Evaluation of Prolonged vs Short Courses of Antibiotic Prophylaxis Following Ear, Nose, Throat, and Oral and Maxillofacial Surgery: A Systematic Review and Meta-analysis

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**IMPORTANCE**
Antibiotic prophylaxis is widely used after surgical procedures operating on the mucosal tissues of the aerodigestive tract, but the optimal duration of these prophylactic therapies is often unclear.

**OBJECTIVE**
To compare short-course antibiotic prophylaxis (≤24-hours) vs extended-course antibiotic prophylaxis (≥72-hours) after ear, nose, throat, and oral and maxillofacial surgery.

**DATA SOURCES AND STUDY SELECTION**
Literature searches of PubMed were completed in October 2017 and included prospective trials that compared antibiotic prophylaxis courses of 24-hours or less vs 72-hours or more after ear, nose, throat, and oral and maxillofacial surgery. Some studies were also handpicked from reference lists of studies found with the initial search terms. All analysis was performed between September 2017 and October 2018.

**DATA EXTRACTION AND SYNTHESIS**
All review stages were conducted in consensus by 2 reviewers. Data extraction and study quality assessment were performed with the Cochrane data extraction form and the Cochrane risk of bias tool. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were used for reporting. The fixed-effects Mantel-Haenszel method was used for meta-analysis.

**MAIN OUTCOMES AND MEASURES**
Relative risk (RR) of surgical site infections, microbial origins of surgical site infections, adverse events, duration of hospital stay, and treatment costs.

**RESULTS**
Included in the meta-analysis were 21 articles with a cumulative 1974 patients. In patients receiving 24-hours or shorter vs 72-hours or longer antibiotic prophylaxis regimens, no significant difference was found in the occurrence of postoperative infections in the pooled population (RR, 0.90; 95% CI, 0.67-1.19), or in the ear, nose, throat (RR, 0.89; 95% CI, 0.54-1.45), and oral and maxillofacial populations (RR, 0.88; 95% CI, 0.63-1.21), separately. No heterogeneity was observed overall or in the subgroups. Patients receiving extended-course antibiotic prophylaxis were significantly more likely to develop adverse events unrelated to the surgical site (RR, 2.40; 95% CI, 1.20-3.54).

**CONCLUSIONS AND RELEVANCE**
No difference was found in the occurrence of postoperative infections between short-course and extended-course antibiotic prophylaxis after ear, nose, throat, and oral and maxillofacial surgery. Therefore, a short course of antibiotic prophylaxis is recommended unless documented conditions are present that would be best treated with an extended course. Using short-course antibiotics could avoid additional adverse events, antibiotic resistance development, and higher hospital costs. Future research should focus on identifying risk groups that might benefit from prolonged prophylaxis.
To prevent surgical site infections (SSIs), antibiotic prophylaxis is used in most surgical interventions where the surgical site is either clean-contaminated or contaminated.1,2 This is the case in most otorhinolaryngologic (ENT) and oral and maxillofacial (OMF) surgical procedures because of the involvement of the mucosal tissues of the aerodigestive tract, which are covered with high loads of both aerobic and anaerobic bacteria, with the exclusion of tonsillectomies and adenotomies. This makes surgery in ENT and OMF sites prone to postoperative wound infections.1,2

Presently, existing evidence favors short-course postoperative prophylaxis (<24 hours) over prolonged prophylaxis (>72 hours), since little to no additional antimicrobial benefits have been observed after prolonging the postoperative antibiotic prophylaxis period.1,3 In the clinical practice guideline for antimicrobial prophylaxis in surgery published by the Surgical Infection Society, most recommendations concerning surgical antibiotic prophylaxis in the head and neck region were graded with much lower evidence than the recommendations for urology, vascular surgery, neurosurgery, cardiac surgery, and gastroduodenal surgery.1 This contrast highlights the lack of evidence on the postoperative use of antimicrobial prophylaxis in the field of ENT and OMF surgery, especially after those procedures that invade contaminated tissues.

