Okužbe kronične rane

B Beović

- 3% oseb > 60 let ima kronično rano!

- Vzroki

✓ nevropatija
✓ okvara žil
✓ rana zaradi pritiska
✓ poškodba

- > 60% jih je v zadnjih 6 do 12 mesecih prejemalo antibiotike (daljši čas)

Lipsky BA, et al. Clin Infect Dis 2009; 49: 1541-9.

Razmerje med rano in mikroorganizmom

- **Kontaminacija**: bakterij je malo, se ne razmnožujejo, gostitelj ima “nadzor”, rana se celi
- **Kolonizacija**: bakterij je več, se množijo, več je vrst mikroorganizmov, ni znakov invazije tkiva, gostitelj ima “nadzor”, rana se celi
- **Kritična kolonizacija**: gostitelj izgublja “nadzor”
- **Okužba**: bakkterijsko breme je doseglo kritično točko, bakterije so vdrle v tkivo, rana se ne celi, bakterije lahko zaidejo v krvni obtok

Landis SJ. Adv Skin Wound Care 2008; 21:531-40.

Patogeneza in mikrobiologija okužbe kronične rane

- Verjetnost nastanka okužbe =

bakterijsko breme x virulenca / odpornost gostitelja

- Bakterijsko breme: mejna vrednost: $>10^5$ / mm^3
- Prag za bolj virulentne bakterije (betahemolitični streptokoki, S. aureus…) nižji kot za koagulazno negativne stafilokoke, enterokoke…
- V začetku najdemo na rani stafilokoke, streptokoke, pri dolgotrajnejši rani pa po Gramu negativne bacile in še kasneje anaerobe
- Sinergizem bakterij v rani
- Za okužbo morda značilen pojav novih bakterij, posebno betahemolitičnih streptokokov, klostridijev, mikobakterij..

Landis SJ. Adv Skin Wound Care 2008; 21:531-40.

Bakterije, osamljene iz kroničnih ran

Table 1. Bacterial Species Isolated from Various Types of Wounds in 3 Studies Using Optimal Culture and Molecular Techniques

	Type of wound (specimen)					
	Mixed[a]		Venous ulcers (tissue specimens)[b]		Chronic wounds[c]	
Bacterial genus	Chronic (tissue)	Acute (biopsy)	Healers	Nonhealers	Swab culture	Tissue PCR
Staphylococcus	65	60	100	100	28	68
Enterococcus	62	80	…	…	12	18
Pseudomonas	35	20	88	70	32	28
Proteus	24	20	25	30	126	…
Citrobacter	24	20	…	…	8	28
Enterobacter	24	20	…	…	…	…
Streptococcus	22	0	25	60	…	…
Micrococcus	…	…	25	90	…	…
Escherichia	14	0	…	…	…	…
Morganella	8	0	…	…	…	…
Klebsiella	5	0	…	…	…	…
Acinetobacter	5	0	…	…	…	…
Serratia	3	0	…	…	…	…
Corynebacteria	…	…	…	…	0	68
Anaerobes	…	…	50	40	0	70

NOTE. Data are from [12, 13].

[a] Diabetic foot, pressure, or venous stasis ulcers (77 chronic and 16 acute); several anaerobic organisms detected by molecular methods but none were isolated by culture [12].

[b] Specimens from 9 healing and 10 nonhealing chronic venous leg ulcers; 40% of species detected by molecular methods were not detected by standard culture [13].

[c] Specimens from 19 wounds (all but 1 of the lower extremity) [14].

Lipsky BA, et al. Clin Infect Dis 2009; 49: 1541-9.

Diagnostika in zdravljenje okužbe kronične rane

- Zelo malo dobrih raziskav
- Veliko izkušenj in različnih pristopv

Landis SJ. Adv Skin Wound Care 2008; 21:531-40.

Diagnoza okužbe kronične rane

Table 1.

CLINICAL BEDSIDE MNEMONIC TO DIFFERENTIATE CRITICAL COLONIZATION AND INFECTION

Mnemonic	Detail
NERDS	**N**onhealing of the wound,
Critical colonization:	Presence of inflammatory **E**xudate,
Use *topical* agents	Friable or **R**ed granulation tissue,
	Tissue **D**ebris, and **S**mell
STONEES	Increased wound **S**ize,
Progression to infection:	Increased local wound **T**emperature,
Use *systemic* agents	Extension of the wound to bone (**O**s),
	New wound breakdown,
	Exudate/**E**dema/Erythema, **S**mell or odor

Used with permission. Sibbald RG, Woo K, Ayello EA. Increased bacterial burden and infection: the story of NERDS and STONES. Adv Skin Wound Care 2006;19:447–63.

