INTRODUCTION:

The decision to use an antibiotic is a choice the head and neck surgeon must make frequently. The topic of perioperative antibiotics is heavily researched in all areas of surgery, including head and neck surgery, which dates back several decades. The first randomized controlled trial was performed by Ketcham in 1962. The topic is controversial and the literature is often divided. Where the literature is clear and consistent, real-world practices often differ from evidenced-based medicine.

BACKGROUND:

The use of perioperative antibiotics requires balancing between two concepts: surgical site infection and side effects. Underuse of antibiotics can result in wound infections while overuse exposes the patient to the risk of drug reactions and contributes to bacterial resistance. The impact of postoperative infection can be significant for head and cancer patients. Wound infections can increase the length of hospitalization, significantly increase in costs, result in poor wound healing, and delay adjuvant therapy. Drug reactions are relatively rare, but can be severe enough to be life-threatening.

FAVORABLE QUALITIES FOR PERIOPERATIVE ANTIBIOTICS:

Selecting the right antibiotic speaks to how broad the coverage should be. A good perioperative antibiotic provides coverage against the microbes most likely to cause a wound infection at the operative site. Rapid administration is favorable since perioperative antibiotics are most effective when given prior to wound contamination (in animal models). The most recent guidelines specify preoperative antibiotics should be given within 60 minutes of the incision. It should be noted that vancomycin and many quinolones require administration over 2 hours. If they are to be used as perioperative antibiotics, the infusion must be started 120 minutes prior to incision. Highly desirable
perioperative antibiotics also achieve adequate tissue concentration levels at the surgical site, have few side effects, and have a low cost.

**SURGICAL WOUND CLASSIFICATION:**

Wound classification has been standardized by the National Academy of Sciences National Resource Council. This system places surgical wounds into four categories. Each category correlates with the risk of post-operative infection. Clean cases involve sterilized surgical wounds with no mucosal barriers crossed, no bacterial contamination, no breaks in sterile technique, and no inflammation is encountered. Examples include clean neck dissections, thyroidectomy, submandibular gland excision, and parotidectomy. The risk of infection is low even without antibiotics in these cases.

Clean-contaminated cases involve wounds that are initially sterile. As a part of the operation, a mucosal barrier is crossed or a hollow viscus is entered which results in contamination of the wound. Most major head and neck procedures fall into this category including laryngectomy, pharyngectomy, and composite resection of oral cavity tumors.

Contaminated surgery results from a major break in sterile technique or an exposure to acute, non-purulent inflammation. Fresh traumatic wounds or unsterile material contaminating the sterile field fall into this category. Dirty wounds are already infected, such as a deep-space neck abscess.

**CLEAN WOUNDS:**

Less controversy exists in the literature regarding clean head and neck cancer surgery than in other areas. The evidence is limited to multiple retrospective case series and a large, recent randomized clinical trial. Although the literature is fairly conclusive and consistent, the recommendations for clean surgery are not routinely followed. The overall risk of wound infection in clean head and neck surgery is low. Johnson and Wagner published a retrospective review of clean head and neck cases and cited a 0.9% infection rate without perioperative antibiotics (1987). Similar findings of infection rates (around 1%) without antibiotics were also published in a larger case series by Shapiro (1991) and Weber (1992). In 2009, Avenia et al. conducted a multi-institutional randomized double-blind study of 500 patients undergoing thyroidectomy. No statistical difference was found in surgical site infection between the group receiving antibiotics (0.8%) and the group without them (0.4%). It should be noted that patients with risk factors for wound infection such as obesity, diabetes, advanced age (over 80 years), patients receiving neck dissection, patients undergoing revision surgery, and patients with advanced tumors were excluded from the study.

**CLEAN WOUNDS- NECK DISSECTION:**

A growing subset of the literature has been dedicated to clean neck dissection as a possible distinct category of clean head and neck cases requiring perioperative antibiotics. The literature is divided. Proponents of giving antibiotics for neck dissection argue that the procedures are longer and patients experience more blood loss. The drapes get soaked and the patients head is frequently turned for optimal positioning. These factors may result in breaks in sterile technique and increased bacterial
contamination of the wound during the case. The evidence is limited to small retrospective studies with inconsistent conclusions.

