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CELULITIS
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Sažetak

Celulitis predstavlja akutno inflamatorno oboljenje kože i potkožnog tkiva. Može zahvatiti bilo koju regiju tela. Celulitis donjih ekstremiteta je najčešći, javlja se u oko 88% svih celulitisa. Manifestuje se u vidu brzo progredirajućeg edema potkožnog tkiva sa izraženim eritemom, nejasnih granica, koji se pseudopodno širi, i palpatorno toplom i bolnom kožom. Celulitis se može prezentovati u vidu blage, umerene ili teške forme, u zavisnosti od kliničkog nalaza i odsustva ili prisustva sistemskih simptoma. U većini slučajeva, pacijenti sa celulitisom zahtevaju hospitalno lečenje, i potreba za hospitalizacijom raste sa uzrastom pacijenta. U zavisnosti od ispitivane populacije, različita je učestalost određenih patogena. Najčešći uzročnici celulitisa kod imunokompetentnih osoba su beta hemolitički streptokok (grupe A, B, C, G i F) i nešto ređe Staphylococcus aureus. S. aureus rezistantan na meticilin (MRSA) u porastu je od 2000. godine i doveo je do značajnog porasta purulentnih celulitisa, odnosno kolonizacije kod pacijenata. Iako je celulitis široko rasprostranjen, u većini zemalja još uvek nema jasno definisanih vodiča (dijagnostičkih i terapijskih). Terapija celulitisa se uglavnom zasniva na empirijskom iskustvu. Nekomplikovani celulitisi obično zahtevaju samo oralnu primenu antibiotika, a umerene i teške forme terapiju parenteralnim antibioticima. Preteranu upotrebu antibiotika treba izbegavati jer dovodi do stvaranja rezistentnih sojeva.
***Ključne reči**: celulitis; streptokok; stafilokok; antibiotici; antibiotska profilaksa; faktori rizika*

Abstract

Cellulitis is an acute inflammatory disease of the skin, affecting the dermis and subcutaneous tissue. It can affect any region of the body, with cellulitis of the lower extremities being the most common, accounting for 88% of all cases. Typical symptoms include rapidly progressing subcutaneous edema, spreading erythema that is not sharply demarcated, and warm, painful skin upon palpation. The severity of cellulitis can vary from mild to moderate or severe, depending on clinical findings and the presence or absence of systemic symptoms. Hospital treatment is often necessary for patients with cellulitis, and the need for hospitalization increases with age. The most common causative agents of cellulitis in immunocompetent people are beta-hemolytic streptococci (groups A, B, C, G and F), with Staphylococcus aureus being less common. Methicillin-resistant S. aureus (MRSA) has become increasingly prevalent since the 2000s and has contributed to a rise in purulent cellulitides and colonization in affected patients. Despite the widespread occurrence of cellulitis, clear diagnostic and therapeutic guidelines are lacking in many countries. Treatment is typically empiric, with oral antibiotics often sufficient for uncomplicated cellulitis, while moderate to severe cases may require parenteral antibiotics. Overuse of antibiotics should be avoided to prevent the development of resistant strains.
Key words: Cellulitis; Streptococcus; Staphylococcus; Anti-Bacterial Agents; Antibiotic Prophylaxis; Risk Factors

Uvod

Celulitis je relativno često akutno inflamatorno oboljenje kože i potkožnog tkiva, sa učestalošću 22–50 slučajeva na 1.000 osoba godišnje [1, 2]. Javlja se zbog narušenog in-

Introduction

Cellulitis is a relatively common acute inflammatory disease of the skin and subcutaneous tissue, with an incidence of about 22-50 cases per 1000 people per year [1, 2].

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tegriteta kože i prodora mikroorganizama u dublja tkiva. Može se manifestovati blagim oblicima (eritem i edem zahvaćenog dela kože, bez sistemskih simptoma), umerenim (eritem, bol, praćen povišenom temperaturom i markerima inflamacije) i teškim formama (tahikardija, temperatura, hipovolemijski šok) [3]. Nelečeni celulitis, pored mogućih komplikacija, može dovesti i do letalnog ishoda. Stopa mortaliteta je značajno opala od 1930. godine sa uvođenjem sulfonamida, odnosno penicilina četrdesetih godina prošlog veka [1].