Despite the current lack of evidence, the fear of SSIs is still considerably larger than the fear of possible adverse effects or antimicrobial resistance resulting from prolonged antibiotic administration.3,7 As a result, antibiotic prophylaxis regimens are often prolonged when they might not be necessary.3,7 However, in light of the antimicrobial resistance issue, the increased risk of serious postoperative adverse effects, and additional pharmaceutical costs, it is becoming extremely difficult to ignore the need for solid evidence on the ideal duration of postoperative antibiotic prophylaxis. The aim of this study is to systematically review the literature and perform a meta-analysis focused on the association of SSIs with use of short-course antibiotic prophylaxis (<24 hours) vs extended-course antibiotic prophylaxis (>72 hours) after ENT and OMF surgery.

**Methods**

**Search Strategy and Study Selection**
A systematic literature PubMed search was conducted using the search terms listed in eAppendix 1 in the Supplement and was completed on October 9, 2017. All analysis was conducted between September 2017 and October 2018. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines checklist was used during the process of systematic review and meta-analysis (eTable 1 in the Supplement). Additionally, eligible articles were handpicked from the reference lists of studies during the initial search. Publications were included if they met the following inclusion criteria: (1) the study was a prospective clinical trial; (2) postsurgical infections were reported as a dichotomous outcome measure; and (3) the comparison of short-course antibiotic prophylaxis vs extended-course antibiotic prophylaxis was made.

**Risk of Bias Assessment**

The Cochrane collaboration tool for assessing risk of bias in randomized trials6 was used for assessing the methodological quality of the included studies. The risk of bias assessment included randomization, allocation concealment, blinding of participants, personnel involved in the trials (ie, nursing staff, pharmacists, physicians, and outcome assessors), and incomplete outcome data. Bias assessment was performed by the first 2 coauthors separately (M.C.O. and C.Z.).

**Data Extraction**

Data extraction was performed by the first 2 coauthors independently (M.C.O. and C.Z.). To minimize bias, data from included studies were extracted using the 2013 Data Extraction Form7 provided by Cochrane. All relevant data for the present study can be extracted with this form, including information on study characteristics, participants, antibiotic regimens, and outcomes.
Patients and Surgical Procedures
In total, 21 articles with 1974 cumulative participants were included in the meta-analysis, of which 1776 (90%) underwent surgery involving the mucosa of the aerodigestive tract (Table).

Eight of the 21 articles concerned ENT surgery, and 13 articles concerned OMF surgery (Table). The combined 8 ENT surgery studies included a total of 841 patients (range, 30-200), of which 703 (84%) underwent surgery involving the aerodigestive tract. Two studies concerned tympanomastoid surgery, and major head and neck surgery explicitly without involvement of the aerodigestive tract (Table). In total, 1133 patients who underwent OMF surgery (range, 30-181) were included, and just 60 patients did not undergo surgery involving the aerodigestive tract (Table). The included OMF studies mainly concerned mandibular fracture and flap reconstruction. Eight of the included trials studied mandibular fracture repairs; 2 of the 13 trials studied flap reconstruction procedures, 1 trial studied orbital blowout fracture repairs, another studied third molar surgical procedures, and the final trial studied intraoral and extraoral orthognathic surgical procedures (Table).

Statistical Analysis
Once data extraction was completed, the RRs of SSI and secondary outcomes were calculated from the data reported in the included studies. The RRs from each study were pooled using the Mantel-Haenszel method and visualized in a forest plot using the Microsoft Excel add-in MetaXL from Epigear, version 5.3. Heterogeneity was assessed by the same software using the Cochrane Q test and I² statistics. Heterogeneity was decided to be present if P < .10, or if the I² value was 40% or greater.

Results
Identification of Eligible Studies
The flow diagram of the literature search for meta-analysis is shown in Figure 1. The initial search yielded 2318 potentially eligible articles. These articles were all evaluated based on the established inclusion and exclusion criteria. A total of 2201 were excluded. Four handpicked articles were added, totaling 21 articles for the meta-analysis.

Study Characteristics
Patients and Surgical Procedures
In total, 21 articles with 1974 cumulative participants were included in the meta-analysis, of which 1776 (90%) underwent surgery involving the mucosa of the aerodigestive tract (Table).