Mikrobiološka diagnostika

- Bakterije iščemo samo v rani, ki kaže znake okužbe!

- Biopsija: najbolj specifična in senzitivna, lahko kvantitativna, a nepraktična in zahtevna metoda, redka uporaba
- aspiracija tekočine: če gre za tekočinske kolekcije ali abscese
- Brisi: enostavni, dostopni, a le odraz dogajanja na površini, ne moremo osamiti anaerobov

Baranoski S, et al. Wound care essentials. Wolters Kluwer 2008.

Izboljšanje tehnike brisov

- Površino rane pred brisanjem očistimo
- Bris navlažimo

- Z-tehnika (cik-cak)

- **Tehnika po Levinu: bris rotiramo po 1 cm^2 površine z dovolj pritiska, da iztisnemo tekočino iz rane: najbližje bioptičnemu vzorcu**

Baranoski S, et al. Wound care essentials. Wolters Kluwer 2008.

Topična sredstva

- Antiseptiki: širokospektralni, pogosto toksični ta tkivo

- Antibiotiki: delujejo na specifične mikroorganizme, možna odpornost, niso škodljivi za tkivo

Lipsky BA, et al. Clin Infect Dis 2009; 49: 1541-9.

Table 4. Topical Antiseptic Products Available for Treating Chronic Wounds

Product and formulations	Formulation(s)	Bacterial spectrum	Advantages	Disadvantages	Cost[a]	Indications[b] and comments
Acetic acid	0.25%, 0.5%, and 1% solutions	Bactericidal against most gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa*	Inexpensive Shown to eliminate *P. aeruginosa* colonization from burns	Cytotoxic in vitro although maybe not in vivo; limited activity against biofilm	$	No longer as widely used as it was in the past
Cadexomer idine	Gel,[c] ointment, and dressing	Polysaccharide starch lattice; active agent is slowly released free iodine; broad spectrum of activity (same as iodine)	Reduced local toxicity compared to iodine; elemental iodine released on exposure to exudate	Application may cause stinging and erythema but less tissue damage than other iodine products; effect may not persist, and efficacy may be reduced in body fluids	$$	Indicated for use in cleaning wet ulcers and wounds and reducing microbial load in the wound environment
Cetrimide	Solution, 40%	Active against bacteria and fungi; not active against *P. aeruginosa*	May be less toxic to wound tissues than other antiseptics	May be corrosive and is potentially harmful if swallowed	...	Not available in the United States
Chlorhexidine gluconate	Solution, 2% and 4%; liquid, 2% and 4%; hand rinse, 0.5%; wipes, 0.5%; sponge/brush, 4%; and foam, 4%	Active against gram-positive bacteria (eg, *Staphylococcus aureus*) and gram-negative bacteria, including *P. aeruginosa*	Persistent activity up to 6 h after application; few adverse effects	Hypersensitivity, including anaphylaxis, generalized urticaria, bronchospasm, cough, dyspnea, wheezing, and malaise; may cause serious injury to the eye and middle ear; avoid contact with face or head; some resistance reported	$	2% Chlorhexidine indicated as surgical hand scrub, hand wash, preoperative skin, skin wound cleanser, and skin cleaner; polyhexanide is a similar newer biguanide
Hexachlorophene	Liquid, 3%; foam, 0.23% with 56% alcohol	Biguanide that is bacteriostatic against *Staphylococcus* species and other gram-positive bacteria	May retain residual effect on skin for several days	Rapidly absorbed and may result in toxic blood levels; application to burns has resulted in neurotoxicity and death; may cause central nervous system stimulation and convulsions, dermatitis, and photosensitivity reactions	$$$	Not recommended for routine use on wounds because of potential toxicity
