Achieving the best method to classify Eosinophilic Chronic Rhinosinusitis: a systematic review *

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Abstract

**Background:** Chronic Rhinosinusitis is currently classified into eosinophilic and non-eosinophilic, according to the histologic quantification of the number of eosinophils in nasal mucosa biopsy. There is a lack of unanimous histopathologic criteria and methodology for this classification and no consensus regarding a cut-off point for Eosinophils per High power field.

**Methodology:** A systematic electronic search was performed on BVS, PUBMED, PUBMED PMC, SCOPUS, WEB OF SCIENCE, EMBASE, COCHRANE and PROQUEST databases looking for studies that reported a cut point for classification of Eosinophilic Chronic Rhinosinusitis (eCRS), and data concerning methodology of classification was extracted.

**Results:** We identified 142 studies that reported 29 different cut-off values for classification of eCRS, and different methods of histologic analysis. Out of these studies 13 reported their own methodology to establish the cut-off point, and used different reference standards as polyp recurrence, asthma and allergy, immunocytochemistry, quality of life index, standard deviation of the control population and cluster analysis.

**Conclusions:** Further studies are needed to determine a precise cut-off point, especially international multicentered cluster analysis. Moreover, methodologic standardization of biopsy and analysis is needed to certify comparable results. Multiple biopsy sites, densest cellular infiltration area examination and oral steroids restriction at least four weeks before sampling are advisable.

**Key words:** sinusitis, nasal polyps, eosinophils, cell count

Introduction

Chronic rhinosinusitis (CRS) is the inflammation of nasal and sinus mucosa (¹). Nowadays, most otorhinolaryngologists acknowledge the classification of CRS in different phenotypes. These phenotypes lack detailed comprehension of the underlying immunologic and inflammatory mechanisms of CRS. This heterogeneity supports the concept that CRS consists of multiple biological subtypes, or endotypes, which are defined by different pathophysiologic systems that might be recognized by distinct biomarkers (²). The inflammatory patterns of nasal polyps are generally defined to be Type 2 inflammation and Non-Type 2 according to the predominant inflammatory cell type (eosinophils or neutrophils), and mediator or cytokine expression (³). Endotypes of CRS can be classified according to specific immune inflammatory and remodeling profiles, circulating biomarkers, responsive to treatment (effect of immunobiological drugs, resistance to antibiotics and corticosteroids), and aspirin sensitivity (⁴). Facing so many possibilities, the EPOS2020 steering group has chosen to look at CRS in terms of primary and secondary and to divide each into localized and diffuse diseases based on anatomic distribution. In primary CRS, the disease is classified according to endotype dominance, either of type 2 or non-type 2. For diffuse CRS, the clinical phenotypes are predominantly eosinophilic chronic rhinosinusitis (eCRS) and non-eosinophilic Chronic Rhinosinusitis (non-eCRS), determined by the histologic quantification of the number of eosinophils, agreed to be ≥ 10 eosinophils/high power field (eos/HPF) as per the EPOS panel (⁵).
Although a meta-analysis stated that a > 55 eos/HPF cut-off point value is useful in predicting the likelihood of recurrence, the cut-off value to the histologic eCRS classification itself is far from a consensus. The literature has paid increased attention to the differentiation between eCRS and non-eCRS, but there is a lack of unanimous histopathologic criteria for it, given its controversial nature. Some studies defined tissue eosinophilia based on eosinophil count per HPF (400×), while others were based on the proportion of the eosinophil cell count as a percentage of the total inflammatory cell count in the sample. Although some researchers suggested absolute numbers/HPF like 5, 8, 10, 70 100, 120, 350 as appropriate cutoffs, others considered eosinophil percentage ranges like 5, 10, 11, 20 or as high as 50% count as relevant cutoff values of eCRS. Conflicting with the European Rhinologic Society, which suggests a cut-off value of 10 eos/HPF, the Japanese JESREC study established a 70 eos/HPF limit in classifying eCRS. There is an urgent need to unify methodologies and to specify clear and practical values for histopathologic eCRS, in order to expand studies comparison and to tailor personal treatment to different populations around the globe. This study aims to identify the different histological methodologies used to classify eCRS in the literature, and subsequently verify the cut-off points of the eosinophil counting used in this classification.

Materials and methods

Data sources and search strategy

A systematic electronic search was performed on BVS, PUBMED, PUBMED PMC, SCOPUS, WEB OF SCIENCE, EMBASE, COCHRANE and PROQUEST databases until January 20th, 2020. The Medical Subject Headings (MeSH) descriptors used in the preliminary search strategy were “sinusitis”, “nasal polyps”, “eosinophils” and “cell count”. However, in order not to miss important articles, we had to exclude the descriptor “cell count”. A search strategy was designed for each database (Appendix 1) to identify all studies on eCRS with nasal polyps. Duplicities were excluded using Endnote® and manually. A systematic review was performed to identify studies that reported the methodology used for eosinophilic histologic classification of CRS patients. This review was done in accordance with the items described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).

Study selection

The studies were reviewed by two independent authors (MDCT and MAA) and selected according to the eligibility criteria. Titles and abstracts were screened using the Rayyan app for systematic reviews. Conflicts between authors were solved by a third author (ES). In a second phase full texts of the selected abstracts were then analyzed and included if meeting the selection criteria. Lastly, missing studies were searched manually after being identified in the bibliography of included studies.

Eligibility criteria

The studies selected had patients classified with CRS according to the EPOS, and biopsy for histologic eosinophil count evaluation. Articles were included when they presented a clear methodology regarding the classification of eosinophilia by showing a cutoff value, even when classifying it in eosinophilia groups or in clusters. The following study designs were considered: case-control, cross-sectional, experimental and cohort. Studies published after the year of 2000 in English, Spanish, French and Portuguese were included. Case reports, case series, reviews, guidelines, letters, congress abstracts, and editorials were excluded along with animal studies. When other parameters different from histopathologic biopsies analysis, since immunohistochemistry or exclusive clinical classification were used to classify eCRS, papers also were excluded, as well as studies that conducted a subjective histopathologic analysis, with no clear criteria for classifying eosinophilic tissues.

The outcome of interest in our first analysis was the method used to histologically classify eCRS, so all studies that specified a cut-off point for eosinophil counting were included. In our secondary examination to verify the best cut-off point for histological evaluation we searched within the bibliography of the studies included and selected only the articles that demonstrated an original threshold of eosinophil count.

Data extraction

An Excel standardized data-sheet was used to extract relevant data from the selected articles, such as first author name, year of publication, study methodology, population, site of biopsy sampling, the classification of eCRS (clinic score and histologic), the cut-off value for eCRS, treatment when biopsy was performed, cited literature to justify the classification used, and method of eosinophil count (number of examiners, if examiners were blinded, number of HPF counted, and how the HPF were selected). After this initial selection we analyzed the articles that were cited by the authors as references to define the cut-off value, along with those that established an original research to prove an optimal cut-off point, and each of the mentioned articles were examined individually. Data from those studies were extracted using the following topics: First author name, year of publication, nationality of the study, population, study design, cut-off value for eCRS, the reason used to justify the cut-off point, and the method for identification of a specific threshold. Descriptive data were presented in percentages and proportions. Characteristics of the studies and details of the information were summarized in tables. Graphical data were displayed in figures.
Assessment of methodological quality for included studies

Articles that demonstrated their own methodology for assessing the classification of eosinophilia, were then analyzed separately using the Quality Assessment Tool for Observational and Cross-sectional Cohorts developed by the National Heart, Lung, and Blood Institute (NHLBI), with 14 different criteria [10]. The articles were classified by a Score previously published in the literature [11]. Because questions concerning exposure and outcome quality of the studies did not necessarily reflect on the eCRS cut-off point, and cross-sectional designs don’t allow measure of time between exposure and outcome, questions 6-10 were answered and “not applicable”. Every answer “Yes” to the criteria of time between exposure and outcome, questions 6-10 were analyzed separately.

Figure 1. Study selection process based on PRISMA flowchart.

Results

Study selection

The search strategy yielded 2847 studies in total. Additionally, 14 studies were manually included after being identified via other sources. Checking for duplicates decreased the number to 1561. All titles and abstracts were then screened, resulting in 407 studies for assessment. Regarding the two objectives of this study, up to this stage the same criteria were used, and after checking eligibility by reading full texts, 142 studies were included, out of which 4 studies consisted of cluster analysis studies. Those articles were used to analyze the different histological methodologies used to classify eCRS.

Of these 142 studies, 13 were selected after meticulous analysis of the cited literature to justify the cutoff value for counting eosinophils in all articles, as well as the selection of articles that offered an original method for choosing the cutoff value. Those articles were used to verify the optimal cut points of eosinophils counts used to classify eCRS. Figure 1 shows a PRISMA based flowchart of the study selection.

Histological methodologies used to classify eCRS

Summarized information on the 142 studies selected to review methodologic histologic classification of eCRS are shown in Appendix 2.

Population

In addition to subjects with Chronic rhinosinusitis with nasal polyps (CRSsNP), some studies also verified Chronic rhinosinusitis without nasal polyps (CRSsNP) participants, controls. There were 88 studies from Asia, 23 from Europe, 20 from America, 7 from Oceania and 4 collaborations between Eastern and Western countries. China contributed with 32 studies, Japan with 31, the USA with 19, and South Korea with 18 studies.

Biopsy site

A great variety of biopsy sites were reported for CRS participants. One hundred studies reported nasal polyps’ biopsy and nine of them specified the exact location (apex or middle meatus). There are 30 mentions on biopsies of ethmoids, 4 on uncinate process, and 3 on maxillary sinuses. Inferior turbinate and osteomeatal complex tissue were mentioned by one author.

Also, 18 studies did not report a location, and 8 studies reported it nonspecifically as “sinus” or “nasal mucosa”.

