Rethinking Pyogenic Flexor Tenosynovitis: Biofilm Formation Treated in a Cadaveric Model

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Abstract

Introduction Pyogenic flexor tenosynovitis (PFT) of the hand remains a challenging problem that often requires surgical irrigation and parenteral or oral antibiotics. The authors hypothesize that the pathophysiology and microenvironment of PFT can be likened to that of periprosthetic joint infections (PJIs), in which bacteria thrive in a closed synovial space with limited blood supply. As such, they postulate that PFT is also facilitated by bacterial attachment and biofilm formation rendering standard treatments less effective. In this study, they evaluate infected tendons for the presence of biofilm and explore new treatment strategies.

Methods Fresh human cadaveric hand tendons were harvested and divided into 0.5-cm segments. Samples were sterilized and inoculated with 1×10^4 CFU/mL green fluorescent *Staphylococcus aureus* (GFP-SA) for 48 hours at 37°C. After saline washing to remove planktonic bacteria, samples were treated for 24 hours with (1) saline irrigation, (2) antibiotics (vancomycin), (3) corticosteroids, or (4) antibiotics/corticosteroid combined. Samples were visualized using confocal laser scanning microscopy (CLSM) and scanning electron microscopy (SEM).

Results Following bacterial challenge, CLSM revealed heterogeneous green fluorescence representing bacterial attachment with dense biofilm formation. SEM at $> 3,000\times$, also demonstrated bacterial colonization in grape-like clusters consisted with a thick matrix characteristic of biofilm. Bacterial load by direct colony counting decreased by 18.5% with saline irrigation alone, 42.6% with steroids, 54.4% with antibiotics, and 77.3% with antibiotics/steroids combined ($p < 0.05$).

Conclusion *Staphylococcus aureus* readily formed thick biofilm on human cadaveric tendons. The addition of both local antibiotics and corticosteroids resulted in greater decreases in biofilm formation on flexor tendons than the traditional treatment of saline irrigation alone. We suggest rethinking the current treatment of PFT and recommend considering a strategy more analogous to PJI management with the adjunctive use of local antibiotics, corticosteroids, and mechanical agitation.

Keywords

- pyogenic
- septic
- suppurative
- flexor tenosynovitis
- biofilm

Introduction

Pyogenic flexor tenosynovitis (PFT), also known as septic or suppurative flexor tenosynovitis, is a common closed-space infection of the flexor tendon sheath of the hand and remains

one of the most challenging infections that can be encountered in the realm of hand surgery. The prevalence of this infection has ranged from 2.5 to 9.4%.^{1–3} Once established, it can become a source of significant morbidity and disability to the patient, as well as an economic burden to the healthcare system. Despite

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prompt treatment, many patients develop pain, swelling, stiffness, weakness, loss of composite flexion, and, ultimately, compromised function of the affected hand.^{1–3} Moreover, in severe cases with delayed or inadequate treatment, PFT can result in tendon adhesions, tendon rupture, spread of the infection, soft-tissue necrosis, and even amputation.^{1–3}

PFT can occur from local bacterial inoculation as well as hematogenous spread. Although both mono- and poly-microbial infections due to a range of organisms have also been found to cause PFT, the most common pathogen is typically methicillin-resistant *Staphylococcus aureus* (MRSA), a pathogen whose prevalence continues to increase, particularly in urban areas.^{4,5} Currently, there is no standardized protocol for this common but challenging infection presenting a great dilemma for the hand surgeon managing PFT. Treatment commonly includes prompt administration of empiric intravenous antibiotics followed by some combination of surgical decompression and sheath irrigation.^{6–11} However, there remains a debate regarding the need for open surgery or closed-catheter irrigation alone, the method of irrigation used, and the duration and method of antibiotic administration. Furthermore, the role of corticosteroids in the treatment of PFT has not been systematically evaluated and is currently unknown. Regardless of timing and type of irrigation, surgical intervention remains the treatment of choice for the more advanced cases of PFT.² However, even with prompt treatment, complication rates can reach 38%.⁴ Moreover, despite successful eradication of the infection, a significant proportion of patients will suffer from continuing pain, swelling, stiffness, loss of composite flexion, weakness, and recurrence, potentially requiring multiple surgeries and even amputation.