Iodine compounds and iodine tincture[c]	Solution, 2% and 2.4%; and NaI strong iodine (Lugols), 5% and 10% KI; for iodine tincture, 2% and 2.4% NaI with 47% alcohol; and 7%, 5% KI in 83% EtOH	Microbicidal against bacteria, fungi, viruses, spores, protozoa, and yeasts	Broad spectrum	Highly toxic if ingested or significantly absorbed; do not use with occlusive dressings; causes pain and stains skin and clothing; use cautiously in patients with thyroid disorders	$	Iodine compounds are now rarely used for wound management; cadexomer iodine and povidone iodine products are less toxic
Povidone iodine[c]	Ointment, 1%, 4.7%, and 10%; solution, 1% and 10%; and wash, scrub, cleanser, gel, aerosol, gauze pad, swab, and others	Broad spectrum includes *S. aureus* and enterococci; active ingredient is liberated free iodine; shares spectrum but is less potent than iodine	Less irritating to skin and allergenic than iodine. Can be covered with dressings. Clinically significant resistance very rare	Antibacterial action requires at least 2 min contact; may cause stinging and erythema; effect may not persist, and efficacy may be reduced in body fluids; prolonged use may cause metabolic acidosis; stains skin and clothing; possible interaction with starches in dressings	$	Indicated for perioperative skin cleansing and for cleansing and prevention of infection in superficial burns, incisions, and other superficial wounds
Sodium hypochlorite[c] (Dakin's solution and EUSOL)	Solution, 0.0125%, 0.125%, 0.25%, and 0.5%	Vegetative bacteria, viruses, and some spores and fungi	Inexpensive. No known systemic toxicity	May require prolonged contact for antibacterial action; inactivated by pus; toxic to fibroblasts and keratinocytes, and may cause pain or lyse blood clots	$	Concentrations ≤0.025% may be useful to reduce bioburden
Hydrogen peroxide[c]	Solution, 1% and 3%; and cream, 1%	Oxidizing agent active against many gram-positive and gram-negative bacteria	Broad-spectrum, bactericidal, inexpensive; no known resistance	May cause some discomfort	$	Commonly used, but few clinical studies
Silver nitrate	Solution 0.5%, 10%, 25%, and 50%; ointment, 10%; and swabs, 25%–50%	Silver ions are bactericidal against a broad spectrum of gram-positive and gram-negative bacteria	Low cost; easily applied	Painful on application; stains tissues; may delay healing; concentrations >0.5% cause cauterization; inactivated by wound exudates and chlorine	$	Although it was previously widely used, it has now been largely replaced by other compounds, including newer silver dressings
Sliver dressings	At least 6 approved products with different properties	Slowly released silver ions have broad-spectrum, including MRSA and VRE	Provide sustained levels of active silver ions; microbial resistance is rare; less painful and few adverse effects than silver nitrate; variety of products adaptable to different types of wounds; infrequent application required	Levels of silver ions at wound interface not well defined; may cause silver staining of tissues; may delay epithelialization; relatively expensive; few published comparative trials	$$	Should not substitute for nonmedicated dressings for uninfected wounds; may be useful for subclinically infected, highly colonized wounds or for wounds being prepared for skin grafting

NOTE. EUSOL, Edinburgh University Solution of Lime; MRSA, methicillin-resistant *S. aureus;* VRE, vancomycin-resistant enterococci.

[a] Costs are approximate in US$ per day for treating 100-cm^2 wound, as follows: $, <$3; $$, $3–$15; and $$$, >$15.

[b] US Food and Drug Administration–approved indications.

[c] Available without prescription.

