Five Predictors Affecting the Prognosis of Patients with Severe Odontogenic Infections

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Abstract

Background: For over ten years, dental cellulitis management is not so longer simple: more and more patients need long-time hospitalization, several surgical interventions and intensive care follow-up. This prospective study seeks to highlight criteria that can split patients with severe odontogenic infection into two main groups: those with simple evolution after treatment of the infection and those for whom complex management is necessary to obtain healing.

Methods: All patients with severe odontogenic infection (namely patients which necessitated hospital admission, intravenous antibiotherapy and general anesthesia) were prospectively recorded between January 2004 and December 2014. Statistical tests used were: chi-square test (or Fisher's exact test when appropriate) for categorical data, and Student t-test (or Mann & Withney test when appropriate) for continuous data; statistics were computed with STATA V12 (Stata Corp, College Station, Texas, USA) and with R (R version 3.0.2; The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org).

Results: A total of 653 patients were included in the study, 611 (93.6%) had one surgery, 42 (6.4%) had more than one surgery (range 2 – 15 surgeries) before healing. In multivariate analysis, objectives criteria which emerge are: C-reactive protein (CRP) level (CRP>200 mg/l, p=0.01, OR=4.12 IC95%=[1.33-12.72]), alcohol abuse (p=0.03, OR=2.70 IC95%=[1.09-6.7]), penicillin allergy (p=0.001, OR=5.47 IC95%=[1.99-15-09]), mandibular molar infection (p= 0.02, OR=2.74 IC95%=[1.16-6.48]). A conditional inference tree (CTREE) illustrated the association of prognostic factors and the need of multiple surgery.

Conclusion: Four subgroups of patients with severe odontogenic infection have a relative risk range between 25 % and 33% to have several surgical intervention associated with complications as intensive unit care follow-up, tracheotomy or death: 1- patients with CRP>200 mg/l; 2- patients with CRP between 50 and 200 mg/l and penicillin allergy; 3- patients with CRP between 50 and 200 mg/l, without penicillin allergy but with molar mandibular infection and psychiatric disorders; 4- patients with CRP ≤ 50 mg/l or unknown CRP level and immunodepression.

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Background

Long-time ago, odontogenic infections were considered as a severe even a lethal disease. With the advent of antibiotics as penicillin and dental care, they were considered as an easy treatable condition. Basis of the therapy are now well known. Typically infection is attributable to decayed or non-vital teeth, postoperative infections, periodontal disease and inflammation of the pericoronal tissues [1–4]. Surgical incision and drainage of the purulent collections in combination with concerned tooth or teeth extraction, oral cavity rehabilitation and probabilistic antibiotic therapy remain the principles of the treatment [5]. Nevertheless for over ten years, dental cellulitis management is not so longer simple: more and more patients need longtime hospitalization, several surgical interventions and intensive care follow-up to heal

[2,6,7]. The clinical symptoms as dysphonia, dyspnea, anterior floor edema, limitation of tongue protraction, oropharyngeal edema promptly alert Odontologists, Oral and Maxillofacial surgeons on the severity of the infection but are often misjudged in current practice. Moreover patients with few symptoms of severe odontogenic infection may have unfavorable evolution. Many criteria could be involved, the growing number of patients with underlying diseases as alcohol abuse, immunodepression or long-terme diabetes could explain the tendency to more severe infections [2,7,8]. Diagnostic delay with several antibiotics or anti-inflammatory prescription don't cure but lessen the symptoms of the infection.

The present study was conducted to identify objectives and simple preoperative criteria that can split patients with severe odontogenic infection in two main groups: those for whom one surgical intervention with tooth extraction and collection drainage combined with probabilistic antibiotic is enough to treat infection and those for whom several surgical interventions, multiple antibiotic adjustment, intensive care unit follow up and longer hospitalization is necessary to obtain healing. This will allow clinicians to better be able to inform patients about the risks incurred and to better anticipate patient's evolution.

Methods

The aim of this prospective observational study is to identify predictors which may affect the prognosis of patients with severe odontogenic infections

Recruitment

Adult patients who meet the following criteria: odontogenic infection which need hospitalization in our department of Oral and Maxillofacial surgery (Clermont-Ferrand University Hospital, France), intravenous antibiotics and surgical management were enrolled in this study between January 2004 and December 2014. All patients gave informed written consent. Non-inclusion criteria were pregnancy, limitations of self-expression, and patients under tutorship or curatorship.

Patient management

Severe odontogenic infections are managed with a standardized protocol. Medical workup was initially performed, including history, clinical examination, C-Reactive Protein (CRP) assay and anesthesiologist consultation. Preoperative images were dental panoramic and cervicofacial CT-scan. Airways are secured and patient anesthetized. Aseptic conditions required for any surgery were respected, Povidone betadine (ASTA Medica) was used as antiseptic solution to disinfect the facial, cervical area and oral cavity, Chlorhexidine 2% was used in case of allergy to iodine-based products. Causal tooth was extracted to liberate purulent flow. At this time, sampling of pus was performed. Bacteriological sample are cultured in aerobic and anaerobic conditions. Incision, drainage and debridement were performed for all anatomic cervical fascial spaces involved by infection. Collections were drained with intraoral or transcervical or combined approach. Delbet drains were placed through the opened incisions and retained with a suture

to realize large lavages by 0.9% saline. Every day, patients had clinical examination, irrigation and dressing. Postoperative CT-scan, and CRP assay was based on patient's progress. After surgery, all patients were fed by naso-gastric tube to enable drainage and oral healing.

