The Development of an Evidence-Based Approach to **Leg Amputation Prevention**

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Our clinical experiences have focused our research efforts. Our research findings have evolved our clinical practice. This summary is presented not to promote our published works but rather to describe the basis of our novel clinical approaches and to provide examples demonstrating how collaborative clinical research focused on practical questions can improve clinical outcomes.

The Management of Foot Infection

Because of our vascular team's ownership of limb salvage, we have had a primarily surgical approach to the management of foot infections, including osteomyelitis. Specifically, 92% of our patients have had surgical biopsies and cultures taken as part of their operative treatment. These have been used to select an antimicrobial regimen directed to the organisms identified. Antimicrobial regimens have consisted predominately of oral antibiotics (95%) since 2011[1]. Ceftriaxone is the primary empiric antibiotic given to patients who have not yet had operative treatment or whose culture results are pending. We use empiric vancomycin only for patients who have a positive nares swab or who have clinical signs of an abscess based on prevalence rates we found in a prior analysis. Finally, contrary to guidelines emphasizing the importance of Gram positive organisms, our analyses have shown that Gram negative organisms are associated treatment failure[2] and that methicillin-resistant Staphylococcus aureus is not[3]; for this reason, we have focused more attention on improving outcomes in patients with these organisms. We re-biopsy if treatment failure occurs, as we have observed shifts in microbial species involved during treatment[4].

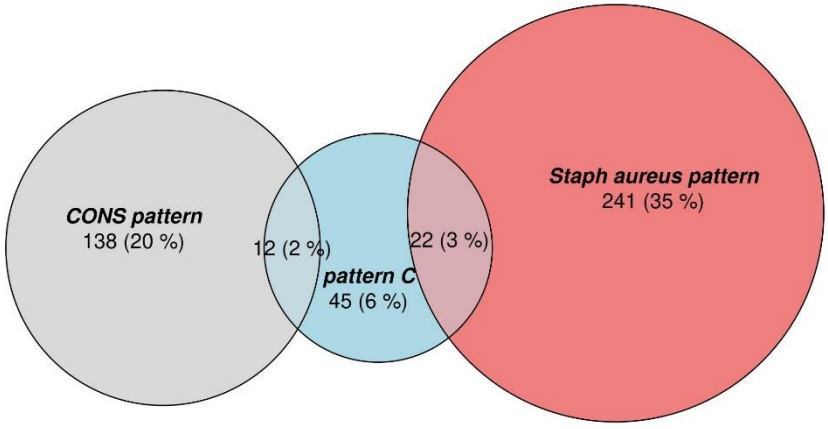
[1] Barshes NR, Mindru C, Ashong C, Rodriguez-Barradas M, Trautner BW. Treatment failure and leg amputation among patients with foot osteomyelitis. *The International Journal of Lower Extremity Wounds* 2016; 15: 303–12.

[2] Barshes NR, Clark NJ, Bidare D, Dudenhoeffer J-H, Mindru C, Rodriguez-Barradas MC. Polymicrobial foot infection patterns are common and associated with treatment failure. *Open Forum Infectious Diseases*. Oxford University Press US, 2022: ofac475.

[3] Ashong CN, Raheem SA, Hunter AS, Mindru C, Barshes NR. Methicillin-resistant staphylococcus aureus in foot osteomyelitis. *Surgical Infections* 2017; 18: 143–8.

[4] Barshes NR, Mindru C, Trautner BW, Rodriguez-Barradas MC. Discordant isolates in bone specimens from patients with recurrent foot osteomyelitis. *European Journal of Clinical Microbiology & Infectious Diseases* 2019; 38: 767–9.

