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Submandibular space infection: a potentially lethal infection

Paolo Boscolo-Rizzo *, **Maria Cristina Da Mosto**

Department of Medical and Surgical Specialities, Otolaryngology Clinic — Regional Center for Head and Neck Cancer, University of Padua, School of Medicine, Treviso Regional Hospital, Treviso, Italy

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Summary
Objectives: The aims of this study were to review the clinical characteristics and management of submandibular space infections and to identify the predisposing factors of life-threatening complications.
Design and methods: This was a retrospective study at a tertiary academic center. We retrieved and evaluated the records of all patients admitted to the University of Padua Otolaryngology Clinic at Treviso Regional Hospital with the diagnosis of submandibular space infection for the period 1998—2006. The following variables were reviewed: demographic data, pathogenesis, clinical presentation, associated systemic diseases, bacteriology, imaging studies, medical and surgical treatment, and complications. A multivariate logistic regression analysis was undertaken using a forward stepwise technique.
Results: Multivariate analysis identified four risk factors for complications. Anterior visceral space involvement (odds ratio (OR) 54.44; 95% confidence interval (CI) 5.80—511.22) and diabetes mellitus (OR 17.46; 95% CI 2.10—145.29) were the most important predictive factors in the model. Logistic regression analysis also confirmed other comorbidities (OR 11.66; 95% CI 1.35—100.10) and bilateral submandibular swelling (OR 10.67; 95% CI 2.73—41.75) as independent predictors for life-threatening complications.
Conclusions: Airway obstruction and spread of the infection to the mediastinum are the most troublesome complications of submandibular space infections. Therefore, the maintenance of a secure airway is paramount. Patients with cellulitis and small abscesses can respond to antibiotics alone. Surgical drainage should be performed in patients with larger abscesses, Ludwig's angina, anterior visceral space involvement, and in those who do not respond to antibiotic treatment. Moreover, the clinical assessment in patients with comorbidities, especially diabetes mellitus, requires a high level of suspicion for potential life-threatening complications. Early surgical drainage should always be considered in these patients, even in seemingly less critical cases.

* Corresponding author. Tel.: +39 0422 322320; fax: +39 0422 322379.
E-mail address: paolo.boscolorizzo@unipd.it (P. Boscolo-Rizzo).

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Introduction

Despite a decrease in the incidence and mortality of deep neck infections (DNIs) as a result of the advent of antibiotics and improved dental care, these infections are not unusual and present a challenging problem because of the complex anatomy and potentially fatal complications that may occur.[1–6]

The deep neck spaces are regions of loose connective tissue filling the areas between the three layers of deep cervical fascia (superficial, middle, and deep layer). The fascial layers may limit the spread of infection. However, the spaces of the neck communicate with one another forming avenues by which infections may spread over large areas.[7] An unsuspecting physician may underestimate an initially localized infection, which could shortly present as airway collapse or descending mediastinitis.

Several reports have indicated that the origins of most DNIs are odontogenic infections. Consistent with this finding, the submandibular space is frequently involved in these infections.[4,6,8,9] The submandibular space is limited above by the oral mucosa of the floor of the mouth and below by the superficial layer of the deep cervical fascia as it extends from the mandible to the hyoid bone. Mylohyoid muscle divides the submandibular space into the sublingual or superior space, containing the sublingual glands, the deep smaller portion of the submandibular gland, and Wharton's duct, and the submaxillary or inferior space, containing the larger superficial portion of the submandibular space and its lymph nodes. These spaces communicate freely around the posterior border of the mylohyoid muscle. The submaxillary space may be further divided into a central submental space, between the anterior bellies of the digastric muscles, and lateral submaxillary spaces.[7]

As well as occurring secondary to dental infections, submandibular space infections may be a consequence of submandibular gland sialadenitis, lymphadenitis, trauma, or surgery. Furthermore, the submandibular space may be involved secondary to an infection that has developed in other deep neck spaces. Ludwig's angina is a potentially life-threatening bilateral diffuse gangrenous cellulitis of the submandibular and sublingual spaces.[10] It is named after the German physician, Wilhelm Frederick von Ludwig who first described this entity in 1836. In this condition, swelling of the submandibular tissues occurs rapidly and may cause an elevation of the tongue with consequent respiratory distress.[10]

The aims of this study were to review the clinical characteristics and management of submandibular space infections and to identify the predisposing factors of life-threatening complications.

