Diabetic Foot Infection Guideline Updates: Data That May Change Your Practice

Whitney Hartlage, PharmD

Infectious Diseases & Antimicrobial Stewardship Pharmacist

Clinical Infectious Diseases

IDSA GUIDELINES

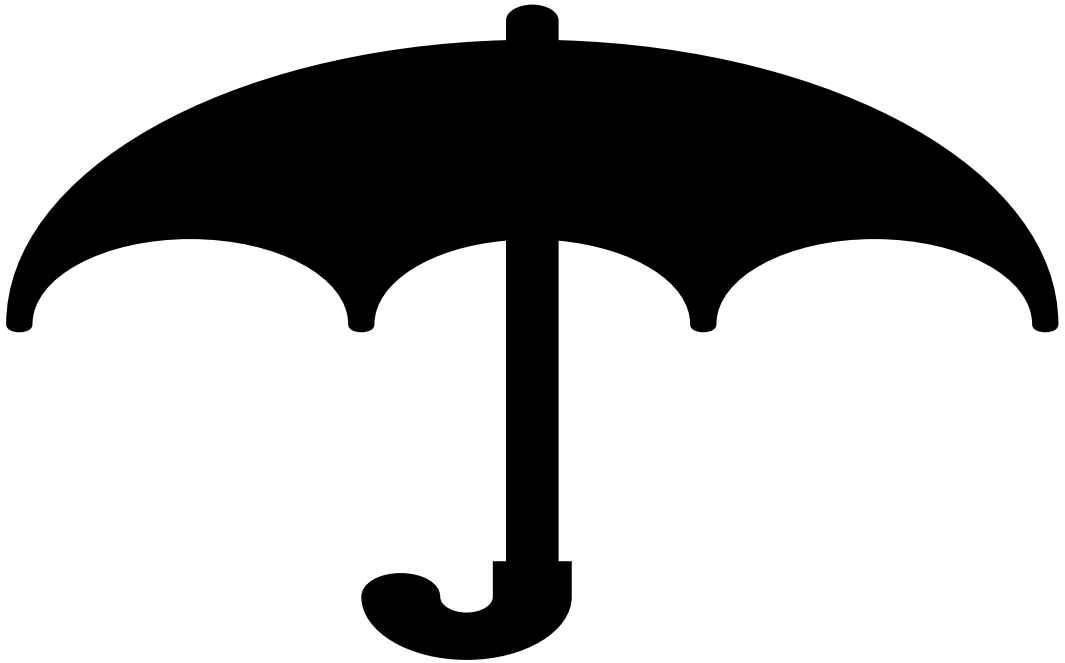
IWGDF/IDSA Guidelines on the Diagnosis and Treatment of Diabetes-related Foot Infections (IWGDF/IDSA 2023)

Éric Senneville,[1,2] Zaina Albalawi,[3] Suzanne A. van Asten,[4] Zulfiqarali G. Abbas,[5] Geneve Allison,[6] Javier Aragón-Sánchez,[7] John M. Embil,[8] Lawrence A. Lavery,[9] Majdi Alhasan,[10] Orhan Oz,[11] Ilker Uçkay,[12] Vilma Urbančič-Rovan,[13] Zhang-Rong Xu,[14] and Edgar J. G. Peters[15,16,17]