We hypothesize that the challenge in infection eradication, tendon healing, and subsequent recovery is related to the poor vascularity of the flexor tendon. Specifically, the vascularity of the flexor tendon sheath is predominantly provided by the synovial fluid and the vincula, which are responsible not only for the influx of nutrients but also for the delivery of systemic antibiotics to the site.¹² In this manuscript, we propose that the living tendon is a substrate for bacterial biofilm formation, explaining the antibiotic recalcitrance of these difficult infections. Specifically, vascularity to the tendons is limited, thereby making the local conditions ripe for bacterial colonization of the nearly avascular tendons.¹³ In that regard, PFT can be likened to a prosthetic joint infection (PJI), sharing many common characteristics. For one, they are both considered a closed-space synovial infection of a poorly vascularized substrate (tendon or prosthesis). Furthermore, bacterial invasion and replication in a nutrient-rich synovial fluid environment is encountered in both processes promoting inflammatory-cell recruitment, and leading to tissue destruction and morbidity.¹⁴ Under local conditions of poor antibiotic delivery, low immune surveillance, and nearly avascular substrate, colonizing bacteria show a predilection for biofilm formation. In addition, the presence of physiologic fluid, for example synovial fluid, has been shown to increase bacterial adhesion to proteins and matrix,¹⁵ as well as production of the thick glycocalyx matrix. In this state, antibiotic penetrance is further inhibited, and the body's immune surveillance is subverted;

the infection thrives and remains recalcitrant to standard treatment, as is common for infections in the presence of prostheses or allograft bone.^{16–18} Like in large joint PJIs, local mechanical debridement, local antibiotic delivery, or complete removal of the affected substrate is required to eradicate the glycocalyx and subsequent infection.¹⁵

Though there is active research in the field of PJI and prosthetic colonization, there is a paucity of literature exploring the microbiological processes taking place in the infections of tendons in the hand. Previous studies have shown, however, that corticosteroids given in conjunction with antibiotics significantly improve clinical outcomes associated with the treatment of septic arthritis.^{19–22} Recently, Draeger et al reported promising results with local injection of antibiotics into the tendon sheath and the addition of locally administered corticosteroids in the treatment of PFT in an animal model.²³ Just as corticosteroids have been shown to decrease morbidity in other closed-space infections, they found that corticosteroids decreased digit stiffness associated with PFT.

In this study, we use a laboratory cadaveric PFT model with harvested human flexor tendons. We inoculated this model with fluorescently labeled MSSA and assessed the effect of local administration of corticosteroids and antibiotics, either together or separately, on MSSA colonization and biofilm formation using visual assays as well as direct bacterial counts.

Methods

With institutional review board (IRB) review, exemption was granted as no human or animals were being studied.

Experimental Outline

Fresh cadaveric hands were dissected to harvest flexor tendons from zones 3 and 4 of each finger, divided in 0.5-cm segments, and placed in 24 well plates (►Fig. 1). Samples were sterilized by incubation in 70% ethanol and inoculated with 1×10^6 colony-forming unit (CFU)/mL green fluorescent protein (GFP)-expressing methicillin-sensitive *Staphylococcus aureus* (MSSA) for 24 hours at 37°C under static conditions²⁴ (►Fig. 2). After gentle washing with PBS to remove planktonic bacteria, samples were divided into the following experimental categories: (A) controls (no further treatment), (B) saline irrigation, (C) saline irrigation + antibiotic incubation, (D) saline irrigation + corticosteroid incubation, and (E) saline irrigation + antibiotic + corticosteroid incubation. After treatments, tendons were washed and bacterial colonization visualized using confocal laser scanning microscopy (CLSM) (►Fig. 3). Alternatively, the colonized tendons were visualized after fixation and dehydration by SEM (►Fig. 4). Finally, adherent bacteria were resuspended and total numbers of released bacteria determined by dilution and plating.

Sample Harvest

Fresh cadaveric hands were dissected to harvest flexor digitorum sublimis (FDS) and flexor digitorum profundus (FDP) tendons from each finger and divided into 0.5-cm segments. About 8 samples on average were obtained per

Fig. 1 Confocal laser microscopy imaging at 20X of colonized tendons. (A) Control tendon sample without bacteria shows no background fluorescence. (B) Tendon sample after 48 hours incubation with green-fluorescent *Staphylococcus aureus* showing extensive colonization.

finger (depending on the digit). Samples were washed and sonicated extensively with dH₂O until washings were clear, followed by sterilization with 70% ethanol for 15 minutes. Finally, the sterile samples were washed three times with PBS and three times with trypticase soy broth (TSB; BD Biosciences, San Jose, California, United States) immediately prior to incubation with bacteria.