Patients and methods

We retrieved and evaluated the records of all patients admitted to the University of Padua Otolaryngology Clinic at Treviso Regional Hospital with the diagnosis of submandibular space infection for the period 1998—2006.

Clinical charts and imaging and bacteriologic studies were reviewed. Patients with head and neck cancer or post-traumatic submandibular space infections were not included in the study. The following variables were reviewed: demographic data, pathogenesis, clinical presentation, associated systemic diseases, bacteriology, imaging studies, medical and surgical treatment, and complications.

All patients underwent contrast-enhanced computed tomography (CECT). Three-mm slides from the skull base to the superior mediastinum were obtained before and after contrast injection using either the spiral or multi-slice technique. The CECT scan was interpreted as demonstrating an abscess in the presence of an enhancing rim around non-enhancing central density consistent with fluid. The initial CECT scan was extended to include the chest in cases of suspected descending infection. The character of the infection was confirmed by needle aspiration or surgery.

The infection was categorized according to its character (cellulitis versus abscess), side (monolateral, bilateral), and to the other involved spaces (lateral pharyngeal space, retropharyngeal space, prevertebral space, parotid space, masticatory space, visceral vascular space, anterior visceral space). Patients with involvement of two or more spaces were classified as having multiple space infections.

On admission, all patients were placed on intravenous antibiotics. Patients who were clinically unstable (compromised airway, signs and symptoms of sepsis), patients with a descending infection, patients with anterior visceral space involvement, with the abscess involving more than two deep neck spaces, and patients with an abscess larger than 3.0 cm, underwent immediate surgical drainage. In all the other cases, patients were observed for 48 hours. If the patient's symptoms and signs worsened or if no clinical improvement was noted after 48 hours, surgical drainage was performed. On the other hand, if a clinical response was seen, a CECTwas repeated to confirm the clinical judgment. If the repeat CECT did not confirm a regression of collection of pus, surgical intervention was considered. In selected cases, therapeutic needle aspiration of the abscess was considered an alternative to conventional open surgery.

The following parameters were analyzed in order to identify potential risk factors for life-threatening complications: gender, age, diabetes mellitus, other associated diseases, character of infection, type and side of submandibular involvement, anterior visceral space involvement, presence of trismus, fever $>38.0\ ^{\circ}C$, and white blood cell count $>12 \times 10^9/l$.

Fisher's exact test, the Chi-square test, and odds ratios (OR) with 95% confidence intervals (95% CI) were used to compare categorical data. A multivariate logistic regression analysis was undertaken using a forward stepwise technique, in which those risk factors significant in the univariate analysis were included, in order to identify independent risk factors for complications. Tests were two-tailed, and levels of statistical significance have been calculated at the 5% level of probability. Statistical analysis was performed using the SPSS/PC software package (SPSS Inc., Chicago, IL, USA) and the confidence interval analysis program CIA.

Results

Patient characteristics

All descriptive data are reported in Table 1. A total of 81 patients with a submandibular space infection were identi-

Table 1 Descriptive data for the 81 patients with a submandibular space infection.

Variables	Categories	*n*	%
Sex	Females	39	48.1
	Males	42	51.9
Age (years)	<65	56	69.1
	≥ 65	25	30.9
Diabetes mellitus	No	68	84.0
	Yes	13	16.0
Other comorbidities	No	68	84.0
	Yes	13	16.0
Pathogenesis	Odontogenic	38	46.9
	Submandibular sialadenitis	12	14.8
	Pharyngitis	5	6.2
	Parotitis	3	3.7
	Unknown	23	28.4
Character of infection	Abscess	40	49.4
	Cellulitis	41	50.6
Type of submandibular involvement	Primary	68	84.0
	Secondary	13	16.0
Side of the submandibular swelling	Monolateral	66	81.5
	Bilateral	15	18.5
Involvement of other spaces	No	57	70.4
	Yes	24	29.6
Visceral anterior space involvement	No	71	87.7
	Yes	10	12.3
Neck swelling	No	1	1.2
	Yes	80	98.8
Trismus	No	67	82.7
	Yes	14	17.3
Pharyngodynia	No	61	75.3
	Yes	20	24.7
Dysphagia	No	52	64.2
	Yes	29	35.8
Dysphonia	No	68	84.0
	Yes	13	16.0
Dyspnea	No	69	85.2
	Yes	12	14.8
Fever ($>38.0\ ^{\circ}C$)	No	62	76.5
	Yes	19	23.5
WBC $>12 \times 10^9/l$	No	51	63.0
	Yes	30	37.0
Complications	No	69	85.2
	Yes	12	14.8
Treatment	Medical alone	56	69.1
	Medical and surgical	25	30.9