Eight of the 21 articles concerned ENT surgery, and 13 articles concerned OMF surgery (Table). The combined 8 ENT surgery studies included a total of 841 patients (range, 50-200), of which 703 (84%) underwent surgery involving the aerodigestive tract. Two studies concerned tympanomastoid surgery, and major head and neck surgery explicitly without involvement of the aerodigestive tract (Table). In total, 1133 patients who underwent OMF surgery (range, 30-181) were included, and just 60 patients did not undergo surgery involving the aerodigestive tract (Table). The included OMF studies mainly concerned mandibular fracture and flap reconstruction. Eight of the included trials studied mandibular fracture repairs; 2 of the 13 trials studied flap reconstruction procedures, 1 trial studied orbital blowout fracture repairs, another studied third molar surgical procedures, and the final trial studied intraoral and extraoral orthognathic surgical procedures (Table).

Short- and Extended-Course Regimens
Short-course antibiotic regimens were similar for all included ENT and OMF studies. In both arms, most studies used a short-course regimen of 24 hours (ENT, 5 of 8; OMF, 8 of 13). Other short-course regimens were defined as 12 hours, intraoperatively only, or preoperatively only (Table). In contrast, differences in extended-course lengths existed between the OMF and ENT studies. Whereas most OMF studies (9 of 13) used an extended course of 5 days, half of the ENT studies (4 of 8) used an extended-course length of 7 or 8 days (Table). Short-course antibiotic prophylaxis regimens in both the OMF and ENT subgroups were administered preoperatively in all studies. However, Baliga et al and Miles et al did not specify when their short-course antibiotic regimens began. All but 1 study started administration of their extended antibiotic prophylaxis regimen at the same time as the short course. Andrews et al decided to only administer antibiotics postoperatively in the extended arm, whereas antibiotic prophylaxis was started at induction of anesthesia in the short arm.

Antibiotics Used
Generally, in both the ENT and OMF studies, β-lactams were the preferred antimicrobial agents of choice (ENT, 5 of 8; OMF, 13 of 13). The 3 studies that did not use β-lactam antibiotics each used clindamycin. Most studies used the same doses and routes of administration for their short- and extended-course regimens. The study by Miles et al did not mandate in their study protocol which antimicrobial agents had to be used for the preoperative period. Instead, preoperative antibiotics used during their trial varied between penicillin G with or without metronidazole, cephalosporins, or clindamycin. Finally, it should be noted that Cioacã et al performed 2 separate trials in their study, 1 trial in which they administered intravenous amoxicillin-clavulanic acid in both their short and extended treatment arms, and 1 trial in which they administered intravenous cefazolin in both short and extended treatment arms. A detailed overview of the antimicrobial agents used in all included studies can be found in eTable 2 in the Supplement.

Risk of Bias Assessment
After performing the risk of bias (Davis, 2017) for risk of
incomplete outcome data, owing to analyzing the number actually treated after a considerable loss to follow-up. In 1 study, no risk of bias was found. The other studies did not clearly report or perform a part of their randomization sequence generation, allocation concealment, or blinding protocols (Figure 2). A more detailed description of the risk of bias assessment can be found in eAppendix 2 of the Supplement.

### Meta-analysis

#### Primary Outcome

No heterogeneity was found in the overall results (Q = 23.78; $P = .30; I^2 = 12\%$), either in the subgroups of ENT ($Q = 9.35; P = .23; I^2 = 25\%$) or OMF ($Q = 15.40; P = .42; I^2 = 3\%$). Therefore, RRs were pooled to perform the overall meta-analysis. Figure 3 presents these results visualized in a forest plot. The pooled RR of SSI for short-course regimens vs extended-course regimens was 0.90 (95% CI, 0.67-1.19), indicating that there was no difference in SSI between short-course and extended-course prophylaxis. Similar results were obtained for ENT and OMT operations: 0.89 (95% CI, 0.54-1.19) and 0.88 (95% CI, 0.63-1.21), respectively.

