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PREGLEDNI RAD

ULOGA MIKROBIOLOGIJE I INFLAMATORNIH BIOMARKERA U PLANIRANJU REKONSTRUKTIVNOG LEČENJA HRONIČNIH RANA: PREGLED LITERATURE

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SAŽETAK

Hronične rane predstavljaju značajan klinički i javnozdravstveni problem, sa rastućom učestalošću kod starije populacije i pacijenata sa dijabetesom i vaskularnim oboljenjima. Pravovremeno planiranje rekonstruktivnog lečenja zahteva razumevanje mikrobioloških procesa i inflamatornih biomarkera koji odražavaju stanje rane. Cilj ovog preglednog rada je analizirati savremene pristupe u dijagnostici i planiranju rekonstruktivnog lečenja hroničnih rana posebno kroz sagledavanje značaja uloge mikrobiologije i inflamatornih biomarkera. U radu prikazan je pregled 18 relevantnih radova objavljenih u periodu 2010–2025. godine, sa fokusom na mikrobiološki profil, inflamatorne biomarkere i rekonstruktivne modalitete lečenja.Dominantni mikroorganizmi u hroničnim ranama su *Staphylococcus aureus*, *Pseudomonas aeruginosa* i *Acinetobacter baumannii*. Povišeni CRP i IL-6 koreliraju sa infekcijom i lošim ishodom graftova, dok normalizacija ovih vrednosti označava spremnost rane za rekonstrukciju. Epidemiološki podaci pokazuju porast prevalencije hroničnih rana od 8–10% godišnje u Evropi, uz rast rezistencije bakterija. Mikrobiološka kontrola i praćenje inflamatornih biomarkera treba da postanu sastavni deo algoritma planiranja rekonstruktivnih procedura kod hroničnih rana. Ovakav pristup doprinosi boljoj predikciji ishoda, smanjenju komplikacija i racionalizaciji terapije.

Ključne reči: hronične rane, bakterijska flora, rekonstruktivna hirurgija, inflamatorni markeri

Uvod

Hronične rane predstavljaju značajan zdravstveni i socio-ekonomski problem širom sveta. One uključuju ulkuse stopala kod dijabetesa, dekubitusne ulkuse i rane nakon opekotina, koje ne zaceljuju u očekivanom vremenskom okviru i zahtevaju multidisciplinarni pristup (1,2). Procene pokazuju da 1–2% opšte populacije razvija hroničnu ranu tokom života, dok kod starijih od 65 godina, prevalencija može dostići i do 5% (3). Kliničko lečenje hroničnih rana postaje sve efikasnije zahvaljujući razvoju tehnologija za procenu površine rane, razumevanju biofilma i bakterijske kolonizacije, kao i praćenju inflamatornih biomarkera (4–9,10–16).

Cilj ovog preglednog rada je analizirati savremene pristupe u dijagnostici i planiranju rekonstruktivnog lečenja hroničnih rana posebno kroz sagledavanje značaja mikrobiologije i inflamatornih biomarkera.

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ROLE OF MICROBIOLOGY AND INFLAMMATORY BIOMARKERS IN PLANNING RECONSTRUCTIVE TREATMENT OF CHRONIC WOUNDS: LITERATURE REVIEW

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SUMMERY

Chronic wounds represent a significant clinical and public health burden, with increasing prevalence among elderly and patients with diabetes and vascular diseases. Proper planning of reconstructive treatment requires a comprehensive understanding of microbiological processes and inflammatory biomarkers reflecting wound status. The aim of this study was to analyze contemporary approaches to the diagnosis and planning of reconstructive treatment of chronic wounds, emphasizing the role of microbiology and inflammatory biomarkers. Review of 18 studies published between 2010 and 2025 was presented in the paper, focusing on microbial profiles, inflammatory markers, and reconstructive treatment modalities. The most common microorganisms are *Staphylococcus aureus*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*. Elevated CRP and IL-6 levels correlate with infection and poor graft outcomes, while normalization indicates readiness for reconstruction. Epidemiological data show an 8–10% annual increase in chronic wound prevalence in Europe, alongside rising bacterial resistance. Microbiological evaluation and biomarker monitoring should be integral to reconstructive planning protocols in chronic wounds. This approach improves outcome prediction, reduces postoperative complications, and promotes rational therapy use.