WBC, white blood cell count.

fied for this evaluation. The 81 patients consisted of 42 males (51.9%) and 39 females (48.1%) ranging in age from 12 to 96 years (median 57 years). On admission, neck swelling (98.8%, *n* = 80) and dysphagia (35.8%, *n* = 29) were the most common symptoms present. The pathogenesis of infection was identified in 58 patients (71.6%); the most common cause was a dental infection (46.9%, *n* = 38). The pathogenesis remained unknown in 23 patients (28.4%). The submandibular space was the primary site of infection in 68 patients (84.0%). In 13 cases (16.0%), the submandibular space was involved secondary to an infection of the lateral pharyngeal and parotid spaces. In 24 patients (29.6%) the infection involved more than one deep space. A submandibular space infection was more commonly associated with an infection of the lateral pharyngeal spaces (22.2%, *n* = 18). None of patients with lateral pharyngeal space involvement had a visceral vascular space infection with jugular vein thrombosis (Lemierre's syndrome). No prevertebral space infections were observed. The distribution of the spaces involved is shown in Table 2. An abscess was present in 40 patients (49.4%) and cellulitis in 41 patients (50.6%). Twenty-four patients had an associated systemic disease (29.6%). Diabetes mellitus was the most common associated systemic disease occurring in 13 patients (16.0%).

Table 2 Distribution of the deep neck infections (81 patients).

Space	*n*	%
Submandibular space	81	100.0
Lateral pharyngeal space	18	22.2
Anterior visceral space	10	12.3
Parotid space	5	6.2
Masticatory space	1	1.2
Retropharyngeal space	1	1.2

The sum of the percentages exceeds 100 as 24 patients had multiple space involvement.

Microbiology

Microbiological diagnosis was successful in 42 patients (51.9%; Table 3). Anaerobic cultures were not carried out in all cases. Blood cultures were obtained only from more critical patients.

Treatment and incidence of complications

The most frequently used treatment regimen, alone or in combination, was amoxicillin/clavulanate potassium (69.1%, *n* = 56). Second- and third-generation cephalosporins were used in 12 patients (14.8%), metronidazole in 10 (12.3%), clindamycin in nine (11.1%), ampicillin/sulbactam in eight (9.9%), and vancomycin in a single case; these were used to eradicate both aerobic and anaerobic microorganisms.

Twenty-five patients (30.9%) underwent cervical surgical drainage. Twelve patients (14.8%) developed life-threatening complications (Table 4). All these patients underwent cervical surgical drainage; two patients underwent thoracotomy, four patients required a tracheostomy, and three patients underwent fiberoptic intubation.

Table 3 Microbiological findings.

Microorganism cultured	*n*	%[a]
Coagulase-negative staphylococci	16	38.1
Staphylococcus aureus	13	31.0
Streptococcus viridans not typed	10	23.8
Bacteroides spp	4	9.5
Haemophilus influenzae	4	9.5
Peptostreptococcus spp	3	7.1
Klebsiella pneumoniae	3	7.1
Fusobacterium nucleatum	1	2.4
Group F Streptococcus	1	2.4
Gemella morbillorum	1	2.4

The sum of the percentages exceeds 100 because of polymicrobial infections.
[a] Of 42 patients with positive cultures.

Predictors of complications

Univariate analysis (Table 5) showed that age ≥65 years (OR 6.12; 95% CI 1.63—22.89), diabetes mellitus (OR 9.00; 95% CI 2.08—38.95), others comorbidities (OR 5.44; 95% CI 1.72—17.17), secondary submandibular infection (OR 4.76; 95% CI 1.53—14.77), bilateral submandibular swelling (OR 10.67; 95% CI 2.73—41.76), multiple space involvement (OR 10.80; 95% CI 2.59—44.97), and anterior visceral space involvement (OR 26.80; 95% CI 5.95—120.76) significantly correlate with the rate of complications. Results of the multivariate analysis are shown in Table 6. Four risk factors of complications were identified. Anterior visceral space involvement (OR 54.44; 95% CI 5.80—511.22) and diabetes mellitus (OR 17.46; 95% CI 2.10—145.29) were the most important predictive factors in the model. An anterior visceral space involvement was identified in 10 patients. The etiology of the infection was identified in only five patients:

Table 4 Characteristics of patients with life-threatening complications.

