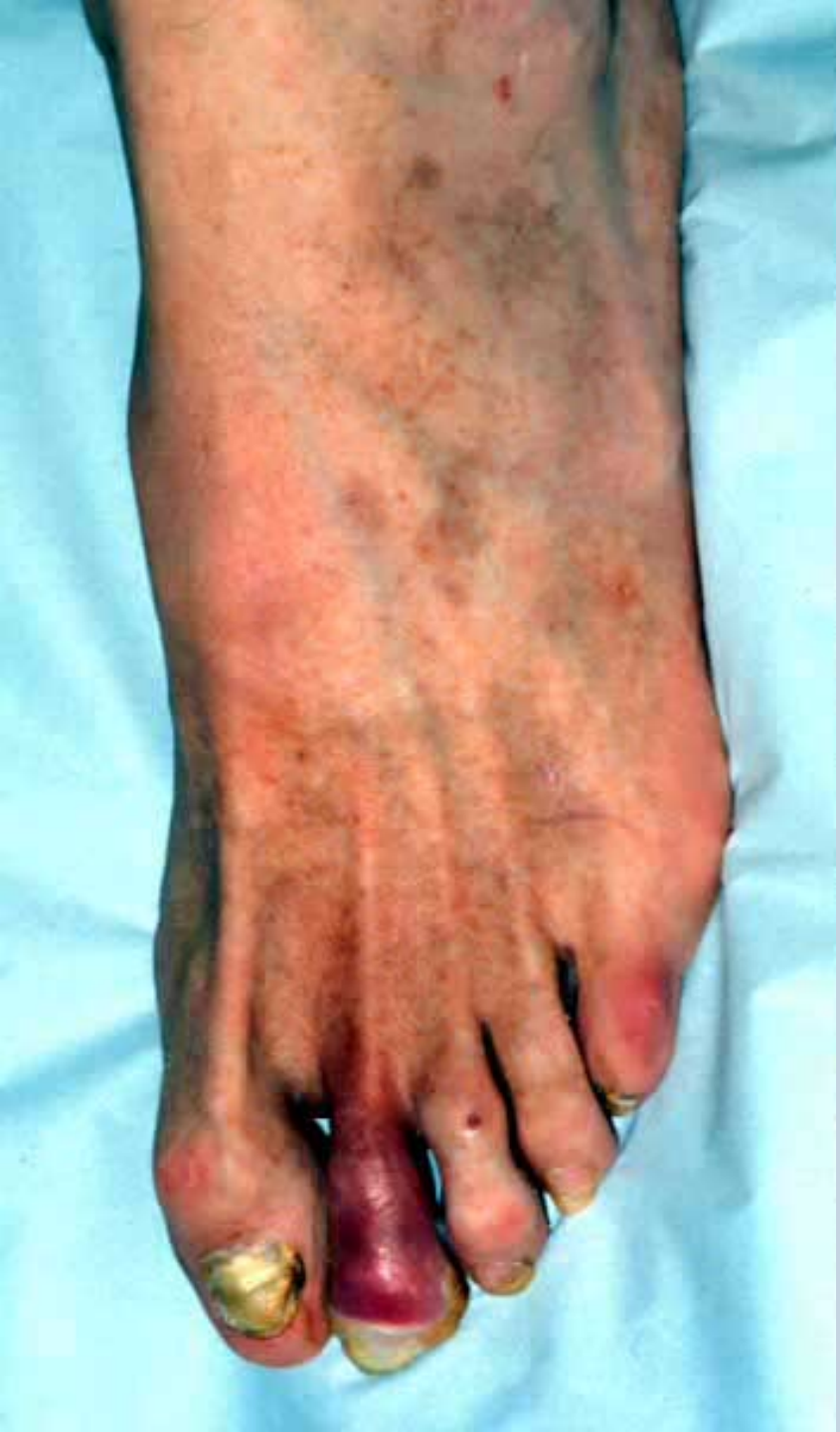

Diagnosis and Treatment of Diabetes-related Foot Infections

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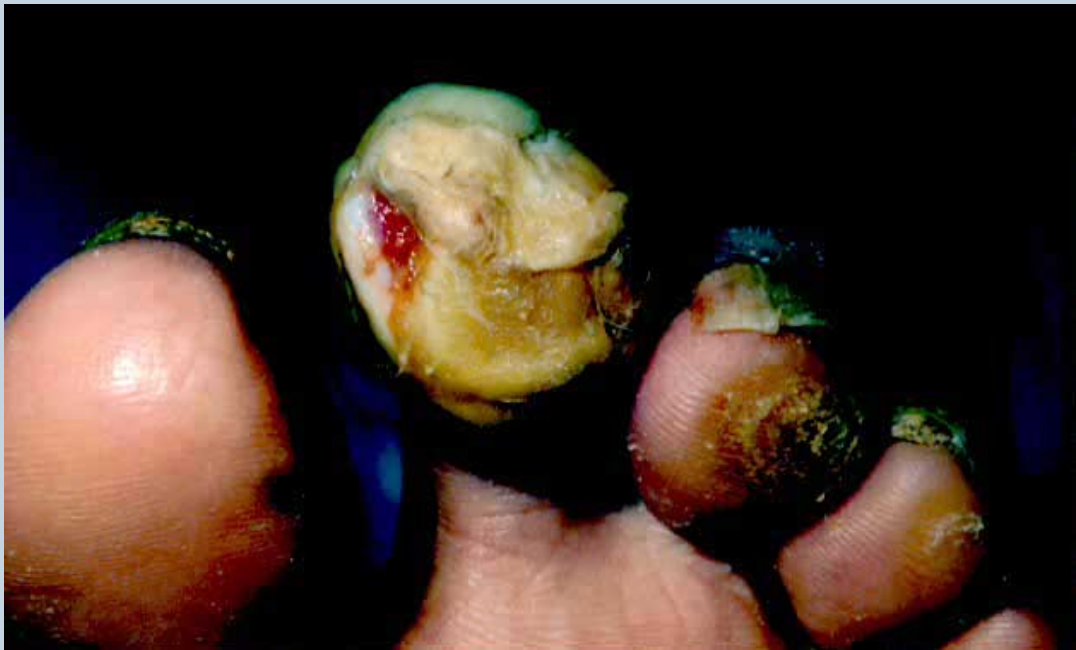


Objectives

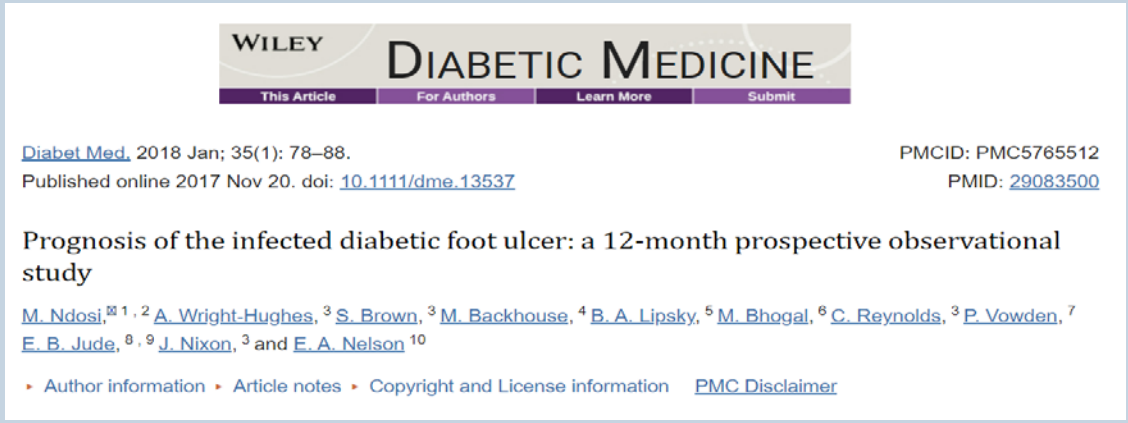
- Classifications of Diabetic Foot Infection
- Evaluating the Patient with a DFI
- Treatment

INTRODUCTION

- The prevalence of diabetes continues to increase globally and the International Diabetes Foundation has estimated that 537 million adults aged between 20 and 79 years worldwide were living with diabetes in 2021.

- DFIs remain the most frequent diabetes-related complications requiring hospitalization and the most common precipitating events leading to lower extremity amputation.

International Diabetes Federation. IDF Diabetes Atlas. 10th ed. Belgium; 2021.