[1]Gustave Dron Hospital, Tourcoing, France; [2]Univ-Lille France, Lille, France; [3]Department of Medicine, Division of Endocrinology, Memorial University, St. John's, Newfoundland and Labrador, Canada; [4]Department of Medical Microbiology, Leiden University Medical Centre, Leiden, The Netherlands; [5]Abbas Medical Centre, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania; [6]Department of Medicine, Tufts Medical Center, Boston, Massachusetts, USA; [7]La Paloma Hospital, Las Palmas de Gran Canaria, Spain; [8]Department of Medicine, Section of Infectious Diseases, University of Manitoba, Winnipeg, Manitoba, Canada; [9]Department of Plastic Surgery, UT Southwestern Medical Center, Dallas, Texas, USA; [10]Department of Medicine, Prisma Health-Midlands, Columbia, South Carolina, USA; [11]UT Southwestern Medical Center, Dallas, Texas, USA; [12]Balgrist University Hospital, Zurich, Switzerland; [13]Faculty of Medicine, University Medical Centre, University of Ljubljana, Ljubljana, Slovenia; [14]Diabetes Centre, Beijing, China; [15]Department of Internal Medicine, Amsterdam UMC, Vrije Universiteit Amsterdam, Section of Infectious Diseases, Amsterdam, The Netherlands; [16]Amsterdam Movement Sciences, Rehabilitation and Development, Amsterdam, The Netherlands; and [17]Amsterdam Infection & Immunity, Infectious Diseases, Amsterdam, The Netherlands

Published: October 2023

Diabetic Foot Infections (DFIs)



Soft tissue infection alone

Soft tissue infection with bone involvement (osteomyelitis)

How to Classify Infection

- Many published classification schemes
- Not compared in large prospective studies
- No consensus on which to use
  - Varied severity definitions in comparative studies of antibiotic therapy
- IDSA severity staging for DFI predicts outcomes and **not** microbiology

Severity	Criteria	Hospitalization	Amputation
Mild	Local infection involving only the skin and subcutaneous tissue as defined by ≥ 2 of the following: • Local swelling or induration • Erythema 0.5 – 2 cm around ulcer • Local tenderness or pain • Local warmth • Purulent discharge	4%	3%
Moderate	Local infection + erythema > 2 cm around ulcer OR Local infection + deeper structure involvement (abscess, osteomyelitis, septic arthritis, fasciitis)	52%	46%
Severe	Local infection + ≥ 2 SIRS criteria	89%	70%

Lipsky BA, et al. Clin Infect Dis. 2012 Jun;54(12):e132-73.
Senneville, et al. Clin Infect Dis. 2023

Osteomyelitis should be considered:

- If ulcer is present for more than a month
- Probe to bone (Has high NPV, not PPV)
- Unexplained high ESR
- Abnormal x-ray

- Up to 20% of patients with mild to moderate DFI have osteo, and up to 60% of patients with severe DFI.

Senneville, et al. Clin Infect Dis. 2023

Microbiology of DFIs

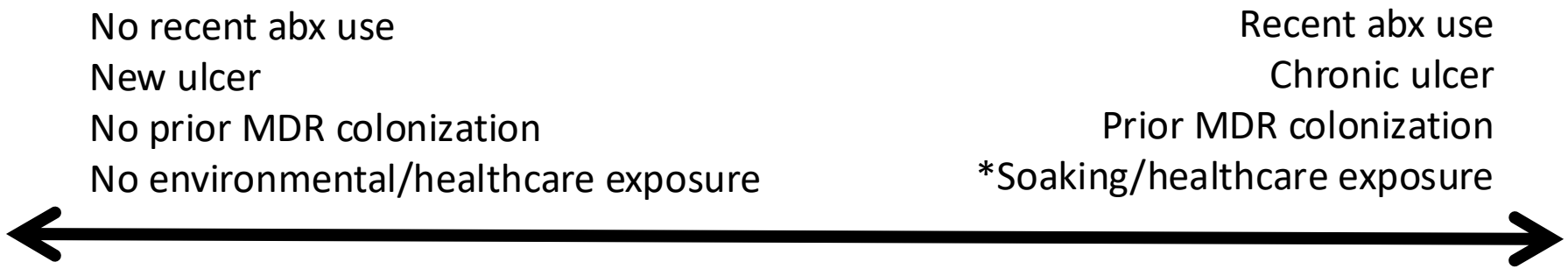
Microbiology is influenced by:

1) Recent antibiotic use (last 30 days)
2) Ulcer chronicity and depth
3) Previous colonization
4) Recent environmental and healthcare exposures

Microbiology of DFIs

Microbiology is influenced by:

1) Recent antibiotic use (last 30 days)
2) Ulcer chronicity and depth
3) Previous colonization
4) Recent environmental and healthcare exposures



Microbiology of DFIs

Microbiology is influenced by:

1) Recent antibiotic use (last 30 days)
2) [illegible]
3) [illegible]
4) [illegible]

It's not that more severe infections are more likely to be Gram negative, or drug resistant, or polymicrobial. However, **willingness to be wrong is lower, so empiric coverage is broader**.