Treatment at time of biopsy

Many treatments were described before the nasal biopsy, the majority restricting one or more medications. In total, 36 studies did not mention any drugs used at time of biopsy. Antileukotrienes were restricted in 13 studies, antihistamines and immunosuppressant drugs instead of restriction. Five studies had patients both on restriction of a drug category and prescription of other drugs category.

Systemic steroids were the most restricted drug. Twenty-nine studies restricted antibiotics for 4 weeks prior to biopsy. Antileukotrienes were restricted in 13 studies, antihistamines in 12 and immunomodulators in general, in 17. The use of anti-inflammatory drugs, decongestants, immunotherapy, non-steroidal and anti-IgE drugs were cited as restricted, but less frequently.

Method of eosinophil counting

The number of pathologists or researchers that independently
counted the eosinophils were not reported in 76 studies (53.5%). Forty studies reported two independent examiners, 20 had a sole pathologist, and six articles reported 3 examiners. Forty-nine studies (34.5%) reported the pathologists’ blindness to the patient’s clinical data. Almost half of the studies (42.3%) did not report the number of High-Power Fields (HPF X 400) used to count eosinophils and 25 (17.6%) considered 10 HPF. The HPF selection was random in 20.4% of cases, and the densest area of cellular infiltration was chosen in 58.5% of the studies.

Eighty-four studies (59.2%) used the absolute average of eosinophils/HPF to determine the cut-off value of eCRS, while 51 (35.9%) used a percentage of eosinophils/number of inflammatory cells for the classification. Four experiments used both the absolute and the percentile count. One author counted the number of eosinophils/mm², one used the ratio of eosinophils/inflammatory cells associated with a thickened basal membrane, and one classified as eCRS when two or more HPF met the cut-off value.

Classification of CRS

Most studies (88%) used histologic eosinophil counting alone to classify CRS as eosinophilic or non-eosinophilic. Two of these classified as eCRS whenever the percentage of double-folded eosinophils exceeded twice the standard deviation (SD) of the mean of controls. Twelve studies (8.5%) combined the JESREC criteria associated with the histologic eosinophil count. Two classified as eosinophilic the combination of the histologic eosinophil count with the evidence of nasal polyps and allergic mucin.

There were 29 different cut-off values for the reported eCRS, 17 being absolute counts, 11 percentages of eosinophils/inflammatory cells, and one study reporting an absolute number of eos/mm². We decided to merge cut-off point values that only differentiate using the ≥ symbol (>5/≥5; >10/≥10; >70/≥70).

The most frequent cut-off value was > 10%, mostly representing Chinese studies, followed by the absolute count of > or ≥10, and > or ≥ 70, mostly representing Japanese studies (Figure 3).

Only 4 cluster analysis studies were included. Nakayama et al. conducted a retrospective study in Japan with 435 patients presenting CRS. Five factors within 16 variables were chosen to perform cluster analysis: symptom score, perennial allergy, disease severity (CT polyp score), asthma and eosinophil count. The patients were divided into 4 clusters and eosinophil count ≥80.5 was the optimal cut-off point value. Lou et al. included only CRSWNP patients. Five clusters were created: Cluster 1: Plasma-cells dominant phenotype; Cluster 2: Lymphocyte dominant phenotype; Cluster 3: Mixed inflammatory phenotype (Mean eos% 40.55); Cluster 4: Neutrophil-dominant phenotype; Cluster 5: Eosinophil-dominant phenotype (Mean eos% 79.28). The cut-off value for eCRS and Cluster 5 was 54.5%, and this cluster had the highest recurrence rate (98.5%). Liao et al. enrolled 246 CRS patients. The eCRS was used as classification when polyp or ethmoid samples had more
Table 1. Cut point for e-CRS classification: summary of findings of studies presenting its own methodology to establish a cut-off value.

<table>
<thead>
<tr>
<th>Author</th>
<th>Nation-ality</th>
<th>Population</th>
<th>Study Design</th>
<th>Cut-off Value</th>
<th>Reason of Cut-off</th>
<th>Method for the Cut-off establishment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cao 2009 (14)</td>
<td>China</td>
<td>50 Controls 94 CRSwNP (70 e-CRS and 81 non-e-CRS)</td>
<td>Prospective, Observational, Cross-sectional study</td>
<td>&gt;10% of the inflammatory cells</td>
<td>Twice the SD of the mean of controls</td>
<td>CRS were classified as eosinophilic when percent eosinophils exceeded twice the SD of the mean of controls (4.77%+2 X 2.47%= 9.71%)</td>
</tr>
<tr>
<td>Gao 2016 (24)</td>
<td>China</td>
<td>153 CRSwNP (75 e-CRS)</td>
<td>Prospective, Observational, Cross-sectional study</td>
<td>&gt;10% of the inflammatory cells</td>
<td>Median proportion of eosinophils</td>
<td>Median proportions of eosinophils and neutrophils hovered around 10% of all inflammatory cells (preliminary study)</td>
</tr>
<tr>
<td>Ikeda 2013 (44)</td>
<td>Japan</td>
<td>130 CRSwNP (42 e-CRS and 88 non-e-CRS)</td>
<td>Prospective, Observational, Cohort</td>
<td>&gt;100 Eos/HPF Polyps recurrence</td>
<td>ROC curve (number of patients with polyp recurrence X number of eosinophils)</td>
<td></td>
</tr>
<tr>
<td>Jeong 2011 (40)</td>
<td>South Korea</td>
<td>118 CRSwNP (74 e-CRS/ 44 non-eCRS)</td>
<td>Prospective, Observational, Cohort</td>
<td>&gt;11% Eos/inflammatory cells</td>
<td>Asthma and allergy</td>
<td>ROC curve (Number of patients with asthma and allergy X number of eosinophils)</td>
</tr>
<tr>
<td>Jiang 2011 (36)</td>
<td>China</td>
<td>42 CRS 10 Controls</td>
<td>Prospective, observational, cross-sectional study</td>
<td>&gt;8% ratio of eos/inflammatory cells</td>
<td>Twice the SD of the mean of controls</td>
<td>CRS were classified as eosinophilic when percent eosinophils exceeded twice the SD of the mean of controls (4.4%+2 X 1.7%= 7.8%)</td>
</tr>
<tr>
<td>Kountakis 2004 (38)</td>
<td>USA</td>
<td>47 CRS (28 e-CRS and 19 non-e-CRS)</td>
<td>Prospective, observational, cross-sectional study</td>
<td>&gt;5 eos/ HPF EG2 stained tissue</td>
<td>All tissue slides with more than five eosinophils/HPF stained with EG2.</td>
<td></td>
</tr>
<tr>
<td>Lou 2015 (34)</td>
<td>China</td>
<td>387 CRSwNP</td>
<td>Retrospective observational, cross-sectional study</td>
<td>≥27% of Eos/inflammatory cells or &gt;55 eos/HPF Polyps recurrence</td>
<td>ROC curve (number of patients with polyp recurrence X number of eosinophils)</td>
<td></td>
</tr>
<tr>
<td>Lou 2016 (3)</td>
<td>China</td>
<td>366 CRSwNP</td>
<td>Retrospective observational study with cluster analysis</td>
<td>≥54.5% of Eos/inflammatory cells</td>
<td>Cluster analysis</td>
<td>Cluster analysis (5 clusters Plasma-cells dominant phenotype; lymphocyte dominant phenotype; mixed inflammatory phenotype; neutrophil-dominant phenotype; eosinophil-dominant phenotype)</td>
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<td>Nakayama 2011 (45)</td>
<td>Japan</td>
<td>223 CRS</td>
<td>Prospective, observational, longitudinal study</td>
<td>≥70 eos/HPF Polyps recurrence</td>
<td>ROC curve (number of patients with polyp recurrence X number of eosinophils)</td>
<td></td>
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<tr>
<td>Nakayama 2012 (12)</td>
<td>Japan</td>
<td>425 CRS</td>
<td>Retrospective, observational study with cluster analysis</td>
<td>≥80.5 eos/HPF Cluster analysis</td>
<td>Cluster analysis: 5 factors within 16 variables were chosen to perform cluster analysis: Symptom score, Perennial allergy, disease severity (CT polyp score), Asthma and Eosinophil Count.</td>
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<tr>
<td>Soler 2010 (42)</td>
<td>USA</td>
<td>102 CRS</td>
<td>Prospective, observational, longitudinal study</td>
<td>≥10 Eos/HPF Disease-specific QOL improvement</td>
<td>6 cut-points were compared including: &gt;1, &gt;5, &gt;10, &gt;50, &gt;100, and &gt;250 eosinophils/HPF. The optimal cut-point was the largest absolute difference in disease-specific QOL change scores (postoperative minus preoperative) and smallest corresponding p-value.</td>
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<td>Tokunaga 2015 (6)</td>
<td>Japan</td>
<td>1716 CRS (672 e-CRS and 1044 non-e-CRS)</td>
<td>Retrospective multi-centered observational study</td>
<td>≥70 eos/HPF CRS recurrence</td>
<td>ROC curve (number of patients with polyp recurrence X number of eosinophils)</td>
<td></td>
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<tr>
<td>Yamada 2019 (43)</td>
<td>Japan</td>
<td>37 CRS</td>
<td>Prospective, observational, longitudinal study</td>
<td>≥55 Eos/HPF CRS recurrence</td>
<td>ROC curve (number of patients with polyp recurrence X number of eosinophils)</td>
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Table 2. Quality assessment tool for observational cohort and cross-sectional studies.

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<th>Author (year)</th>
<th>Q1</th>
<th>Q2</th>
<th>Q3</th>
<th>Q4</th>
<th>Q5</th>
<th>Q6</th>
<th>Q7</th>
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<th>Q9</th>
<th>Q10</th>
<th>Q11</th>
<th>Q12</th>
<th>Q13</th>
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</table>

NA = not applicable; NR = not reported

Questions (Q1-Q14).
1. Was the research question or objective in this paper clearly stated?
2. Was the study population clearly specified and defined?
3. Was the participation rate of eligible persons at least 50%?
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?
5. Was a sample size justification, power description, or variance and effect estimates provided?
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
10. Was the exposure(s) assessed more than once over time?
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?
12. Were the outcome assessors blinded to the exposure status of participants?
13. Was loss to follow-up after baseline 20% or less?
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?
than 10% eos/inflammatory cells, as reported by Cao, 2009. Patients were divided into 7 clusters. Cluster 1: Type 2 eCRSwNP had a median eosinophil count of 29.5% eos/inflammatory cells, and had poor treatment outcome, with 50% of difficult to treat cases.

