with a viral pathogenesis) or elderly (with a bacterial pathogenesis) [8]. We found a mean age of 53 years, and only 8% had active medically predisposing factors, and the majority of the cases were admitted from their own home. The percentage of active smokers was found to be higher in ASI patients (34%) than in the Danish population in general (16%) [7], and the abscess groups in particular showed a high prevalence of smokers (46% and 55% in the PG and SMG group, respectively). Smoking is known to promote

TABLE 2 / Bacterial findings in 90 patients with sialadenitis. The values are n (%).

	Parotid gland		Submandibular gland	
	abscess	Stensen's duct	abscess	Wharton's duct
Cultures:	23	32	9	26
Positive cultures	16 (70)	19 (59)	8 (89)	10 (38)
With polymicrobiology	4 (17)	9 (28)	3 (33)	6 (23)
Staphylococcus aureus	6 (26)	11 (34)	0	2 (8)
Streptococci:				
Viridans	5 (22)	9 (28)	4 (44)	8 (31)
Pyogenic	1 (4)	1 (3)	2 (22)	0
Streptococcus pneumoniae	1 (4)	0	0	0
Haemophilus influenzae	0	0	0	1 (4)
Fusobacterium necrophorum	0	1 (3)	0	0
Other species with oral origin[a]	10 (43)	16 (50)	4 (44)	20 (77)
Mixed anaerobic flora	3 (13)	1 (3)	3 (33)	2 (8)
Other[b]	4 (17)	4 (17)	0	1 (4)

a) *Neisseria* sp., coagulase-negative staphylococci, *Veillonella* sp., *Aggretibacter* sp., *Eikenella* sp.
b) Enterobacterales, enterococci, fungi.

TABLE 3 / Demographic and clinical data from patients with sialadenitis divided in infections caused by *Staphylococcus aureus*, other bacteria and bacteria with oral origin/no samples.

	Staphyloccus aureus				Other bacteria				Oral origin/no samples			
	parotid gland		submandibular gland		parotid gland		submandibular gland		parotid gland		submandibular gland	
	abscess (n = 6)	inflammation (n = 11)	abscess (n = 0)	inflammation (n = 2)	abscess (n = 10)	inflammation (n = 8)	abscess (n = 8)	inflammation (n = 8)	abscess (n = 8)	inflammation (n = 46)	abscess (n = 4)	inflammation (n = 46)
Age, yrs, median (range)	60.5 (37-82)	77 (40-93)	-	49.5 (20-79)	67 (42-91)	51 (21-91)	53 (32-77)	50.5 (7-73)	65 (52-69)	31 (3-83)	63 (55-82)	47.5 (9-92)
Duration of symptoms, days, median (range)	6 (4-30)	3.5 (1-7)	-	1.5 (1-2)	5 (2-14)	4 (1-9)	7 (4-21)	4 (1-16)	7.5 (2-30)	3 (1-12)	3.5 (1-9)	4 (1-28)
Duration of admission, days, median (range)	7 (6-10)	6 (3-9)	-	3.5 (3-4)	4.5 (2-10)	4 (2-5)	4 (3-8)	3 (2-5)	3 (2-12)	3 (1-6)	3 (2-4)	3 (2-8)
CRP concentration, mg/l, mean (± SD)	219 (± 144)	170 (± 71)	-	79 (± 109)	120 (± 103)	77 (± 53)	103 (± 82)	88 (± 88)	85 (± 60)	80 (± 75)	82 (± 71)	77 (± 76)
Absolute neutrophil count, $\times 10^9$/l, mean (± SD)	13.0 (± 4.5)	14.9 (± 4.8)	-	7.6 (± 2.0)	10.3 (± 3.9)	9.7 (± 1.9)	11.1 (± 2.9)	9.7 (± 4.8)	5.7 (± 3.6)	8.3 (± 5.2)	7.7 (± 1.7)	8.1 (± 4.3)

CRP = C-reactive protein; SD = standard deviation.

upper airway infections and we have previously shown that smoking promotes peritonsillar abscess [9]. In this study, smoking was associated with abscess formation in both PG and SMG infections.

In our study, 14% received antidepressants or antipsychotics. This proportion was statistically – non-significantly larger (p = 0.453, Fisher's exact test) in the SMG group (18%) than in the PG group (12%). Several types of antidepressants and antipsychotics are known to have an anticholinergic effect, thus reducing saliva production and potentially changing the oral microbial flora and promoting ASI. From 2001 to 2017, the use of antidepressants in Denmark increased by 43%; and in 2017, 4% of the Danish population received selective serotonin reuptake inhibitor (SSRI) treatment [10]. In our study, 6% (8/132) received SSRI.