Wound chronicity and prior exposure to antibiotics are what influence the microbiology.

Streptococcus species
Staphylococcus aureus

Streptococcus species
MSSA
MRSA
Enterobacteriaceae
Pseudomonas

Empiric antipseudomonal coverage is usually NOT necessary

- Pseudomonas is rare in DFIs in the US (4-4.5%)[1,2]
- RCT comparing upfront ertapenem to pip/tazo for mod/severe DFI was equivalent[3]
  - Interestingly, clinical response rates were higher with ertapenem (83%, n=15/18) than pip/tazo (70%, n=7/10) when *P. aeruginosa* was isolated
- Indications[4]:
  - Isolated from culture of the affected site within the previous few weeks
  - Moderate to severe infection in person who resides in Asia or North Africa

1) Young H, et al. J Am Podiatr Med Assoc. 2015.
2) Nebraska Medicine. Diabetic Foot Infections.
3) Lipsky B, et al. Lancet. 2005.
4) Senneville, et al. Clin Infect Dis. 2023

Empiric Antibiotics for DFI/DFO

Recommended Empiric Antibiotics for DFI			
Severity	**Pathogens**	**Considerations**	**Antibiotics**
Mild *Local/skin & soft tissue infection*	Gram positives: *Staph aureus*, Streptococcus species	Non-purulent	• Cephlex
		Purulence OR history of MRSA in foot wound	• TMP/SMX or Doxy

Senneville, et al. *Clin Infect Dis*. 2023

Empiric Antibiotics for DFI/DFO

Recommended Empiric Antibiotics for DFI			
Severity	**Pathogens**	**Considerations**	**Antibiotics**
Mild *Local/skin & soft tissue infection*	Gram positives: *Staph aureus*, Streptococcus species	Non-purulent	• Cephlex
		Purulence OR history of MRSA in foot wound	• TMP/SMX or Doxy
Moderate *Deeper involvement*	Gram-positives ± Enterobacteriaceae	No previous antibiotics (1 month)	• Cefazolin • If purulence: add vanco
		Previous antibiotics (1 month)	• Amp/sul or Ceftriaxone + metro • If purulence: add vanco

Senneville, et al. *Clin Infect Dis*. 2023

Empiric Antibiotics for DFI/DFO

Recommended Empiric Antibiotics for DFI			
Severity	**Pathogens**	**Considerations**	**Antibiotics**
Mild *Local/skin & soft tissue infection*	Gram positives: *Staph aureus*, Streptococcus species	Non-purulent	• Cephlex
		Purulence OR history of MRSA in foot wound	• TMP/SMX or Doxy
Moderate *Deeper involvement*	Gram-positives ± Enterobacteriaceae	No previous antibiotics (1 month)	• Cefazolin • If purulence: add vanco
		Previous antibiotics (1 month)	• Amp/sul or Ceftriaxone + metro • If purulence: add vanco
Severe *Systemic infection*	Gram-positives ± Enterobacteriaceae ± obligate anaerobes	No previous antibiotics (1 month)	• Amp/sul or Ceftriaxone + metro • If purulence: add vanco
		Previous antibiotics (1 month)	• Cefepime + metro • If purulence: add vanco