Keywords: chronic wounds, microbiology, reconstructive surgery, inflammatory biomarkers

Introduction

Chronic wounds are a significant global health and socio-economic problem. They include diabetic foot ulcers, pressure ulcers and post-burn wounds, which fail to heal within the expected time frame and require a multidisciplinary approach (1,2). Estimates suggest that 1-2% of the general population experience a chronic wound in their lifetime, while in persons over 65 years of age, the prevalence may reach up to 5% (3). The clinical treatment of chronic wounds is becoming more effective thanks to the development of technologies for evaluating surface areas of chronic wounds, understanding of biofilm and bacterial colonization, as well as monitoring of inflammatory biomarkers (4-9, 10-16).

The aim of this review article was to analyze contemporary approaches to diagnosis and planning of reconstructive treatment of chronic wounds, emphasizing the significance of microbiology and inflammatory biomarkers.

Metode

U okviru ovog preglednog rada uključeni su svi radovi koji su objavljeni u periodu 2010-2025. godine, a koji su se bavili ispitivanjem značaja bakterijske flore i inflamatornih biomarkera za planiranje rekonstruktivnog lečenja hroničnih rana. Ovim radom obuhvaćeni su rezultati 18 relevantnih radova objavljenih na engleskom u navedenom šesnaestogodišnjem periodu. Pretraživanje radova je sprovedeno korišćenjem PUBMED baze podataka, a ključne reči koje su korišćene su: hronična rana, bakterijska flora, inflamatorni markeri, dijagnostika, lečenje, epidemiologija i rekonstruktivna hirurgija.

Epidemiologija hroničnih rana

Hronične rane predstavljaju složen medicinski problem čija učestalost raste sa starenjem populacije i povećanom prevalencijom hroničnih bolesti. Najčešći tipovi hroničnih rana su dijabetički ulkusi koji su pak česti kod pacijenata sa dijabetesom tipa 1 i 2, a javljaju se uglavnom na stopalima. Istraživanja pokazuju da su dominantni patogeni *Staphylococcus aureus* i gram-negativne bakterije, koje su često multirezistentni (6,8). Zatim dekubitusne rane (engl. Pressure ulcers). Ove rane nastaju usled produženog pritiska na kožu, posebno kod nepokretnih i hospitalizovanih pacijenata. Prevalencija u bolničkim ustanovama dekubitusnih rana kreće se od 5 do 15% pacijenata (3,5). Opekotine i rane nakon traume. Duboke opekotine ili postoperativne rane koje ne zarastaju očekivano, zahtevaju poseban hirurški pristup i monitoring inflamatornih biomarkera (7). Hronične postoperativne rane i infekcije. One su često povezane sa polimikrobnom kolonizacijom bakterija i rizikom od biofilma, što produžava trajanje lečenja i povećava stopu komplikacija (4,9).

Faktori koji značajno utiču na razvoj i hronicitet su hronične bolesti **(**dijabetes, vaskularne bolesti, imunodeficijencije), **s**tariji uzrast i fiziologija **(**smanjena regenerativna sposobnost kože i dugotrajna imobilizacija), **i**nfekcije i biofilm **(**prisustvo zrelog biofilma produžava upalu i odlaže zarastanje) i **s**ocio-ekonomski faktori **(**otežan pristup zdravstvenoj zaštiti i nedostatak edukacije o samonezi rana (4,5).