#### Secondary Outcomes

### Microbial Etiology

Four ENT surgery studies (Andrews, 2006; Bartella, 2017; Liu, 2007; Mustafa, 1993) reported outcomes of microbiology analysis. Not enough data were available to compare protocol groups. Overall, *Staphylococcus aureus* (16 of 76; 21%) was the most common SSI-causing pathogen in the field of ENT, followed by *Pseudomonas aeruginosa* (11 of 76; 14%), *Escherichia coli* (9 of 76; 12%), and *Klebsiella pneumoniae* (8 of 76; 11%). Rarely reported species consisted of *Branhamella catarrhalis*, *Salmonella*, *Moranella morganii*, *Citrobacter koseri*, *Acinetobacter baumannii*, *Haemophilus influenzae*, and α-hemolytic *streptococcus*. A complete overview of the reported pathogens isolated from

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**Table. Study Characteristics of Included ENT and OMF Studies**

<table>
<thead>
<tr>
<th>Source</th>
<th>Patients, No.</th>
<th>Procedure (Involvement of Aerodigestive Tract, Yes/No)</th>
<th>Regimens</th>
</tr>
</thead>
<tbody>
<tr>
<td>Andrews et al, 2006</td>
<td>164</td>
<td>Septorhinoplasty (yes)</td>
<td>12 h vs 7 d</td>
</tr>
<tr>
<td>Bartella et al, 2017</td>
<td>50</td>
<td>Surgical resection of squamous cell carcinoma (yes)</td>
<td>Intraoperative vs 5 d</td>
</tr>
<tr>
<td>Bidkar et al, 2014</td>
<td>78</td>
<td>Tympanomastoid surgery (no)</td>
<td>1 d vs 8 d</td>
</tr>
<tr>
<td>Carroll et al, 2003</td>
<td>74</td>
<td>Surgical ablation of malignancies/flap reconstructions (yes)</td>
<td>1 d vs 5 d</td>
</tr>
<tr>
<td>Liu et al, 2007</td>
<td>53</td>
<td>All head and neck surgeries (yes)</td>
<td>1 d vs 3 d</td>
</tr>
<tr>
<td>Mustafa et al, 1993</td>
<td>60</td>
<td>Major head neck surgery (no)</td>
<td>1 d vs 7 d</td>
</tr>
<tr>
<td>Rajan et al, 2005</td>
<td>200</td>
<td>Septorhinoplasty (yes)</td>
<td>Preoperative vs 7 d</td>
</tr>
<tr>
<td>Righi et al, 1996</td>
<td>162</td>
<td>Oncological surgery of the oral cavity/larynx/pharynx (yes)</td>
<td>1 d vs 3 d</td>
</tr>
<tr>
<td><strong>Total ENT</strong></td>
<td>841</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Oral and maxillofacial surgery</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abubaker and Rollert, 2001</td>
<td>30</td>
<td>Mandibular fracture surgery (yes)</td>
<td>1 d vs 5 d</td>
</tr>
<tr>
<td>Baliga et al, 2014</td>
<td>60</td>
<td>Open reduction/internal fixation of facial fractures (yes)</td>
<td>Preoperative vs 5 d</td>
</tr>
<tr>
<td>Bentley et al, 1999</td>
<td>30</td>
<td>Intraoral/extracranial oromaxillary surgery (yes)</td>
<td>Intraoperative vs 4 d</td>
</tr>
<tr>
<td>Bhatnarna and Kavara, 1998</td>
<td>50</td>
<td>Major flap reconstruction (yes)</td>
<td>1 d vs 5 d</td>
</tr>
<tr>
<td>Cioaca et al, 2002</td>
<td>140</td>
<td>All maxillofacial surgeries (yes)</td>
<td>Preoperative vs 5 d</td>
</tr>
<tr>
<td>Davis et al, 2017</td>
<td>171</td>
<td>Le Fort I osteotomies/BSSOs/FGs or any combination (yes)</td>
<td>1 d vs 3 d</td>
</tr>
<tr>
<td>Johnson et al, 1986</td>
<td>109</td>
<td>Pedicled flap reconstruction (yes)</td>
<td>1 d vs 5 d</td>
</tr>
<tr>
<td>Kang et al, 2009</td>
<td>56</td>
<td>Le Fort I/bilateral intraoral vertical ramus osteotomies (yes)</td>
<td>1 d vs 3 d</td>
</tr>
<tr>
<td>López-Cedrín et al, 2011</td>
<td>89</td>
<td>Third molar surgery (yes)</td>
<td>Preoperative vs 5 d</td>
</tr>
<tr>
<td>Miles et al, 2006</td>
<td>181</td>
<td>Mandibular fracture surgery (yes)</td>
<td>Pre-op vs 5-7 d</td>
</tr>
<tr>
<td>Schaller et al, 2013</td>
<td>59</td>
<td>Mandibular fracture surgery (yes)</td>
<td>1 d vs 5 d</td>
</tr>
<tr>
<td>Soong et al, 2014</td>
<td>98</td>
<td>Zygomatic complex/Le Fort I, II and III fractures (yes)</td>
<td>1 d vs 5 d</td>
</tr>
<tr>
<td>Zix et al, 2013</td>
<td>60</td>
<td>Orbital blowout fracture repairs (no)</td>
<td>1 d vs 5 d</td>
</tr>
<tr>
<td><strong>Total OMF</strong></td>
<td>1133</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BSSO, bilateral sagittal split osteotomy; ENT, ear, nose, throat; FG, functional genioplasty; OMF, oral and maxillofacial.
SSIs can be found in eTable 3 of the Supplement. One ENT study by Liu et al\textsuperscript{14} isolated multiple pathogens from the surgical site in almost half of the SSIs (6 of 14; 46.2%). Most of the SSIs in the study by Liu et al\textsuperscript{14} contained at least \textit{P aeruginosa} (9 of 13; 69.2%). The 1OMF surgery study mostly found \textit{Pseudomonas}, \textit{Acinetobacter}, and \textit{Enterococcus} species, but did not clarify in what frequencies these pathogens were found.\textsuperscript{21}