All patients received intravenous probabilistic antibiotherapy effective against oral mucosa flora. The French Health Products Safety Agency [9] (ANSM) recommendations are monoantibiotherapy by Amoxicillin and Clavulanic Acid (1 gramme every 8 hour); in case of penicillin allergy: Clindamycin (300 mg every 8 hours) and Metronidazole (500 mg every 8 hours). Secondly, if necessary, antibiotics were adapted to bacteriological results.

Data collection

The following data were collected for each patient:

- socio-demographic data: age, sex, associate medical condition (penicillin allergy, smoking status, consumption of alcohol, diabetes, asthma, psychiatric disorder);
- number and type of space involved by the infection;
- treatment on admission: ongoing antibiotic (family and duration of treatment) and/or anti-inflammatory treatment (corticosteroids or Nonsteroidal anti-inflammatory drugs, NSAIDs)
- Duration of hospital stay and number of surgery
- Bacteriological results, results of culture and sensitivity, antibiotics adaptation
- Complications [10]

Statistical analysis

Descriptive statistics are expressed as mean and range (min-max), according to their distribution, and number of patients (%) for categorical data. In order to assess the performance of CRP in classifying at-risk patients, namely patients with several surgeries, we used Receiver Operating Characteristic (ROC) curves methods. Aera under the ROC curve is plotted with its 95% confidence interval. Besides, sensivity, specificity, true/false predictive values and positive/negative likelihood ratios are shown at some arbitrary chosen cut-points (>50, >100, >200). Patients at risk to have several surgeries are compared using chi-square test (or Fisher's exact test when appropriate) for categorical data, and using Student t-test (or Mann & Withney test when appropriate) for continuous data. A multivariable logistic regression was performed, adjusted for factors that were statistically significant, factors statistically significant but related to clinical symptoms of severity were deliberately not sample in the multivariate analysis because they are often misjudged, only objectives and simple criteria which emerge were taken in consideration. Adjusted Odd Ratios (aOR) are shown with their 95% confidence interval. In other hand, a conditional inference tree (CTREE) was built to illustrate the association of prognostic factors and the need of several surgeries. Statistics were computed with STATA V12 (Stata Corp, College Station, Texas, USA) and with R

(R version 3.0.2; The R Foundation for Statistical Computing, Vienna, Austria; http://www.r-project.org/). Tests were two-sided and a p-value<0.05 was considered statically significant.

Results

Baseline characteristics.

A total of 653 patients were recorded, 386 (59%) male and 267 (41%) female with a mean age of 37 years (range 8—88). Of them, 375 (57%) were smokers, 78 (12%) were regular drinkers, 54 (8%) were addicts to drugs, 62 (9.5%) had psychiatric disorders and 20 (3%) were immunodepressed. Forty-seven patients (7.2%) were allergic to penicillin.

The average number of visits before hospitalization in our department was 1.7 (range 0 - 7). About the course of care, 338 (51%) patients were directly addressed by the dentist, 237 (36%) by the emergency department and 144 (22%) by the general practitioner and 28 (4%) were addressed otherwise. About 189 (29%) patients have consulted 2 different doctors before being addressed to our department (general practitioner, dentist or emergency doctor), 32 (5%) 3 different doctors and 9 patients at least 4 different doctors (general medical practitioner, general dentist practitioner or emergency practitioner). None of them have had tooth extraction, roots treatment or collection incision.

A total of 378 (64%) patients had antibiotics treatment orally before presenting to hospital. The treatment was prescribed by the general practitioner, the dentist or the emergency doctor or due to self-medication. Treatment duration before presenting to the Oral and Maxillofacial Department was 4.6 days (range 1—60). Most patients (231; 61%) were prescribed Amoxicillin or Amoxicillin and Clavulanic Acid, 75 (20%) an association of spiramycine—metronidazole, 37 (10%) pristinamycine, 36 (9.5%) metronidazole and 2 (0.5%) clindamycine. Among the 47 patients allergic to penicillin, 33 (70%) patients received antibiotics before admission in our Department but only 5 (11%) patients received the first-line antibiotics specifically recommended by ANSM: azithromycine, 500 mg per day or clarithromycine 1000 mg per day or spiramycine 9 MUI per day or clindamycine 1200 mg per day. In the event of treatment failure, métronidazole 1500 mg per day must be add. For all of those patients a new antibiotic therapy was prescribed. A total of 329 (50%) patients had anti-inflammatory treatment orally before presenting to hospital, 50 (7.6%) received corticosteroids, 242 (37%) received NSAIDs and 37 (5.6%) both.