Teže forme celulitisa viđaju se u zemljama u razvoju i kod osoba lošeg socioekonomskog statusa [3]. Celulitis se može se javiti na bilo kojoj regiji kože. Celulitis donjih ekstremiteta je čest, javlja se u oko 88% svih celulitisa [4]. Obično je zahvaćen jedan ekstremitet, bilateralni celulitis je izuzetno redak [5], i potrebno je ponovo razmotriti dijagnozu, najverovatnije da se ne radi o celulitisu [1]. Nekomplikovani celulitis u većini slučajeva ne zahteva hospitalno lečenje. Između 7 do 10% pacijenata sa celulitisom potrebno je hospitalizovati, procenat se značajno povećava sa uzrastom pacijenta [5]. Kod osoba uzrasta 85 godina i više, i do pet puta više u odnosu na one starosti 54 godine [6]. Prema podacima iz literature, postoji tendencija stalnog porasta hospitalizovanih pacijenata sa celulitisom i poslednjih decenija se broj hospitalizacija utrostručio [6–10]. Iako je celulitis široko rasprostranjen, u većini zemalja još uvek nema jasno definisanih vodiča (i dijagnostičkih i terapijskih).

Erizipel (Erysipelas) je dugo razdvajan od celulitisa, budući da postoje kliničke i etiološke razlike. Pojedini autori erizipel smatraju kliničkom varijantom celulitisa [11]. U poslednje vreme sve se manje govori o dva različita entiteta budući da postoje brojna preklapanja. I erizipel i nekomplikovani celulitis imaju isti terapijski pristup [1]. Eritem kod erizipela je oštro ograničen, infekcija zahvata površnije slojeve kože, izazivač je skoro isključivo streptokok (Streptococcus pyogenes, Streptococcus agalactiae i Streptococcus dysgalactiae sp. equisimilis (C i G) [11]. Rezultati skorijih istraživanja su pokazali skoro podjednaku učestalost zlatnog stafilokoka i kod celulitisa i kod erizipela [5, 12]. Kako se ova dva entiteta ne mogu sa jasnom sigurnošću ni klinički razlikovati, oba su, prema predlogu američke škole grupisani, predložen je naziv „infekcije kože i potkožnog tkiva“ (engl. skin and soft tissue infections, SSTI) kojim je

It occurs due to compromised skin integrity allowing microorganisms to penetrate deeper tissues. Cellulitis can manifest as mild forms (characterized by erythema and edema without systemic symptoms), moderate forms (involving erythema and pain accompanied by fever and inflammation markers), and severe forms (with symptoms like tachycardia, fever, and hypovolemic shock) [3]. If left untreated, cellulitis can lead to complications, and in severe cases, even a fatal otucome. The introduction of sulfonamides in the 1930s and penicillin in the 1940s significantly reduced mortality rates associated with cellulitis [1].

Severe cellulitis is more prevalent in developing countries and among individuals with lower socioeconomic status [3]. While cellulitis can affect any skin region, it most commonly affects the lower extremities (about 88% of cases) [4]. Bilateral cellulitis is extremely rare [5], necessitating consideration of differential diagnoses [1]. Although most cases of uncomplicated cellulitis do not require hospitalization, approximately 7-10% of patients with cellulitis require hospital treatment, with hospitalization rates increasing significantly with age [5]. Patients aged 85 years and older have up to five times higher hospitalization rates than those aged 54 years [6]. There has been a constant increase in hospitalization among cellulitis patients over recent decades, with hospitalizations tripling in number [6–10]. Despite the prevalence of cellulitis, many countries lack clearly defined guidelines for its diagnostic and treatment.

Erysipelas, historically distinguished from cellulitis based on clinical and etiological differences, is now considered by some to be a clinical variant of cellulitis due to overlapping characteristics [11]. Both erysipelas and uncomplicated cellulitis are managed similarly [1]. Erysipelas is characterized by sharply demarcated erythema affecting superficial skin layers and is predominantly caused by streptococci (Streptococcus pyogenes, Streptococcus agalactiae, and Streptococcus dysgalactiae spp. equisimilis (C and G) [11]. Recent studies have shown similar prevalence rates of Staphylococcus aureus in cellulitis and erysipelas cases [5, 12]. Because of the difficulty in clinically distinguishing between these conditions, they are often grouped under the term “skin and soft tissue infections” (SSTI), which encompasses various skin infections with diverse clinical manifestations and course [13]. The Infectious Diseases