WILEY DIABETIC MEDICINE

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Diabet Med. 2018 Jan; 35(1): 78–88.
Published online 2017 Nov 20. doi: 10.1111/dme.13537
PMCID: PMC5765512
PMID: 29083500

Prognosis of the infected diabetic foot ulcer: a 12-month prospective observational study

M. Ndosi,[✉1,2] A. Wright-Hughes,[3] S. Brown,[3] M. Backhouse,[4] B. A. Lipsky,[5] M. Bhogal,[6] C. Reynolds,[3] P. Vowden,[7] E. B. Jude,[8,9] J. Nixon,[3] and E. A. Nelson[10]

Author information ▸ Article notes ▸ Copyright and License information PMC Disclaimer

Outcomes in patients presenting with an infected diabetes-related foot ulcer (DFU) are suboptimal

prospective study, at the end of 1 year, the ulcer had healed in only 46% (and it later recurred in 10% of these), while 15% had died and 17% required a lower extremity amputation.

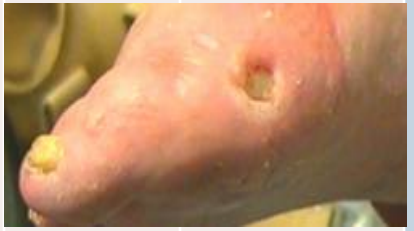
Diabet Med. 2018; 35(1):78–88

Risk Factor for DFI

- Ulcer >30d
- Positive PTB
- Recurrent foot ulcers
- Peripheral vascular disease
- Walking barefoot
- Renal insufficiency
- Loss of protective sensation
- Previous amputation
- Traumatic foot wound
- Chronic hyperglycemia

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

Infectious Diseases Society of America and International Working Group on the Diabetic Foot Classifications of Diabetic Foot Infection

Clinical Manifestation of Infection	PEDIS Grade	IDSA Infection Severity
No symptoms or signs of infection	**1**	**Uninfected**
Infection present, as defined by the presence of at least 2 of the following items: **• Local swelling or induration** **• Erythema** **• Local tenderness or pain** **• Local warmth** **• Purulent discharge (thick, opaque to white or sanguineous secretion)**		

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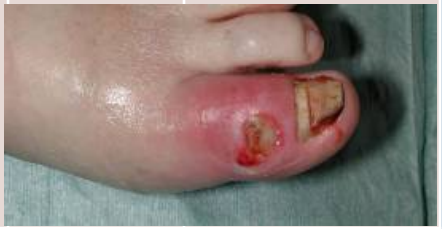
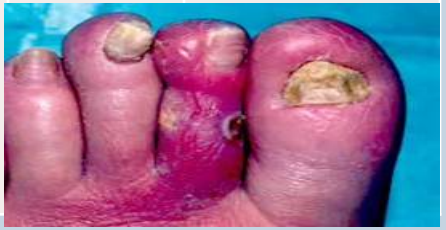
Infectious Diseases Society of America and International Working Group on the Diabetic Foot Classifications of Diabetic Foot Infection

Clinical Manifestation of Infection	PEDIS Grade	IDSA Infection Severity
Local infection involving only the skin and the subcutaneous tissue (without involvement of deeper tissues and without systemic signs as described below). If erythema, must be >0.5 cm to ≤2 cm around the ulcer. Exclude other causes of an inflammatory response of the skin (eg, trauma, gout, acute Charcot neuro-osteoarthropathy, fracture, thrombosis, venous stasis).	2	Mild
Local infection (as described above) with erythema > 2 cm, or involving structures deeper than skin and subcutaneous tissues (eg, abscess, osteomyelitis, septic arthritis, fasciitis), and No systemic inflammatory response signs (as described below)	3	Moderate





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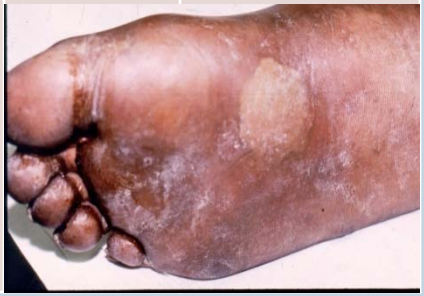
Infectious Diseases Society of America and International Working Group on the Diabetic Foot Classifications of Diabetic Foot Infection

Clinical Manifestation of Infection	PEDIS Grade	IDSA Infection Severity
Local infection (as described above) with the signs of SIRS, as manifested by ≥2 of the following: **• Temperature >38°C or <36°C** **• Heart rate >90 beats/min** **• Respiratory rate >20 breaths/min or PaCO2 <32 mm Hg** **• White blood cell count >12 000 or <4000 cells/µL or ≥10% immature (band) forms**	**4**	**severe**