Kim et al. conducted a retrospective study with 375 CRSwNP patients. When polyp eosinophil count surpassed 20% of the total inflammatory cells, it was classified as e-CRS as reported by Kim 2013. Six variables were defined for clustering: Comorbidity airway disease, blood eosinophil, tissue eosinophil, Lund-Mackay score (Ethmoid/Maxillary or E/M score), Mean Lund-Mackay score, and age. Four factors were then used, age ≥35, asthma, tissue eosinophilia, and E/M score ≥2.2. Patients were divided in 6 clusters. The clusters with a higher risk of revision surgery were A2 (asthmatic, eosinophilic polyp patients), NA2 (non-asthmatic, non-eosinophilic polyp patients with younger age) and NA4 (non-asthmatic, eosinophilic polyp patients with higher E/M ratio).

Optimal cut-off points for eosinophils
All the 142 articles were screened for references that justified the cut-off point value together with articles that demonstrated their own methodology for establishing the cutoff value for eosinophilia. A total of 53 different papers were found in this search, and 40 were excluded for the following reasons: use of immunohistochemistry for eosinophil counting, review article, absence of cut-point value, or not having specified or described the reason or methodology to demonstrate the value for eCRS. The remaining 13 articles are summarized in Table 1.

Methodological quality assessment
The evaluation of methodological quality was performed only in the 13 cut-off studies. The Quality Assessment Tool for Observational and Cross-sectional Cohorts developed by the National Heart, Lung, and Blood Institute (NHLBI) was used in this assessment, with 14 different criteria. The result is presented in Table 2. Two articles were classified as “good” quality, eleven as “fair”, and none as having “poor” quality. The most common caveats were the lack of sample size justification, and not describing participation rate of eligible persons or follow-up rate.

We also determined that the use of standard deviation of controls, immunohistochemistry, asthma and allergy, quality of life (QoL) scores had a high risk of bias, while polyp recurrence and combined parameters in cluster analysis had a low risk of bias.

Discussion
In an era of personalized and precision medicine, endotype driven potential therapies like use of immunobiologics is becoming more and more important. Histopathology, therefore, is a simple but sophisticated method to assist in CRS endotyping. The classification of eCRS is in vogue worldwide, and our study demonstrated a divergence in the cut-off point value for eCRS in different countries. Zhang et al. demonstrated in 2008, a higher eosinophilic infiltration in Belgians CRSwNP patients compared to Chinese patients, establishing a division into predominant eCRS in western countries and predominant non-eCRS in eastern countries. Although studies suggest that genetic factors contribute to this difference, it may also have a tendency of growth of CRS in eastern countries. We also found that there is a higher threshold on classification of eosinophilic pattern in eastern countries, especially in Japanese studies, which could increase the discrepancy between the prevalence of eCRS between eastern and western countries. Still, most Chinese articles use the relative >10% eosinophil count based on Cao et al. This review exposes a clear lack of standardization in the method of biopsy and histologic evaluation among the articles. Some authors use a subjective classification grading scale of eosinophil infiltration, Gao et al. also showed a positive correlation between objective and subjective classification of NP, however, that can lead to inter-examiners bias and is very difficult to reproduce accurately. To objectively assess those classifications, Snidvongs et al described a structured histopathology report to uniform CRS evaluation.

Thaikrakool et al showed a significant difference in eosinophil count when comparing biopsies of polyp apex and ethmoid mucosa, but no difference was found when comparing polyp pedicle with polyp apex and ethmoid mucosa. Most articles did not specify the site of nasal polyp biopsy, and a minority of the studies used ethmoid mucosa as the site of analysis. Sampling at least three sites of mucosa may reduce risk of a false negative eCRS. Considering the recommendation of classification both CRSwNP and CRSSNP as eosinophilic or non-eosinophilic, ethmoid mucosa biopsy should be contemplated. The number of different examiners is seemingly non-significant as Bhathachayaya et al. showed a strong interrater and intrarater reliabilities between pathologists. The same researchers demonstrated a significant correlation within the same individual microscopic slide of tissue, when searched for the area of the densest cellular infiltrate. The use of blinded pathologists is important to reduce risk of bias in a diagnosis test, and although there is not a consensus, most histopathologists assess the densest inflammatory areas. In this context, using a higher number of HPF for eosinophil counts can reduce the bias that the distribution of eosinophils may not be homogenous. A great risk of bias may be introduced by the medications used prior to biopsy. Akiyama reported a 15% chance of false negative diagnosis of eCRS, considering a 70 eos/HPF cut-off point when short-term low dose oral steroids were administered prior to surgery, which can be reduced by collecting multiple polyp samples. De Borja Callejas et al. also proved a significant eo-
sinophil infiltrate decrease after 2 weeks of combined oral and intranasal steroids, and after 10 weeks of only intranasal steroids maintenance [30]. Jankowski et al. also demonstrated a reduction of 3/4 of eosinophil infiltration in nasal polyps tissue in patients without asthma after oral steroids, and a 2/3 reduction in patients with asthma and nasal polyps [31]. Interestingly, there was no difference when topical steroids were used alone, which the author attributed to a possible decrease in the activation of eosinophils, rather than a decrease in the number of cells [31]. Similarly, Mastruzzo et al. showed no difference in the density of cellular infiltration in NP after topical steroids, however a significant decrease in eosinophils and EG2+ cells [32].

Among all articles, almost 60% used the absolute count of eosinophils / HPF to classify eCRS instead of using the relative count of eosinophils / inflammatory cells. There is no consensus in the literature about the best method. Absolute count may be simpler for the pathologist, but can also be biased by a low cell density in the high power field [33]. Garin et al. demonstrated that both absolute and relative counting methods for quantifying tissue eosinophilia have statistical correlation [33]. Lou et al. compared both methods as a predictor for polyp recurrence, and demonstrated that the percentage tissue eosinophil was superior to the absolute tissue eosinophil count [34].

Although classification of different eosinophils counts in groups or grades might be interesting as CRS may have a great number of endotypes, this different degree of eosinophils usually has a cut-off point that correlates to clinical eCRS [21,31,33]. Probably the key question concerning a cut-off point for eCRS is the best reference parameter to use as a comparison of the index test threshold of eosinophils. In this study we identified the following parameters used as reference: standard deviation of controls, immunohistochemistry, asthma and allergy, quality of life (QoL) scores, polyp recurrence and combined parameters in cluster analysis.

In normal nasal mucosa, there are none or very few eosinophils [33]. Studies that used twice the standard deviation of the mean controls and applied the median proportion of eosinophils, had a cut-off point ranging between 8 and 10% [14,24,36]. Although Wenzel et al. used this method to classify eosinophilic asthma by endobronchial biopsy, we believe that this parameter can introduce a great risk of bias, as the presence of eosinophil may occur in a mixed inflammatory response [13,37]. Kountakis used an eosinophil activation marker (EG2+) as the single parameter of eosinophil cut-off point. This may be biased as high IL-5 response may have negative eosinophil activation marker [18,39].

The use of clinical parameters may have a significant relevance in medical practice. A cut-off point of 11% was determined when correlating eosinophil infiltration with asthma and allergy [40]. A cohort study by Gitomer et al. showed that patients with mild asthma had significantly elevated levels of tissue eosinophils when compared with patients with severe asthma, which can be explained by the increased need for steroids in severe symptomatic patients [41]. Kirtsreesakul's findings indicated that there was no association between a positive skin test and eosinophilic infiltration in nasal polyps [25]. Snidvongs, using a 10 eos/HPF cut-off point, found no correlation with asthma [25]. Moreover, a multicentric study of CRS inflammatory endotypes based on cluster analysis of biomarkers demonstrated that although most Th2 positive biomarkers correlate to clinical asthma, a group of non-asthmatic IL-5 positive endotype was observed [19]. Therefore, using allergy and asthma as a reference parameter may introduce bias.

Conventional clinical features of the eCRS phenotype, such as worse symptom and image scores, quality of life outcome and relapse of disease are not automatically good markers for the presence of eosinophilia in the sinus mucosa [25]. Soler et al. was cited by many other authors using the >10 eos/HPF cut-off point. The presence of this mucosal eosinophilia threshold predicted less improvement in both disease-specific and general QOL after FESS, but the presence of mucosal eosinophilia did not affect QOL for patients with NP, which can be explained by the removal of polyps done during ESS dramatically improving nasal obstruction, contributing to improve quality of life despite of eosinophilia [42]. Hence, quality of life in itself may not be a good parameter for classification.