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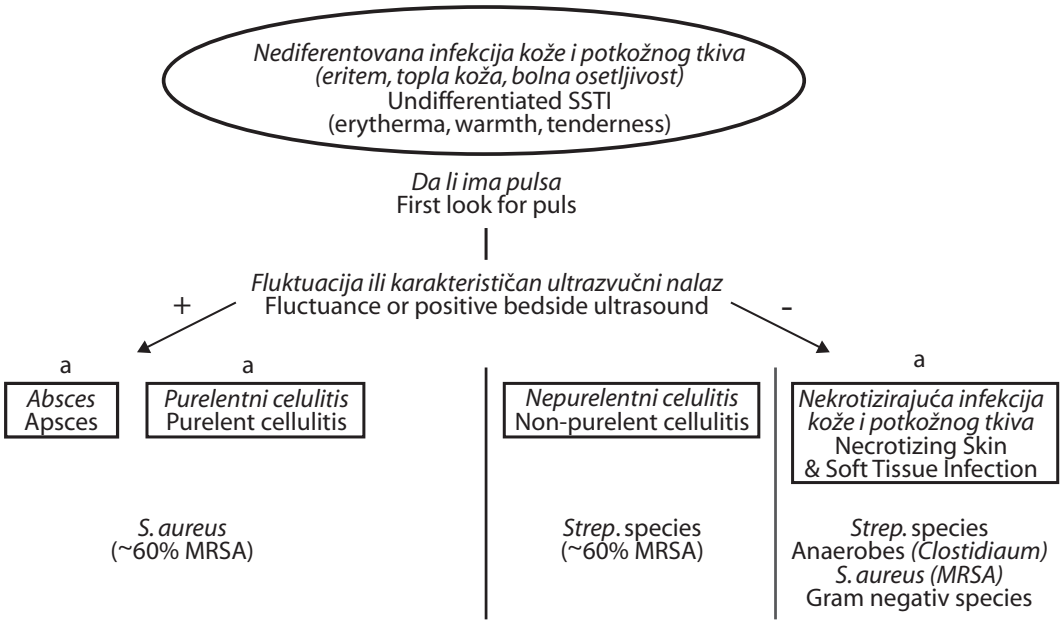

Dijagram 1. *Klasifikacija infekcija kože i potkožnog tkiva (Breyre, 2018)*
Diagram 1. Classification of skin and subcutaneous tissue infections (Breyre, 2018)

obuhvaćen veći broj različitih infekcija kože, sa različitim kliničkim manifestacijama i tokom [13]. Prema IDSA (engl. The Infectious Diseases Society of America) razlikuju se tri vrste SSTI – 1) nekomplikovane infekcije poršnog dela kože, 2) komplikovane infekcije koje zahvataju dublje strukture i 3) infekcije sa nekrozom tkiva (kao što su nekrozantni fasciitis i mionekroza [14]. U infekcije kože i potkožnog tkiva ubrajaju se celulitis i erizipel, kao i purulentni oblici celulitisa ***(Dijagram 1)*** *[5, 13]. Pojedini autori pak razdvajaju purulentni celulitis, ne svrstavajući ga u kategoriju celulitisa, opisujući ga kao zapaljenje oko primarnog infektivnog žarišta, kao što je pustule, apscess, furunkul [14].*

Etiopatogeneza i faktori rizika

Do razvoja celulitisa dolazi kada je narušen integritet epiderma što omogućava prodor bakterija do potkožnog tkiva. Različiti faktori rizika koji mogu dovesti do narušenog integriteta epiderma, mogu se podeliti na opšte i lokalne [6, 15] ***(Tabela 1).***

Infektivni agens se u etiologiji celulitisa često ne može utvrditi, te učestalost određenih sojeva bakterija nije moguće odrediti. Najčešći uzročnici celulitisa kod imunokompetentnih osoba su beta hemolitički streptokok (grupe A, B, C, G i F) i nešto ređe Staphylococcus

Society of America (IDSA) classifies SSTIs into three types: uncomplicated infections of superficial skin, complicated infections involving deeper structures, and infections leading tissue necrosis (e.g. necrotizing fasciitis and myonecrosis) [14]. Skin and subcutaneous tissue infections include cellulitis, erysipelas, and purulent forms of cellulitis **(Diagram 1)** [5, 13]. Some authors separate purulent cellulitis from non-purulent cellulitis, describing it as inflammation around primary infectious foci such as pustules, abscesses, and furuncles [14].

Etiopathogenesis and risk factors

Cellulitis develops when the integrity of the epidermis is compromised, allowing bacteria to penetrate the subcutaneous tissue. There are various risk factors that can lead to this impairment, categorized as general or local **(Table 1)** [6, 15]**.**

The infective agent responsible for cellulitis is often unidentified, making it challenging to determine the frequency of specific bacterial strains. However, in immunocompetent individuals, the most common causative agents of cellulitis are beta-hemolytic streptococci (groups A, B, C, G and F), and less frequently, Staphylococcus aureus [13, 14, 16, 17]. The frequency of certain pathogens varies depending

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Tabela 1. *Faktori rizika za razvoj celulitisa*
Table 1. Risk factors for the development of cellulitis