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Characteristics suggesting a more serious diabetes-related foot infection (DFI)

A. Findings suggesting a more serious diabetes-related foot infection	
Wound specific	
Wound	Penetrates to subcutaneous tissues (e.g., fascia, tendon, muscle, joint, or bone)
Cellulitis	Extensive (>2 cm), distant from ulceration, or rapidly progressive (including lymphangitis)
Local signs/symptoms	Severe inflammation or induration, crepitus, bullae, discolouration, necrosis or gangrene, ecchymoses or petechiae, and new anaesthesia or localised pain
General	
Presentation	Acute onset/worsening or rapidly progressive
Systemic	Fever, chills, hypotension, confusion, and volume depletion
Laboratory tests	Leucocytosis highly elevated C-reactive protein, or erythrocyte sedimentation rate, severe or worsening hyperglycemia, acidosis, new/worsening azotaemia and electrolyte abnormalities tests
Complicating features	Presence of a foreign body (accidently or surgically implanted), puncture wound, deep abscess, arterial or venous insufficiency, lymphoedema, immunosuppressive illness or treatment, acute kidney injury
Failing treatment	Progression while on apparently appropriate antibiotic and supportive therapy

B. Factors that should lead to considering hospitalisation
Severe infection (see findings suggesting a more serious diabetes-related foot infection above)
Metabolic or haemodynamic instability
Intravenous therapy needed (and not available/appropriate as an outpatient)
Diagnostic tests needed that are not available as an outpatient
Severe foot ischaemia is present
Surgical procedures (more than minor) required
Failure of outpatient management
Need for more complex dressing changes than patient/caregivers can provide
Need for careful, continuous observation

The presence of osteomyelitis does not necessarily require hospitalization, since many of these patients are clinically stable and can be treated with oral antibiotic agents.

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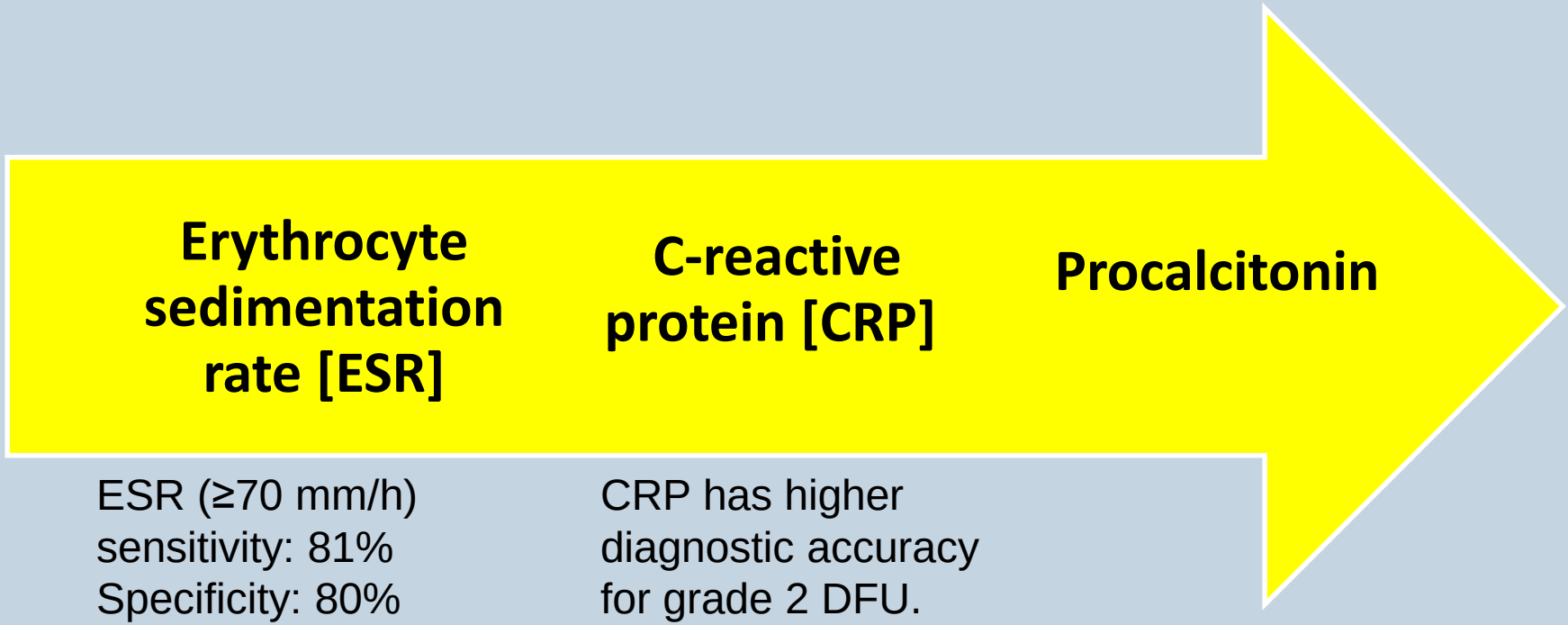
Evaluating the Patient with a DFI Laboratory