Bacterial Inoculation

GFP-expressing (maintained through growth in chloramphenicol) MSSA (GFP-MSSA) was cultured in TSB containing 10% glucose, 10 µg/mL chloramphenicol, 250 rpm (revolutions per minute), 37°C, 12 to 14 hours (overnight culture), and diluted to 1×10^6 CFU/mL using a turbidity meter standardized to a 0.5 McFarland standard ($\sim 1 \times 10^8$ CFU/mL, $OD_{600} = 0.10$).²⁴ From the diluted culture, 2 mL was added to the sterilized samples in

TSB. Samples were then incubated for 24 hours at 37°C under static conditions.

Sample Treatments

After 24 hours, samples were washed three times with sterile PBS, transferred to a fresh well, and washed another three times to remove nonadherent bacteria. At this time, samples were divided into groups. First, five samples were removed and placed aside as the control, that is, group (A). The remaining samples were copiously irrigated with saline, placed on a rotary shaker at 100 rpm for 10 minutes at room temperature, and then rinsed and transferred to new well plates. The prepared flexor tendons were then divided into the four more groups, as described previously, starting with the first treatment group: (B) *irrigation only*. The remaining samples were then placed in 3×12 well plates representing the rest of the experimental

Fig. 2 Scanning electron microscopy imaging of tendon edge samples at 500 to 10,000X magnification. *Top row:* Control tendon without bacteria showing the natural topographical features. *Bottom row:* Tendon sample after 48 hours incubation with green-fluorescent *Staphylococcus aureus*, demonstrating grape-like clusters of spherical structures (~ 1 µm diameter), typical of *S. aureus* that are higher magnification show evidence of a thick film covering the colonies, which is characteristic of glycocalyx matrix.

Fig. 3 Confocal laser microscopy imaging of colonized tendons at 20X after various treatments. (A) Control tendon samples were only lightly rinsed to rid of plank tonic bacteria. (B) Irrigation samples were placed on a shaker at 100 rpm for 10 minutes. (C) Vancomycin samples were treated with 20 μ g/mL of vancomycin for 4 hours. (D) Steroid group was allowed to incubate in dexamethasone at 2 mg/mL for 4 hours. (E) Vanc and steroids group was allowed to incubate in vancomycin at 20 μ g/mL and dexamethasone at 2 mg/mL for 4 hours. (F) Vanc/steroids/sonication group was allowed to incubate in vancomycin at 20 μ g/mL and dexamethasone at 2 mg/mL for 4 hours followed by a 10-minute sonication treatment. All samples were shaken at 40 rpm, 37°C during treatment, and washed with PBS to remove nonadherent bacteria before visualization.

Fig. 4 Scanning electron microscopy imaging of tendon samples at 10,000X magnification after various treatments. (A) Control tendon samples were only lightly rinsed to rid of plank tonic bacteria. (B) Irrigation samples were placed on a shaker at 100 rpm for 10 minutes. (C) Vancomycin samples were treated with 20 μ g/mL of vancomycin for 4 hours. (D) Steroid group was allowed to incubate in dexamethasone at 2 mg/mL for 4 hours. (E) Vanc and steroids group was allowed to incubate in vancomycin at 20 μ g/mL and dexamethasone at 2 mg/mL for 4 hours. (F) Vanc/steroids/sonication group was allowed to incubate in vancomycin at 20 μ g/mL and dexamethasone at 2 mg/mL for 4 hours followed by a 10-minute sonication treatment. All samples were shaken at 40 rpm, 37°C during treatment, and washed with PBS to remove nonadherent bacteria. Samples were also dehydrated, fixed, and sputter-coated.

Fig. 5 Experimental outline indicating the number of sample needed for each repeat, experimental groups and the analysis performed for each.

groups, as follows: (C) *antibiotic group*: vancomycin at 20 µg/mL (~10 times the MIC of SA), (D) *corticosteroid group*: dexamethasone (Vedco, St. Joseph, Missouri, United States) at 2 mg/mL, and (E) *combined group*: vancomycin at 20 µg/mL + dexamethasone at 2 mg/mL. Last, all five groups were then incubated with shaking at 40 rpm, 37°C for 4 hours. At the end of the incubation, samples were washed five times with PBS to remove nonadherent bacteria (► Fig. 5).

Surface Assessment

To determine bacterial colonization and biofilm formation, the GFP-MSSA samples were washed six times with PBS and visualized by CLSM with z-sectioning and image reconstruction. Total areas of surface colonization were determined from multiple fluorescent images analyzed using a macro on Adobe Photoshop and expressed as percentage of cell CFU totals.