Five studies demonstrating the method for the cut-off point selection used recurrence as main parameter [34,43-45]. This may be the most relevant parameter for phenotype division and was therefore chosen as a factor of low risk of bias, even though follow-up time for classifying recurrence also varied greatly. All of these studies were from eastern countries, and all restricted use of oral steroids although two did not specified for how long. Ikeda et al detected a 100 eos/HPF cut-off point [46], in a study selecting only CRSwNP. Both Nakayama and Tokunaga identified a 70 eos/HPF cut point [47], and Yamada and Lou found 55 eos/HPF as an optimal cut-off point, although Lou stressed that the relative count of >27% was superior to detect recurrence risk [19,41]. McHugh et al. accomplished a Meta-analysis with 11 individual studies, all reporting recurring rates in eCRS, and the highest overall sensitivity, and specificity was identified with a cut-off value >55 eos/HPF [19]. Interestingly, out of the five studies discussed here, only Yamada’s was not included in this Meta-analysis, and it also corroborate with the 55 eos/HPF value [4,43]. Hypothesis-free cluster analysis is probably the best research tool to evaluate a cut-off point as it considers both clinical and laboratorial features of eCRS [17]. In Lou et al., a cut-off point >54.4% of eosinophils was defined. Comorbid asthma, FeNo concentration, peripheral eosinophilia, and olfactory dysfuncti- on mirrored tissue eosinophilia across the five clusters. Moreover, high eosinophilic clusters were associated with the highest
recurrence rate. Nakayama et al. found a >80.4 eos/HPF cut-off point, after using the following factors: symptom score, perennial allergy, disease severity (CT polyp score), asthma and eosinophil count. Although the study did not examine recurrence, this value is close to the 70 eos/HPF demonstrated in a previous study. This review provides a broad overview of the techniques and parameters used for histological classification of CRS. However, it is limited due to the lack of consistency of the studies as well as the methodology used, patient selection and treatment, and the reference criteria used for classification, making it difficult to compare studies. On the other hand, it is possible to highlight the importance of global standardization through multi-center studies to systematize the classification and consequently, treatment of CRS.

Conclusion
A multicenter international cluster analysis of CRS endotypes is needed to determine a precise cut-off point for eCRS. Recent publications suggest a range of 55–80 eos/HPF considering polyp recurrence and cluster analysis, which is a greater value than what is usually performed by most researchers. Furthermore, methodological standardization of biopsy and assessment is needed to certify comparable results. Multiple biopsies sites, densest cellular infiltration area examination and oral steroids restriction at least four weeks before sampling are advisable.

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Authorship contribution
MDCT performed the data collection, study selections, data analysis, data interpretation and drafted the article. MAA was involved with data collection, study selection and data analysis. MGAR reviewed the article and was involved with the conception of the work. MSA performed critical analysis of the article and rewied the article. ES was involved with the conception of the work, data interpretation and made critical analysis of the article. All authors gave final approval of the version to be published.

Conflict of interest
All authors have no financial disclosures or conflict of interests.

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23. Kirtreesakul V, Atchariyasathan V. Nasal polyposis: Role of allergy on therapeutic


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## Appendix

### Appendix 1.

<table>
<thead>
<tr>
<th>Source</th>
<th>Strategy</th>
<th>N° of studies</th>
<th>Date</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BVS / BIREME</strong></td>
<td>tw:(tw:(&quot;Nasal Polyps&quot; OR &quot;Polipos Nasales&quot; OR &quot;Pólipos Nasais&quot;) AND (tw:(sinusitis OR sinusites OR sinuses))) AND (tw:(eosinophils OR eosinófilos OR eosinófilos)))</td>
<td>432</td>
<td>20/01/2020</td>
</tr>
<tr>
<td><strong>WEB OF SCIENCE</strong></td>
<td>TÓPICO: (&quot;Nasal Polyps&quot; OR &quot;Nasal Poly&quot; OR &quot;Poly, Nasal&quot; OR &quot;Poly, Nasal&quot;) AND TÓPICO: (Sinusitis OR Sinusitides OR &quot;Sinus Infections&quot; OR &quot;Infection, Sinus&quot; OR &quot;Infections, Sinus&quot; OR &quot;Sinus Infection&quot;) AND TÓPICO: (Eosinophils OR Eosinophil)</td>
<td>277</td>
<td>20/01/2020</td>
</tr>
<tr>
<td><strong>EMBASE</strong></td>
<td>(nose polyt/exp OR (&quot;nose polyt&quot;/syn) AND (&quot;sinusitis&quot;/exp OR &quot;sinusitis&quot;/syn) AND (&quot;eosinophil&quot;/exp OR &quot;eosinophil&quot;/syn) AND (embase/lim NOT (embase/lim AND (medline/lim)))</td>
<td>386</td>
<td>20/01/2020</td>
</tr>
<tr>
<td><strong>COCHRANE LIBRARY</strong></td>
<td>MeSH descriptor: (Nasal Polyps) explode all trees OR (&quot;Nasal Polyps&quot; OR &quot;Poly, Nasal&quot; OR &quot;Poly, Nasal&quot;) AND MeSH descriptor: (Sinusitis) explode all trees OR (Sinusitis OR Sinusitides OR &quot;Sinus Infections&quot; OR &quot;Infection, Sinus&quot; OR &quot;Infections, Sinus&quot; OR &quot;Sinus Infection&quot;) AND MeSH descriptor: (Eosinophils) explode all trees OR (Eosinophil OR Eosinophil)</td>
<td>55</td>
<td>20/01/2020</td>
</tr>
<tr>
<td><strong>PROQUEST</strong></td>
<td>(MJMESH.EXACT.EXPLODE(&quot;Nasal Polyps:C.08.460.572&quot;) OR MJMESH.EXACT.EXPLODE(&quot;Nasal Polyps:C.09.603.557&quot;) OR (&quot;Nasal Polyps&quot; OR (&quot;Poly, Nasal&quot; OR &quot;Poly, Nasal&quot;) AND MJMESH.EXACT.EXPLODE(&quot;Sinusitis:C.01.748.749&quot;) OR MGHEXACT.EXPLODE(&quot;Sinusitis:C.08.692.752&quot;) OR MJMESH.EXACT.EXPLODE(&quot;Sinusitis:C.08.730.749&quot;) OR MJMESH.EXACT.EXPLODE(&quot;Sinusit is:C.08.692.752&quot;) OR (Sinusitis OR Sinusitides OR &quot;Sinus Infections&quot; OR &quot;Infection, Sinus&quot; OR &quot;Infections, Sinus&quot; OR &quot;Sinus Infection&quot;)) AND (MJMESH.EXACT.EXPLODE(&quot;eosinophil:A.15.145.229.637.415.345&quot;) OR MJMESH.EXACT.EXPLODE(&quot;eosinophil:A.15.382.490.315.251&quot;) OR MJMESH.EXACT.EXPLODE(&quot;eosinophil:A.11.627.340.345&quot;) OR MJMESH.EXACT.EXPLODE(&quot;eosinophil:A.11.118.637.415.345&quot;) OR (eosinophil OR Eosinophil))</td>
<td>466</td>
<td>20/01/2020</td>
</tr>
<tr>
<td><strong>TOTAL</strong></td>
<td></td>
<td>2847</td>
<td></td>
</tr>
<tr>
<td><strong>TOTAL OF DUPLICITIES</strong></td>
<td>1215 STUDIES EXCLUDED WITH ENDNOTE OR 85 STUDIES EXCLUDED WITH RAYYAN</td>
<td>1300</td>
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</tr>
<tr>
<td><strong>TOTAL AFTER DUPLICITY EXCLUSION</strong></td>
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<td>1547</td>
<td></td>
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</tbody>
</table>
### Table: Summary of findings on methodological assessment of e-CRS classification (142 articles)