About 645 patients with collected datas, 516 patients (80%) presented during surgery a single facial space involvement by abscess, 95 patients (15%) had 2 spaces involved, 28 (4%) had 3 spaces involved, 5 patients (1%) had 4 spaces involved and 1 patient had 6 spaces involved. The submandibular space and the vestibular space were the most frequently involved with respectively 32% (n = 209) and 28% (n = 182).

Among the 653 patients, 611 (94 %) had no further surgery. Forty-two patients (6%) had more than one surgery (range 2—15 surgeries) to drain all collections, their mean hospitalization duration was 14.6 days

(range 5—37 days). Among this group, 21 were hospitalized in an intensive care unit, 13 needed a tracheotomy and one patient died of acute respiratory distress associated with sepsis.

The results of univariate analysis comparing the 611 patients with single operation and the 42 patients operated several times are displayed in Table 1. In the medical history, alcohol abuse, immunodepression, psychiatric disorder and penicillin allergy are risks factors. Diagnoses and therapeutic erroneous with a higher rate of consultation, anti-inflammatory and antibiotic prescription without tooth extraction are also risks factors. Presence of clinical symptoms of severity as trismus, edema, fever, dysphagia, odynophagia, dysphonia, dyspnea, anterior floor edema, orpharyngeal edema, tongue protraction limitation are linked to a risk of multiple surgeries before healing. The tooth and the number of spaces involved by the infection also affect the course of the patient. Elevate CRP level is highly significate. From an arbitrary base CRP level (< 50, 50–99, 100–199 and ≥ 200 mg/l), can estimate the risk to have more than one surgery (Tab. 2 and Fig.1)

Table 1

Univariate analysis between the 2 groups: patients which necessitate 1 surgery (second column) and patients which necessitate more than one surgery (third column) to obtain healing. The fourth column shows the P values (*< 0.005, i.e., significant effect). Quadrant 1: maxillary incisive and canine, quadrant 2: axillary premolar, quadrant 3: maxillary molar, quadrant 4: mandibular incisive and canine premolar, Quadrant 5: mandibular premolar and quadrant 6: mandibular molar.

Variable	Number of surgical intervention = 1 N=611 (%)	Number of surgical intervention >1 N=42 (%)	p-value
Demographic outcomes			
Gender male	360 (59)	26 (62)	0.70
Age	36.8+/-16.2	39.5+/-15.6	0.30
Medical history			
Smoker	349 (57)	26 (62)	0.54
Drugs abuse	49 (8)	5 (12)	0.38
Alcohol abuse	67 (11)	11 (26)	0.003*
Immunodepression	15 (2)	5 (12)	0.001*
Psychiatric disorder	52 (9)	10 (24)	0.001*
Penicillin allergy	39 (6)	8 (19)	0.002*
Pre-hospitalization management			
Number of consultations	1.7+/-0.9	2.3+/-1.5	0.02*
Anti-inflammatory consummation	297 (54)	32 (78)	0.003*
Antibiotics consummation	350 (63)	28 (70)	0.39
Clinical symptoms at admission			
Trismus	352 (58)	38 (90)	<0.001*
no edema	13 (2)	0 (0)	<0.001*
facial edema	214 (35)	5 (12)	
cervicofacial unilateral edema	371 (61)	32 (79)	
	1 (0)	0 (0)	

cervical unilateral edema cervical bilateral edema	11 (2)	5 (12)	
Fever	159 (26)	23 (55)	<0.001*
Dysphagia/ odynophagia	127 (21)	27 (64)	<0.001*
Dysphonia	20 (3)	8 (19)	<0.001*
Dyspnea	10 (2)	6 (14)	<0.001*
Anterior floor edema	43 (7)	19 (45)	<0.001*
Tongue protraction limitation	24 (4)	6 (14)	0.009*
Oropharyngeal edema	11 (2)	7 (17)	<0.001*
Biological samples			
C-reactive protein level (mg/l)	72.4 (+/- 71.2)	153.9 (+/-97.4)	<0.001*
< 50	224 (37)	3 (7)	
50-99	116 (19)	9 (21)	
100-199	86 (14)	12 (29)	
≥ 200	27 (4)	10 (24)	
Missing values	158 (26)	8 (19)	
Surgical outcomes			
Number of spaces involved	1.2+/-0.5	2.1+/-0.9	<0.001*
Tooth position			
Quadrant 1	56 (9)	0 (0)	0.04
Quadrant 2	69 (11)	2 (5)	0.30
Quadrant 3	70 (11)	2 (5)	0.30
Quadrant 4	24 (4)	0 (0)	0.39
Quadrant 5	47 (8)	5 (12)	0.37
Quadrant 6	360 (59)	34 (81)	0.005*

Table 2

The estimate risk to have more than one surgery according to an arbitrary base CRP level. Abbreviations: PPV, predictive positive value; PNV, predictive negative value; LR+, likelihood ratio positive; LR-, likelihood ratio negative. A likelihood ratio of greater than 1 indicates the test result is associated with the disease. A likelihood ratio less than 1 indicates that the result is associated with absence of the disease

Caracteristics	Sensibility	Specificity	PPV	VPN	LR+	LR-
CRP level						
≥50	91	49	12	99	1.80	0.18
≥100	65	75	16	97	2.59	0.47
≥200	29	94	27	95	4.93	0.75

Predictors of multiple surgeries for severe odontogenic infection.