We have made novel contributions to understanding the systemic impact of foot infection. Specifically, we first described acute kidney injury associated with foot osteomyelitis in 2017[5]. We use the presence of acute kidney injury as a clinical sign of foot infection, we have modified our selection of inpatient and outpatient antibiotics accordingly (selective use of vancomycin based on the aforementioned factors, minimizing use of sulfamethoxazole and trimethoprim). We have also described acute cardiac complications (new myocardial infarctions, worsening heart failure, and new arrhythmias) occurring with severe foot infections[6]. Although the prevalence was only 6.6% among the 274 patients analyzed, patients with these new cardiac events have a significantly higher one-year mortality. We therefore consult our medical teams for further cardiac workup when acute cardiac complications are seen. Lastly, we've described an unusual syndrome of severe anemia, weight loss, hyponatremia, hyopalbuminemia, and uremia and other metabolic derangements occurring in a series of patients with beta-hemolytic streptococci[7]. We are particularly aggressive in controlling infection in patients with this constellation of findings.



pattern C = two or more of "K.E.E.P.S." organisms:
Klebsiella,
Enterococcus fecalis,
Enterobacter,
Escherichia coli,
Proteus, and/or
Streptococcus (alpha-hemolytic)

NEITHER *Bacteroides*
NOR *Corynebacterium*

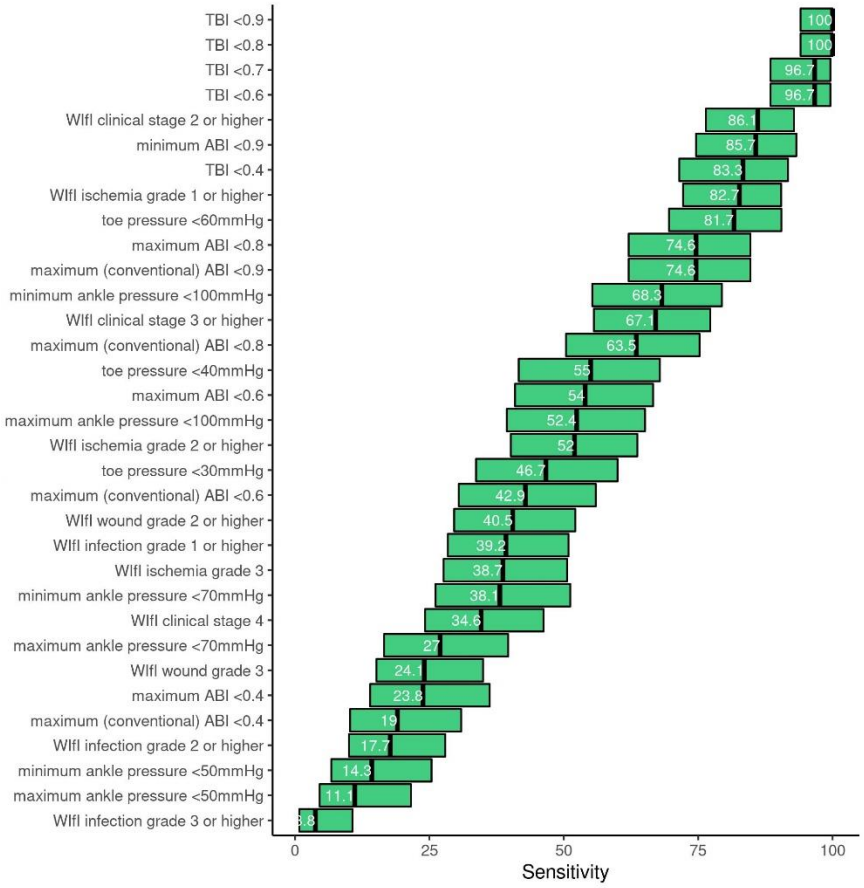
[5] Jiang BC, Cowart JB, Barshes NR. Acute kidney injury associated with foot osteomyelitis. *Clinical Medicine* 2017; 17: 376–6.

[6] Singh M, Khan K, Fisch E, Frey C, Mathias K, Jneid H, Musher DM, Barshes NR. Acute Cardiac Events in Patients With Severe Limb Infection. Acute cardiac events in patients with severe limb infection. *The International Journal of Lower Extremity Wounds* 2018; 17: 261–7.

[7] Den JL, Gay LM, Barshes NR. Severe anemia, anorexia, and uremia associated with diabetic foot infections: A case series. *The Foot* 2022; 53: 101926.