<table>
<thead>
<tr>
<th>Author</th>
<th>Nationality</th>
<th>Method</th>
<th>Population</th>
<th>biopsy local CRS/controls</th>
<th>classification of e-CRS</th>
<th>cut-off value for e-CRS</th>
<th>Treatment at biopsy / period of restriction or use</th>
<th>literature-justification</th>
<th>Nº of Examinators</th>
<th>Blinded Examiners</th>
<th>Nº of HPF</th>
<th>Selection of HPF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akiyama 2019</td>
<td>Japan</td>
<td>P</td>
<td>45 CRS</td>
<td>superficial meatus NP</td>
<td>JESREC scoring system + histologic eosinophil count</td>
<td>&gt;70 eos/HPF</td>
<td>No systemic corticosteroid /3 months* 2nd Biopsy with systemic corticosteroids and No intranasal steroid sprays, antihistamines or anti-leukotriene</td>
<td>Tokunaga 2015</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>areas of densest cellular infiltrate</td>
</tr>
<tr>
<td>Aslan 2017</td>
<td>Turkey</td>
<td>P</td>
<td>53 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>&gt;10 eos/HPF</td>
<td>No topical or systemic corticosteroid or antibiotic therapy/ 4 weeks</td>
<td>Soler 2010</td>
<td>3</td>
<td>NR</td>
<td>1</td>
<td>areas of densest cellular infiltrate</td>
</tr>
<tr>
<td>Baba 2014</td>
<td>Japan</td>
<td>p</td>
<td>36 CRS 8 Controls</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;50 eos/HPF</td>
<td>No systemic corticosteroid or immunomodulators /1 month</td>
<td>Ishitoya 2010</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
<td>random</td>
</tr>
<tr>
<td>Baba 2014</td>
<td>Japan</td>
<td>P</td>
<td>23 CRS 6 Controls</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;50 eos/HPF</td>
<td>No systemic corticosteroid or immunomodulators /1 month</td>
<td>Ishitoya 2010</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
<td>random</td>
</tr>
<tr>
<td>Baba 2015</td>
<td>Japan</td>
<td>P</td>
<td>31 CRS 8 Controls</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;50 eos/HPF</td>
<td>No systemic corticosteroid or immunomodulators /1 month</td>
<td>Ishitoya 2010</td>
<td>2</td>
<td>yes</td>
<td>5</td>
<td>random</td>
</tr>
<tr>
<td>Baba 2017</td>
<td>Japan</td>
<td>P</td>
<td>34 CRS 7 Controls</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;70 eos/HPF</td>
<td>No systemic corticosteroid or immunomodulators /1 month</td>
<td>Tokunaga 2015</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
<td>random</td>
</tr>
<tr>
<td>Barham 2015</td>
<td>Australia</td>
<td>R</td>
<td>259 CRS</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;10 eos/HPF</td>
<td>No systemic corticosteroid /4 weeks</td>
<td>Soler 2010</td>
<td>NR</td>
<td>yes</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Bellussi 2012</td>
<td>China/Italy</td>
<td>P</td>
<td>21 CRS 8 controls</td>
<td>NP and Nasal Mucosa</td>
<td>histologic eosinophil count</td>
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<td>NR</td>
<td>NR</td>
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<tr>
<td>Bonfils 2009</td>
<td>France</td>
<td>P</td>
<td>144 CRS</td>
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<td>&gt;50% ratio of eos/inflammatory cells</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
<td></td>
</tr>
<tr>
<td>Brescic 2015</td>
<td>Italy</td>
<td>P</td>
<td>143 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>&gt;10 eos/HPF</td>
<td>No oral steroid /3 months No nasal steroid/1 month</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Brescia 2016</td>
<td>Italy</td>
<td>P</td>
<td>114 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>≥10 eos/HPF</td>
<td>No oral steroid /3 months No nasal steroid/1 month</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Brescia 2017</td>
<td>Italy</td>
<td>R</td>
<td>115 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>≥10 eos/HPF</td>
<td>No oral steroid /3 months No nasal steroid/1 month</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Brescia 2018</td>
<td>Italy</td>
<td>R</td>
<td>79 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>≥10 eos/HPF</td>
<td>No oral steroid /3 months No nasal steroid/1 month</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Author</td>
<td>Nationality</td>
<td>Method</td>
<td>Population</td>
<td>Biopsy local CRS/controls</td>
<td>Classification of e-CRS</td>
<td>Cut-off value for e-CRS</td>
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<td>Literature-Justification</td>
<td>Nº of Examinators</td>
<td>Blinded Examiners</td>
<td>Nº of HPF</td>
<td>Selection of HPF</td>
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<tr>
<td>Brescia 2019 [18]</td>
<td>Italy</td>
<td>P</td>
<td>58 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>≥10 Eos/HPF</td>
<td>No oral steroids/3 months No nasal steroid/1 month</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
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<tr>
<td>Brescia 2020 [19]</td>
<td>Italy</td>
<td>R</td>
<td>135 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>≥10 Eos/HPF</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
<td>areas of densest cellular infiltrate</td>
</tr>
<tr>
<td>Cao 2009 [24]</td>
<td>China</td>
<td>P</td>
<td>151 CRS</td>
<td>50 controls</td>
<td>NP tissues (apex region) and diseased ethmoid mucosa tissues</td>
<td>classified as eosinophilic when percent eosinophils exceeded twice the SD of the mean of controls</td>
<td>No oral glucocorticoid/3 months No intranasal steroid sprays/1 month Patients received 3 to 5 days of antibiotics before biopsy</td>
<td>Wenzel 1999 [25]/ cutoff value demonstrated in the article itself</td>
<td>2</td>
<td>yes</td>
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<td>random</td>
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<tr>
<td>Chen (D) 2014 [26]</td>
<td>China/Italy</td>
<td>P</td>
<td>41 CRS</td>
<td>9 Controls</td>
<td>NP, ethmoid sinus and uncinate process mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No topical or systemic corticosteroid / 4 weeks</td>
<td>De Gastro 2013 [27]</td>
<td>2</td>
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<tr>
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<td>China</td>
<td>P</td>
<td>53 CRS</td>
<td>NP and UP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>NR</td>
<td>Cao 2009 [29]</td>
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<td>Yes</td>
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<td>random</td>
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<td>China/Singapore</td>
<td>R</td>
<td>606 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>NR</td>
<td>Gao 2016 [32]</td>
<td>2</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Cho (KS) 2014 [33]</td>
<td>South Korea</td>
<td>P</td>
<td>20 CRS</td>
<td>11 Controls</td>
<td>NP / Inferior Turbinate mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;75% ratio of eos/ inflammatory cells</td>
<td>No oral or topical corticosteroids, nonsteroidal anti-inflammatory drugs, macrolide antibiotics, or antihistamines /4 weeks</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
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<td>Nº of Examinators</td>
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<td>Cho (SN) 2014</td>
<td>South Korea</td>
<td>P</td>
<td>40 CRS 20 Controls</td>
<td>NP / Inferior Turbinates mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>no oral or nasal corticosteroids, antibiotics or antileukotrienes/ 4 weeks</td>
<td>Cao 2009 [26]</td>
<td>NR</td>
<td>NR</td>
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<td>Czerny 2014</td>
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<td>P</td>
<td>33 CRS 7 Controls</td>
<td>Ethmoid Bulla</td>
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<td>&gt;10 Eos/HPF</td>
<td>No systemic steroids/ 3 weeks.</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Brazil</td>
<td>P</td>
<td>20 CRS 6 Controls</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>&gt;30% ratio of eos/ inflammatory cells</td>
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<td>Ingels 1997 [17]</td>
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<td>Yes</td>
<td>4</td>
<td>NR</td>
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<td>Do 2016</td>
<td>Australia</td>
<td>P</td>
<td>110 CRS</td>
<td>maxillary or ethmoid sinus</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No oral corticosteroids/ 4 weeks</td>
<td>Snidvongs 2012 [8]</td>
<td>NR</td>
<td>NR</td>
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<td>Dutsch-Wicher 2010</td>
<td>Poland</td>
<td>P</td>
<td>50 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
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<td>NR</td>
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<td>1</td>
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<td>P</td>
<td>39 CRS</td>
<td>anterior ethmoid sinus</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>no oral steroids or Immunotherapy / 4 weeks</td>
<td>Soler 2010 [44]</td>
<td>2</td>
<td>yes</td>
<td>5</td>
<td>NR</td>
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<tr>
<td>Feng 2016</td>
<td>USA</td>
<td>P</td>
<td>26 CRS 9 Controls</td>
<td>NP / sinus mucosa</td>
<td>histologic eosinophil count</td>
<td>≥5 Eos/HPF</td>
<td>NR</td>
<td>Mattos 2011 [44]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Feng 2019</td>
<td>USA</td>
<td>P</td>
<td>33 CRS 6 Controls</td>
<td>NP / sinus mucosa</td>
<td>histologic eosinophil count</td>
<td>≥5 Eos/HPF</td>
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<td>P</td>
<td>22 CRS 10 Controls</td>
<td>NP / Nasal mucosa</td>
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<td>NR</td>
<td>NR</td>
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<td>Gao 2016</td>
<td>China / Singapore</td>
<td>P</td>
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<td>NP</td>
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<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>NR</td>
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<td>Garin 2008</td>
<td>Spain</td>
<td>P</td>
<td>40 CRS 12 controls</td>
<td>NP / Middle turbinate</td>
<td>histologic eosinophil count</td>
<td>≥5 Eos/HPF</td>
<td>No systemic corticosteroids/ 2 months</td>
<td>Jankowski [44]</td>
<td>NR</td>
<td>NR</td>
<td>4</td>
<td>NR</td>
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<tr>
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<td>Literature - Justification</td>
<td>Nº of Examinators</td>
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<tr>
<td>Gitomer 2016</td>
<td>USA</td>
<td>R</td>
<td>70 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>NR</td>
<td>Snidvongs 2012</td>
<td>1</td>
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<td>Gracic 2015</td>
<td>Croatia</td>
<td>P</td>