- Assess inflammatory serum biomarkers such as CRP, ESR, or PCT in a person with diabetes and a possible infected foot ulcer for whom the clinical examination is diagnostically equivocal or uninterpretable.



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Evaluating the Patient with a DFI Laboratory

- In a person with suspected soft tissue DFI, consider a sample for culture to determine the causative microorganisms, preferably by aseptically collecting a tissue specimen (by curettage or biopsy) from the wound.

- In cases of an **acute, non-severe DFI** in a patient who **has not recently received antibiotic** therapy and has **no other risk factors for unusual or antibiotic-resistant pathogens**, selecting empiric therapy without culture may be reasonable.

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Specimen(s) for culture

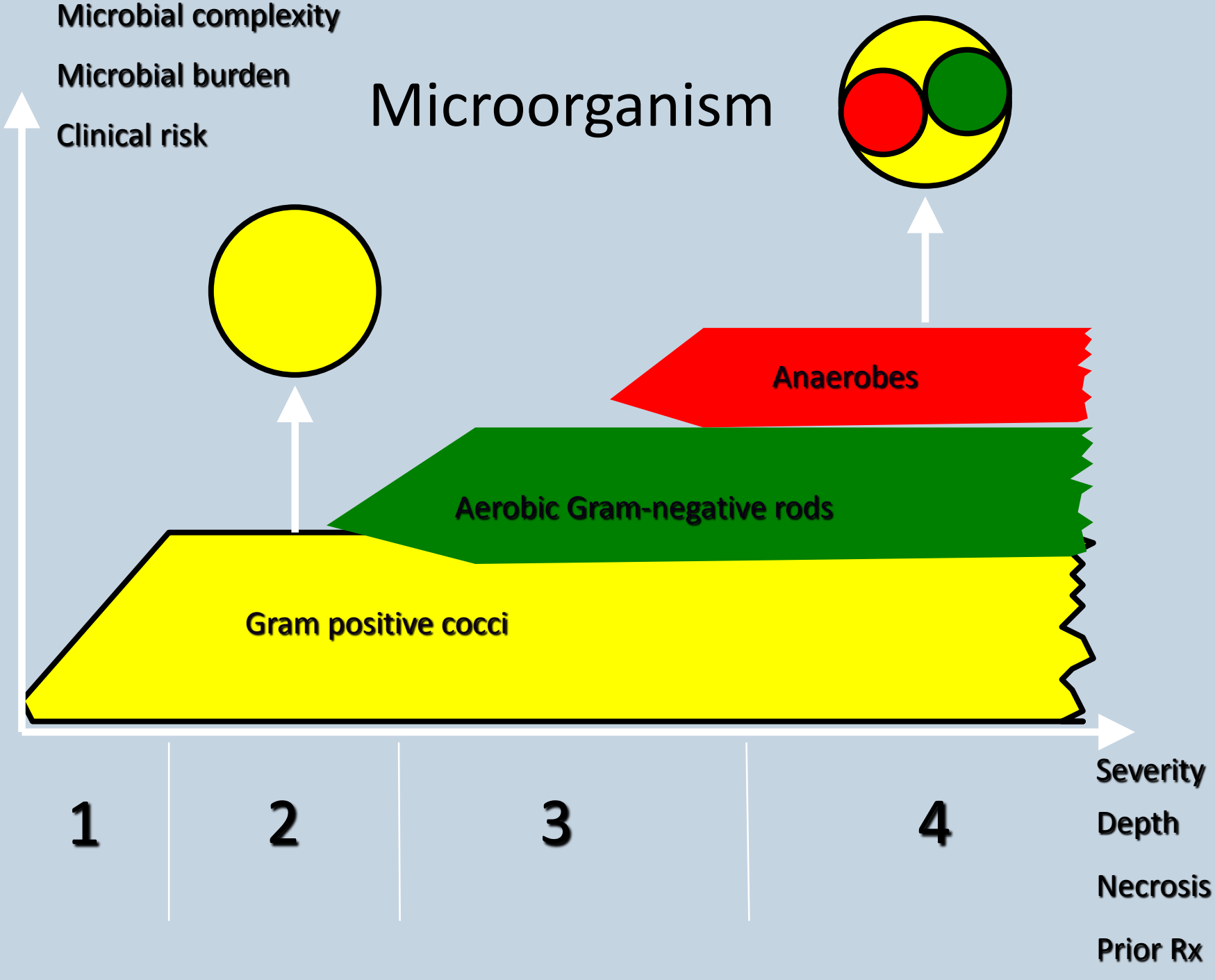
Deep tissue, obtained by biopsy or curettage after the wound has been cleansed and debrided.