Epidemiološki značaj mikrobiologije i inflamatornih biomarkera

Mikrobiološki nadzor i praćenje inflamatornih biomarkera predstavljaju neophodne alate za prevenciju komplikacija i optimizaciju lečenja hroničnih rana. Identifikacija bakterijske flore i ispitivanje oseljivosti omogućava selektivnu primenu antibiotika i smanjuje rizik od širenja multirezistentnih sojeva (6,8). Praćenje inflamatornihbiomarkera (CRP, IL-6, TNF-α) pomaže u proceni stepena upale, predviđanju razvoja hroniciteta rane i određivanju optimalnog vremena za rekonstruktivne intervencije (7,9). Studije pokazuju da kombinovanjemikrobiološke analize i praćenje inflamatornih biomarkera može doprineti proceni ishoda zarastanja rane, što ima direktan uticaj na smanjenje morbiditeta i dužine trajanja hospitalizacije (7,9).

Ključni bakterijski patogeni za nastanak hronične rane

Biofilm je organizovani mikrobiološki sloj koji se formira na površini rane i sastoji se od bakterija ugrađenih u sloj polisaharidne komponente ćelije. Ovaj sloj štiti mikroorganizme od antibiotika i imunološkog odgovora domaćina (4,5). *Wolcott* i saradnici (4) su pokazali da zrelost biofilma direktno utiče na terapijski prozor, odnosnorano uklanjanje biofilma (mehaničkim ili oštrim debridmanom) povećava efikasnost antibiotske terapije. Najčešće bakterije koje se identifikuju u biofilmu hroničnih rana su: *Staphylococcus aureus* (uključujući MRSA sojeve), *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Escherichia coli i Klebsiella pneumoniae* (5–8). Harika i saradnici (5), kao i kasniji epidemiološki i sistematski pregledi (6–8), ukazuju da infekcije hroničnih rana uzrokovane biofilm-producentima često ne reaguju adekvatno na monoterapiju. Na osnovu profila rezistencije, u kliničkoj praksi se najčešće primenjuju kombinacije antipseudomonasnih β-laktama sa aminoglikozidima ili fluorohinolonima kod gram-negativnih patogena, dok se kod MRSA infekcija koriste glikopeptidi ili linezolid, često u sklopu kombinovanog režima kod polimikrobnih rana. Ovakav pristup, uz obavezno mehaničko uklanjanje biofilma, povezan je sa boljim terapijskim odgovorom. (5–8)

Chelkeba i Melaku (8) su u sistematskoj reviziji u Etiopiji pokazali da gram-negativne bakterije čine više od 60% izolatahroničnih rana, sa visokom stopom rezistencije na β-laktamske antibiotike, fluorohinolone i aminoglikozide. Ovakvi podaci su zabrinjavajući jer direktno utiču na mortalitet i morbiditet, posebno u niskoresursnim sredinama gde su mogućnosti za mikrobiološko testiranje ograničene. *Shimekaw i Tigabu* (6) su potvrdili sličan obrazac, pri čemu je *Pseudomonas aeruginosa* najčešći uzročnik hronične rane kod pacijenata sa dijabetičkim ulkusima i dekubitusom, dok je *S. aureus* dominantan u ranama nakon hirurških intervencija.

Liu i saradnici (9) naglašavaju da prisustvo multi-

Methods

This review article includes the studies published between 2010 and 2025, which examined the significance of bacterial flora and inflammatory biomarkers for planning the reconstructive treatment of chronic wounds. This study encompasses the results of 18 relevant articles published in English in the aforementioned sixteen-year period. The literature search was conducted using the PubMed database, while the following key words were used: chronic wound, bacterial flora, inflammatory biomarkers, diagnosis, treatment, epidemiology, and reconstructive surgery.

Epidemiology of chronic wounds

Chronic wounds are a complex health problem, whose incidence increases with the aging of the population and the increased prevalence of chronic diseases. The most common types of chronic wounds are diabetic ulcers, which are common in patients with type 1 and 2 diabetes, and occur mainly on feet. Research has shown that the dominant pathogens are *Staphylococcus aureus* and gram-negative bacteria which are often multidrug-resistant (6,8).

Pressure ulcers. These wounds occur due to the prolonged pressure on the skin, especially in immobile and hospitalized patients. The prevalence of pressure ulcers in hospitals ranges from 5 to 15% of patients (3,5).

*Burns and wounds after trauma. D*eep burns or postoperative wounds that fail to heal as expected require a special surgical approach and monitoring of inflammatory biomarkers (7).