Bacterial Plating

After washing six times with PBS, colonized samples were sonicated in 0.3% Tween-80 for 10 minutes to suspend adherent bacteria. The sonicate was then serially diluted, plated on PetriFilms, and incubated for 24 hours to allow bacterial growth. CFUs were manually counted and tabulated.

Confocal Laser Scanning Microscopy

Samples were imaged using an Olympus Fluoview 300 CLSM set to detect green fluorescence. Image acquisition was performed with z-sectioning, followed by reconstruction. To determine areas of bacteria and biofilm population, more than three fields were recorded and used for morphometric analysis of the fluorescent areas representing viable adherent bacteria.

Scanning Electron Microscopy

Samples were rinsed six times with dH₂O and fixed for 1 hour with 4% paraformaldehyde. Samples were then sequentially dehydrated by a graded ethanol series, incubated in Freon, and vacuum-dried overnight. Samples were then affixed onto a metal plate, sputter-coated with palladium, and visualized using a Hitachi TM-1000 SEM (Ibaraki, Japan) at magnifications 2,000 to 5,000X. At these magnifications, individual bacteria can be distinguished, which allows for the evaluation of the bacterial organization as well as the topographic characteristics of biofilm formation.

Statistics

All quantitative data derived from the experimental condition were presented as means ± standard errors. Statistical analyses was performed on normal equally variant data using a

one- or two-way analysis of variance (ANOVA) with statistical difference defined as $p \leq 0.05$.

Results

Bacteria Readily Colonize Tendons

To first discern whether bacteria attach to tendons, tendons from fresh-frozen cadaverous fingers were incubated with green-fluorescent *Staphylococcus aureus* (GFP-SA) for 48 hours. Using CLSM at 20X magnification (►Fig. 1), control tendon samples without bacteria showed no background fluorescence (►Fig. 1A). Tendon samples that had been challenged with GFP-SA demonstrated abundant fluorescence, representative of extensive colonization by the GFP-SA (►Fig. 1B). Microcolonies, as well as the denser areas typical of biofilm, were apparent across the surface.

Bacteria Biofilm Formation on Tendons

To confirm that GFP-SA readily colonized the tendons, we next compared colonization on control and GFP-SA contain-

ing tendons. Following bacterial inoculation, SEM was performed at magnifications of 500 to 10,000X. Control tendon samples demonstrate their typical morphology with parallel collagen fibers apparent at all magnifications without biofilm formation (►Fig. 2—top row). The GFP-SA incubated samples are not markedly different from control samples at the lowest magnification (500X), but at magnifications $> 3,000X$, grape-like clusters of bacteria, typical of *Staphylococcus aureus*, can be distinguished (►Fig. 2—bottom row). Higher magnifications revealed dense colonies covered by a thick slimy veil characteristic of biofilm.

Visualization of Contaminated Tendons after Treatment with Antibiotics, Steroids and Sonication

The authors then asked what effect the different treatments had on bacterial colonization of tendon samples. Using CLSM and SEM, irrigation alone had little effect on the qualitative appearance of the tendon surfaces with little to no decrease in the morphologic distribution of bacteria as compared with controls (►Figs. 3A, 4A), as seen by the green fluorescent

Fig. 6 Direct CFU counts after sonication and plating following various treatments for 24 hours. (A) Irrigation alone resulted in 18.5% decrease in bacterial colonization, whereas the addition of antibiotics decreased bacteria by 54.4%. Steroids by themselves resulted in a moderate decrease of 42.6%, but when combined with antibiotics, yielded the most decrease in any condition with 77.3% reduction in bacteria. (B) When comparing antibiotic and steroids with antibiotic and steroids followed by a 10-minute sonication period, a further 75% decrease in attached bacteria is achieved. Bars = $\pm$ SE.

signal emitted by the bacteria (►Fig. 3B) as well as direct visualization (►Fig. 4B). Vancomycin and steroid treatment individually yielded some decrease in the overall attachment, but the distribution pattern on the surface remained unaffected (►Figs. 3C, 4C and ►Figs. 3D, 4D). Following treatment with vancomycin and steroids combined, the fluorescent signal appeared more sparse (►Fig. 3E) whereas scanning microscopy revealed that the remaining bacteria were organized in discrete colonies rather than in a homogeneous distribution (►Fig. 4E).

Numbers of Adherent Methicillin-Sensitive *Staphylococcus aureus* Colonies with or without Treatment

Finally, we determined the number of adherent bacteria after treatment of the colonized tendon samples. Bacterial count normalization relative to the control is illustrated in (►Fig. 6). Irrigation with saline alone yielded a modest approximately 18.5% decrease in bacteria burden; steroids, a 42.6% decrease; antibiotics, a 54.4% decrease; and antibiotics/steroids combined, a 77.3% decrease ($p < 0.05$).