**Adverse Events** | In total, 9 studies reported on adverse events: 5 OMF studies\textsuperscript{22,26,28-30} and 4 ENT studies.\textsuperscript{12,13,16,17} This analysis therefore included a total of 920 patients, of which 32 who were given short-course prophylaxis developed adverse events compared with 77 patients in the extended-course prophylaxis groups (RR, 2.40; 95% CI, 1.20-3.54). The most common distant adverse event in the extended course was diarrhea (14 of 77; 18%), followed by nausea (11 of 77; 14%) and rash (8 of 77; 10%). In the short course, rash (5 of 32; 16%), gastric pain (3 of 32; 9%), and hyperpyrexia without localization (3 of 32; 9%) were the most commonly reported adverse events.

Some studies reported adverse effects other than SSI without clearly reporting their nature or location. In a separate sensitivity analysis of adverse events, these particular studies were excluded to ensure that the RR adequately represents distant adverse events and not surgical site issues. In this analysis (842 patients), 22 of 420 short course participants developed distant adverse effects, compared with 51 of 422 of participants in the long course (RR, 2.31; 95% CI, 1.43-3.73).

**Other Secondary Outcomes** | Other reported secondary outcomes included length of hospital stay, treatment costs, and pain scores. Five studies\textsuperscript{11,12,14,22,23} included length of hospital stay as a secondary outcome in their study, of which 4 did not find a significant difference in the length of hospital stay between the different regimens.\textsuperscript{11,14,22,23} The study by Bidkar et al\textsuperscript{12} found that the participants receiving the extended-course regimen were hospitalized significantly longer (mean days [SD], 3.05 [0.72]) than participants in the short-course regimen. The included studies and their corresponding numbers of patients, with risk ratios (RRs) and 95% confidence intervals (CIs), are outlined on the left. Results were plotted for ear, nose, throat (ENT), and oral and maxillofacial (OMF) surgery separately, and also for the total results. A relative risk greater than 1 favors the use of short-course antibiotic prophylaxis, while a relative risk less than 1 favors the use of extended-course antibiotic prophylaxis.
Discussion

This meta-analysis of 21 studies is, to our knowledge, the largest to date that has assessed SSI outcomes in short-course antibiotic prophylaxis (<24 hours) vs extended-course antibiotic prophylaxis (>72 hours) in a broad range of ENT and OMF surgical procedures. We found that short-course antibiotic prophylaxis was associated with similar rates of SSI as extended prophylaxis. However, an extended course of prophylactic antibiotics was associated with more than 2-fold increased risk of adverse events.