Out of the independent outcomes for which the univariate analysis reached significance, the following ones were kept for multivariate analysis: alcohol abuse, psychiatric disorders, immunodepression, penicillin allergy, anti-inflammatory consummation, mandibular molar and CRP level. Factors statistically significant but related to clinical symptoms of severity as number of space involved, dysphagia, dysphonia, dyspnea, tongue protraction limitation, oropharyngeal edema and anterior flour edema were deliberately not sample in the multivariate analysis, by definition they are severity risk factors but unfortunately are often misjudged. Only objectives and simple criteria which emerge are taken in consideration. The multivariate analysis reveals that the risk to have several surgeries in severe odontogenic infection is associated with CRP level: CRP<50 mg/l (p = 0.02, OR = 0,18 IC95% = [0.05–0.72]), CRP between 50 and 99 mg/l (OR = 1), CRP between 100 and 199 mg/l (p = 0.38, OR = 1.55 IC95% = [0.59–4.13]), CRP>200 mg/l (p = 0.01, OR = 4.12 IC95% = [1.33–12.72]), alcohol abuse (p = 0.03, OR = 2.70 IC95% = [1.09–6.7]), penicillin allergy (p = 0.001, OR = 5.47 IC95% = [1.99–15–09]), mandibular molar infected (p = 0.02, OR = 2.74 IC95% = [1.16–6.48]). To a lesser extent, it is associated with anti-inflammatory consummation used to ease pain (p = 0.06, OR = 2.20 IC95% = [1.16–6.48]), psychiatric disorders (p = 0.02, OR = 3.02 IC95% = [1.21–7.55]), immunodepression (p = 0.07, OR = 3.32 IC95% = [0.9–12.31]). Data are reported in Table 3.

Table 3

Multivariate analysis (MVA) between the 2 groups: patients which necessitate 1 surgery and patients which necessitate more than one surgery to obtain healing. MVA involves observation and analysis of pertinent data which emerged in the univariate analysis. The second column shows the Odd Ratio (OR), the third column shows the Confident Intervals stated at 95% (CI 95%), the fourth column shows the P values (*< 0.005, i.e., significant effect). Quadrant 6 corresponds to mandibular molar. C-reactive protein level is dosed in milligrams per liter (mg/l), the interval 50-99 is taken as reference to display the interval CRP<50 as protective.

Characteristics	OR	CI95%	p-value
Medical history			
Alcohol abuse	2.70	1.09 - 6.7	**0.03***
Immunodepression	3.32	0.9 - 12.31	0.07
Psychiatric disorder	3.02	1.21 - 7.55	**0.02***
Penicillin allergy	5.47	1.99 - 15.09	**0.001***
Pre-hospitalization management			
Anti-inflammatory consummation	2.20	0.97 - 4.99	0.06
Tooth position			
Quadrant 6	2.74	1.16 - 6.48	**0.02***
Biological samples			
C-reactive protein level (mg/l)			
<50	0.18	0.05 - 0.72	**0.02***
50-99	1	-	
100-200	1.55	0.59 - 4.13	0.38
200	4.12	1.33 - 12.72	**0.01***
Missing values	0.79	0.27 - 2.34	0.68

Antibiotics and infection evolution

A total of 378 (64%) patients had antibiotics treatment orally before presenting to hospital. Treatment duration before admission was 4.6 days (range 1—60). Most patients (231; 61%) were prescribed amoxicillin or amoxicillin and clavulanic acid, 75 (20%) spiramycine and metronidazole, 37 (10%) pristinamycine, 36 (9.5%) metronidazole and 2 (0.5%) clindamycine. Among the 47 patients allergic to penicillin, 11 (23%) received any antibiotic therapy and 34 (73%) received antibiotics before admission in our Department; 1/6 (25%) patients with adapted antibiotic therapy, 6/28 (21%) patients with unadapt antibiotic therapy and 1/13 (8%) none treated patients had unfavourable course. In the univariate analyse, antibiotics consummation before hospitalisation does not affect the probability to have complications ($p = 0.39$). A propensity score matching based on the above cited criteria as clinical symptoms gravity, patient characteristics and molar mandibular was performed to identify the complications according to “taking antibiotics” before hospitalization. There is no significate effect of the antibiotics on the same level of severity of infection ($p = 0.24$), even if 50% of patients with favorable evolution versus 35% of patients with unfavorable evolution had had antibiotics before hospitalization.

Conditional inference tree (CTREE) construction (Fig. 2).