Table 5. Topical Antibiotic Products Available for Treating Chronic Wounds

Product	Formulation(s)	Bacterial spectrum	Advantages	Disadvantages	Cost[a]	Indications[b] and comments
Bacitracin[c]	Ointment, 500 units/g; and powder combinations with neomycin, polymixin B, and zinc	Many gram-positive organisms, including aerobic staphylococci and streptococci, corynebacteria, anaerobic cocci, and clostridia; inactive against most gram-negative organisms	Activity not impaired by blood, pus, necrotic tissue, or large bacterial inocula; resistance is rare but increasing among staphylococci; no cross-resistance with other antibiotics; minimal absorption	May cause allergic reactions, contact dermatitis, and (rarely) anaphylactic reactions; may lead to overgrowth of drug-resistant organisms, including fungi	$	Widely used for many years; indicated for prevention of infection in minor skin injuries
Fusidic acid	Cream, 2%; ointment, 2%; and gel, 2%	*Staphylococcus aureus,* streptococci (in topical concentrations), corynebacteria, and clostridia	Penetrates intact and damaged skin as well as crust and cellular debris	Occasional hypersensitivity reactions; resistance among staphylococci is emerging; must apply 3 times daily	$$	Not available in the United States
Gentamicin	Cream, 0.1%; and ointment, 0.1%	Streptococci, staphylococci, *Pseudomonas aeruginosa, Enterobacter aerogenes, Escherichia coli, Proteus vulgaris,* and *Klebsiella pneumoniae*	Broad spectrum; inexpensive	Must be applied 3–4 times daily; may drive resistance to an agent used systemically	$	Indicated for primary skin infections (pyode mas) and for secondary skin infections, cluding infected excoriations, and for bac terial superinfections
Mafenide acetate	Solution, 5%; and cream, 85 mg/g	A sulfonamide that is bacteriostatic against many gram-negative organisms, including *P. aeruginosa,* and some gram-positive organisms, but minimal activity against staphylococci and some obligate anaerobes	Remains active in the presence of pus and serum, and its activity is not affected by acidity of environment	Systemic absorption may occur; dug and metabolites may inhibit carbonic anhydrase, potentially causing metabolic acidosis; use cautiously in patients with renal impairment; pain on application; hypersensitivity reactions	$$$	Indicated as adjunctive therapy in second- and third-degree burns; may be used in rapidly progressing bacterial necrotizing fasciitis; limited use in other wounds
Metronidazole	Cream, 0.75%; gel, 1%; lotion, 0.75%	Many clinically important anaerobic bacteria	May reduce odor associated with anaerobic infections; application only 1–2 times daily	Relatively expensive; systemic formulations available; could drive resistance to these	$–$$	Indicated for inflammatory papules and pus tules of rosacea
Mupirocin and mupirocin calcium	Ointment, 2%; for mupirocin calcium, cream, 2.15%;[c] and nasal ointment, 2.15%;[c] (equivalent to 2% mupirocin)	Gram-positive aerobes, including *S. aureus* (most MRSA), *Staphylococcus epidermidis, Staphylococcus saprophyticus,* and streptococci (groups A, B, C, and G) but not enterococci, some gram-negative aerobes (not *P. aeruginosa*), corynebacteria, and obligate anaerobes	Minimal potential for allergic reactions	Rare local burning and irritation; applying ointment to large wounds in azotemic patients can cause accumulation of polyethylene glycol; long-term use can lead to resistance among staphylococci, which is increasing	$$	Indicated for topical treatment of impetigo and eradication of nasal colonization with *S. aureus*
Neomycin sulfate[c]	Powder; cream, 0.5%, combinations with polymixin B and pramoxine; and ointment, 0.5%, combinations with bacitracin, polymixin B, lidocaine, and pramoxine	Good for gram-negative organisms but not *P. aeruginosa;* active against some gram-positive bacteria, including *S. aureus,* but streptococci are generally resistant; inactive against obligate anaerobes	Low cost; applied only 1–3 times daily; may enhance reepithelialization	Topical powder in wound irrigating solution may cause systemic toxicity (FDA banned); use other formulations cautiously on large wounds, especially with azotemia; hypersensitivity reaction in 1%–6%, often with chronic use or history of allergies	$	Use of topical powder alone or in solution not recommended; cream and ointment, in combination with other agents are ind cated for prevention of infection in mino skin injuries
Nitrofurazone	Solution, 0.2%; ointment, 0.2%; and cream, 0.2%	Broad gram-positive and gram-negative activity, including *S. aureus* and streptococci, but not *P. aeruginosa*	Used mainly for burn wounds	Hypersensitivity reactions; polyethylene glycols (in some formulations) may be absorbed and can cause problems in azotemic patients	$$	Indicated as adjunctive to prevent infection in patients with second- and third-degree burns
Polymixin B[c]	Cream, 5000 units/g or 10,000 units/g, in combination with other agents	Bactericidal against many gram-negative organisms, including *P. aeruginosa;* minimal activity against gram-positive bacteria; activity may be neutralized by divalent cations	Inexpensive	Some hypersensitivity and neurological or renal adverse reactions reported; may show cross-reaction with bacitracin	$	Only available in combination with other agents, including bacitracin and neomyci indicated for prevention of infection in m nor skin injuries
Retapamulin	Ointment, 1%	Active against staphylococci (but uncertain for MRSA) and streptococci and some obligate anaerobes	May be active against some mupirocin-resistant *S. aureus* strains; broader activity than mupirocin	Not evaluated for use on mucosal surfaces; may cause local irritation	$$$	Indicated for impetigo, due to *S. aureus* (methicillin-susceptible only) or *S. pyogenes*
Silver sulfadiazine	Cream, 1%	A sulfonamide; the released silver ions are the primary active ingredient; active against many gram-positive and gram-negative organisms, including *P. aeruginosa*	Applied only once or twice daily; soothing application; low rate of hypersensitivity reaction	Potential cross-reaction with other sulfonamides; may rarely cause skin staining	$	Indicated as adjunctive treatment to preve infections in patients with second- and third-degree burns.
Sulfacetamide Na[+]	Lotion, 10%	Bacteriostatic against many gram-positive and gram-negative pathogens	Broad spectrum; can be combined with sulphur	Systemic absorption and rarely severe side effects occur with application to large, denuded areas; hypersensitivity reactions may occur	$$$	Indicated for secondary bacterial skin infec tions due to susceptible organisms and for acne vulgaris in adults