Two notable studies have provided evidence that neck dissections are a distinct type of clean head and neck surgical case that would benefit from perioperative antibiotics. Coskun et. al. performed a retrospective review and published a smaller subset of patients undergoing clean radical neck dissection. They found that 13% (N=54) of patients undergoing clean radical neck dissections developed wound infections despite use of antibiotics (2000). The infection rate was higher than that found in other clean cases in the series (1%) which served as a control. This finding achieved statistical significance. In 2004, Seven et al. performed a non-randomized prospective study comparing patients who received perioperative unasyn vs no antibiotics when undergoing clean neck dissections. 1/57 (1.2%) patients receiving antibiotics developed wound infections compared to 7/51 (13.2%) patients in control group.

Other studies have found no difference between clean neck dissections and other clean cases with respect to wound infection rate. Slattery et al. published a retrospective review of 120 patients undergoing clean neck dissection with the use of perioperative antibiotics (1995). They reported a 0% infection rate. It should be noted that 70% of these patients had received previous radiation therapy. This data argues against neck dissections as a special category of clean head and neck surgery case. Since the evidence is mixed and low in quality, only a placebo-controlled randomized controlled trial would be able to prove definitively if clean neck dissections were a distinct category of case requiring antibiotics. Since the wound infection rate in neck dissection is low, such a study would require a large number of patients enrolled which may be prohibitive.

CLEAN-CONTAMINATED CASES:

The role of antimicrobials in clean-contaminated head and neck cancer surgery is controversial. Since most major head and neck procedures fall into this category the topic is heavily studied. The microbiology of head and neck clean-contaminated cases is unique since the wound is exposed to saliva. Both clean and clean-contaminated cases are exposed to skin flora (staph epidermidis, beta-hemolytic step). A typical wound infection occurs with a bacterial load of 100,000 cells/gram of tissue. In saliva, often 100,000,000 cells/mL are found. In 1998, Gerard found that post-operative wound infections in head and neck cancer surgery are often polymicrobial with aerobic and anaerobic bacteria. Gram negative bacterial are not common in the saliva of healthy patients, but they are more commonly found in head and neck oncology patients. They are also more likely to be found in hospitalized or debilitated patients. Species frequently recovered from head and wound infections as published by Ottoline in 2009 can be seen below:
Evidence-Based Use of Perioperative Antibiotics and Head and Neck Cancer Surgery  May 2014

Multiple risk factors for wound infection have been proposed in clean-contaminated head and neck surgery. Many of these have been cited in published case series, although the mechanisms have not been conclusively proven. Diabetes can cause poor wound healing and make patients more prone to infection from hyperglycemia. Advanced stage of disease and extent of surgery frequently coincide, although their mechanisms of action may be different. Larger, more extensive tumors may harbor a larger bacterial load of altered flora while the extent of dissection and operative time with larger wounds may be more susceptible to infection. A tracheostomy may contribute to wound infection through soiling of the wound from the trach site. Previous radiation therapy may decrease blood supply through a chronic-vasculitis mechanism.

**SHOULD ANTIBIOTICS BE USED IN CLEAN-CONTAMINATED CASES?**

The literature is fairly clear regarding whether or not perioperative perioperative antibiotics should be used in clean-contaminated head and neck surgery operations. It contains several small, early randomized-controlled clinical trials demonstrating significantly decreased risk of wound infection when perioperatives antibiotics are used compared to placebo. The number of patients involved in these studies was small, but the findings were consistent. In several of these trials, the disparity was so great that the study was stopped early. They can be found below:

<table>
<thead>
<tr>
<th>Author</th>
<th>study design</th>
<th>Infection Without Abx (placebo)</th>
<th>Infection rate with abx</th>
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</thead>
<tbody>
<tr>
<td>Ketcham '62</td>
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<td>22.2% (n=9)</td>
</tr>
<tr>
<td>Dor et al '73</td>
<td>Double blind RCT</td>
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<td>17.3% (n=52)</td>
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<td>87% (n=23)</td>
<td>38% (n=32)</td>
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<tr>
<td>Saginur '87</td>
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<td>55% (n=9)</td>
<td>33% (n=11)</td>
</tr>
<tr>
<td>Sepehr '09</td>
<td>Retrospective review</td>
<td></td>
<td>7% (n=202) short 13% (n=205) long</td>
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<table>
<thead>
<tr>
<th>Gram Positive</th>
<th>Gram Negative</th>
<th>Anaerobic</th>
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</thead>
<tbody>
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<td>Staph aureus</td>
<td>Klebsiella pneumonia</td>
<td>Peptococcus</td>
</tr>
<tr>
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<td>E. Coli</td>
<td>Peptostreptococcus</td>
</tr>
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<td>Enterobacter sp.</td>
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</tr>
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<td>-</td>
<td>Hemophilus sp.</td>
<td>Anaerobic strep</td>
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<tr>
<td>-</td>
<td>Proteus sp.</td>
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</table>
WHICH ANTIBIOTIC SHOULD BE USED IN CLEAN-CONTAMINATED CASES?

The question of which antibiotic to use speaks to how broad should coverage should be in head and neck cancer surgery. It is widely accepted that skin flora and expected upper aero-digestive tract flora should be covered (gram positives and anaerobes). Anaerobes are 10 times more common in oropharyngeal secretions than aerobes. Several studies have examined the importance of directing perioperative antibiotics against them. Robbins et. al performed a randomized prospective study in 1990 of patients undergoing clean-contaminated head and neck cancer operations. Patients were randomized to receive either ancef or ancef plus metronidazole. The group with ancef only experienced a 23.9% wound infection rate compared to 11.9% when receiving ancef and metronidazole. Johnson et al. found that patients receiving only perioperative ancef had a higher rate of infection (25%) compared to patients receiving a combination of clindamycin/gentamycin (5.4%) (1987). Despite a fairly broad consensus, other studies have found no statistically significant difference between covering skin flora only and covering skin flora plus anaerobes. Rodrigo et al conducted a double-blind randomized controlled trial comparing groups of patients receiving ancef, unasyn, and clindamycint + gentamicin (1997). The study was fairly large (n=159) and had an overall infection rate of 22%. The ancef-only group had the highest rate of infection (26%), but this was not statistically significant.

Controversy exists regarding the need for gram negative coverage. Weber and Frankenthaler compared unasyn and clindamycin in clean-contaminated head and neck surgery in 1992. They found significantly more wound infections in the clindamycin group (27%) than the unasyn group (13%). A higher percentage of the wound infections in the clindamycin group were gram negative bacteria. A similar study performed by Johnson and Wagner in 1992, however, found no difference in infection rates between the same two antibiotics. The clindamycin group did have a higher rate of C. diff colitis.

In 2007, Skitaralec et. al. randomized patients undergoing clean-contaminated head and neck surgery into groups receiving ancef alone vs amoxicillin/clavulanate. The study was under-powered, but found no statistically significant difference. The literature remains divided, but unasyn has been found to be at least as effective as clindamycin and has a favorable side effect profile. It also has the added benefit of providing coverage against gram positives, anaerobes, and some gram negatives.

PERIOPERATIVE ANTIBIOTIC DURATION IN CLEAN-CONTAMINATED SURGERY:

In theory, the contamination of the wound stops once the wound is irrigated and closed. It can be reasoned that a short course of antibiotics to suppress bacterial contamination that occurred during the surgery should be as effective as a long course. Multiple studies have found no benefit of perioperative antibiotics beyond 24 hours after surgery. The evidence is consistent and high quality.

In 1986 Johnson performed a randomized trial comparing 1 day vs 5 days of cefoperazone in patients with flaps. No statistically significant difference in infection rate was found. Righi performed a prospective randomized trial of 162 patients undergoing clean-contaminated head and neck surgery. Patients were randomized to 1 or 3 days of a clindamycin/cefonicid regimen. The patients in the 1 day group experienced a 2.5% infection rate compared to 3.7% infection rate in the 3 day group. The difference was not statistically different. In 2003 Carroll et. al. conducted a randomized, blinded,
prospective trial of clean-contaminated head and neck cancer patients undergoing tumor resection with free flap reconstruction. Patients received either 1 or 3 days of clindamycin. No difference was found in infection rate.