The Identification of Peripheral Artery Disease

Our approach to identifying peripheral artery disease (PAD) has also evolved based on research findings. With award funding from the Society for Vascular Surgery, we performed a formal decision analysis with a probabilistic Markov which we expected would support our approach at that time: selective angiography done based on the results of non-invasive arterial testing (specifically, toe pressure <60mmHg). Findings from the analysis, however, suggested that the sensitivity in identifying PAD might be increased by deciding on angiography simply based on weak or absent pedal pulses and using non-invasive testing to instead corroborate adequate arterial perfusion in patients with palpable pedal pulses[8]. A subsequent observational study has corroborated these findings and have suggested that a toe-brachial index of <0.7 may be even more sensitive still, especially in patients without medial artery calcification of pedal vessels as seen on plain radiography[9].

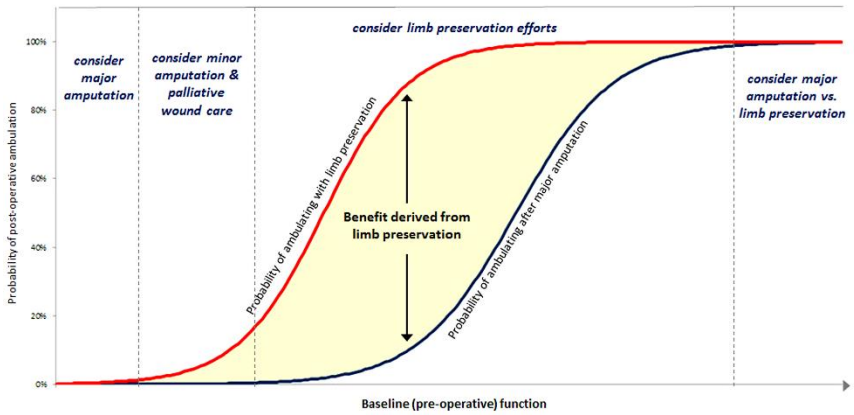


[8] Barshes NR, Flores E, Belkin M, Kougias P, Armstrong DG, Mills Sr JL. The accuracy and cost-effectiveness of strategies used to identify peripheral artery disease among patients with diabetic foot ulcers. *Journal of Vascular Surgery* 2016; 64: 1682–90

[9] Choi JC-B, Miranda J, Greenleaf E, Conte MS, Gerhard-Herman MD, Mills JL Sr, Barshes NR. Lower-extremity pressure, staging, and grading thresholds to identify chronic limb-threatening ischemia. *Vascular Medicine* 2023; 28: 45–53

Decision Making: Revascularization and Limb Salvage, Leg Amputation or Palliative Wound Care

Leg amputation is generally still the only alternative that many surgeons provide to patients who are not candidates for revascularization and limb salvage. It had been ours prior to the aforementioned cost-utility study[10]. In this study, wound care alone (i.e. without revascularization) was included as a strategy analyzed with the intent of demonstrating the clinical harms associated with missing the diagnosis of PAD. Unexpectedly, the model predicted the strategy of wound care alone would actually produce better health outcomes and lower total costs than leg amputation[11]. We subsequently reported outcomes of this "palliative wound care" alternative to leg amputation for a selected group of patients with advanced comorbid conditions; these research findings[12] and much more clinical experience since have confirmed that it is indeed a good and generally preferable alternative to leg amputation.



[10] Barshes NR, Chambers JD, Cohen J, Belkin M, Ischemic Extremities 1 (MOVIE) Study Collaborators MTOHV in, et al. Cost-effectiveness in the contemporary management of critical limb ischemia with tissue loss. *Journal of Vascular Surgery* 2012; 56: 1015–24.

[11] Barshes NR, Chambers JD, Cohen J, Belkin M, Ischemic Extremities 1 (MOVIE) Study Collaborators MTOHV in, et al. Cost-effectiveness in the contemporary management of critical limb ischemia with tissue loss. *Journal of Vascular Surgery* 2012; 56: 1015–24.

[12] Barshes NR, Gold B, Garcia A, Bechara CF, Pisimisis G, Kougias P. Minor amputation and palliative wound care as a strategy to avoid major amputation in patients with foot infections and severe peripheral arterial disease. *The International Journal of Lower Extremity Wounds* 2014; 13: 211–9.

We therefore generally pursue surgical revascularization and limb salvage – even in patients with advanced comorbidities[13] or marginal functional status[14], and especially in patients with a contralateral leg amputation[15]. We favor endovascular interventions for patients with end-stage renal disease[16].

