Protocol #: 13-2819
Project Title: Treatment of tracheostomy granulomas
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I. Hypotheses and Specific Aims:

Specific Aims:
Examine standard of care by comparing the effectiveness of different treatments of tracheostomy granulomas: steroid application, silver nitrate, betadine.

Hypotheses:
We surveyed the thirteen attending doctors at Children's Hospital Colorado and the satellite clinic in Colorado Springs, CO regarding which method of treatment they deem as most successful. The most commonly reported preferred method of treatment was silver nitrate (75%). We hypothesize that treatment with steroid application or betadine may result in less frequent recurrence of tracheostomy granulomas compared to silver nitrate use.

II. Background and Significance:

The incidence of tracheostomy granulation tissue is between 10-80% of all tracheostomy tubes[1,2,3] . Granulation tissue can cause bleeding, difficulty with tracheostomy tube changes, and respiratory distress if it occludes the end of the tracheostomy tube. Reports of death due to obstruction from granulation tissue exist[1]. There is no significant data on the best course of treatment to prevent granulation tissue and to remove granulation tissue once it develops[1,2]. The purpose of this study is to evaluate treatment of tracheostomy granulation tissue and determine if any significant difference in the frequency and extent of granulation tissue formation with different topical treatments. Each treatment has minimal morbidity and side effects. Granulation tissue is caused by fibroblasts, collagen and blood vessels formed in the proliferative phase of healing. Suggested causes of hypergranulation include prolonged inflammation from infection, foreign body irritation, external friction, and allergens. Studies have shown that steroid treatment is effective in treating granulation tissue. Silver nitrate works as chemical cautery by reacting with water in the blood and forming nitric acid[4]. Anti-septic solutions, such as betadine, are known to be toxic for fibroblasts and also help with chronic low-grade infections, and therefore, are helpful in treatment of granulation tissue[5].

III. Preliminary Studies/Progress Report:

To our knowledge, none of the faculty in the pediatric otolaryngology department at CHC has conducted any research studies the effectiveness of different treatments of tracheostomy granulomas.

IV. Research Methods

A. Outcome Measure(s):

1. Success or failure of treatment method
    a. Definition of success: We are defining successful treatment of tracheostomy granulomas as a clinically significant decrease in the size of granuloma (greater than 50% improvement) over a six week observation period using the assigned treatment.
    b. Definition of failure: We are defining a treatment as a failure as if there is less than 50% reduction in size of tracheostomy granulomas at the conclusion of the six week observation period or if worsening occurs requiring alternative treatments.
2. Categorical Improvement (Degree of Improvement)
    a. At each time point, the size of the granuloma will be measured and recorded. The percent circumference will also be measured
    b. The approximate percent decrease in the granuloma size will be determined to determine the category subject's change in granuloma:
        i. Complete resolution: >90% improvement (Score = 4)
        ii. Improvement: 50 - 90% improvement (Score = 3)
        iii. Minimal improvement: < 50% improvement (Score = 2)
        iv. No improvement (Score = 1)
        v. Worsening (Score = 0)

B. Description of Population to be Enrolled:

The population to be enrolled in this study includes all Children's Hospital Colorado patients, 31 days to 18 years of age inclusive, who are being treated for a tracheostomy granuloma and consent to participating in the study. We anticipate 45 patients will be needed for this pilot study to determine the effect size and variation in granuloma change.

C. Study Design and Research Methods:

The study will be a prospective comparison of three different treatment methods for patients with tracheostomy granulomas at Children's Hospital Colorado. The current standards of care for tracheostomy granulomas that we will be examining include: steroid application, silver nitrate and betadine. Patients or parents will be consented or assented during the initial physician visit prior to any administration of treatment by the provider. The treatment method will be assigned starting at the time the patient is enrolled in the study.

1. The three treatment methods (steroid application, silver nitrate, and betadine) will be assigned sequentially #1, #2, or #3. (See below for description)
2. Patients will be assigned a treatment method based on the sequential allocation done prior to enrollment. To reduce potential bias, the enrolling physicians will be unaware of the previous patient's allocated treatment group.
3. The treatment method for the patient given at the initial visit will be documented in Epic. During the six week observation period, the study team will collect follow-up data on the degree of improvement for each treatment method. Our primary time point will be 6 week follow up.
4. Each patient will be followed for an observation period of six weeks, with follow-up appointments, per standard of care, every two weeks (+/- 3 days) in order for a physician to evaluate the degree of improvement for each treatment method. If the investigator determines further follow-up is not necessary, per standard of care, the observation period will end.
5. If during a follow-up visit, the physician determines the patient's granuloma is worsening, the follow-up period will end and the patient's participation in the study will be complete. If

other treatments are utilized, we will analyze with the intent to treat analysis based on the treatment the subject was received.

6. In addition, if a patient is given a different form of treatment, such as in the emergency department or through a primary care physician, the follow-up period will end and the patient's participation in the study will be complete.