The similar SSI outcomes when using extended prophylaxis vs short-course prophylaxis in OMF and ENT patients is in line with other studies in this field and other fields of surgery. Nevertheless, risk groups may exist that substantially benefit from prolonged antibiotic prophylaxis where the general population does not. This has, for example, been found in women with obesity undergoing cesarean section.31 However, to date, such a subgroup has not been identified among patients undergoing OMF/ENT surgery, despite 2 meta-analyses addressing this question in more complex operations. The study by Vila et al32 compared the efficacy of prolonged prophylaxis with short prophylaxis in adults undergoing ENT oncology surgery in a meta-analysis of 4 studies, but found no differences.

Another recent meta-analysis by Haidar et al33 included studies on antibiotic prophylaxis in head and neck microvascular free-flap reconstruction, and showed an increased risk in patients receiving antibiotics for over 24 hours. However, after post hoc correcting for antibiotic type, this outcome proved to be caused by antibiotic choice (clindamycin) rather than duration.33 This illustrates the fact that the antibiotic should match the susceptibility profiles of the pathogens causing SSI, and that the choice of antibiotics besides dose and duration need careful consideration for every type of surgery.

Additional results showed that in patients undergoing an antibiotic prophylaxis regimen of more than 72 hours, an increased risk of adverse events was found as compared to those undergoing a regimen of (less than) 24 hours. Furthermore, the use of more antibiotics inherently leads to increased hospital costs, even costs unrelated to increased adverse events.34 Furthermore, it has widely been recognized that inappropriate use of antibiotics leads to antibiotic resistance, and needlessly prolonging antibiotic prophylaxis therefore contributes to the current antimicrobial resistance crisis.

Limitations

One limitation of this study was the sole use of the PubMed library for article extraction. However, since PubMed extracts references from MEDLINE, PMC, and NCBI, and the search term was not limited to MeSH controlled vocabulary, it is doubtful whether this has affected any outcomes. Furthermore, even though only the PubMed library was used, this meta-analysis is at present the largest in this field of surgery, to our knowledge. Another limitation of this meta-analysis is the lack of appropriate reporting or conducting randomization and blinding in the included studies. This might introduce bias, but it can be argued that randomization and blinding does not actually influence SSI development, so these studies were included. Moreover, there is a large amount of interest in this particular aspect of surgery as it relates to the use of implants; however, no articles comparing antibiotic prophylaxis regimens in implant surgery fit our inclusion criteria, so our findings cannot be extrapolated to these interventions. Finally, a limitation of the present study was the differences between included studies; every trial used different short-course and prolonged-course prophylaxis regimens and used different classes of antibiotics, which might have influenced the outcome of this literature study. However, most of the included studies reported an insignificant association between SSI and the different courses, and the studies that did find a significant association did not seem to be related to the same antibiotic agent, but this was not tested.

Conclusions

No association was found between SSI and antibiotic prophylaxis for 24 hours or less vs 72 hours or more after ENT and OMF surgery. However, administering antibiotic prophylaxis for an extended period was associated with significantly more adverse events compared with administering antibiotic prophylaxis up to 24 hours. These results suggest that short-course antibiotic prophylaxis is recommended unless risk groups are found to benefit from an extended course. In the future, placebo-controlled randomized clinical trials need to be conducted to identify these risk groups who might benefit from different protocols.

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Drafting of the manuscript: Oppelaar, Zijtveld, Wertheim.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Oppelaar, Zijtveld.
Administrative, technical, or material support: Oppelaar, Zijtveld, Oever, Weijs, Wertheim.
Study supervision: Kuipers, Oever, Honings, Weijs, Wertheim.

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