Opšti/General
Uzrast pacijenta/Age of the patient
Gojaznost/Obesity
Hronične bolesti: Diabetes mellitus, maligniteti/Chronic diseases: Diabetes mellitus, malignancies
Alkoholizam/Alcoholism
Pušenje/Smoking
Imunosupresija/Immunosuppression
Socioekonomski položaj (beskućnici)/Socioeconomic position (homeless)
Lokalni/Local
Varikoziteti, pozitivna anamneza u smislu tromboflebitisa/flebotromboze, vaskularni operativni zahvati (venektomija) Varices, a positive history of thrombophlebitis/phlebothrombosis, vascular surgery (venectomy)
Neurološki poremećaji/Neurological disorders
Zračna terapija/Radiation therapy
Hronične venske ulceracije i ulceracije druge etiologije Chronic venous ulcerations and ulcerations of other etiology
Stazni dermatitis i pruriginozne dermatoze (ekskorijacije) Stasis dermatitis and pruriginous dermatoses (excoriations)
Gljivične infekcije stopala/Fungal infections of the feet
Limfedem/Lymphedema
Depigmentišući topikalni preparati/Depigmenting topical preparations

aureus [13, 14, 16, 17]. U zavisnosti od ispitivane serije/populacije, različita je učestalost određenih patogena. Beta hemolitički streptokok je izolovan kod 73% pacijenata sa celulitisom (i 96% sa erizipelom) [1]. U pojedinim istraživanjima, stafilokok je bio primarni uzročnik celulitisa i češće je uzročnik tzv. purulentnih celulitisa [18]. Pored tzv. konvencionalnih patogena, uzročnici celulitisa su i tzv. nekonvencionalni koji se izoluju sporadično i kod određenog broja pacijenata (imunokompromitovani, alkoholičari, dijabetičari i sl) [8, 19]. S. aureus rezistentan na meticilin (MRSA) koji je do pre deset-petnaest godina bio isključivo bolnički soj, od 2000. godine je u porastu i kod zdravih individua (koji nisu boravili u hospitalnim uslovima, tzv CA MRSA (engl. Community associated MRSA) i doveo je do značajnog porasta purulentnih celulitisa [13, 20, 21]. MRSA je uzročnik preko 60% purulentnih celulitisa, odnosno kolonizacije kod pacijenata (prethodna upotreba antibiotika, hospitalizovani pacijenti, intravenska terapija, prethodne

on the series/population studied. Beta-hemolytic streptococci have been isolated in 73% of patients with cellulitis (and 96% with erysipelas) [1]. In some studies, staphylococcus was the primary cause of cellulitis, particularly in cases of purulent cellulitis [18]. In addition to conventional pathogens, cellulitis can be caused by unconventional pathogens, which are sporadically isolated in specific patient groups such as immunocompromised individuals, alcoholics, and patients with diabetes [8, 19]. Methicillin-resistant S. aureus (MRSA), historically a hospital-acquired strain, has increasingly been observed in healthy individuals (Community-Associated MRSA or CA-MRSA) since the 2000s. This trend has led to a significant increase in purulent cellulitis [13, 20, 21], with MRSA being responsible for over 60% of such cases, i.e. colonization in patients (previous use of antibiotics, hospitalized patients, intravenous therapy, previous surgeries, etc.) [9, 13]. Individuals at high risk of developing purulent cellulitis due to CAMRSA include athletes, children, homosexuals, prison-

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Tabela 2. *Uzročnici celulitisa u odnosu na komorbiditete i faktore rizika (Raff, 2016; Gunderson 2011)*
Table 2. Causes of cellulitis in relation to comorbidities and risk factors *(Raff, 2016; Gunderson 2011)*