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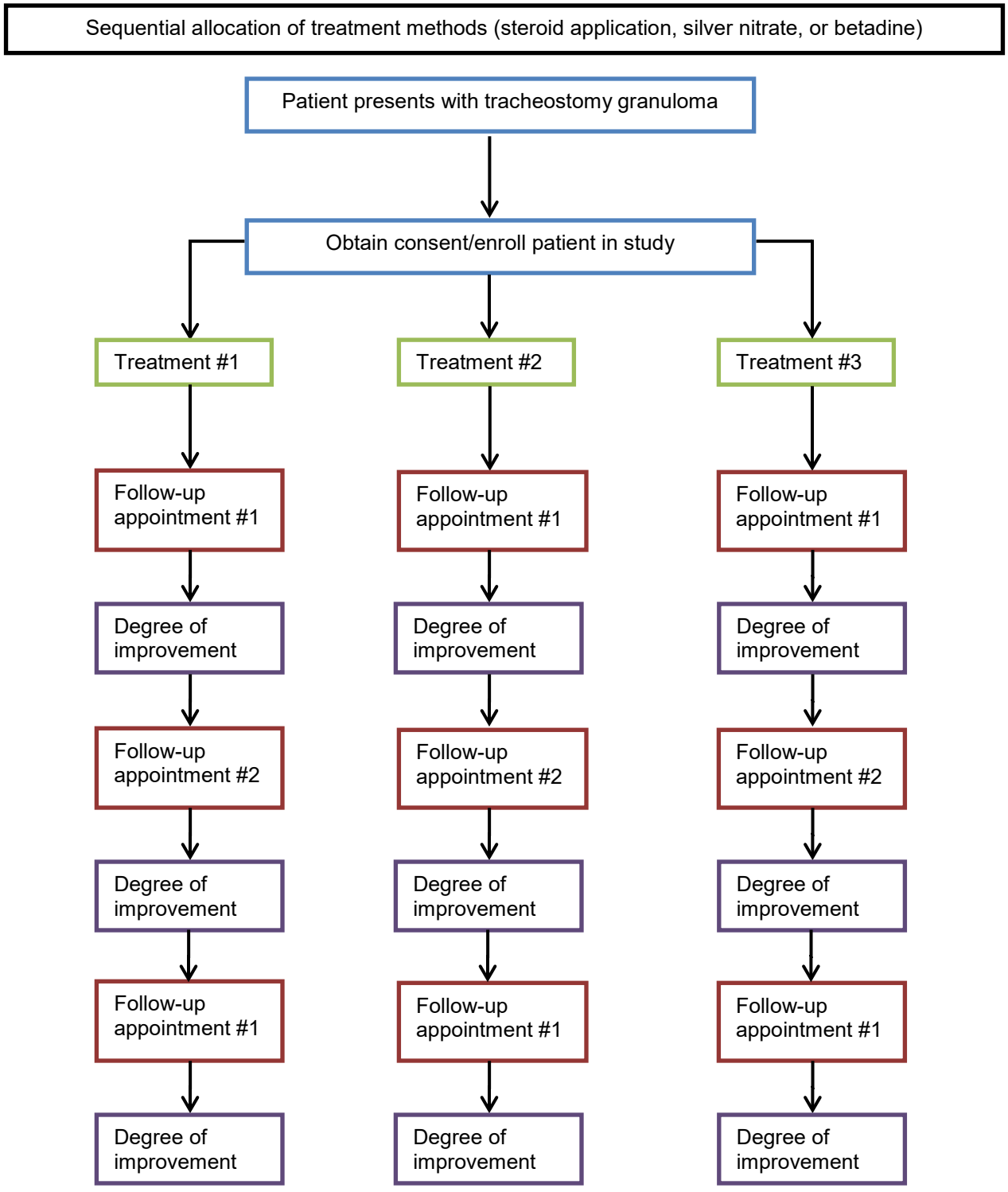
Treatments:

1) Silver nitrate – Silver nitrate will be applied to the tracheostomy site granuloma after enrollment. Parents will be instructed to keep the site dry for 14 hours. Residual granuloma will be treated similarly at Follow up #1 and #2, but not at Follow up #3.
2) Betadine solution will be used to topically treat the tracheostomy site BID for 2 weeks (until Follow up #1). If residual granuloma is present, an additional week will be recommended and this treatment duration recorded.
3) Hydrocortisone 1% topical will be used to topically treat the tracheostomy site BID for 2 weeks (until Follow up #1). If residual granuloma is present, an additional week will be recommended and this treatment duration recorded.

Study Design Flow Chart



Definition of success: We are defining successful treatment of tracheostomy granulomas as a clinically significant decrease in the size of granuloma (greater than 50 percent reduction) over a 6 week month period using the assigned treatment method.