**Topical Antibiotics:**

Patients undergoing clean-contaminated head and neck surgeries requiring flap reconstruction have high infection rates even with antibiotics. Studies have shown altered oral/oropharyngeal flora in these patients. Topical antibiotics can be delivered at concentrations more than 100 times IV dosing. Several studies have examined if topical swish and swallow perioperative antibiotics would decrease infection rates. Simmons et. al. performed a prospective, randomized trial of clean contaminated head and neck cases (2001). Patients received either perioperative IV zosyn or perioperative IV zosyn plus topical zosyn. Patients in the latter group gargled with zosyn mouthwash on call to the operating room and then twice daily for 2 days. Zosyn was also added to the irrigation solution intraoperatively. The difference between the two groups was not statistically significant.

Staph aureus is an important microbe in wound infection and MRSA infections are difficult to treat. Many asymptomatic patients are staph carriers. Mupirocin has been used intra-nasally to treat patients colonized with MRSA. Previous literature in orthopedics and cardiac surgery has shown decreased infection rates with decolonization prior to surgery. Shuman examined this topic with a prospective randomized trial in 2012 of head and neck cancer patients. Patients were randomized to topical decolonization with mupriocin plus topical chlorhexadine plus IV antibiotics or IV antibiotics alone. Patients in the first group used muperocin intranasally for 5 days prior to surgery and added chlorhexadine to their daily bathing for 2 days prior to surgery. No statistically significant difference was found between the two groups.

**SUMMARY:**

1. No good evidence in literature to support routine use of prophylactic antibiotics in clean head and neck surgery
2. There is strong evidence to support use of prophylactic antibiotics in clean-contaminated head and neck surgery
   a. Gram positive and anaerobes should be covered- coverage of gram negatives is controversial
   b. Literature supports limiting duration of antibiotics to 24 hours after surgery
3. Topical antibiotics for head and neck surgery are controversial- more studies needed
4. ASHP Guidelines recommend administration of prophylactic antibiotics within 60 minutes of start of procedure and re-dosing after 2 half-lives of the drug.
Faculty Discussant: Vicente A. Resto, MD, PhD, FACS

Dr. Patton, that’s a very nice review of the literature that’s out there. It’s certainly an important topic as we progress in medicine with our decreased spectrum of choice of antibiotics for surgical infections. There are some really critical risk factors that we have come to understand as we come late to his topic. I didn’t catch a whole lot of discussion in these papers about them. For example, we know diabetes is an issue as well as radiotherapy and importantly chemoradiotherapy. These are significant issues in the head and neck. From personal experience, even in cases where you do clean neck dissections status post chemoradiotherapy, you get the sense that things perhaps are different there.

The first question for you is how many of these papers really broke down their cohorts in such ways as to early dichotomize any kind of treatment recommendation? Has there been anybody putting forth a recommendation regarding prophylaxis with this level of categorization?

The level of intervention and the cost of failure are important drivers in decision making. You look at large composite resections with reconstructions in patients that need to move forward to adjuvant therapy in a timely fashion for what we understand will be better outcomes. Your cost of failure defined as postoperative infection with either failure the cost of that is you come up with a second solution or simply a delay to the completion of the treatment package which can be rather high.

We can have academic discussions about this issue but up until there is a definitive study with good methodology that really assesses some of these important risk factors that I believe most people agree likely play some role. I think that most of us who treat these patients are simply going to be more aggressive with antibiotic coverage. My suspicion is that has been and remains the case across the country. I hope that in the future there is such an initiative. It would be complicated and the numbers would have to be quite high. We are entering the era of databases and patient information categorization and the like so it could be that we are moving forward to a time where these questions can be asked appropriately. I don’t believe that they have been thus far, not in a way that will change most people’s practice.
Bibliography:


Russel MD, Goldberg AN. What is the evidence for use of antibiotic prophylaxis in clean-contaminated head and neck surgery? Laryngoscope 2012. 122:944-946