*Chronic postoperative wounds and infections. T*hey are often associated with polymicrobial colonization and the risk of biofilm, which prolongs the duration of treatment and increases the rate of complications (4,9).

Factors that significantly affect the development and chronicity are chronic diseases (diabetes, vascular diseases, immunodeficiencies), older age and physiology (reduced regenerative capacity of the skin and long-lasting immobilization), infections and biofilm (the presence of a mature biofilm prolongs inflammation and delays healing) and socio-economic factors (difficult access to health care and lack of education on self-care) (4,5).

Epidemiological significance of microbiology and inflammatory biomarkers

Microbiological surveillance and monitoring of inflammatory biomarkers are necessary tools for the prevention of complications and optimization of chronic wound treatment. The identification of bacterial flora and susceptibility testing enable the selective application of antibiotics and reduce the risk of the spread of multidrug-resistant strains (6,8). Monitoring inflammatory biomarkers (CRP, IL-6, TNF-α) helps in assessing the degree of inflammation, predicting the development of wound chronicity and determining the optimal time for reconstructive interventions (7,9). Studies have shown that combining microbiological analysis and monitoring of inflammatory biomarkers can contribute to the assessment of wound healing outcomes, which directly affects the reduction in morbidity and the length of hospitalization (7,9).

Key bacterial pathogens for the occurrence of chronic wounds

A biofilm is an organized microbiological layer that is formed on the surface of the wound and it consists of bacteria embedded in the layer of the polysaccharide component of the cell. This layer protects microorganisms from antibiotics and the host's immune response (4,5). *Wolcott et al.* (4) showed that the biofilm maturity directly affects the efficiency of the therapeutic window, that is, early removal of the biofilm (by mechanical or sharp debridement) increases the effectiveness of antibiotic therapy. The most common bacteria identified in the biofilm of chronic wounds are: *Staphylococcus aureus* (including MRSA strains), *Pseudomonas aeruginosa*, *Proteus mirabilis*, *Escherichia coli* and *Klebsiella pneumoniae* (5–8). *Harika et al.* (5), as well as subsequent epidemiological and systematic reviews (6-8) indicate that biofilm-related infections of chronic wounds often do not respond adequately to monotherapy. Based on the resistance profile, in clinical practice combinations of anti-pseudomonal ß-lactams with aminoglycosides and fluoroquinolones are most frequently used for gram-negative pathogens, while in MRSA infections, glycopeptides or linezolid are used often as part of a combined regimen for polymicrobial wounds. This approach, with mandatory mechanical removal of the biofilm, is associated with a better therapeutic approach (5-8).

Chelkeba and *Melaku* (8) in their systematic review in Ethiopia showed that gram-negative bacteria account for more than 60% of isolates of chronic wounds, with a high rate of resistance to ß-lactam antibiotics, fluoroquinolones and aminoglycosides. Such data are worrying because they directly affect mortality and morbidity, especially in low-resource settings where opportunities for microbiological testing are limited. *Shimekaw* and *Tigabu* (6) confirmed a similar pattern, while *Pseudomonas aeruginosa* was the most common causative agent of chronic wounds in patients with diabetic ulcers and pressure ulcers, and *S. aureus* was dominant in wounds after surgical interventions.

Liu and associates (9) emphasize that the presence of multidrug-resistant bacteria in chronic

rezistentnih bakterija u hroničnim ranama pojačava lokalnu i sistemsku inflamatornu reakciju, aktivirajući mrežu citokina koja vodi u perzistentnu upalu i inhibiciju regeneracije tkiva. Ovaj "začarani krug" infekcije i inflamacije često je razlog neuspeha konzervativne terapije i potrebe za rekonstruktivnim zahvatima.

Inflamatornibiomarkeri

Inflamatorni biomarkeri su biološki pokazatelji koji odražavaju stepen upalnog odgovora organizma i mogu pomoći u proceni težine infekcije i efikasnosti terapije. Njihova klinička primena u lečenju hroničnih rana postaje sve važnija jer omogućava objektivno praćenje stanja rane, pored klasičnih mikrobioloških analiza (7,9). Ključni biomarkeri uhroničnim ranama su:C-reaktivni protein (CRP), interleukini, tumorski nekrozni faktor alfa (TNF- α)itd.