<td>30 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>&gt;20 Eos/HPF</td>
<td>NR</td>
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<td>10</td>
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<td>Gu 2011</td>
<td>China</td>
<td>P</td>
<td>41 CRS 11 Controls</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No steroids, nonsteroidal anti-inflammatory drugs, antihistamines, or macrolide antibiotics/ 4 weeks</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>NR</td>
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<td>Gunel 2017</td>
<td>Turkey/ USA</td>
<td>P</td>
<td>39 CRS</td>
<td>ethmoid sinus mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No topical or oral steroids/ 4 weeks Preoperative amoxicillin–clavulanic</td>
<td></td>
<td>1</td>
<td>yes</td>
<td>NR</td>
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<td>Hamad 2018</td>
<td>Lebanon</td>
<td>R</td>
<td>76 CRS</td>
<td>Not Reported</td>
<td>histologic eosinophil count</td>
<td>≥5 Eos/ HPF</td>
<td>NR</td>
<td>Kountakis 2004</td>
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<td>NR</td>
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<td>Hauser 2017</td>
<td>USA</td>
<td>P</td>
<td>59 CRS 10 Controls</td>
<td>ethmoid bulla/ Ethmoid sinus, sphenoid face</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No systemic steroids/ 4 weeks</td>
<td>Barham 2015,Snidvongs 2012, Soler 2010, Soy 2013</td>
<td>1</td>
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<td>Japan</td>
<td>P</td>
<td>70 CRS</td>
<td>NP located in the middle meatus</td>
<td>histologic eosinophil count</td>
<td>&gt;200 Eos/ HPF</td>
<td>No antibiotics, systemic or topical corticosteroids, or other immune-modulating drugs / 1 month</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
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<tr>
<td>Hirotsu 2014</td>
<td>Japan</td>
<td>P</td>
<td>35 CRS 15 Controls</td>
<td>NP located in the middle meatus/ Sphenoid sinus mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;100 Eos/HPF</td>
<td>No antibiotics, systemic or topical corticosteroids, or other immune-modulating drugs / 1 month</td>
<td>Ikeda 2013, Saitoh 2010</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>areas of densest cellular infiltrate</td>
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<td>Ho 2015</td>
<td>Australia</td>
<td>P</td>
<td>26 CRS 9 Controls</td>
<td>Ethmoid sinuses/ Sphenoid sinus</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No systemic steroids/ 4 weeks</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Ho 2018</td>
<td>Australia</td>
<td>P</td>
<td>345 CRS</td>
<td>Sinuses mucosal</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No systemic steroids/ 4 weeks</td>
<td>Barham 2015, Snidvongs 2012</td>
<td>NR</td>
<td>yes</td>
<td>2</td>
<td>NR</td>
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<tr>
<td>Author</td>
<td>Nationality</td>
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<td>Classification of e-CRS</td>
<td>Cut-off value for e-CRS</td>
<td>Treatment at biopsy / period of restriction or use</td>
<td>Literature-Justification</td>
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<td>Hu 2012</td>
<td>China</td>
<td>P</td>
<td>155 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No oral glucocorticoid/ 3 months No intranasal steroid/ 1 month</td>
<td>Cao 2009 [24]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Hupin 2013</td>
<td>Belgium</td>
<td>P</td>
<td>23 CRS 10 Controls</td>
<td>CRS</td>
<td>histologic eosinophil count</td>
<td>≥ 2 Eos/HPF</td>
<td>no oral and nasal corticosteroids or antibiotics/ 3 weeks</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
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<td>Iinuma 2015</td>
<td>Japan</td>
<td>P</td>
<td>69 CRS 16 Controls</td>
<td>CRS</td>
<td>histologic eosinophil count</td>
<td>&gt;70 Eos/HPF</td>
<td>no systemic steroids/4 weeks</td>
<td>Nakayama 2011 [26]</td>
<td>2</td>
<td>yes</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Ikeda 2013</td>
<td>Japan</td>
<td>P</td>
<td>130 CRS</td>
<td>NP tissue middle meatus</td>
<td>histologic eosinophil count</td>
<td>&gt;100 Eos/HPF</td>
<td>NR</td>
<td>cutoff value demonstrated in the article itself</td>
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<td>NR</td>
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<td>Ito 2019</td>
<td>Japan</td>
<td>R</td>
<td>68 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;70 eos/HPF</td>
<td>no systemic or nasal steroids/1 month</td>
<td>Tokunaga 2015 [27]</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>areas of densest cellular infiltrate</td>
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<tr>
<td>Jang 2018</td>
<td>South Korea</td>
<td>P</td>
<td>31 CRS 7 Controls</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No decongestants, antibiotics, topical or systemic corticosteroids/4 weeks</td>
<td>Cao 2009, Lee 2016 [28]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Jeong 2010</td>
<td>South Korea</td>
<td>P</td>
<td>118 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>≥11% ratio of eos/ inflammatory cells</td>
<td>No antihistamine, systemic or intranasal corticosteroids / 1 month</td>
<td>cutoff value demonstrated in the article itself</td>
<td>2</td>
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<td>Jiang 2011</td>
<td>China</td>
<td>P</td>
<td>42 CRS 10 Controls</td>
<td>NP</td>
<td>classified as eosinophilic when the percentage of eosinophils exceeded twice the SD of the mean controls</td>
<td>&gt;8% ratio of eos/ inflammatory cells</td>
<td>No glucocorticoid, antihistamine, and antibiotic therapy/ NR</td>
<td>Wenzel 1999 [29]</td>
<td>2</td>
<td>yes</td>
<td>10</td>
<td>random</td>
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<tr>
<td>Jin 2014</td>
<td>South Korea</td>
<td>P</td>
<td>40 CRS 15 Controls</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/inflammatory cells</td>
<td>No oral or nasal corticosteroids, antibiotics, antileukotrienes/4 weeks</td>
<td>Cao 2009 [24]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Author</td>
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<td>Biopsy local CRS/controls</td>
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<td>Cut-off value for e-CRS</td>
<td>Treatment at biopsy / period of restriction or use</td>
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<td>Nº of Examinators</td>
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<td>Jung 2019</td>
<td>South Korea</td>
<td>P</td>
<td>32 CRS</td>
<td>NP/ Uncinate Process</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No systemic or topical steroids, antibiotics or antihistamine /4 weeks</td>
<td>NR</td>
<td>2</td>
<td>yes</td>
<td>NR</td>
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<td>Kagaoya 2015</td>
<td>Japan</td>
<td>P</td>
<td>33 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;50 eos/HFP</td>
<td>No systemic corticosteroids or other immunomodulating drugs /1 month</td>
<td>NR</td>
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<td>Yes</td>
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<td>Kambara 2017</td>
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<td>P</td>
<td>45 CRS</td>
<td>NR</td>
<td>JESREC scoring system + histologic eosinophil count</td>
<td>&gt;70 eos/HFP</td>
<td>No Systemic or topical steroids / NR Inhaled steroids were not restricted</td>
<td>Tokunaga 2015</td>
<td>NR</td>
<td>NR</td>
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<td>Kato 2018</td>
<td>Japan</td>
<td>P</td>
<td>114 CRS</td>
<td>NP</td>
<td>JESREC scoring system + histologic eosinophil count</td>
<td>&gt;70 eos/HFP</td>
<td>NR</td>
<td>Tokunaga 2015</td>
<td>NR</td>
<td>NR</td>
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<td>Kawanomo 2012</td>
<td>Japan</td>
<td>P</td>
<td>17 CRS</td>
<td>NP/ Sphenoid sinus</td>
<td>histologic eosinophil count</td>
<td>&gt;350 Eos/HFP</td>
<td>No systemic corticosteroids or immunomodulating drugs / NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>South Korea</td>
<td>P</td>
<td>56 CRS</td>
<td>NP/ UP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No antibiotics, systemic or topical corticosteroids, or immunomodulating drugs /4 weeks</td>
<td>Cao 2009, Jeong 2011</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>South Korea</td>
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<td>160 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;70 eos/HFP</td>
<td>No antibiotics, systemic or topical corticosteroids, or immunomodulating drugs /4 weeks</td>
<td>Tokunaga 2015</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Kim (DW) 2016</td>
<td>South Korea</td>
<td>P</td>
<td>133 CRS</td>
<td>uncinate process or NP tissues</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No oral or topical steroids and oral antibiotics /4 weeks</td>
<td>Shin 2015, Mahdavinia 2015</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Kim (DW) 2017</td>
<td>South Korea</td>
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<td>130 CRS</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No antibiotics, systemic or topical corticosteroids, or other immunomodulating drugs /4 weeks</td>
<td>NR</td>
<td>NR</td>
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<td>South Korea</td>
<td>P</td>
<td>30 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;5% ratio of eos/ inflammatory cells</td>
<td>No Systemic or topical steroids / NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>5 NR</td>
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<tr>
<td>Kim (JW) 2018</td>
<td>South Korea</td>
<td>R</td>
<td>375 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;20% ratio of eos/ inflammatory cells</td>
<td>No systemic corticosteroids / 4 weeks</td>
<td>Kim 2013</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Kim (JY) 2019</td>
<td>South Korea</td>
<td>P</td>
<td>15 CRS</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No oral or spray steroids / 3 months</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
<td>5 Random</td>
<td></td>
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<tr>
<td>Author</td>
<td>Nationality</td>
<td>Method</td>
<td>Population</td>
<td>Biopsy local CRS/ controls</td>
<td>Classification of e-CRS</td>
<td>Cut-off value for e-CRS</td>
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</tr>
<tr>
<td>Kim (SJ) 2013</td>
<td>South Korea</td>
<td>P</td>
<td>230 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;5 Eos/HPF</td>
<td>No systemic or topical steroids/ 2 weeks</td>
<td>Kountakis 2004 [50]</td>
<td>2</td>
<td>NR</td>
<td>10</td>
<td>areas of densest cellular infiltrate</td>
</tr>
<tr>
<td>Kim (SY) 2013</td>
<td>South Korea</td>