Leg amputation is typically now recommended to patients who are not a candidate for revascularization and limb salvage but have one or more of the following characteristics: infection that is not controlled by surgical therapy (e.g. minor amputation) and limited-course antibiotics and causing secondary infection or other systemic effects (ex. weight loss, anorexia, malaise); pain that is not controlled by medications or image-guided nerve injections; wounds that patients or care providers cannot or will not manage due to voluminous fluid output or foul odor; or mobility that is impaired by the foot wound and that may improve with leg amputation.

We generally recommend and offer leg amputation at the transtibial (below-knee) level, but we may suggest more proximal levels, such as through-knee or transfemoral, for patients with ischemic pains and "no-option" peripheral artery disease because of a significantly higher rate of revision to more proximal levels following transtibial amputation in these patients[17].

[13] Barshes NR, Menard MT, Nguyen LL, Bafford R, Ozaki CK, Belkin M. Infrainguinal bypass is associated with lower perioperative mortality than major amputation in high-risk surgical candidates. *Journal of Vascular Surgery* 2011; 53: 1251–9.

[14] Barshes NR, Kougias P, Ozaki CK, Pisimisis G, Bechara CF, Henson HK, Belkin M. Cost-effectiveness of revascularization for limb preservation in patients with marginal functional status. *Annals of Vascular Surgery* 2014; 28: 10–7.

[15] Sharath S, Henson H, Flynn S, Pisimisis G, Kougias P, Barshes NR. Ambulation and independence among Veterans with nontraumatic bilateral lower-limb loss. *Journal of Rehabilitation Research & Development* 2015; 52:851-8.

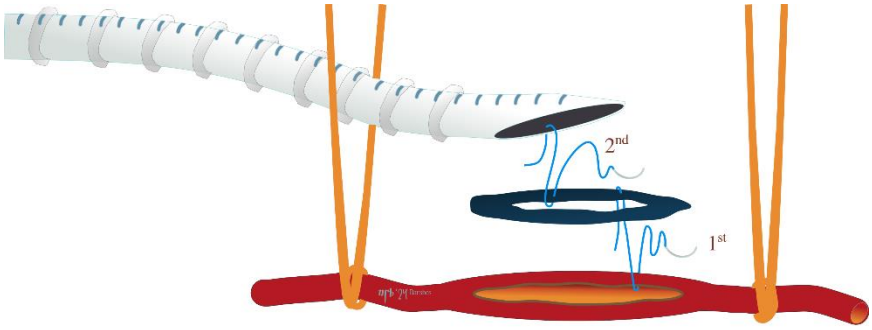
[16] Barshes NR, Kougias P, Ozaki CK, Goodney PP, Belkin M. Cost-effectiveness of revascularization for limb preservation in patients with end-stage renal disease. *Journal of Vascular Surgery* 2014; 60: 369–74.

[17] Khouqer A, Uribe-Gomez A, Sharath SS, Kougias P, Barshes NR. Wound complications and reoperations after transtibial amputation of the leg. *Annals of Vascular Surgery* 2020; 69:292-7.

Revascularization for PAD

Our approach to treating PAD has been informed by cost-utility studies that suggest infrainguinal bypass may be more clinically effective and cost-effective that endovascular intervention[13,]. Spliced vein conduits seem better in patients without adequate single-segment saphenous vein, but bypasses done with polytetrafluoroethylene (PTFE) and a distal vein patch provide good outcomes too[18,19]. In 2011, cryopreserved allograft vein was the conduit used for 9% infrainguinal bypasses, but this has been eliminated because of findings suggesting it was associated with poorer clinical outcomes and higher costs[15]. Similarly, we reduced the usage of stent-grafts used in infrainguinal endovascular interventions from 28% in 2011 to 9% in 2017 and <5% currently based on findings suggesting a significantly poorer patency and higher rate of acute limb occlusion with these devices[20]. We employ bundled interventions (pre-operative nasal and skin decontamination for methicillin-sensitive Staphylococcus aureus, routine perioperative antibiotics, chlorhexidine/alcohol skin preparation, wound closure using subcuticular sutures, and incisional negative pressure wound therapy dressings for groin wounds) that has lead to a 5-fold reduction in superficial or deep surgical site infections[21].