Poskus priporočil za sistemsko zdravljenje (STONES)

po Landis SJ. Adv Skin Wound Care 2008; 21:531-40.

Vrsta kronične rane	**Kompleksna: diabetična noga, ishemija, globoke rane zaradi pritiska, malignomi**	**Enostavna: venski ulkusi, drugo**
Pogosti povzročitelji	**stafilokoki, streptokoki, enterični bacili, anaerobi. *Pseudomonas aeruginosa***	**stafilokoki, streptokoki**
Klinična slika	**Izkustveno zdravljenje**	**Izkustveno zdravljenje**
Blaga okužba, brez sistemskih znakov vnetja, ambulantno zdravljenje	**amoksi/klav** **ciprofloksacin/klindamicin*** **moksifloksacin**	**protistafilokokni penicilin** **klindamicin** **1. generacija cefalosporinov**
Zmerna okužba, sistemski znaki, brez osteomielitisa, še možno ambulantno zdravljenje	**ciprofloksacin/klindamicin***	**amoksi/klav** **ciprofloksacin/klindamicin***

*po Gramu negativni anaerobi so v Sloveniji slabo občutljivi za klindamicin, ciprofloksacin pa slabo deluje na stafilokoke in še slabše na streptokoke

2012 Infectious Diseases Society of America Clinical Practice Guideline for the Diagnosis and Treatment of Diabetic Foot Infections[a]

Benjamin A. Lipsky,[1] Anthony R. Berendt,[2] Paul B. Cornia,[3] James C. Pile,[4] Edgar J. G. Peters,[5] David G. Armstrong,[6] H. Gunner Deery,[7] John M. Embil,[8] Warren S. Joseph,[9] Adolf W. Karchmer,[10] Michael S. Pinzur,[11] and Eric Senneville[12]

Clinical Infectious Diseases 2012;54(12):132–173

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)		
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
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 $PaCO_2$ <32 mm Hg • White blood cell count >12 000 or <4000 cells/μL or ≥10% immature (band) forms	4	Severe[a]

IDSA smernice 2012

Izbira antibiotika IDSA 2012

Stopnja okužbe	Povzročitelj	Antibiotik
blaga	stafilokoki, streptokoki	protistafilokokni penicilin klindamicin 1. gen. cefalosporinov levofloksacin amoksi / klav
	MRSA	doksiciklin, TMP/SMX
zmerna (P.O.) huda (I.V.)	stafilokoki, streptokoki, po Gramu negativne bakterije, anaerobi	levofloksacin ceftriakson moksifloksacin ampi/sulbaktam ertapenem tigeciklinl ciprofloksacin/levofloksa + klindamicin/metronidazol imipenem protipsevdomonasni antibiotiki antibiotiki, ki delujejo na MRSA

Zdravila, registrirana za zdravljenje okužb kože in mehkih tkiv na podlagi študij, ki so izključevale diabetično stopalo (npr ceftarolin), niso navedena.

Trajanje antibiotičnega zdravljenja

Diabetična noga, IDSA smernice 2012:

- Glede na potek zdravljenja

✓ Blaga: 1 do 2 tedna

✓ Srednje huda: 1 do 3 tedne

✓ Huda: 2 do 4 tedne

Lipsky BA, et al. Clin Infect Dis 2012

- Druge kronične rane: blaga do zmerna: 2 tedna (?)

Landis SJ. Adv Skin Wound Care 2008