Case	Age	Sex	Spaces	Microbiology	Pathogenesis	Complications	Treatment	Outcome
1	70	M	Pp—Sm—Avs	*Klebsiella pneumoniae*	Unknown	Airway obstruction	Drainage	Good
2	73	M	Pp—Sm—Avs	No growth	Unknown	Airway obstruction	Drainage	Good
3	75	M	Sm—Pp—Rp	*Gemella morbillorum*	Odontogenic	Mediastinitis, pneumonia	Tracheotomy, drainage	Good
4	54	F	Sm—Avs	Group F Streptococcus	Odontogenic	Airway obstruction, sepsis	Tracheotomy, drainage	Good
5	85	F	Sm—Avs	No growth	Odontogenic	Airway obstruction	Drainage	Good
6	67	M	Pp—Sm	No growth	Pharyngitis	Airway obstruction	Drainage	Good
7	44	M	Sm—Avs	No growth	Odontogenic	Airway obstruction	Drainage	Good
8	70	M	Sm—Avs	*Peptostreptococcus spp*	Odontogenic	Airway obstruction	Intubation, drainage	Good
9	57	F	Sm	No growth	Sialadenitis	Airway obstruction	Tracheotomy, drainage	Good
10	78	M	Pp—Sm	No growth	Parotitis	Airway obstruction	Intubation, drainage	Good
11	65	F	Sm—Pp	*Streptococcus viridans*	Unknown	Airway obstruction	Intubation, drainage	Good
12	59	M	Pp—Sm—Avs	No growth	Unknown	Mediastinitis	Tracheotomy, drainage	Good

Pp, parapharyngeal space; Sm, submandibular space; Avs, anterior visceral space; Rp, retropharyngeal space.

Table 5 Patient characteristics and complications (univariate analysis).

Variables	Categories	With complications	Without complications	*p*-Value	OR (95% CI)
Sex	Males	8	34	0.266 [a]	2.06 (0.57–7.48)
	Females	4	35		
Age (years)	≥65	8	17	0.006 [b]	6.12 (1.63–22.89)
	<65	4	52		
Diabetes mellitus	Yes	5	7	<0.001 [b]	9.00 (2.08–38.95)
	No	5	63		
Other comorbidities	Yes	8	5	0.021 [b]	5.44 (1.72–17.17)
	No	7	61		
Character of infection	Abscess	6	34	0.963 [a]	1.03 (0.30–3.51)
	Cellulitis	6	35		
Type of submandibular involvement	Secondary	60	9	0.029 [b]	4.76 (1.53–14.77)
	Primary	7	5		
Side of the submandibular swelling	Bilateral	7	8	0.001 [b]	10.67 (2.73–41.76)
	Monolateral	5	61		
Involvement of other spaces	Yes	9	15	0.001 [b]	10.80 (2.59–44.97)
	No	3	54		
Anterior visceral space involvement	Yes	8	2	<0.001 [b]	26.80 (5.95–120.76)
	No	4	67		
Trismus	Yes	1	13	0.681 [b]	0.39 (0.05–3.31)
	No	11	56		
Fever (>38.0 °C)	Yes	2	17	0.722 [b]	0.61 (0.12–3.07)
	No	10	52		
WBC $>12 \times 10^9$/l	Yes	6	24	0.345 [b]	1.87 (0.54–6.45)
	No	6	45		

OR, odds ratio; CI, confidence interval; WBC, white blood cell count.
[a] Chi-square test.
[b] Fisher's exact test.

dental infections in three cases and submandibular sialadenitis in two cases. Diabetic patients tended to have a higher prevalence of anterior visceral space involvement (Fisher's exact test, $p = 0.008$).

Logistic regression analysis also confirmed other comorbidities (OR 11.66; 95% CI 1.35–100.10) and bilateral submandibular swelling (OR 10.67; 95% CI 2.73–41.75) as independent predictors for life-threatening complications.