CRP je najčešće korišćen biomarker u kliničkoj praksi. Povećane vrednosti CRP-a ukazuju na sistemsku upalu i često koreliraju sa bakterijskom infekcijom. Kod postojanja hronične rane, CRP se koristi za praćenje odgovora na terapiju i odluku o trenutku za rekonstruktivni zahvat.

Interleukin-6 (IL-6) je proinflamatorni citokin koji ima direktnu ulogu u aktivaciji neutrofila i stimulaciji akutne faze inflamacije. *Liang* i saradnici (7) su pokazali da je koncentracija IL-6 značajno povećana kod pacijenata sa dubokim opekotinama ekstremiteta i da njeno smanjenje tokom terapije korelira sa boljim ishodom zarastanja. TNF-α je važan indikator aktivne upale i prediktor nastanka hronične rane. Povećane vrednosti TNF-α povezane su sa usporenim epitelizacijama i češćom potrebom za hirurškim rekonstrukcijama. Interleukin-8 (IL-8) je marker hronične inflamacije, posebno kod rana sa perzistentnim biofilmom i multirezistentnim bakterijama (9).

Integracija biomarkera inflamacije sa mikrobiološkim podacima omogućava personalizovani pristup lečenju. U praksi, povećane vrednosti CRP-a i IL-6 signaliziraju da rana još nije spremna za rekonstruktivnu intervenciju. Stabilizacija biomarkera i smanjenje inflamatorne aktivnosti smatraju se ključnim preduslovom za uspeh transplantacije tkiva, grafta ili flapa (7,9).

Integracija mikrobioloških nalaza, inflamatornih biomarkera i rekonstruktivnih strategija za različite tipove hroničnih rana prikazana je u Tabeli 1."

Tabela 1. Patogeni, biomarkeri i hirurški pristup po vrstama hroničnih rana

Vrsta hronične rane	Dominantni mikroorganizmi	Inflamatorni biomarkeri (serumski i lokalni)	Hirurški pristup / rekonstruktivne mere	Klinički kriterijumi za rekonstrukciju	Reference
Dijabetični ulkus	Staphylococcus aureus, Pseudomonas aeruginosa; česta multirezistencija i biofilm formacija	CRP, IL-6, TNF-α — značajno povišeni kod infekcija i nekroze	Serijski debridman, VAC terapija, split-thickness skin graft (STSG) nakon mikrobiološke kontrole	CRP <10 mg/L, sterilna kultura, IL-6 u padu	[5], [8], [9], [18]
Venski ulkus potkolenice	Enterococcus spp., E. coli, ponekad Proteus mirabilis u sekundarnoj infekciji	CRP, IL-6 — umereno povišeni, korelacija sa površinom rane	Lokalni debridman i kožni graft, rekonstrukcija nakon eradikacije bakterijske kolonizacije	Smanjenje CRP i IL-6 ≥ 30% pre grafta	[6], [8], [11]
Arterijski (ishemijski) ulkus	Klebsiella pneumoniae, P. aeruginosa — visoka otpornost na cefalosporine i fluorohinolone	CRP, TNF-α, IL-8 — visoki nivoi kod nekroze i infekcije	Rekonstruktivni flap (lokalni ili slobodni) nakon revaskularizacije i antibiotske terapije	CRP <15 mg/L, negativna kultura	[7], [8], [9]
Dekubitalne (pritisne) rane	Proteus mirabilis, Enterobacter spp., Pseudomonas spp., S. aureus	IL-6, TNF-α — povišeni kod dubokih infekcija	Rotacioni mišićni flap ili fasciokutani flap nakon potpunog uklanjanja nekroze	Stabilizovani inflamatorni markeri i sterilna rana	[6], [7], [9]
Posttraumatske hronične rane	Polimikrobne infekcije (mešovita flora uključujući Enterobacter, Acinetobacter, S. aureus)	CRP, IL-6 — povišeni kod reinfekcije; pad u fazi granulacije	Sekvencijalni debridman i mikrovaskularni free flap	CRP normalizovan, IL-6 u padu ≥ 40%	[5], [9], [13], [16]
Hronične rane nakon opekotina	Staphylococcus spp., Pseudomonas spp., Klebsiella spp. — dominantni uzročnici infekcija	IL-6 i TNF-α — korelacija sa dubinom opekotine i ishodom	Višefazna rekonstrukcija (autotransplantati i lokalni flapovi)	IL-6 <40 pg/mL, CRP u trendu pada	[7], [9]