CTREE analysis of the prognostic power of the objectives and simple preoperative criteria yielded seven diagnostic nodes, resulting from a decision tree consisting of the following parameters: CRP level, penicillin allergy, immunodepression, mandibular molar infection and psychiatric disorders. The conditional inference tree model to determine the ranking of the factors showed that four subgroups of patients with increased risk of multiple surgeries have emerged: 1- patients with a CRP level higher than 200 mg/l have a risk factor of 27% (IC95% = [14–44], n = 37), 2- patients with a CRP level between 50 and 200 mg/l and allergic to penicillin have a risk factor of 30%, (IC95% = [12–54], n = 20), 3- patients with a CRP level between 50 and 200 mg/l, mandibular molar infection and psychiatric disorder but without penicillin allergy have a risk factor of 33% (IC95% = [14–44], n = 37), 4- patients with CRP < 50 mg/l or CRP level unknown and immunodepression, have a risk factor of 25% (IC95% = [3–65], n = 8). Contrary, patients with CRP < 50 mg/l or CRP level unknown and any immunodepression have a risk factor of 2%, (IC95% = [1–4], n = 385) to need multiple surgeries. Patients with CRP level between 50 and 200 mg/l without any penicillin allergy presenting a cellulitis not due to a mandibular molar have a risk factor equal to 0 (IC95% = [0–4], n = 81) to have complications. For patients with CRP level between 50 and 200 mg/l without penicillin allergy nor psychiatric disorders but with infection involving mandibular molar, the risk factor is only 9% (IC95% = [5–17], n = 107) to need several surgical interventions.

Discussion

We investigated the clinical course of patients with severe odontogenic infection. Two third of patients had antibiotic therapy before hospitalisation and their evolution is substantially the same than for the third of patients who did not receive antibiotics before hospitalisation. All patients addressed did not

have tooth extraction and/or collection drainage. However, after a well performed treatment, evolution is favourable for the immense majority. Only 6% present an unfavourable course. To gain a better understanding of this group, we looked for predictors of complications based on patient general status, tooth involved and biological markers: 5 predictors were identified: penicillin allergy, CRP level > 200 mg/l, molar mandibular infection, psychiatric disorders and alcohol abuse.

This study is part of the rare prospective studies about severe odontogenic infection [3,11,12], with over 653 patients included, it was one of the largest. Our population with a mean age of 37 years-old, a male dominance, a poor health status, a maximum of mandibular molar infected with submandibular and perimandibular space involvement is similar to the literature [1,3–8,11–17]. Penicillin allergic reported is 7% in our study, 4.1% in Zirk et al. study and 8% in Flynn et al study [3,17]. Multiple tooth involvement, multiple space infected, systemic disease, prescription of non-penicillin antibiotic or of antibiotic combination, empirical antibiotic treatment changed after microbiologic assessment are predictors of hospitalization in patients with acute odontogenic infection [15]. Comparing our population to the data reported by the Institut National de prevention et d'Education pour la santé (INPES), showed that it is more vulnerable than general population with a higher proportion of alcohol, nicotine and drug abuse.

We voluntary focused on simple, objective and presurgical criteria to determine patients with a high risk to need several surgical interventions. Indeed, clinical symptoms of severity as number of spaces involved, dysphagia, dysphonia, dyspnea, tongue protraction limitation, oropharyngeal edema and anterior floor edema are well known by the experimented Oral and Maxillofacial surgeons but are misjudged by other actors as general practitioners, pharmacologists or residents. Moreover, those symptoms sometime worsen during or after surgery. That is why we removed them from the multivariate analysis. CRP level, penicillin allergy, mandibular molar infection, psychiatric disorders and immunodepression allow us to characterize 4 profiles of patients linked to a risk level higher than 25% to need several surgical interventions and to have complex course.

We started from a principle that CRP is frequently measured on admission when infection is suspected. Its measure is objective and repeatable over time. Daily measurement is useful in the detection of sepsis and it is more sensitive than body temperature or white blood cell count [18]. This inflammatory biomarker rise in most pathological situations associated with inflammation as bacterial, viral infection, trauma, systemic disease flare (excepted lupus) or post-surgical period. Normal human CRP concentrations is less than 1mg/l. Its level increases in the first 6 hours after stimulation by interleukine–6 (IL–6) and can reach peak levels approaching 350–400 mg/l after approximately 48 hours; its half-life is of 20 to 24 hours [19]. It is commonly considered that mild inflammation and viral infections cause elevation of CRP in the 10–40 mg/l range. Active inflammation and bacterial infection leads to a CRP level from 40 to 200 mg/l. Levels over 200 mg/l are found in severe bacterial infections and burns [20]. Historically, a plasma CRP level of 50 mg/l or more was highly suggestive of sepsis (sensitivity 98.5%, specificity 75%) [18]. We were guided by those considerations to arbitrary define four level of CRP: <50, 50 to 99, 100 to 199 and > 200 mg/l. Nevertheless, most studies failed to objective correlation between CRP level and severity of the sepsis [21]. Meili et al., (2016), demonstrated that CRP < 100 mg/l is significantly

associated with worst acute respiratory tract infections but have moderate prognostic accuracy in primary care patients to predict clinical outcomes [22]. CRP help to diagnose equivocal cases of appendicitis, cholecystitis, pancreatitis and pelvic inflammatory disease but faster and more interpretable tests are available. Moreover, the cut-off is variable between those different diseases: CRP > 12 mg/l have a sensitivity of 98% to diagnose appendicitis, CRP > 30 mg/l have a sensitivity of 78% to diagnose cholecystitis, CRP levels > 210 mg/l discriminated between patients with clinically mild and severe pancreatitis with a sensitivity of 83% and a specificity of 85% [20]. The CRP level linked with severe infection is variable between the different diseases. Ylijoki et al., (2001) study showed to a statistically significant degree ($p < 0.001$) that CRP concentration on admission is linked with the complicated course of disease, respectively 140.2 mg/l (± 67.5) for patients admitted in intensive care unit [1]. However, it is difficult to define an objective CRP level cut-off between patients with severe odontogenic infection with a high risk of unfavorable evolution. It might be necessary to study systematically CRP level in odontogenic infection. Yet, in the inference tree, the level of CRP > 200 mg/l is self-sufficient to have 27% of risk to need multiple surgical intervention with a complex evolution.