Discussion

The management of DNIs remains particularly troublesome due to the complex anatomy of the neck, polymicrobial etiology, and life-threatening complications that may arise.[1–6] Furthermore, the inappropriate use of antibiotics, steroids, and nonsteroidal anti-inflammatory drugs may mask signs of infection and change the clinical presentation, making it more elusive, and also lead to a slow course of disease, delayed recovery, and the development of complications.[6]

The mainstay of treatment of DNIs consists of airway control, antibiotic medical treatment, and, if necessary, surgical drainage. The maintenance of a safe and secure airway is mandatory in submandibular space infections. In patients with bilateral submandibular swelling, an airway obstruction can be the result of the tongue pushing against the roof of the mouth and the posterior pharyngeal wall, or be a consequence of anterior visceral space involvement with laryngeal edema.[6,10]

In multivariate analysis, anterior visceral space involvement was the most important independent factor in predicting life-threatening complications, including airway obstruction. In seven cases, anterior visceral space involvement occurred in association with an infection of both the submandibular and lateral pharyngeal space. Both these spaces communicate inferiorly with the anterior visceral space, representing a route of spread of these infections. The anterior visceral space extends from the hyoid bone down to the superior mediastinum. This space contains the

Table 6 Patient characteristics and complications (multivariate analysis).

Variables	Regression coefficient	*p*-Value	OR (95% CI)
Diabetes mellitus	2.86	0.008	17.46 (2.10–145.29)
Other comorbidities	2.46	0.025	11.66 (1.35–100.10)
Bilateral submandibular swelling	2.36	0.001	10.67 (2.73–41.75)
Anterior visceral space involvement	3.99	<0.001	54.44 (5.80–511.22)

OR, odds ratio; CI, confidence interval.

larynx, thyroid gland, trachea, and cervical esophagus. Therefore, this space may play a key role in determining airway obstruction as well as the spread of infection to the anterior mediastinum.

Conventional endotracheal intubation and tracheotomy under general anesthesia may be problematic, notably in patients with Ludwig's angina. Considering that patients with airway collapse are not infrequently diabetic with morbid obesity, attempts at airway management may be heroic. Therefore, airway control remains a challenging task for otolaryngologists and anesthesiologists. Awake tracheotomy under local anesthesia, blind nasal intubation, and intravenous or gaseous induction followed by laryngoscopy and intubation are possible, but not risk-free, options for managing airways in patients with DNIs.[11] Fiberoptic guided awake endotracheal intubation is considered a more appropriate procedure for many anesthesiologists faced with treating a cooperative patient with an upper airway obstruction.[12] This procedure allows spontaneous breathing to be maintained during intubation and enables the surgeon to explore an anatomically distorted upper aerodigestive tract. The procedure is operator-dependent and relies on the adequate preparation of the patient.[11]

In agreement with others reports,[1,4,8,9] dental infection was the most common cause of submandibular space infections found. The cause of the infection was not identified in 28.4% of cases. A proportion of these patients may have had a suppuration of the deep lymph nodes not recognized in clinical and imaging studies. No cases due to acute suppurative thyroiditis or to infection of congenital cysts of the neck were observed.

With the exception of prevertebral space infection secondary to hematogenous vertebral osteomyelitis mostly due to *Staphylococcus aureus*, no correlation usually exists between the anatomical region and microbiology of neck space infections. The microbiological pattern of DNIs is generally polymicrobial, including aerobes and anaerobes. As a consequence, an empiric antibiotic therapy should be targeted at aerobic and anaerobic pathogens.

The predominant anaerobic organisms isolated in deep neck infections are *Prevotella*, *Porphyromonas*, *Fusobacterium*, and *Peptostreptococcus spp*; aerobic organisms are group A streptococcus, viridans streptococci, *Staphylococcus aureus*, and *Haemophilus influenzae*. More than two thirds of deep neck infections contain beta-lactamase producing organisms. The most efficacious antimicrobial agents comprise the combination of a penicillin and a beta-lactamase inhibitor (amoxicillin/clavulanate, ticarcillin/clavulanate, piperacillin/tazobactam), cefoxitin, carbapenem, or clindamycin.[13,14] Macrolides or ketolides plus metronidazole should be considered in patients with a penicillin allergy.