Avoiding swab specimens

Specimen(s) for culture

- Repeating cultures may be useful for a patient who is not responding to apparently appropriate therapy, but this may result in isolating antibiotic-resistant strains likely to be contaminants rather than pathogens.

- Use conventional, rather than molecular, microbiology techniques for the first-line identification of pathogens from soft tissue or bone samples in a patient with a DFI.


Microbial complexity
Microbial burden
Clinical risk
Microorganism
Anaerobes
Aerobic Gram-negative rods
Gram positive cocci
1
2
3
4
Severity
Depth
Necrosis
Prior Rx

osteomyelitis

- In a person with diabetes, consider using a combination of probe-to-bone test, plain X-rays, and ESR, or CRP, or PCT as the initial studies to diagnose osteomyelitis of the foot.
- PTB:
- Sensitivity was 0.87 and specificity 0.83. in diagnosing DFO, the PTB test suggests the diagnosis if it is positive in a high-risk patient and helps rule it out if it is negative in a low-risk patient.

Imaging

- All patients presenting with a new DFI have plain radiographs of the affected foot to look for bony abnormalities (deformity, destruction) as well as for soft tissue gas and radio-opaque foreign bodies.

- New or evollistaving radiographic features[a] on serial radiographs,[b] including:
  - Loss of bone cortex, with bony erosion or demineralisation
  - Focal loss of trlistaabecular pattern or marrow radiolucency (demineralisation)
  - Periosteal reaction or elevation
- Bone sclerosis, with or without erosion
- Abnormal soft tissue density in the subcutaneous fat, or gas density, extending from skin towards underlying bone, suggesting a deep ulcer or sinus tract
- Presence of sequestruma: devitalised bone with radiodense appearance separated from normal bone
- Presence of involucrum[a]: layer of new bone growth outside previously existing bone resulting, and originating, from stripping off the periosteum
- Presence of cloacae[a]: opening in the involucrum or cortex through which sequestrum or granulation tissue may discharge

[a]some features (e.g., sequestrum, involucrum, and cloacae) are seen less frequently in diabetes-related foot osteomyelitis than in younger patients with osteomyelitis of larger bones.

[b]usually spaced several weeks apart.

Features characteristic of diabetes-related osteomyelitis of the foot on plain X-rays.

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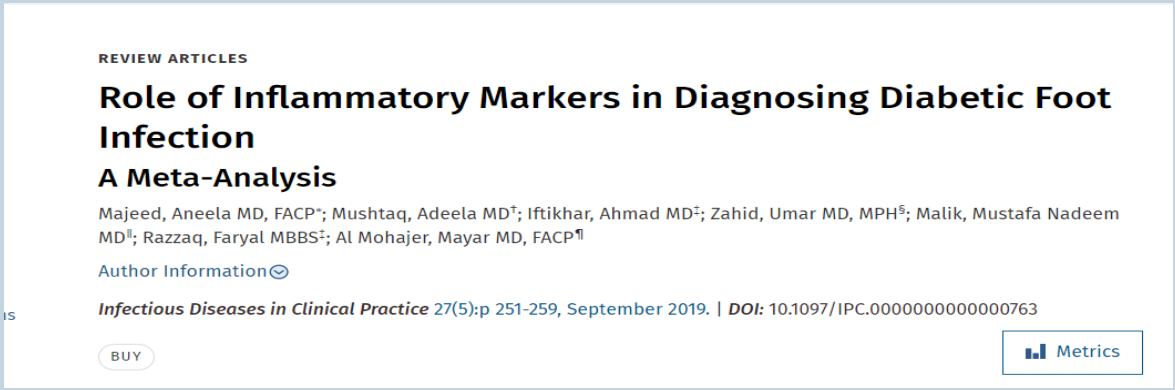
Imaging

- Because plain X-rays are insensitive to acute osteomyelitis, it is often useful to repeat a normal examination in 2–3 weeks when the suspicion of osteomyelitis is still high.