In contrast, when CRP level is lower than 50 mg/l or unknown, immunodrepression is self-sufficient to have a risk level of 25% to need multiple surgeries. General health status of patients significantly impact the course and outcome of severe odontogenic infection. Seppänen et al., (2008), showed in their study that among patients with odontogenic infection, 85% of healthy patients developed local complications whereas 75% of medically compromised patients developed systemic infection complications with a need for longer hospital and a higher risk to die [8]. In Optiz et al. (2015), study, among 816 patients included, 14 (1.7%) where affected by severe complications after odontogenic infections [7]. All of them had predisposing factors such as diabetes mellitus, obesity, immunosuppression and arterial hypertension with its systemic consequences. In this group, long-term alcohol and nicotine abuse where also noticied. In our multivariate analysis, alcohol abuse appeared as a statistically significant risk factor to have severe complication but this factor does not stand out in the inference tree. Tung-Yiu et al., (2000), reported among 422 odontogenic infection 11 cases of cervical necrotizing fasciitis, 7 of them had immunocompromising conditions [23]. Patients with relevant comorbidities are known to have a worse prognosis and longer hospitalisation compared to patients without concomitant diseases.

If CRP level is between 50 and 200 mg/l and the patient allergic to penicillin, the risk factor to have multiple surgeries is 30%. Among the 47 patients allergic to penicillin, 33 (70%) received antibiotic therapy but only 5 received the first-line antibiotics specifically recommended by ANSM before admission in our Department. Still before being admitted, face to the failure of the antibiotic treatment, all patients had a non-justified antibiotic therapy modification and any causal tooth extraction. This contradicts guidelines from the ANSM which state that antimicrobials should be prescribed as an adjunct to removal of the source of infection. Therefore prescription of oral antibiotics without operative intervention represents an inadequate level of treatment for dentoalveolar infections. Prescription of oral antibiotics alone expose patients to more courses of antibiotics which can lead to development of antibiotic resistance. The incidence of routinely antibiotics resistance in deep space head and neck infection is: in the aerobic spectrum, 18% for clindamycin, 14% for macrolides and 7% for penicillin G, in the anaerobes 11% for

clindamycin, 6% for metronidazole and 8% for penicillin G [24]. In Farmahan et al. study resistance to amoxicillin was 26.6% and to both amoxicillin and metronidazole was 18.7% [14]. But in Poeshl et al. study they did not observe any clinical antibiotic failure for patients treated by an association of amoxicillin and clavulanic acid. In contrast, for patients treated by clindamycin, they observed 3 clinical failures, which necessitated further surgical interventions and a change in the antibiotic regime [24]. The first line antibiotic therapy recommended by ANSM in severe odontogenic infection is an association between amoxicillin and clavulanic acid. For patients allergic to penicillin, the impossibility to use this first choice is a loss of chance. Moreover the high resistance rate for clindamycin is a matter of concern for those patients. Combination of high resistance rate for clindamycin and of a second choice antibiotic may explain most unfavourable course of patients allergic to penicillin.

If CRP level is between 50 and 200 mg/l and the patient not allergic to penicillin, two criteria must be add to obtain a risk factor of 33%: mandibular molar infection and psychiatric disorders. Mandibular molar is the most frequent tooth involved in severe odontogenic infection [3,5,7,11,13,14] and is responsible of infection spreading preferentially in the submandibular space [13,15,17,25,26]. Moreover, in our study it is also strongly correlate with unfavourable evolution. When the point of departure of the infection is the mandibular molar, the submandibular space is often involved, followed by floor oedema and tongue protraction limitation or extension to masseter and pterygoid muscles provoking trismus [25]. Then infection can spread into the parapharyngeal space and be responsible of respiratory distress and dysphagia [25,27] and along jugular and carotidien vessels to mediastinum [10,26,28,29]. The issue then was to understand why infection stay compartmentalised or dispersed. However, mandibular molar infection is not sufficient to have adverse evolution, it requires an association with psychiatric disorders. Patients with mental illness have markedly elevated rates of physical disorders compared to the general population. It is widely linked to factors as lifestyle, adverse psychotropic effects, alcohol and drugs abuses and poor health care [30]. A large review of the literature from Matevosyan et al. (2010) reports that patients with psychiatric disorders have more missing teeth, gross caries, decay, periodontal disease and xerostomia [31]. The worst predictive factors of oral health outcomes in this population are old age, type and onset mental illness. A lack of awareness and a poor perception in oral health are associated with poor oral hygiene and excessive consumption of sugar and lipids. Moreover those patients have poor access to dental care [31]. The use of treatments or drugs limiting pain perception, late consultation and limited access to appropriate treatment determine the risk for low-noise infection spreading to cervico-facial space and oral health adverse outcomes among adults with psychiatric disorders.