Discussion

PFT of the hand remains a challenging problem that currently requires surgical irrigation and parenteral or oral antibiotics. Regardless of timing and type of irrigation, surgical intervention remains the treatment of choice for most recalcitrant cases of PFT. However, despite prompt treatment, complication rates can reach 38%.⁴ We hypothesized that PFT shares many similarities to peri-PJIs due to the tendons' limited blood supply and closed-space nature of the tendon sheath. Specifically, bacteria within these spaces can attach and form a biofilm on the substrate, rendering standard treatments of local irrigation and/or parenteral antibiotics less effective. Furthermore, previous studies have demonstrated that local administration of corticosteroids in conjunction with antibiotics can improve treatment outcomes in patients with septic arthritis and in animal models^{20,22} of PFT.^{21,23} In this study, we hypothesized and demonstrated that bacteria indeed readily form a biofilm on the tendon surface, and the local administration of corticosteroids and antibiotics, either together or separately, can act directly on the adherent bacteria, and the combined treatment yields greatest reduction in bacterial colonization and biofilm formation.

The genesis of this study is based on the hypothesis that PFT infection eradication and tendon recovery are related to the vascularity of the flexor tendon as well as extent of bacterial biofilm formation. In terms of vascularity, flexor tendon sheath perfusion is predominantly provided by the vincula, which is responsible not only for the influx of nutrients but also for the delivery of systemic antibiotics to the site.¹² In the setting of infection, vascularity to the tendons becomes limited, thereby potentially compromising antibiotic delivery and penetration.¹³ In terms of biofilm formation, bacteria can form a thick glycocalyx matrix on the flexor tendon, similar to those found on PJIs, further preventing antibiotic penetration and immune surveillance. Thus, the infection potentiates and remains recalcitrant to standard treatment, similar to infections invol-

ving prosthetic joints.¹⁴ Therefore, like in PJIs, local mechanical debridement, local antibiotic delivery, and/or complete removal of the prosthesis are required to eradicate the glycocalyx and subsequent infection.¹⁶

This study findings, which are consistent with those in the study by Draeger et al.,²³ also further reinforced the potential benefit of corticosteroids in inhibiting the activity of infections. Conventionally, the use of systemic corticosteroids in the setting of an infection is contraindicated as it could dampen the body's systemic immune response. However, this study further supports the theory that the local placement of corticosteroids can dampen the bacteria's local invasion and damage while not limiting the body's systemic immune response of the antibiotic's effectiveness. Although we recognize that this may be paradoxical as the main function of steroids is to reduce immune reaction, we would speculate that the augmenting effect of the corticosteroid on decreasing biofilm and bacterial might be related to its inhibitory effect on bacterial and biofilm adherence.

To the best of our knowledge, this is the first study that demonstrates that *S. aureus* can readily form biofilm on human hand flexor tendons. This may render current PFT treatment of surgical drainage and/or antibiotics less effective contributing to the common sequelae of pain, swelling, stiffness, weakness, and persistent infection that is common following PFT infections. The addition of both local antibiotics and corticosteroids resulted in considerable decrease in cell colony count and biofilm formation on cadaveric flexor tendons. As such, these treatments can serve as a starting point for further in vivo animal studies, as described by Draeger et al.,²¹ to arrive at a more optimized uniform treatment protocol that includes not only surgical drainage and/or antibiotics but possibly also local delivery of antimicrobial and antiinflammatory agents to prevent tendon colonization and recalcitrant biofilm formation.

There are several limitations to this study. First, it is a cadaveric study and cannot yet speak to the clinical applicability in a living host. Specifically, despite being hypovascular, tendons benefit from some inherent immune support and response in a live individual. In addition, the study is based on MSSA, and its ability to form biofilm may also not be applicable to other bacterial infections of human flexor tendons. Future study directions include investigating this study design and hypothesis in an animal model, and ultimately humans.

Based on the data that we have presented, we suggest rethinking the current treatment of PFT of surgical drainage, lavage, and catheter irrigation, and would recommend considering a strategy more analogous to PJI management with the adjunctive use of local antibiotics and corticosteroids to limit bacterial count and biofilm formation to better eradicate the infection.

Note

This study was conducted at the Rothman Institute at the Thomas Jefferson University, Philadelphia, Pennsylvania, United States.

Funding

None.

Conflict of Interest

None.

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