<td>R</td>
<td>432 CRS</td>
<td>NP or inflamed ethmoid sinus mucosa and NP</td>
<td>histologic eosinophil count</td>
<td>&gt;20% ratio of eos/ inflammatory cells</td>
<td>No oral glucocorticoid/ 1 month</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Kountakis 2004</td>
<td>USA</td>
<td>P</td>
<td>52 CRS</td>
<td>sinus mucosal and NP</td>
<td>histologic eosinophil count</td>
<td>&gt;5 Eos/HPF</td>
<td>No oral Corticosteroids/2 weeks</td>
<td>cutoff value demonstrated in the article itself</td>
<td>NR</td>
<td>Yes</td>
<td>5</td>
<td>NR</td>
</tr>
<tr>
<td>Koyama 2018</td>
<td>Japan</td>
<td>P</td>
<td>71 CRS 13 Controls</td>
<td>NP/UP</td>
<td>JESREC scoring system + histologic eosinophil count</td>
<td>&gt;70 eos/HPF</td>
<td>No oral corticosteroids/ 8 weeks</td>
<td>No macrolide antibiotics and intranasal corticosteroids/ 3 weeks</td>
<td>Tokunaga 2015 [57]</td>
<td>1</td>
<td>Yes</td>
<td>3</td>
</tr>
<tr>
<td>Kuhar 2017</td>
<td>USA</td>
<td>P</td>
<td>114 CRS</td>
<td>ethmoid sinus tissue</td>
<td>histologic eosinophil count</td>
<td>&gt;5 Eos/HPF</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lee (M) 2015</td>
<td>South Korea</td>
<td>P</td>
<td>46 CRS 11 Controls</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No antibiotics and topical steroids/ 2 weeks</td>
<td>No oral corticosteroids/ NR</td>
<td>Cao 2009 [24]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Lee (W) 2017</td>
<td>China</td>
<td>R</td>
<td>61 CRS 27 Controls</td>
<td>NP /UP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No Steroids or antibiotics/ 1 month</td>
<td>Cao 2009 [24]</td>
<td>2 (3 in case of disagreement)</td>
<td>NR</td>
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<tr>
<td>Loesel 2001</td>
<td>USA</td>
<td>R</td>
<td>54 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>&gt;75% ratio of eos/ inflammatory cells</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Author</td>
<td>Nationality</td>
<td>Method</td>
<td>Population</td>
<td>Biopsy location</td>
<td>CRS/controls</td>
<td>Classification of e-CRS</td>
<td>Cut-off value for e-CRS</td>
<td>Treatment at biopsy / period of restriction or use</td>
<td>Literature-Justification</td>
<td>Nº of Examinators</td>
<td>Blinded Examiners</td>
<td>Nº of HPF</td>
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<tr>
<td>Lou et al. 2015</td>
<td>China</td>
<td>R</td>
<td>387 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;27% ratio of Eos/Inflammatory cells or &gt;55 eos/HPF</td>
<td>No antibiotics or corticosteroids/4 weeks</td>
<td>cutoff value demonstrated in the article itself</td>
<td>2</td>
<td>Yes</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>Lou et al. 2016</td>
<td>China</td>
<td>R</td>
<td>366 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>≥54.5% ratio of Eos/Inflammatory cells</td>
<td>NR</td>
<td>cutoff value demonstrated in the article itself</td>
<td>2</td>
<td>yes</td>
<td>10</td>
<td>NR</td>
</tr>
<tr>
<td>Ma et al. 2016</td>
<td>China</td>
<td>P</td>
<td>177 CRS</td>
<td>NP from middle meatus/inferior turbinate mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/Inflammatory cells</td>
<td>No oral glucocorticoid/3 months No intranasal steroid spray/1 month No antileukotrienes or immunotherapy</td>
<td>Cao 2009 [24]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Marino et al. 2019</td>
<td>Japan</td>
<td>R</td>
<td>56 CRS</td>
<td>NP or sinus mucosa</td>
<td>CRS with nasal polyps + histologic eosinophil count or eosinophilic mucin</td>
<td>&gt;120 Eos/HPF</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>yes</td>
<td>3</td>
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<tr>
<td>Meng et al. 2016</td>
<td>China</td>
<td>P</td>
<td>200 CRS</td>
<td>Ethmoid sinus</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/Inflammatory cells</td>
<td>No antibiotics or corticosteroids/4 weeks</td>
<td>Cao 2009 [24]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>Mori et al. 2013</td>
<td>Japan</td>
<td>P</td>
<td>621 CRS</td>
<td>NP or sinus mucosa</td>
<td>CRS with nasal polyps + histologic eosinophil count or eosinophilic mucin</td>
<td>&gt;120 Eos/HPF</td>
<td>NR</td>
<td></td>
<td>Meltzer 2006 [101]</td>
<td>NR</td>
<td>Yes</td>
<td>3</td>
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<tr>
<td>Mortuaire et al. 2015</td>
<td>France</td>
<td>P</td>
<td>36 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;50% of Eos/Inflammatory cells</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>2</td>
<td>yes</td>
<td>1</td>
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<tr>
<td>Nakayama et al. 2011</td>
<td>Japan</td>
<td>P</td>
<td>223 CRS</td>
<td>NP or mucosa of the ethmoid sinus</td>
<td>JESREC scoring system + histologic eosinophil count</td>
<td>&gt;70 eos/HPF</td>
<td>No oral steroid or antimicrobial agents/4 weeks</td>
<td>cutoff value demonstrated in the article itself</td>
<td>3</td>
<td>yes</td>
<td>NR</td>
<td>areas of densest cellular infiltrate</td>
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<tr>
<td>Nakayama et al. 2012</td>
<td>Japan</td>
<td>R</td>
<td>435 CRS</td>
<td>NR</td>
<td>histologic eosinophil count (Cluster analysis)</td>
<td>≥80.5 Eos/HPF</td>
<td>No oral steroid or antimicrobial agents/4 weeks</td>
<td>cutoff value demonstrated in the article itself</td>
<td>3</td>
<td>yes</td>
<td>NR</td>
<td>areas of densest cellular infiltrate</td>
</tr>
<tr>
<td>Author</td>
<td>Nationality</td>
<td>Method</td>
<td>Population</td>
<td>Biopsy local CRS/controls</td>
<td>Classification of e-CRS</td>
<td>Cut-off value for e-CRS</td>
<td>Treatment at biopsy / period of restriction or use</td>
<td>Literature-Justification</td>
<td>N° of Examinators</td>
<td>Blinded Examiners</td>
<td>N° of HPF</td>
<td>Selection of HPF</td>
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<tr>
<td>Nakayama 2016</td>
<td>Japan</td>
<td>P</td>
<td>36 CRS</td>
<td>5 Controls</td>
<td>JESREC scoring system + histologic eosinophil count</td>
<td>&gt;70 eos/HPF</td>
<td>No oral steroid or antimicrobial agents/4 weeks</td>
<td>Tokunaga 2015 [2]</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>areas of densest cellular infiltrate</td>
</tr>
<tr>
<td>Tokunaga 2015</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>No oral steroid or antimicrobial agents/4 weeks</td>
<td>Tokunaga 2015 [2]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Okada 2018</td>
<td>Japan</td>
<td>P</td>
<td>22 CRS</td>
<td>7 controls</td>
<td>JESREC scoring system + histologic eosinophil count</td>
<td>≥70 eos/HPF</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Ono 2013</td>
<td>Japan</td>
<td>P</td>
<td>59 CRS</td>
<td>20 Controls</td>
<td>histologic eosinophil count</td>
<td>&gt;100 Eos/HPF</td>
<td>No systemic corticosteroids or other immune-modulating drugs/1 month</td>
<td>Ikeda 2013 [5]</td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
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<tr>
<td>Papagianopoulos 2018</td>
<td>USA</td>
<td>P</td>
<td>107 CRS</td>
<td>ethmoid sinus tissue</td>
<td>histologic eosinophil count</td>
<td>&gt;5 Eos/HPF</td>
<td>NR</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Papagianopoulos 2019</td>
<td>USA</td>
<td>R</td>
<td>222 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>&gt;5 Eos/HPF</td>
<td>+immunosuppressive therapy</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Parrino 2018</td>
<td>Italy</td>
<td>P</td>
<td>194 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>≥10 Eos/HPF</td>
<td>Oral steroids/ 3 months nasal steroid/ 1 month</td>
<td>NR</td>
<td>1</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
</tr>
<tr>
<td>Payne 2008</td>
<td>USA</td>
<td>P</td>
<td>2 CRS</td>
<td>2 Controls</td>
<td>histologic eosinophil count</td>
<td>≥ 5 Eos/HPF</td>
<td>No oral steroids/NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
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<tr>
<td>Payne 2011</td>
<td>USA</td>
<td>P</td>
<td>105 CRS</td>
<td>17 Controls</td>
<td>histologic eosinophil count</td>
<td>≥ 5 Eos/HPF</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>Yes</td>
<td>10</td>
<td>random</td>
</tr>
<tr>
<td>Author</td>
<td>Nationality</td>
<td>Method</td>
<td>Population</td>
<td>Biopsy local CRS/controls</td>
<td>Classification of e-CRS</td>
<td>Cut-off value for e-CRS</td>
<td>Treatment at biopsy / period of restriction or use</td>
<td>Literature-Justification</td>
<td>N° of Examinators</td>
<td>Blinded Examiners</td>
<td>N° of HPF</td>
<td>Selection of HPF</td>
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<tr>
<td>Plewka</td>
<td>Poland</td>
<td>P</td>
<td>40 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No topical or systemic glucocorticoids and antihistaminic/4 weeks</td>
<td>Cao 2009, Fokkens 2012 [90,113]</td>
<td>NR</td>
<td>NR</td>
<td>10</td>
<td>NR</td>
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<tr>
<td>Rosati</td>
<td>Italy</td>
<td>P</td>
<td>44 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;20% ratio of eos/ inflammatory cells</td>
<td>No antibiotic and oral or nasal steroids/4 weeks No antileukotrienes/2 weeks</td>
<td>Nakayama 2011 [83], Kountakis 2004 [95], Soler 2009 [115], Kim 2013 [90], Wen 2012 [116], Soler 2010 [95], Ikeda 2013 [83], Mori 2013 [100], Matsuwaki 2008 [90], Yao 2009 [117], Kim 2007 [81], Cao 2009 [24], Jankowski 2002 [95], Hu 2012 [95], Jeong 2011 [81], Bonfils 2009 [11], Tecomter 2015 [116], Tikaran 2013 [119], Bhattacharyya 2001 [120]</td>
<td>1</td>
<td>yes</td>
<td>10</td>
<td>NR</td>
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<tr>
<td>Seif</td>
<td>Iran</td>
<td>P</td>
<td>35 CRS</td>
<td>NP / Inferior turbinate</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No systemic or nasal corticosteroids, antibiotics, antihistamines, decongestants, and anti-leukotrienes/4 weeks</td>
<td>Cao 2009 [24]</td>
<td>1</td>
<td>yes</td>
<td>5</td>
<td>random</td>
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<tr>
<td>Shen</td>
<td>Taiwan</td>
<td>P</td>
<td>100 CRS</td>
<td>Ostialomental complex mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No oral Steroids/3 months</td>
<td>Kountakis 2004 [90], Soler 2009 [115], Snidvongs 2013/2012 [5,120]</td>
<td>1</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Author</td>
<td>Nationality</td>
<td>Method</td>
<td>Population</td>
<td>Biopsy local CRS/controls</td>
<td>Classification of e-CRS</td>
<td>Cut-off value for e-CRS</td>
<td>Treatment at biopsy / period of restriction or use</td>
<td>Literature-Justification</td>
<td>Nº of Examinators</td>
<td>Blinded Examiners</td>
<td>Nº of HPF</td>
<td>Selection of HPF</td>
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<tr>
<td>Shi 2013</td>
<td>China P</td>