Definition of failure: We are defining a treatment as a failure if after 6 weeks of treatment there is less than 50% reduction in the size of tracheostomy granulomas.

D. Description, Risks and Justification of Procedures and Data Collection Tools:

These methods of treatment do not represent a deviation of the standard of care for tracheostomy granulomas and incur the standard amount of risk.

The risks for administering steroid application include thinning of skin, local infection, and systemic absorption. Silver nitrate can cause superficial burning on normal tissue that is exposed. Betadine can cause skin irritation.

E. Potential Scientific Problems:

Potential scientific problems include the following:

1. Inability to enroll the number of patients needed to obtain data pertaining the success or failure of the three methods of treatment
2. Potential for bias in early failure between the 3 treatment arms. For example, it is possible that one treatment would work quickly and another would work slowly. If we discontinue follow-up too early, we would bias towards the early treatment effect. To minimize this risk we will continue to follow patients clinically with the treatment provided unless there is worsening of the granuloma that would require a change in treatment. There is the potential that this study is under powered. There is no data on the treatment of tracheotomy site granulomas and therefore the mean and variance in the treatment effect may be different than that estimated in our power analysis below. This study is powered to detect a clinically important difference and will additionally provide data to determine the sample size needed for future studies. We feel this potential is reasonable given that this study is a pilot study.

F. Data Analysis Plan:

Success and failure rates for each treatment method and the length of time between initial administration of the treatment and the determination of treatment success or failure will be utilized to compare the three standard of care treatment methods to better define and improve the current standard of care treatment of tracheostomy granulomas.

All variable will be analyzed for distribution and cleaned. For inconsistencies, we will refer back to the source data. Data will be checked for normalcy and non-parametric tests will be utilized for non-normal data. All analyses will utilize an alpha of 0.05 with two tails. The study will utilize an intent to treat analysis where subjects are analyzed according to the treatment they were assigned to regardless of treatments they receive.

Aim 1: Test for difference in treatment failure between the three treatment arms
Hypothesis 1: At the primary time point (6 weeks), there will be a clinically important difference between the silver nitrate treatment and the topical treatments.

Aim 2: Test for difference in categorical granuloma improvement in the three treatment arms
Hypothesis 2: At the primary time point (6 weeks), there will be more categorical improvement in the silver nitrate treatment group compared to and the topical treatments.

Aim 3: Describe the treatment effects of the three treatment arms including average number of treatments needed (silver nitrate), duration of topical medication administration (Betadine and Hydrocortisone, i.e. two weeks versus three weeks)
Hypothesis 3: Descriptive aim, no specific hypothesis in this pilot study.

Power Analysis:
Power analysis is based on aim 2. Because tracheotomy site granulomas have not been rigorously studied in the literature, the degree of improvement that will be found in the treatment groups is unclear. We hypothesize that the standard deviation for this 5 point scale will be one unit of measure. We determined the power to detect a difference of one unit of measure between treatment groups (from partial response to resolution or from minimal improvement to improvement). Assuming a sample size of 15 and an alpha of 0.05, our study will have an 80% power to detect a 1.1 point difference in categorical granuloma improvement. Table 1 below shows the power to detect differences between two treatment groups.

Table 1: Power analysis for Aim 2

Treatment A mean	Treatment B mean	% Diff	Power
3.4	2.4	42%	78%
3.4	2.2	55%	91%
3.4	2.1	62%	94%
3.5	2.5	40%	78%
3.6	2.5	44%	85%
3.7	2.5	48%	90%

The power to detect differences in treatment success (Aim 1) is shown in table 2. This study has an 80 percent power to detect a clinically important (50 percentage point) difference in treatment success between two treatment arms.

Treatment A Success (%)	**Treatment B Success (%)**	**Relative Risk***	**Power**
60%	73%	0.67	12%
53%	73%	0.57	20%
47%	73%	0.5	30%
40%	73%	0.44	44%
33%	73%	0.4	60%
27%	73%	0.36	74%
20%	73%	0.33	87%

*protective effect of treatment B

G. Summarize Knowledge to be Gained:

Currently, there is no “gold” standard of care for the treatment of tracheostomy granulomas in children. The knowledge gained by comparing the effectiveness of different treatments will better define and improve the current standard of care. The knowledge to be gained will expectantly benefit future patients by reducing the frequency of recurring tracheostomy granulomas as well as minimizing office visits with inconsistent forms of treatment. This pilot study is powered to detect a clinically important difference in treatment effects with a modest sample size but additionally provide further estimates for sample sizes needed for future studies of this clinically important problem in pediatric otolaryngology.

H. References

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4. McShane Diana B and Jane S. Bellet. Treatment of Hypergranulation Tissue with High Potency Topical Corticosteroids in Children. Pediatric Dermatology Vol. 29 No. 5 675–678, 2012
5. Habif: Clinical Dermatology, 5th ed. Chap 27: Dermatologic Surgical Procedures