Senneville, et al. *Clin Infect Dis*. 2023

Empiric Antibiotics for DFI/DFO

Recommended Empiric Antibiotics for DFI			
Severity	**Pathogens**	**Considerations**	**Antibiotics**
Mild *Local/skin & soft tissue infection*	Gram positives: *Staph aureus*, Streptococcus species	Non-purulent	• Cephlex
		Purulence OR history of MRSA in foot wound	• TMP/SMX or Doxy
Moderate *Deeper involvement*	Gram-positives ± Enterobacteriaceae	No previous antibiotics (1 month)	• Cefazolin • If purulence: add vanco
		Previous antibiotics (1 month)	• Amp/sul or Ceftriaxone + metro • If purulence: add vanco
Severe *Systemic infection*	Gram-positives ± Enterobacteriaceae ± obligate anaerobes	No previous antibiotics (1 month)	• Amp/sul or Ceftriaxone + metro • If purulence: add vanco
		Previous antibiotics (1 month)	• Cefepime + metro • If purulence: add vanco
Severe + hypotension or organ dysfunction *(requiring ICU admission)*	Gram-positives ± Enterobacteriaceae ± obligate anaerobes ± *P aeruginosa*		• Cefepime + metro + vanco

Senneville, et al. *Clin Infect Dis*. 2023

Definitive Therapy Selection

- Tailor antibiotics to ***appropriately obtained*** culture results

- Role of histology and bone cultures:
  - Histology: helps determine if remaining osteo after debridement
  - Bone culture: helps guide which definitive regimen is selected

- IV to PO: switch when patient is improving and taking oral meds
  - “As treatment with **oral antibiotics regimens** for residual osteomyelitis are **associated with failure rates similar to those with intravenous regimens**, this may help reduce the length of stay in those patients."

Senneville, et al. Clin Infect Dis. 2023

Duration of therapy – SSTI alone (no bone involvement)

- **5 days** (same as any other SSTI; max 10 days)

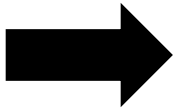
- *Note: Guidelines recommend treatment duration up to 2 weeks.
  - Recommendation is mainly based on opinion and “no new studies to justifying modifying our previous recommendation”. Not because shorter durations < longer
  - Studies looking at shorter antibiotic durations for SSTI included those with diabetes
  - **Why max of 10 days and not 14??** Pilot RCT that compared 10-day duration versus 20 days with equivalent clinical outcome
    - Duration for study was selected based on practice preference at investigator site (“surgeons round down to 10 days or up to 20 days”)

Senneville, et al. Clin Infect Dis. 2023

Duration of therapy – Bone or joint involvement

2012 IDSA Guideline for the Diagnosis and Treatment of Diabetic Foot Infections

Bone or Joint	Duration of Therapy
No residual infected tissue (eg, postamputation)	2-5 days
Residual infected soft tissue (but no bone)	1-3 weeks
Residual infected (but viable) bone	4-6 weeks
No surgery, or residual dead bone postoperatively	≥3 months



2023 IDSA Guideline for the Diagnosis and Treatment of Diabetic-related Foot Infections

Bone or Joint	Duration of Therapy
Resected	2-5 days
Debrided (soft tissue infection only)	1-2 weeks
Positive ~~culture or~~ histology or bone margins after bone resection or minor amputation	3 weeks
No surgery or dead bone	6 weeks

Senneville, et al. Clin Infect Dis. 2023

Clinical Infectious Diseases

MAJOR ARTICLE

Three Weeks Versus Six Weeks of Antibiotic Therapy for Diabetic Foot Osteomyelitis: A Prospective, Randomized, Noninferiority Pilot Trial

Karim Gariani,[1,a] Truong-Thanh Pham,[2,3,a] Benjamin Kressmann,[2,3] François R. Jornayvaz,[1] Giacomo Gastaldi,[1] Dimitrios Stafylakis,[3] Jacques Philippe,[1] Benjamin A. Lipsky,[2,4] and Ilker Uçkay[2,3,5,6]