Imunosupresija (HIV/AIDS, pacijenti sa transplantiranim organom, sistemske bolesti veziva) Immunosuppression (HIV/AIDS, transplant patients, systemic connective tissue diseases)	Streptococcus pneumoniae Escherichia coli Campylobacter Serratia marcescens Shewanella putrefaciens	Helicobacter cinaedi Cryptococcus neoformans Cryptococcus gattii Haemophilus influenzae
Hronične bolesti jetre i hronična bubrežna insuficijencija Chronic liver disease and chronic kidney insufficiency	Vibrio spp (V vulnificus ili V cholerae) Pseudomonas aeruginosa Acinetobacter Neisseria gonorrhoeae Burkholderia cepacia Enterobacteriaceae spp Aeromonas spp Streptococcus iniae	Campylobacter E coli S putrefaciens Neisseria meningitidis V alginolyticus Shewanella spp Mycobacterium marinum Erysipelothrix rhusiopathiae
Ubodi insekata, životinjski ujedi, ljudski ugrizi Insect bites, animal bites, human bites	Pasteurella Streptococcus spp Corynebacterium spp Fusobacterium Prevotella Propionibacterium Eikenella corrodens Porphyromonas Fusobacterium	Neisseria Staphylococcus Moraxella Porphyromonas Bacteroides Clostridium spp Bacteriodes fraglis Peptostreptococcus Veillonello
Hospitalno lečenje ili hirurška intervencija u poslednjih godinu dana. Hemodijaliza, prethodna infekcija MRSA ili kolonizacija. Skora upotreba antibiotika. Kontaktni sportovi, ubod pauka. Boravak u kolektivnom smeštaju – vojnici, zatvorenici, beskućnici. Homoseksualci, intravenski zavisnici Hospitalization or surgical intervention in the last year. Hemodialysis, previous MRSA infection or colonization. Recent use of antibiotics. Contact sports, spider bite. Residence in collective housing- soldiers, prisoners, homeless individuals. Homosexuals, intravenous addicts	*MRSA*/MRSA	

MRSA – meticilin rezistentan stafilokok/MRSA – methicillin resistant staphylococcus

operacije i slično) [9, 13]. Pacijenatima sa visokim rizikom od razvoja purulentnog celulitisa, izazvanog CA MRSA, smatraju se atletičari, deca, homoseksualci, zatvorenici, vojnici, narkomani, osobe koje su bile izložene MRSA [12].

Kod većine nekomplikovanih i nepurulentnih celulitisa, ne izoluju se Gram-negativne bakterije. One su uglavnom izolovane kod imunokompromitovanih pacijenata i kod pacijenata sa cirozom jetre. Konvencionalni i nekonvencionalni patogeni uzročnici celulitisa kod pa-

ers, soldiers, drug addicts, and those exposed to MRSA [12].

In most uncomplicated and non-purulent cellulitis cases, gram-negative bacteria are not isolated. Gram-negative bacteria are primarily found in immunocompromised patients and those with liver cirrhosis. **Table 2** illustrates a range of conventional and unconventional pathogens responsible for cellulitis in patients with different comorbidities and risk factors.

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cijenata sa različitim komorbiditetom i sa različitim faktorima rizika prikazani su u ***Tabeli 2.***

Histopatološki nalaz

Biopsija se retko radi, dijagnoza je klinička. Biopsija se radi kod sumnje na drugu dijagnozu. Histopatološki nalaz kod celulitisa je nespecifičan, prisutan je edem u dermu, difuzan perivaskularni neutrofilni infiltrat, dilatacija limfnih sudova. U kasnijem toku mogu se naći limfociti, histiociti i formiranje granuloma [13].

Klinička prezentacija

Celulitis se manifestuje u vidu brzoprogredirajućeg edema potkožnog tkiva sa izraženim eritemom i palpatorno toplom i bolnom kožom [9, 12, 19]. Eritem je nejasnih granica koji se pseudopodno širi ***(Slika 1)****. Celulitis se može javiti na bilo kojoj regiji kože. Češći su poremećaji opšteg stanja – jeza, febrilnost kod 22–77% [1], malaksalost, koji se mogu javiti i pre pojave promena na koži. Simptomi su uglavnom manje naglašeni nego kod erizipela i odsutni ili blagi kod nekomplikovanih celulitisa [13]. Takođe se mogu javiti vezikule i/ili bule, obično seroznog sadržaja. Limfedem može biti manje ili više naglašen i daje koži karakterističan izgled "pomorandžine kore"* ***(Slika 2)****. Često su prisutni i lim-*

Slika 1. *Nekomplikovani celulitis – edem, eritem nejasnih granica, distenzivna skvama*
Figure 1. Uncomplicated cellulitis – edema, erythema with unclear boundaries, distensive squama

Slika 2. *Bulozni celulitis: vezikule, bule, limforeja, izgled pomorandžine kore*
Figure 2. Bullous cellulitis: vesicles, blisters, lymphorrhea, orange peel appearance

Histopathological findings

Biopsies are rarely performed for cellulitis diagnosis, and it is primarily clinical. Biopsies are considered in cases where a second diagnosis is being considered. Histopathological findings in cellulitis are nonspecific and typically include edema in the dermis, diffuse perivascular neutrophilic infiltrate, and dilation of lymphatic vessels. As the condition progresses, lymphocytes, histiocytes and granuloma formation may be observed [13].