wounds enhances the local and systemic inflammatory reaction, thus activating a cytokine network which leads to persistent inflammation and inhibition of tissue regeneration. This "vicious circle" of inflammation and inhibition is often the reason for the failure of conservative therapy and the need for reconstructive procedures.

Inflammatory biomarkers

Inflammatory biomarkers are biological indicators that reflect the degree of inflammatory response of the body and they can help assess the severity of the infection and the effectiveness of therapy. Their clinical application in the treatment of chronic wounds is becoming more and more important because it enables objective monitoring of the condition of the wound, in addition to classical microbiological analyses (7,9). Key biomarkers for chronic wounds are: C-reactive protein (CRP), interleukins, tumor necrosis factor alpha (TNF-α) etc.

CRP is the most commonly used biomarker in clinical practice. Elevated CRP values indicate systemic inflammation and often correlate with bacterial infection. In chronic wounds, CRP is used to monitor the response to therapy and to make a decision on the appropriate moment for reconstructive surgery.

Interleukin-6 (IL-6) is a pro-inflammatory cytokine that directly affects the activation of neutrophils and stimulation of the acute phase of inflammation. *Liang* et al. (7) showed that the concentration of IL-6 was significantly elevated in patients with deep burns of the extremities and that its decrease during therapy correlated with a better healing outcome. TNF-α is an important indicator of active inflammation and a predictor of chronic wound formation. The elevated values of TNF-α are associated with slow epithelialization and more frequent need for surgical reconstructions. Interleukin-8 (IL-8) is a marker of chronic inflammation, especially in wounds with persistent biofilm and multidrug-resistant bacteria (9).

The integration of inflammatory biomarkers with microbiological data enables a personalized treatment approach. In practice, the elevated values of CRP and IL-6 are markers that signal that the wound is not ready for reconstructive surgery. The stabilization of biomarkers and reduction of inflammatory activity are considered to be the key prerequisite for the success of tissue transplantation, graft or flap (7,9).

The integration of microbiological findings, inflammatory biomarkers and reconstructive strategies for different types of chronic wounds is shown in Table 1.

Table 1. Pathogens, biomarkers and surgical approach according to types of chronic wounds

Type of chronic wound	Dominant microorganisms	Inflammatory biomarkers (serum and local)	Surgical approach / reconstructive measures	Clinical criteria for reconstruction	Reference
Diabetic ulcus	Staphylococcus aureus, Pseudomonas aeruginosa; frequent multidrug resistance and biofilm formation	CRP, IL-6, TNF-α — significantly elevated in infections and necrosis	Serial debridement, VAC therapy, split-thickness skin graft (STSG) after microbiological control	CRP <10 mg/L, sterile culture, IL-6 decreasing	[5], [8], [9], [18]
Venous leg ulcer	Enterococcus spp., E. coli, sometimes Proteus mirabilis in secondary infection	CRP, IL-6 — moderately elevated, correlation with wound surface area	Local debridement and skin graft, reconstruction after eradication of bacterial colonization	Decrease in CRP and IL-6 ≥ 30% before graft	[6], [8], [11]
Arterial (ischemic) ulcus	Klebsiella pneumoniae, P. aeruginosa — high resistance to cephalosporins and fluoroquinolones	CRP, TNF-α, IL-8 — high levels in necrosis and infection	Reconstructive flap (local or free) after revascularization and antibiotic therapy	CRP <15 mg/L, negative culture	[7], [8], [9]
Pressure wounds	Proteus mirabilis, Enterobacter spp., Pseudomonas spp., S. aureus	IL-6, TNF-α — elevated in deep infections	Rotation muscle flap or fasciocutaneous flap after complete removal of necrosis	Stabilized inflammatory markers and sterile wound	[6], [7], [9]
Posttraumatic chronic wounds	Polymicrobial infections (mixed flora including Enterobacter, Acinetobacter, S. aureus)	CRP, IL-6 — elevated in reinfection; decrease in granulation phase	Sequential debridement and microvascular free flap	CRP normalized, IL-6 decreasing ≥ 40%	[5], [9], [13], [16]
Chronic wounds after burns	Staphylococcus spp., Pseudomonas spp., Klebsiella spp. — dominant causes of infections	IL-6 and TNF-α — correlation with the depth of the burn and outcome	Multistage reconstruction (autotransplantation and local flaps)	IL-6 <40 pg/mL, a CRP decrease trend	[7], [9]