[1]Service of Endocrinology, Diabetes, Hypertension and Nutrition, Geneva University Hospitals, Geneva, Switzerland, [2]Service of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland, [3]Orthopedic Surgery Service, Geneva University Hospitals, Geneva, Switzerland, [4]Department of Medicine, University of Washington, Seattle, Washington, USA, [5]Infectiology, Balgrist University Hospital, University of Zurich, Zurich, Switzerland, and [6]Unit for Clinical and Applied Research, Balgrist University Hospital, University of Zurich, Zurich, Switzerland

- Prospective, randomized, noninferiority trial
- Patients with diabetic foot osteomyelitis (DFO) who underwent surgical debridement
  - Excluded those that had total clinical amputation of all infected tissue
- 3-week (n=44) vs 6-week treatment duration (n=49)
- Clinical remission of DFO at 2 months after the designated end of treatment

Gaiani, et al. Clin Infect Dis. 2020;73(7):e1539-e1545.

Clinical Infectious Diseases

MAJOR ARTICLE

Three Weeks Versus Six Weeks of Antibiotic Therapy for Diabetic Foot Osteomyelitis: A Prospective, Randomized, Noninferiority Pilot Trial

Karim Gariani,[1,a] Truong-Thanh Pham,[2,3,a] Benjamin Kressmann,[2,3] François R. Jornayvaz,[1] Giacomo Gastaldi,[1] Dimitrios Stafylakis,[3] Jacques Philippe,[1] Benjamin A. Lipsky,[2,4] and Ilker Uçkay[2,3,5,6]

[1]Service of Endocrinology, Diabetes, Hypertension and Nutrition, Geneva University Hospitals, Geneva, Switzerland, [2]Service of Infectious Diseases, Geneva University Hospitals, Geneva, Switzerland, [3]Orthopedic Surgery Service, Geneva University Hospitals, Geneva, Switzerland, [4]Department of Medicine, University of Washington, Seattle, Washington, USA, [5]Infectiology, Balgrist University Hospital, University of Zurich, Zurich, Switzerland, and [6]Unit for Clinical and Applied Research, Balgrist University Hospital, University of Zurich, Zurich, Switzerland

- Prospective, randomized, noninferiority trial
- Patients with diabetic foot osteomyelitis (DFO) who underwent surgical debridement
  - Excluded those that had total clinical amputation of all infected tissue
- 3-week (n=44) vs 6-week treatment duration (n=49)
- Clinical remission of DFO at 2 months after the designated end of treatment

- *Staphylococcus aureus* (47%), streptococci (11%), gram-negative pathogens (30%), and polymicrobial (52%)
- **Duration of IV therapy**, median: 2 days (1 day in 3-week vs. 3 day in 6-week)
- Agents: amox/clav (63%), levofloxacin (22%), clindamycin (17%)

Characteristic	Duration of Antibiotic Therapy: 3 Weeks (n = 44)	6 Weeks (n = 49)	*P* Value[a]
Outcome			
Complete remission	37 (84)	36 (73)	.21
Microbiological recurrence only	3 (7)	5 (10)	.56
Adverse events	17 (39)	16 (33)	.54
Serious adverse events	5 (11)	9 (18)	.35
Antibiotic-related adverse events	4 (9)	7 (14)	.44
Complete wound healing after therapy	28 (64)	29 (59)	.67

<u>Conclusion</u>: A postdebridement antibiotic course for DFO of 3 weeks gave similar (and statistically noninferior) incidence of remission to a course of 6 weeks

Gariani K, et al. Clin Infect Dis. 2021;73(7):e1539-e1545.

Duration of Therapy Summary

- **Soft tissue infection alone**: 5 days (max 10)

- **Soft tissue infection with bone involvement (osteomyelitis):**
  - No remaining infected bone after resection: 2-5 days
  - No remaining infected bone but residual soft tissue infection: see above
  - Positive histology of proximal bone margins after bone resection or minor amputation: 3 weeks
  - No surgery or dead bone: 6 weeks

Key points

- **Non-infection-related factors** are more important in ultimate success
- **Wound chronicity and prior exposure to antibiotics** are what influence the microbiology
- **Appropriately obtained** cultures are everything
- **Multidisciplinary approach** used to optimize management