Clinical presentation

Cellulitis typically presents as rapidly progressing edema of the subcutaneous tissue accompanied by pronounced erythema and palpatory warm, tender skin [9, 12, 19]. The erythema often has unclear borders that spread pseudopod-like (**Figure 1**). Cellulitis can affect any region of the skin. Common systemic symptoms associated with cellulitis include chills, fever (present in 22-77% of cases), malaise, which can precede the skin changes and are generally less pronounced compared to erysipelas, and may be absent or mild in uncomplicated cellulitis [13]. Other manifestations can include vesicles and/or bullae filled with serous fluid, along with lymphedema that gives the skin

Slika 3. *Purulentni celulitis*
Figure 3. Purulent cellulitis

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fangiitis i bolna regionalna limfadenopatija [1, 6]. Ponekad se mogu videte petehije i ekhimoze. Pored najčešće lokalizacije na donjim ekstremitetima, promene se mogu javiti i na gornjim ekstremitetima, kod intravenskih zavisnika [6], kao i na drugim anatomskim regijama kao što su orbita, vulvarna, ingvinalna regija i sl. [1].

Nepurulentni celulitis

Promene se javljaju nakon narušenog integriteta kože, i/ili narušenog imunskog sistema odnosno poremećene cirkulacije [13]. Mogu se javiti i širenjem infekcije iz udaljenog žarišta ili u sklopu bakterijemije [16]. Zato su najznačajniji faktori rizika razvoja nepurulentnog celulitisa Diabetes mellitus tip 2*, gojaznost, venska insuficijencija, kompromitovana limfna drenaža, starija populacija [13].*

Purulentni cellulitis

Purulentni celulitis se definiše kao celulitis sa secernacijom/drenažom purulentnog sadržaja bez postojanja vidljivog apscesa [12]. Purulentni celulitis je udružen sa purulentnim fokusom kao što su apscess, pustula, ulceracija ***(Slika 3)****. Izazivač je u najvećem broju slučajeva Staphylococcus aureus [13]. U većini slučajeva, oko purulentnog fokusa formira se eritem i induracija, a u ređim, celulitis je van granica suspektnog purulentnog fokusa [13]. Potencijalna komplikacija celulitisa je pojava nekrozantnog fasciitisa (NF) koji se manifestuje brzoširećom destrukcijom mekih tkiva i, superficijalne ili duboke fascije, i mišića [12]. Kod NF može postojati i eritem kože mada je obično odsutan, izrazitim bolom zahvaćene regije, evl. bulama, krepitacijama, visokom temperaturom [6]. Purulentni celulitis spada u SSTI, odvojen je entitet od klasičnog celulitisa [2].*

Recidivantni celulitis

Visok procenat pacijenata, 16−29%, koji su imali epizodu celulitisa (nekomplikovanog) imaće jedan ili više recidiva [22]. Prema definiciji, prethodna epizoda celulitisa predstavlja faktor rizika razvoja recidiva, čak je prema istraživanjima jedne grupe autora bila jedini značajni prognostički faktor recidiva [12]. Klinička prezentacija je ista, faktori rizika za rekurentni celulitis slični su kao i za primarni celulitis [6] ***(Tabela 1)****. Zbog oštećenja limfnih sudova usled više ponavljanih epizoda celulitisa, dolazi do trajnog limfedema koji može bitI i jako naglašen − elefantijaze.*

a characteristic “orange peel” appearance **(Figure 2).** Additionally, lymphangitis and painful regional lymphadenopathy may occur [1, 6]. Petechiae and ecchymoses may also be visible. While cellulitis commonly affects the lower extremities, it can also occur on the upper extremities, particularly in intravenous drug users [6], and in other anatomical regions such as the orbit, vulvar area, inguinal region, etc. [1].

Nonpurulent cellulitis

Changes occur following compromised skin integrity, a weakened immune system, or impaired circulation [13]. They can also result from the spread of infection from a distant focus or as part of bacteremia [16]. The primary risk factors for developing nonpurulent cellulitis include type 2 Diabetes mellitus, obesity, venous insufficiency, compromised lymphatic drainage, and advancing age [13].

Purulent cellulitis

Purulent cellulitis is characterized by cellulitis with secretion/drainage of purulent content without a visible abscess [12]. Purulent cellulitis is associated with a purulent focus such as an abscess, pustules, or ulceration **(Figure 3).** The most common causative agent is Staphylococcus aureus [13]. Typically, erythema and induration develop around the purulent focus, while, in rare cases, cellulitis may extend beyond the borders of the suspected purulent focus [13]. A potential complication of cellulitis is the development of necrotizing fasciitis (NF), which is characterized by rapid and extensive destruction of soft tissues, fascia, and muscles – both superficial and deep [12]. Necrotizing fasciitis may present with severe pain in the affected region, vesicles, crepitus, and high fever [6]. While related to SSTIs, purulent cellulitis is considered a distinct entity from classic cellulitis [2].