Dinamika inflamacije i ishod lečenja

Liu i saradnici (9) ističu da kontinuirana inflamacija izazvana multirezistentnim bakterijama dovodi do tzv. "zapaljenskog zarobljavanja rane" — stanja u kojem je proces zarastanja blokiran. U takvim slučajevima, cilj terapijeje da prekine upalne spirale kroz:

mehaničko uklanjanje biofilma, precizno ciljanu antibiotsku terapiju, imunomodulatorne tretmane i praćenje biomarkera u realnom vremenu.

Uporna bakterijska infekcija aktivira transkripcijske faktore (NF-κB i STAT3) koji stimulišu produkciju IL-6 i TNF-α, čime se pokreće samoodržavajuća inflamacija (9). Ova interakcija objašnjava zašto standardne terapije često ne daju rezultate i zašto praćenje biomarkera ima sve veću kliničku vrednost.

Najnovije studije ističu potrebu za integrisanim modelima praćenja hroničnih rana koji kombinuju mikrobiološku kulturu, analizu biofilma i serumske biomarkere. Takav pristup omogućava: objektivnu procenu težine rane, pravovremenu odluku o rekonstruktivnoj intervenciji**,** smanjenje nepotrebne antibiotske upotrebe **i** kraće vreme hospitalizacije (6–9).

U praksi, to znači da mikrobiološki i imunološki podaci treba da budu deo standardnog evaluacionog protokola svake hronične rane, jednako kao i digitalna merenja površine rane(13–16,18).

Ključni rezultati radova uključenih u ovaj pregled, grupisani prema tematskim celinama i njihovom kliničkom značaju, sumirani su u Tabeli 2.

Tabela 2. Komparativna analiza radova po tematskim celinama

Autori	Godina	Fokus istraživanja	Ključni nalazi	Klinički značaj
Bovis et al.	2023	Procena površine rana	Vizuelna procena varira >25%	Potreba za digitalnim merenjem
Yao et al.	2021	Površina rana - pravilo palca	Praktičan metod za kliničku procenu	Jednostavna klinička primena
Wolcott et al.	2010	Biofilm i terapijski prozor	Debridman otvara „window of opportunity"	Bolje vreme za antibiotsku terapiju
Harika et al.	2020	Biofilm i rezistencija	Biofilm povezan s višom rezistencijom	Potreba za agresivnijom terapijom
Chelkeba & Melaku	2021	Gram-negativne infekcije	Visoka prevalencija u Africi	Regionalni antibiotik protokoli
Liang et al.	2022	Biomarkeri kod opekotina	IL-6 i TNF-α kao prognostički faktori	Individualizacija terapije
Liu et al.	2025	Multirezistencija u hroničnim ranama	Inflammacija + rezistencija = loš ishod	Integrisana dijagnostika