Serum biomarkers



REVIEW ARTICLES

Role of Inflammatory Markers in Diagnosing Diabetic Foot Infection

A Meta-Analysis

Majeed, Aneela MD, FACP*; Mushtaq, Adeela MD†; Iftikhar, Ahmad MD‡; Zahid, Umar MD, MPH§; Malik, Mustafa Nadeem MD‖; Razzaq, Faryal MBBS‡; Al Mohajer, Mayar MD, FACP¶

Author Information

Infectious Diseases in Clinical Practice 27(5):p 251-259, September 2019. | **DOI:** 10.1097/IPC.0000000000000763

BUY

Metrics

- Erythrocyte sedimentation rate has the highest AUROC of 0.91 followed by PCT (0.84) and CRP (0.80) to diagnose DFI.

Infect Dis Clin Pract. 2019; 27(5):251–259

Meta-Analysis > PLoS One. 2022 Apr 27;17(4):e0267412. doi: 10.1371/journal.pone.0267412. eCollection 2022.

The efficacy of inflammatory markers in diagnosing infected diabetic foot ulcers and diabetic foot osteomyelitis: Systematic review and meta-analysis

Harman Sharma [1], Sandhli Sharma [2], Anirudh Krishnan [1], Daniel Yuan [1], Venkat N Vangaveti [1 3], Usman H Malabu [1 3], Nagaraja Haleagrahara [1]

Affiliations + expand

PMID: 35476639 PMCID: PMC9045669 DOI: 10.1371/journal.pone.0267412

Free PMC article

Systematic review and meta-analysis published in 2022 found that PCT had the highest diagnostic test accuracy when compared to that of ESR, WBC and ESR with sensitivity, specificity, and AUC of 0.85, 0.67 and 0.844 at a cutoff value of 0.33 ng/mL.

PLoS One. 2022; 17(4):e0267412.

Serum biomarkers

- A large-scale retrospective single-centre study with high risk of bias that used the results of culture and/or histology of bone samples as a reference standard found that ESR >60 mm/hr plus CRP ≥80 mg/L had a high positive predictive value, but a modest negative predictive value, for the diagnosis of DFO.

- In another study, the combination of elevated ESR (>43 mm/h) with a positive PTB test showed a high correlation with having positive bone culture and/or histology results.

Clin Orthop Relat Res. 2019; 477(7):1594–1602

Serum biomarkers

- Overall, neither plain x-ray, inflammatory biomarkers (ESR, CRP and PCT) nor probe-to-bone tests can one their own solely and reliably rule in or rule out the diagnosis of DFO. When diagnostic doubt persists after the clinical assessment and review of plain X-rays of the foot, we recommend testing for ESR, CRP, or PCT.

MRI

- Perform MRI when the diagnosis of diabetes-related osteomyelitis of the foot remains in doubt despite clinical, plain X-rays and laboratory findings.

- Consider using PET, leucocyte scintigraphy, or SPECT as an alternative to MRI for the diagnosis of diabetes-related osteomyelitis of the foot.

Bone Biopsy

- In a person for whom there is suspicion of osteomyelitis of the foot (before or after treatment), consider obtaining bone (rather than soft tissue) samples for culture, either intraoperatively or percutaneously.

- To avoid a false-negative culture, some experts suggest delaying BeBoP in a patient who is receiving antibiotics until they have been off therapy for at least a few days, and ideally for at least 2 weeks.

Treatment

- Do not treat clinically uninfected foot ulcers with systemic or local antibiotic therapy when the goal is to reduce the risk of new infection or to promote ulcer healing.