Recurrent cellulitis

Recurrence of cellulitis is a common issue, with a significant percentage of patients (16-29%) experienceing one or more episodes after an initial bout of uncomplicated cellulitis [22]. Previous cellulitis episodes serve as a major risk factor for recurrence, and in some studies, they have been identifies as the sole significant prognostic factor for recurrence [12]. The clinical presentation and the risk factors for recurrent cellulitis are similar to those of primary cellulitis **(Table 1)** [6]. Damage to lymphatic vessels re-

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Smatra se da zbog inflamacije kod celulitisa i posledičnog oštećenja tkiva i fibroze, dolazi do smanjenog protoka i usporene eliminacije toksina. Sa smanjenim protokom i ponovljenim infekcijama doći će do insuficijencije limfnog sistema što će dalje uticati na smanjen imunološki odgovor [22]. Recidivantni celulitis se javlja u 16–53% slučajeva, unutar tri godine [23]. Recidivi celulitisa su često uzrokovani beta hemolitičkim streptokokom (grupa A, B, C ili G).

Učestalost recidiva je viša sa uzrastom [3, 6, 22]. Faktori rizika su različiti udruženi komorbiditeti, gljivične infekcije stopala, hronična venska insuficijencija, hronični limfedem, limfadenektomija i druge prethodne operacije [1, 2, 9, 13, 24]. Radi lečenja, odnosno profilakse potrebno je lečiti faktore rizika [24].

Klinička klasifikacija celulitisa

Postoje različite predložene klasifikacije celulitisa (odnosno SSTI), prema težini kliničke slike (lokalni nalaz i udruženi simptomi). Eronova klasifikacija koja je u širokoj upotrebi je prikazana u ***Tabeli 3****, sa modifikacijama ili bez njih [25, 26]. Takođe su predloženi CREST (engl. Clinical Resource Efficiency Support Team) kriterijumi na osnovu Eronove klasifikacije [27]. Klasifikacija celulitisa (infekcija kože i mekih tkiva) može se izvršiti i na blage, umerene i teške, a u zavisnosti od prisustva ili ne sistemskog inflamatornog sindroma (engl. Systemic Inflammatory Response Syndrome - SIRS) (****Tabela 4)*** *[14]****.***

sulting from repeated cellulitis episodes can lead to permanent lymphedema, which may be severe and result in elephantiasis. Inflammation and subsequent tissue damage and fibrosis impair lymphatic flow, leading to decreased toxin elimination and immune response [22]. Recurrent cellulitis occurs in a substantial percentage of patients within a few years, ranging from 16 53% within a three-year period [23]. Beta-hemolytic streptococcus (group A, B, C or G) is a common cause of recurrent cellulitis.

The frequency of recurrences increases with age [3, 6, 22]. Risk factors include various associated comorbidities, fungal foot infections, chronic venous insufficiency, chronic lymphedema, lymphadenectomy, and previous surgeries [1, 2, 9, 13, 24]. Treatment and prevention require addressing the risk factors [24].

Clinical classification of cellulitis

There are several commonly used classifications for cellulitis (i.e. SSTI) based on the severity of the clinical presentation (local findings and associated symptoms). Eron's classification, which is widely used, is shown in **Table 3**, with or without modifications [25, 26]. The Clinical Resource Efficiency Support Team (CREST) criteria have been proposed based on Eron's classification [27]. Cellulitis (skin and soft tissue infections) can also be classified as mild, moderate, or severe, depending on the pres-

Tabela 3. *Klasifikacija celulitisa (infekcija kože i potkožnog tkiva) (Eron, 2003)*
Table 3. Classification of cellulitis (infection of the skin and subcutaneous tissue) (Eron, 2003)

Klasa/Class	*Karakteristike*/Characteristics
I	*Oboleli bez sistemskih parametara bolesti, bez udruženih značajnih komorbiditeta, terapija se sprovodi peroralnim antibioticima, vanbolnički*/Patients without systemic disease parameters, without associated significant comorbidities, therapy is carried out with oral antibiotics outside the hospital
II	*Oboleli sa minornim sistemskim znacima bolesti, ili bez sistemskih manifestacija sa komorbitetima (periferna vaskularna bolest, gojaznost i hronična venska insuficijencija), moguće komplikacije ili produženo trajanje bolesti*/Patients with minor systemic signs of the disease, or without systemic manifestations with comorbidities (peripheral vascular disease, obesity and chronic venous insufficiency), possible complications or prolonged duration of the disease
III	*Oboleli sa izraženim sistemskim manifestacijama (akutna konfuzija, tahikardija, tahipnea, hipotenzija), sa udruženim komorbitetima koji se pogoršavaju usled infekcije* Patients with pronounced systemic manifestations (acute confusion, tachycardia, tachypnea, hypotension), with associated comorbidities that worsen due to infection
IV	*Oboleli sa znacima sepse ili teškim infekcijama koje ugrožavaju život (evl. nekrotišući fascitis)* Patients with signs of sepsis or severe life-threatening infections (e.g. necrotizing fasciitis)