Conclusion

In conclusion, about 6% of patients may have complications during severe odontogenic infections combining multiple surgeries and intensive care unit hospitalisation, long-time intubation, tracheotomy and even dying. Objective presurgical criteria significantly predict the risk to have worse evolution, they allow us to individualize 4 subgroups at risk to need multiples surgeries: 1- a group of patients with as CRP level higher than 200 mg/l, 2- a group of patients with as CRP level inferior to 50 mg/l and with immunodrepression condition, 3- a group of patients with an association CRP level between 50 and 200

mg/l and penicillin allergy and 4- a group of patients with an association CRP level between 50 and 200 mg/l and mandibular molar infection and psychiatric disorders.

Abbreviations

CTREE: conditional inference tree

CRP: C-reactive protein

CT-scan: computerized tomography—scanner

ANSM: French Health Products Safety Agency

ROC: Receiver Operating Characteristic

aOCR: Adjusted Odd Ratios

OR: Odd Ratios

IC: Interval confidence

NSAIDs: Nonsteroidal anti-inflammatory drugs

Declarations

Ethics approval and consent to participate:

Study ethics approval was obtained on Comité d'Ethique et Centre d'investigation Clinique de l'interrégion Rhône Alpes Auvergne CECIC Rhône-Alpes-Auvergne, Grenoble, IRB 5921, at the date of 03/22/2012

IRB number : CE-CIC-GREN–12–08

Consent for publication

All the participants were informed and sign a consent to participate in the study

Availability of data and material:

To have access to the datasets contact the Authors by using the e-mail: nphamdang@chu-clermontferrand.fr.

Competing interests:

The authors declare that they have no competing interests

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Authors' contributions:

all authors have read and approved the manuscript

CD collected datas

NPD design the study

AM performed the stats

LD reviewed the manuscript

IB reviewed the manuscript

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Figures

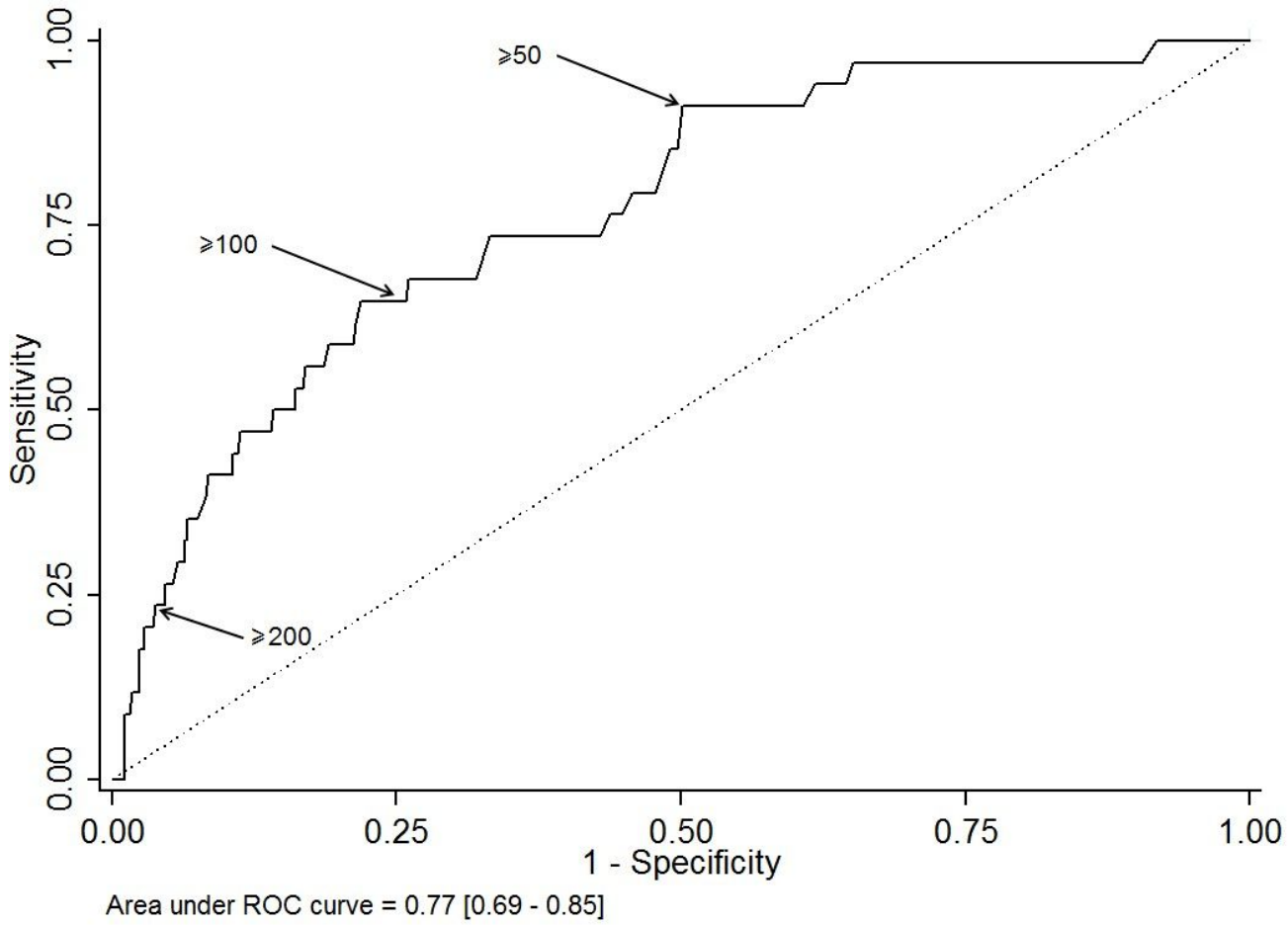

Figure 1

The receiver operating characteristic (ROC) curve for the CRP test results of the study cohort

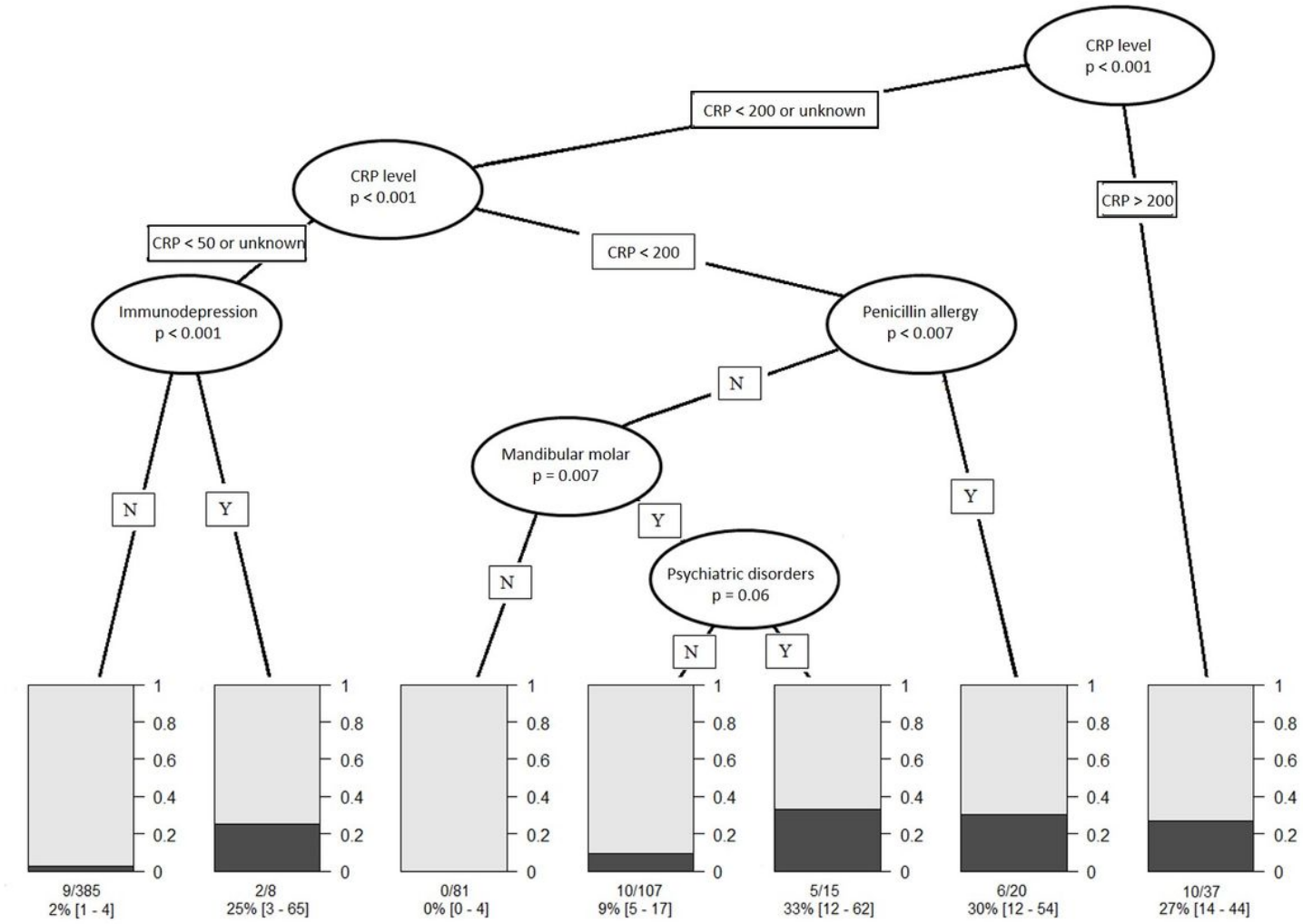

Figure 2

Results of conditional inference tree (CTREE) showing the most predictive indicators to have more than one surgery in case of severe odontogenic infection. Seven nodes where identified (N, no for absent; Y, yes for present). Bar diagrams show the probability to have on surgery in grey and the probability to have more than one surgery in black according the different nodes