We have employed a strategy of surgical closure of many foot wounds early after revascularization[22]. This approach was initially based on the post-operative care of the incident foot ulcer being identified as a cost-driver for the overall strategy of revascularization and limb salvage[13].



[18] Barshes NR, Ozaki CK, Kougias P, Belkin M. A cost-effectiveness analysis of infrainguinal bypass in the absence of great saphenous vein conduit. *Journal of Vascular Surgery* 2013; 57: 1466–70.

[19] Branco BC, Kougias P, Braun JD, Mills Sr JL, Barshes NR. Distal vein patch use and limb events after infragenicular prosthetic bypasses. *Journal of Vascular Surgery* 2018; 68: 145–52.

[20] Zamani N, Sharath SE, Browder RC, Barshes NR, Braun JD, Mills JL Sr, Kougias P, Younes HK. Outcomes after endovascular stent placement for long-segment superficial femoral artery lesions. *Annals of Vascular Surgery* 2021; 71: 298–307.

[21] Zamani N, Sharath SE, Vo E, Awad SS, Kougias P, Barshes NR. A multi-component strategy to decrease wound complications after open infra-inguinal re-vascularization. *Surgical Infections* 2018; 19: 87–94.

[22] Barshes NR, Bechara CF, Pisimisis G, Kougias P. Preliminary experiences with early primary closure of foot wounds after lower extremity revascularization. *Annals of Vascular Surgery* 2014; 28: 48–52.

Ensuring Adequate Access to Timely Specialty Care

Data available through the VHA Support Service Center helped us recognize that our hospital system had half the number of podiatrists and also lower rates of podiatry clinic visits for veterans at moderate and high risk (PAVE II and III, respectively) than VHA hospitals of comparable size. We proposed an action plan that has resulted in successfully hiring two additional podiatrists, and we have a plan to increase the frequency of podiatry clinic visits for these at-risk patients.

We have done work with state-level data has helped us identify groups of people within Texas who experience high rates of leg amputation: persons categorized as black or Hispanic and persons living in specific geographic locations[23,24,25,26]. Based on findings suggesting higher rates of leg amputations and poorer access to specialty care among people in east Texas, one of the authors (N.R.B.) began seeing vascular surgery patients at VHA community-based outpatient VHA clinic in Lufkin, a town of 35,000 people located 127 miles from Houston.

Primary Prevention of Foot Ulcers

Data analyses have helped us direct our primary prevention efforts. An economic model suggested that primary prevention efforts had a much higher potential for cost-savings that limb salvage treatment, including efforts that might be low effectiveness but have low cost[27]. Based on this, we developed a 500-word plain language trifold brochure that discusses preventative care actions[28].

With the help of the information technology specialists, we generated lists of veterans of all races/ethnicity living in high amputation-rate zip codes in our region and mailed them our brochures with an explanatory cover letter, timed along with April as "Amputation Awareness & Prevention Month." We have now completed two rounds of mailings, with brochures and letters sent during the last round to 3,512 veterans. Several of our specialty clinics have in-person or video-based outpatient clinic within the identified area of high amputation rates.

[23] Barshes NR, Sharath S, Zamani N, Smith K, Serag H, Rogers SO. Racial and geographic variation in leg amputations among texans. *Texas Public Health Journal* 2018; 70: 22.

[24] Cao J, Sharath SE, Zamani N, Barshes NR. Health care resource distribution of texas counties with high rates of leg amputations. *Journal of Surgical Research* 2019; 243: 213–9.

[25] Barshes NR, Uribe-Gomez A, Sharath SE, Mills Sr JL, Rogers Jr SO. Leg amputations among texans remote from experienced surgical care. *Journal of Surgical Research* 2020; 250: 232–8.

[26] Bidare D, Sharath S, Cerise F, Barshes NR. Specialist access and leg amputations among Texas Medicaid patients. *Seminars in Vascular Surgery* 2023: 36: 49–57.

[27] Barshes NR, Saedi S, Wrobel J, Kougias P, Kundakcioglu OE, Armstrong DG. A model to estimate cost-savings in diabetic foot ulcer prevention efforts. *Journal of Diabetes and its Complications* 2017; 31: 700–7.

[28] Barshes NR. Healing feet, avoiding amputation. 2023. https://nealbarshes.github.io.