Zaključak

Hronične rane predstavljaju složen klinički problem u kojem se mikrobiološki status, inflamatorni odgovor i pravovremeno planiranje rekonstruktivnog lečenja međusobno prožimaju i određuju krajnji ishod terapije. Dominantna prisutnost multirezistentnih bakterijskih sojeva i formiranje biofilma produžavaju inflamatornu fazu i otežavaju epitelizaciju, dok praćenje biomarkera kao što su CRP, IL-6 i TNF-α omogućava objektivnu procenu aktivnosti infekcije i spremnosti tkiva za rekonstrukciju. Uvođenje savremenih digitalnih metoda za merenje površine rana i doprinosi standardizaciji procene zarastanja i racionalnijem planiranju terapijskih intervencija. Integrisan pristup koji povezuje mikrobiološku dijagnostiku, praćenje biomarkera i rekonstruktivne tehnike omogućava personalizovano lečenje, smanjenje broja komplikacija, kraće trajanje hospitalizacije i bolji funkcionalni ishod. Takav multidisciplinarni model predstavlja savremeni okvir za efikasno zbrinjavanje hroničnih rana i optimizaciju resursa u kliničkoj praksi.

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Dynamics of inflammation and treatment outcomes

Liu and associates (9) emphasize that the continuous inflammation caused by the multidrug-resistant bacteria leads to the so-called "inflammatory wound entrapment" – a condition in which the healing process is blocked. In such cases, the goal of the therapy is to break the inflammatory spiral through: mechanical biofilm removal, precisely targeted antibiotic therapy, immunomodulatory treatments and real-time monitoring of biomarkers.

A persistent bacterial infection activates transcription factors (NF-kB and STAT3) that stimulate the production of IL-6 and TNF-α, thus initiating the self-perpetuating cycle of inflammation (9). This interaction explains why standard therapies do not give results and monitoring biomarkers have rapidly increasing clinical significance.

The latest studies emphasize the need for integrated models of monitoring chronic wounds that combine microbiological culture, biofilm analysis and serum biomarkers. This approach enables: objective assessment of wound severity, making a timely decision on reconstructive intervention, reduction of unnecessary use of antibiotics and shorter hospitalization time (6-9).

In practice, this means that microbiological and immunological data should be part of the standard evaluation protocol of all chronic wounds, as well as digital measurements of the wound surface area (13-16,18).

The key results of studies included in this review, which were grouped according to thematic units and their clinical significance, are summarized in Table 2.

Table 2. Comparative analysis of studies according to thematic units

Authors	Year	Research focus	Key findings	Clinical significance
Bovis et al.	2023	Evaluating wound surface area	Visual assessment varies >25%	Need for digital measurement
Yao et al.	2021	Surface area of wounds – rule of thumb	Practical method for clinical evaluation	Simple clinical implementation
Wolcott et al.	2010	Biofilm and therapeutic window	Debridement opens „window of opportunity"	Better time for antibiotic therapy
Harika et al.	2020	Biofilm and resistance	Biofilm associated with higher resistance	Need for more aggressive therapy
Chelkeba & Melaku	2021	Gram-negative infections	High prevalence in Africa	Regional antibiotic protocols
Liang et al.	2022	Biomarkers in burns	IL-6 and TNF-α as prognostic factors	Individualization of therapy
Liu et al.	2025	Multidrug resistance in chronic wounds	Inflammation + resistance = poor outcome	Integrated diagnostics

Conclusion

Chronic wounds are a complex clinical problem, in which the microbiological status, inflammatory response and timely planning of reconstructive treatment are correlated and determine the final treatment outcome. The dominant presence of multidrug-resistant bacterial strains and biofilm formation prolong the inflammatory phase and make the epithelialization difficult, while the monitoring of biomarkers, such as CRP, IL-6 and TNF-α enables the objective assessment of infection activity and the tissue readiness for reconstruction. The introduction of modern digital methods for the measurement of surface areas of chronic wounds contributes to the standardization of the evaluation of healing and more rational planning of therapeutic interventions. An integrated approach that connects microbiological diagnostics, monitoring of biomarkers and reconstructive techniques enables the personalized treatment, reduction in the number of complications, shorter hospitalization and better functional outcome. Such a multidisciplinary model represents a modern framework for the efficient management of chronic wounds and optimization of resources in clinical practice.

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