<td>P</td>
<td>148 CRS</td>
<td>33 controls</td>
<td>Ethmoid sinus mucosa or NP tissues/ inferior turbinate</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>NR</td>
<td></td>
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<td>Cao 2009 [24]</td>
<td></td>
<td>2</td>
<td>yes</td>
<td>NR</td>
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<tr>
<td>Snidvongs 2012</td>
<td>Australia P</td>
<td>P</td>
<td>51 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No oral steroid/ 4 weeks</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Snidvongs 2013</td>
<td>Australia P</td>
<td>P</td>
<td>88 CRS</td>
<td>NR</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No oral steroid/ 4 weeks</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>3</td>
<td>NR</td>
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<tr>
<td>Snidvongs 2013</td>
<td>Australia P</td>
<td>P</td>
<td>70 CRS</td>
<td>Ethmoid Bulla</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No oral steroid/ 4 weeks</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Soler 2009</td>
<td>USA P</td>
<td>P</td>
<td>147 CRS</td>
<td>Ethmoid mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;5 Eos/HPF</td>
<td>+ oral prednisone taper and oral antibiotics/ 7 days + topical nasal steroid</td>
<td>NR</td>
<td>1</td>
<td>YES</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Soler 2010</td>
<td>USA P</td>
<td>P</td>
<td>147 CRS</td>
<td>Ethmoid mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>+ oral prednisone taper and oral antibiotics/ 7 days + topical nasal steroid</td>
<td>cutoff value demonstrated in the article itself</td>
<td>1</td>
<td>YES</td>
<td>NR</td>
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<td>Soler 2010</td>
<td>USA P</td>
<td>P</td>
<td>110 CRS</td>
<td>ethmoid sinus</td>
<td>histologic eosinophil count</td>
<td>&gt;5 Eos/HPF</td>
<td>+ oral prednisone taper and oral antibiotics/ 7 days + topical nasal steroid</td>
<td>Soler 2009 [115]</td>
<td>1</td>
<td>YES</td>
<td>NR</td>
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<tr>
<td>Soy 2013</td>
<td>Turkey P</td>
<td>P</td>
<td>57 CRS</td>
<td>ethmoid sinus</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>NR</td>
<td></td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Szucs 2002</td>
<td>Belgium R</td>
<td>P</td>
<td>47 CRS</td>
<td>ethmoid sinus</td>
<td>histologic eosinophil count</td>
<td>&gt;3% ratio of eos/ inflammatory cells</td>
<td>+ antibiotics/3 weeks (8 patients) + Oral corticosteroids/ 12 days (4 patients) + topical corticosteroids (1 patient) + cetirizine (10 patients)</td>
<td>Rothemberg 1998 [130]</td>
<td>1</td>
<td>NR</td>
<td>10</td>
<td>Random</td>
</tr>
<tr>
<td>Tajudeen 2018</td>
<td>USA P</td>
<td>P</td>
<td>101 CRS</td>
<td>sinus tissue</td>
<td>histologic eosinophil count</td>
<td>&gt;5 Eos/HPF</td>
<td>Prednisone use was at the discretion of the surgeon</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Tang 2018</td>
<td>China P</td>
<td>P</td>
<td>70 CRS</td>
<td>NP/ Inferior turbinate</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/ inflammatory cells</td>
<td>No oral or topical corticosteroids, antihistamines, and antibiotics/ 1 month</td>
<td>Cao 2009 [124]</td>
<td>NR</td>
<td>NR</td>
<td>10</td>
<td>Random</td>
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<td>Tecimer 2014</td>
<td>Turkey P</td>
<td>P</td>
<td>40 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;50% ratio of eos/ inflammatory cells</td>
<td>+ Topical steroids / 6 months</td>
<td>NR</td>
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<td>NR</td>
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<td>Teranishi 2016</td>
<td>Finland</td>
<td>R</td>
<td>80 CRS/29 Controls</td>
<td>NP/Inferior turbinate</td>
<td>histologic eosinophil count</td>
<td>&gt;20% ratio of eos/ inflammatory cells</td>
<td>No aspirin desensitization, allergen immunotherapy or anti-IgE/ NR</td>
<td>NR</td>
<td>2</td>
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<td>Thaitrakool 2018</td>
<td>Thailand</td>
<td>P</td>
<td>30 CRS</td>
<td>NP apex, NP pedicle and ethmoid mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;10 eos/HPF</td>
<td>No antibiotics, topical corticosteroids or systemic corticosteroids/ 4 weeks</td>
<td>Snidvongs 2012, Soler 2010 [4,5]</td>
<td>1</td>
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<td>NR</td>
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<td>R</td>
<td>1716 CRS</td>
<td>NP or ethmoid polyoid mucosa</td>
<td>histologic eosinophil count</td>
<td>&gt;70 eos/HPF</td>
<td>No systemic or topical corticosteroids/NR</td>
<td>cutoff value demonstrated in the article itself</td>
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<td>Japan</td>
<td>R</td>
<td>60 CRS</td>
<td>NP</td>
<td>JESREC scoring system + histologic eosinophil count</td>
<td>&gt;70 eos/HPF</td>
<td>NR</td>
<td>Tokunaga 2015 [2]</td>
<td>NR</td>
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<td>Finland</td>
<td>P</td>
<td>41 CRS</td>
<td>NP</td>
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<td>NR</td>
<td>Holopainen 1979 [138]</td>
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<td>Vlaminck 2014</td>
<td>Belgium</td>
<td>P</td>
<td>221 CRS</td>
<td>Mucosa tissue</td>
<td>histologic eosinophil count</td>
<td>&gt;5 Eos/HPF</td>
<td>No systemic steroids/ 6 weeks + topical steroids</td>
<td>Soler 2009 [117]</td>
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<td>NR</td>
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<td>NP</td>
<td>histologic eosinophil count</td>
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<td>No antibiotics or steroids/ 4 weeks.</td>
<td>Cao 2009 [144]</td>
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<td>183 CRS</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/inflammatory cells</td>
<td>No systemic corticosteroids/3 months</td>
<td>NR</td>
<td>2</td>
<td>Yes</td>
<td>5</td>
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<td>Wei 2018</td>
<td>China</td>
<td>P</td>
<td>63 CRS 25 Controls</td>
<td>NP/UP</td>
<td>mean value in the healthy control subjects (2.21) plus 2 times the standard deviation (SD)</td>
<td>&gt;7 Eos/HPF</td>
<td>No systemic corticosteroids/4 weeks</td>
<td>NR</td>
<td>NR</td>
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<td>USA</td>
<td>P</td>
<td>10 CRS 10 Controls</td>
<td>NP</td>
<td>histologic eosinophil count</td>
<td>&gt;10 Eos/HPF</td>
<td>No antibiotics, topical or systemic Steroids/4 weeks</td>
<td>Gunel 2017[46]</td>
<td>2</td>
<td>NR</td>
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<td>P</td>
<td>31 CRS 16 Controls</td>
<td>NP/UP</td>
<td>histologic eosinophil count</td>
<td>&gt;8 Eos/HPF</td>
<td>No oral, nasal steroids or other immune-modulating drugs/4 weeks</td>
<td>Wen 2012[116]</td>
<td>NR</td>
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<td>China</td>
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<td>Ethmoid sinus mucosa and NP/ inferior turbinate</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/inflammatory cells</td>
<td>No steroids, nonsteroidal anti-inflammatory drugs, and anti-leukotrienes/3 months</td>
<td>Cao 2009[24]</td>
<td>2</td>
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<td>Xu 2015</td>
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<td>P</td>
<td>83 CRS 20 Controls</td>
<td>NP apex region/ inferior turbinate</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/inflammatory cells</td>
<td>No Oral glucocorticoid/3 months</td>
<td>Hu 2012[256]</td>
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<td>USA</td>
<td>P</td>
<td>97 CRS</td>
<td>NP or polyoid lesions of the ethmoid cavity</td>
<td>histologic eosinophil count</td>
<td>&gt;55 Eos/HPF</td>
<td>No systemic or topical corticosteroids/ NR</td>
<td>Cao 2009[24]</td>
<td>3</td>
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<td>China</td>
<td>P</td>
<td>244 CRS 40 Controls</td>
<td>NP/Inferior turbinate</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/inflammatory cells</td>
<td>No oral glucocorticoid, intranasal steroid spray and anti-leukotriene/4 weeks</td>
<td>Cao 2009[24]</td>
<td>NR</td>
<td>NR</td>
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<tr>
<td>Yang 2017</td>
<td>China</td>
<td>P</td>
<td>60 CRS 16 Controls</td>
<td>NP ethmoid sinus mucosa or uncinate processes/ Inferior turbinate, ethmoid sinus, UP</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/inflammatory cells</td>
<td>No corticosteroids or antibiotics/ 1 month</td>
<td>Cao 2009 [24]</td>
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<td>Yao 2009</td>
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<td>33 CRS</td>
<td>NP located in the middle meatus/ sphenoid sinus</td>
<td>histologic eosinophil count</td>
<td>&gt;350 Eos/HPF</td>
<td>No systemic corticosteroids or other immune modulating Drugs/ NR</td>
<td>NR</td>
<td>2</td>
<td>NR</td>
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<td>Yoshida 2018</td>
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<td>P</td>
<td>70 CRS 33 Controls</td>
<td>NP tissue or ethmoid cavity</td>
<td>histologic eosinophil count</td>
<td>&gt;70 eos/HPF</td>
<td>NR</td>
<td>Tokunaga 2015 [5]</td>
<td>NR</td>
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<td>No local or systemic medications, such as glucocorticoids and macrolides/ 4 weeks</td>
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<td>176 CRS 109 Controls</td>
<td>NP/ Ethmoid sinus or inferior turbinate</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/inflammatory cells</td>
<td>No Oral glucocorticoid/3 months No intranasal steroid sprays/1 month No antileukotrienes or immunotherapy.</td>
<td>Cao 2009 [24]</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
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<td>P</td>
<td>73 CRS 45 Controls</td>
<td>NP/ Inferior turbinate</td>
<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos/inflammatory cells</td>
<td>No Oral glucocorticoid/3 months No intranasal steroid sprays/1 month No antileukotrienes or immunotherapy</td>
<td>Cao 2009 [24]</td>
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<td>NR</td>
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<td>histologic eosinophil count</td>
<td>&gt;10% ratio of eos / inflammatory cells</td>
<td>No Oral glucocorticoid or antihistamines / 3 months No intranasal steroid sprays / 1 month No antileukotrienes or immunotherapy</td>
<td>Cao 2009 [24]</td>
<td>NR</td>
<td>NR</td>
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References


84. Kuchar HN, Tajudeen BA, Hellingoetter A, et al. Distinct histopathologic features of radii...
106. Tajuddeen BA, Ganti A, Kuarth HN, et al. The...