The microbiology in both SMG and PG patients showed a large variety of bacterial species. *S. aureus* was the most frequent pathogen cultured (20%), whereas other potential pathogens such as pyogenic streptococci, pneumococci, *Haemophilus influenzae* or *Fusobacterium necrophorum* were only rarely isolated (Table 2). Of interest, *S. aureus* was more frequent in the PG group (31%) than in the SMG group (6%), whereas viridans streptococci was the most frequent isolate in SMG infections (37%). *S. aureus*-positive cases showed a higher inflammatory response, and *S. aureus* positive patients were hospitalised for statistically significantly longer periods than *S. aureus*-negative cases (p = 0.0108), which indicates that *S. aureus* is a true pathogen and not merely contamination. Even so, it is noteworthy that *S. aureus* was isolated from a relatively low number of abscess cases.

Since the 1960s, *S. aureus* has been described as the major pathogen in bacterial parotitis [5, 11, 12]. In 2002, Brook highlighted the polymicrobial nature of bacterial parotitis, and found anaerobic bacteria in 41% of aspirates from ASI [13]. In our study, *S. aureus* was the major pathogen in PG cases, but was rarely recovered from SMG cases. *S. aureus* has several virulence factors; and in our study, the bacteria seemed to produce a higher inflammatory response than in cases caused by other pathogens.

In their review, Smith et al described the ecology of staphylococcus species in the oral cavity [14]. They found that *S. aureus* was frequently found in gingivitis and periodontal disease. Unfortunately, we were unable to investigate oral hygiene and dental status in relation to ASI in the present study.

Drainage was carried out in abscess cases. In SMG infections where sialolithiasis was found, intraoral opening of the duct and removal of the stone in local anaesthesia was preferable. In this study, 20 cases with SMG infections underwent this procedure. In PG infections, abscesses were either drained by external incision or fine-needle aspiration (FNA). No damage to the facial nerve was observed in any of the cases requiring surgery. None of the patients who had only FNA performed were registered with treatment failure. Therefore, the risk of nerve damage should be taken into consideration when choosing the surgical strategy as FNA seems to be adequate in selected PG infections. The antibiotics prescribed were quite heterogenic, but penicillin as monotherapy was the most frequently prescribed antibiotic – 32% before admission, 19% during admission and 24% upon discharge.

Most of our knowledge regarding pathogens in ASI is from PG infections, whereas information on the microbiology in SMG infections is sparse. With next-generation sequencing techniques, the diversity of the oral microbial flora has become more evident, and some bacteria seem to be more abundant in some people and

even be selective to different subsites in the oral cavity [15, 16]. Sampling within the oral cavity without contamination from the normal oral flora can be difficult, wherefore samples with swaps from Stensen's and Wharton's ducts are more unreliable than pus aspirates. New sampling techniques combined with 16S RNA bacterial testing may yield a different or a more complex composition of pathogens in the future.

This study had a number of limitations. As the treatment of ASI is often conservative, non-ENT wards may be able to treat the condition; and if patients with mild ASI were treated in other departments, this would lead to an underestimation of the number of ASI cases. Microbiological sampling with swaps from the mucosal surface around the ducts may have been contaminated with normal oral flora. Prescription of antibiotics prior to sampling may have affected the proportion of positive samples, but information about compliance with and duration of antibiotics prior to sampling was not available. Comparison between active smokers and SSRI users among ASI patients and the general Danish population is marred by several potential confounders due to the limited reliability of patient-reported data in non-anonymous settings.

The number of consecutive cases was a strength in this study. The inclusion period is also a strength as the study takes into account all data from 2001 to2017, thus giving us an up-to-date status on ASI in Denmark.

CONCLUSIONS

To our knowledge, the present study describes the largest population suffering from ASI in Denmark. Patient characteristics have changed since the 1960s and only 1-2 of 100,000 Danish inhabitants per year are admitted to hospital due to ASI. Our study emphasises *S. aureus* as a significant pathogen in PG infections, but also raises the question if PG and SMG infections are caused by the same pathogens. Future studies should include more advanced microbiological testing (16S sequencing). Antibiotic treatment should address the affected gland and the potential pathogens. As *S. aureus* seems to cause more severe cases with a higher inflammatory response and prolonged duration of admission, sampling for cultures prior to antibiotic prescription is important to identify potentially complicated cases and clarify antibiotic resistance in potential pathogens. Based on this study, we recommend penicillinase-resistant penicillin as first-line treatment.

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