In this series, no bacterial growth was observed in 39 patients, and anaerobes were isolated in only a few cases. A number of factors may have affected the results of microbiological tests: the use of antibiotics prior to admission, high-dosage intravenous antibiotics prior to surgical drainage, improper collection of specimens, and no routine use of anaerobic cultures, as well as difficulty in culturing anaerobes.

Coagulase-negative Staphylococcus was the most common isolate found and was identified in 38.1% of positive cultures. Since these bacteria are usually considered contaminants in most cultures and only 24% of our specimens were from intraoperative collection of pus, this high rate of isolation may reflect the collection of contaminated specimens. As the upper aerodigestive tract is colonized with a wide variety of indigenous microorganisms, it is essential to decontaminate the mucous membrane before obtaining material for microbiological culture. *Staphylococcus aureus* was the second most common isolated microorganism in this series. No methicillin-resistant strains (MRSA) were identified. Considering the expanding role of MRSA in suppurative infections, an increasing rate of MRSA deep neck space infections could be expected in the future. Vancomycin, trimethoprim/sulfamethoxazole, rifampin, and linezolid in different associations should be the options considered for the treatment of MRSA in addition to surgical drainage of the abscess.

Appropriate treatment planning for patients with DNIs requires a clear differentiation between cellulitis and abscess. CECT has a critical role in the identification of DNIs, in the differentiation of deep neck abscesses from cellulitis, in delineation of the involved spaces, in the diagnosis of complications, and in checking the evolution of the infection.[15] In studies with large patient numbers, intra-operative findings confirmed the CECT diagnosis in 68—88% of cases.[16,17] The differential diagnosis between abscess and cellulitis is essentially based on subjective findings and is consequently dependent on the level of experience of the radiologist. An area of low attenuation with a complete circumferential rim of enhancement is considered the hallmark of abscess. Unfortunately, CECT findings may be ambiguous in the transition stages from cellulitis to abscess; specifically, a thin or partial enhanced rim may be present in cellulitis.[16] Another subjective finding, a scalloped contour of the ring-enhancing, was recently proved to be highly predictive of the presence of pus (positive predictive value 94%, sensitivity 64%, and specificity 82%).[18]

Since submandibular space infections frequently have a dental origin, acquisition of high-resolution axial scans of the jaw together with curved and orthoradial multiplanar reconstructions (Dentalscan) are advisable in order to identify periapical infections.[19]

Open surgical incision and drainage are considered the mainstay of treatment for submandibular space abscesses and Ludwig's angina. Currently, our philosophy is to treat all patients with large doses of broad-spectrum intravenous antibiotics (e.g., amoxicillin/clavulanate potassium) until culture results identify the causative organism. In cases of large abscesses or multiple space involvement, an open surgical incision and drainage are promptly performed. In patients with small abscesses, a watch and wait policy is applied for 48 hours; if a lack of response to medical treatment is noted both clinically and by CECT, the patient is treated with an open surgical drainage.

In patients with Ludwig's angina, a more aggressive approach is justified, even if areas of colliquation are not evident. These patients are reported to be more at risk than others for adverse complications.[10] This is consistent with our regression results, which showed a significant impact of bilateral submandibular swelling on the rate of complications.

Data showing that patients with diabetes mellitus and other comorbidities are particularly susceptible to DNIs and tend to have a higher rate of life-threatening complications is

confirmed by our univariate and multivariate analysis.[20] In the light of these considerations, particular attention should be paid to diabetics, and an early surgical drainage should also be considered in apparently less severe cases. Comorbidities and immunosuppression from polypharmacy, frequently occurring in older patients, may predispose these patients to more severe infections as well as make clinical presentation more elusive.

In conclusion, submandibular space infections are potentially lethal infections. Physicians should be aware that the clinical status may quickly and unexpectedly worsen.[21] Airway obstruction and spread of infection to the mediastinum are the most troublesome complications. Therefore, the maintenance of a secure airway is paramount and an aggressive treatment is justified. Patients with cellulitis and small abscesses can respond to antibiotics alone. A surgical drainage should be performed in patients with larger abscesses, Ludwig's angina, anterior visceral space involvement, and in those who do not respond to antibiotic treatment. Nonetheless, each case has to be taken on its merit. Specifically, the clinical assessment in patients with comorbidities, especially diabetes mellitus, requires a high level of suspicion for potential life-threatening complications. In these patients an early surgical drainage should always be considered, even in seemingly less critical cases.

Conflict of interest: No conflict of interest to declare.

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