Empirical antibiotic therapy

Infection severity	Additional factors	Usual pathogen(s)[b]	Potential empirical regimens[c]
Mild	No complicating features	GPC	Semisynthetic penicillinase-resistant penicillin (cloxacillin) 1st generation cephalosporin (cephalexin)
	ß-lactam allergy or intolerance	GPC	Clindamycin; fluoroquinolone (levo/moxi-floxacin); trimethoprim-sulfamethoxazole; doxycycline
	Recent antibiotic exposure	GPC + GNR	ß-lactam- ß lactamase inhibitor1 (amoxicillin/clavulanate, ampicillin/sulbactam) Fluoroquinolone (levo/moxi-floxacin); trimethoprim-sulfamethoxazole
	High risk for MRSA	MRSA	Linezolid; trimethoprim-sulfamethoxazole; clindamycin; doxycycline, fluoroquinolone (levofloxacin, moxifloxacin)
Moderate or severe[d]	No complicating features	GPC ± GNR	ß-lactam- ß lactamase inhibitor1 (amoxicillin/clavulanate, ampicillin/sulbactam) 2nd, 3rd generation cephalosporine (cefuroxime, cefotaxime, ceftriaxone)
	Recent antibiotics	GPC ± GNR	ß-lactam- ß lactamase inhibitor2 (ticarcillin/clavulanate, piperacillin/tazobactam) 2nd, 3rd generation cephalosporine (cefuroxime, cefotaxime, ceftriaxone) group 1 carbapenem (ertapenem); (depends on prior therapy; seek advice)
	Macerated ulcer or warm climate	GNR, including *Pseudomonas* sp.	ß-lactam- ß lactamase inhibitor2 (ticarcillin/clavulanate, piperacillin/tazobactam) semisynthetic penicillinase-resistant penicillin (cloxacillin) + ceftazidime or ciprofloxacin group 2 carbapenem (mero/imi-penem)
	Ischaemic limb/necrosis/ gas forming	GPC ± GNR ± strict anaerobes	ß-lactam- ß lactamase inhibitor1 (amoxicillin/clavulanate, ampicillin/sulbactam) or ß-lactam- ß lactamase inhibitor2 (ticarcillin/clavulanate, piperacillin/tazobactam) Group 1 (ertapenem) or 2 (mero/imi-penem) carbapenem 2nd (cefuroxime)/3rd (cefotaxime, ceftriaxone) generation cephalosporin + clindamycin or metronidazole
	MRSA risk factors	MRSA	Consider adding, or substituting with, glycopeptides (vancomycin, teicoplanin); lILinezolid; daptomycin; fusidic acid, trimethoprim-sulfamethoxazole; doxycycline
	Risk factors for resistant GNR	ESBL	Carbapenem (erta/mero/imi-penem); fluoroquinolone (ciprofloxacin); Aminoglycoside (amikacin); colistin

Antibiotics enclosed in brackets are cited as examples. High risk for MRSA: previous MRSA infection or colonisation. MRSA risk factors: prolonged hospitalisation, intensive care admission, recent hospitalisation, recent antibiotic use, invasive procedures, HIV infection, admission to nursing homes, open wounds, haemodialysis, discharge with long-term central venous access.

Abbreviations: ESBL, extended-spectrum ß-lactamase; GNR, gram-negative rod; GPC, gram-positive cocci (staphylococci and streptococci); HIV, human immunodeficiency virus; MRSA, methicillin-resistant *Staphylococcus aureus*.

[a]Recommendations are based upon theoretical considerations and results of available clinical trials.

[b]Refers to isolates from an infected foot ulcer, not just colonisation at another site.

[c]Given at the usual recommended doses for serious infections. Where more than one agent is listed, only one of them should be prescribed unless otherwise indicated. Consider modifying doses or agents selected for patients with comorbidities such as azotaemia, liver dysfunction, and obesity.

[d]Oral antibiotic agents should generally not be used for severe infections, except as a follow-on (switch) after initial parenteral therapy.

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Duration of therapy

If evidence of infection has not resolved after 4 weeks of apparently appropriate therapy, re-evaluate the patient and reconsider the need for further diagnostic studies or alternative treatments.

	Route	Duration
Infection severity (skin and soft tissues)		
Class 2: Mild	Oral	1–2 weeks[a]
Class 3/4: Moderate/severe	Oral/initially iv	2–4 weeks
Bone/joint		
Resected	Oral/initially iv	2–5 days
Debrided (soft tissue infection)	Oral/initially iv	1–2 weeks
Positive culture or histology of bone margins after bone resection	Oral/initially iv	3 weeks
No surgery or dead bone	Oral/initially iv	6 weeks

Abbreviation: iv, intravenous.

[a]10 days following surgical debridement.

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