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Dijagnoza i diferencijalna dijagnoza

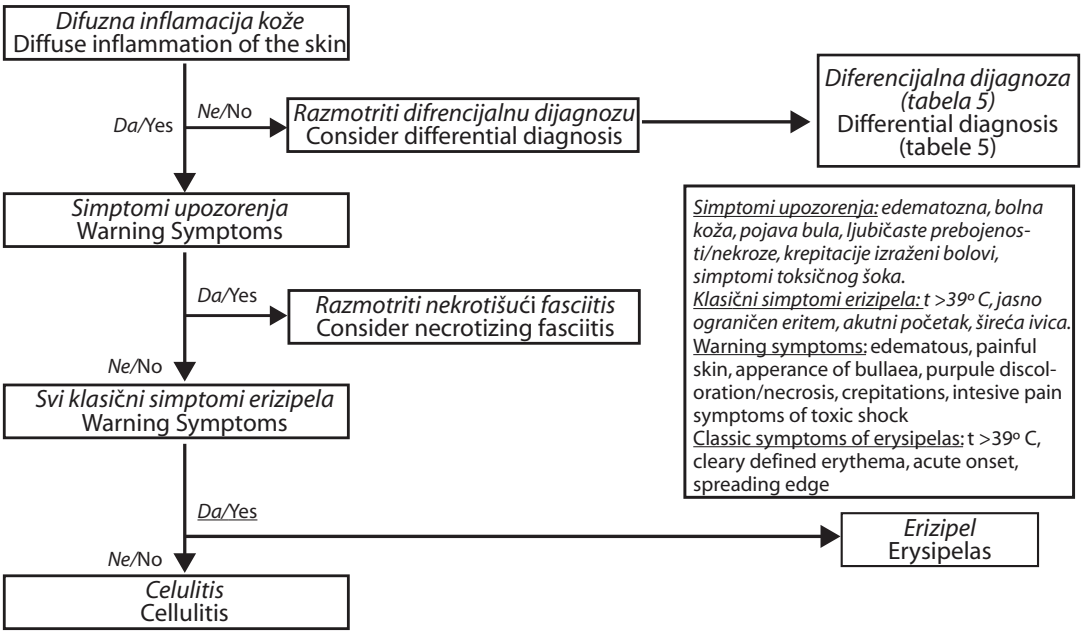
*Dijagnoza se postavlja na osnovu kliničke prezentacije i relevantnih anamnestičkih podataka (faktori rizika – **Tabela 1**), kao i toka bolesti (**Dijagram 2).***

Kod pacijenata sa suspektnim purulentnim celulitisom potrebna je pažljiva palpacija kako bi se otkrila fluktuacija. Ultrazvučni pregled je od pomoći kada se ne palpira fluktuacija ili ju je teško locirati. Apscesne šupljine se obično na ultrazvuku manifestuju kao hipo ili anehogene senke sa perifernom hiperemijom [10, 13]. Isto tako kompjuterizovanom tomografijom mogu se otkriti dublje, supkutani ili intramuskularni apscesi ali se ona retko koristi u dijagnostičke svrhe [13].

Diagnosis and differential diagnosis

The diagnosis of cellulitis relies on the clinical presentation, relevant medical history (risk factors - **Table 1**), and the progression of the disease (**Diagram 2).**

In cases where purulent cellulitis is suspected, careful palpation is necessary to detect fluctuation. Ultrasonography is a valuable tool when fluctuation is challenging to discern or is not palpable. Abscess cavities typically appear as hypoechoic or anechoic shadows with peripheral hyperemia on ultrasound [10, 13]. Similarly, computed tomography can identify deeper, subcutaneous, or intramus-



***Dijagram 2.** Dijagram toka celulitisa, prema holandskom vodiču, 2013.*
Diagram 2. *Cellulitis flow chart, according to the Dutch guidelines, 2013.*

***Tabela 4.** SIRS kriterijumi*
Table 4. SIRS criteria

SIRS kriterijumi/SIRS criteria	
Temperatura/Temperature	> 38°C *ili*/or < 36°C
Tahikardija/Tachycardia	> 90/min
Tahipneja/Tachypnea	> 24 *respiracija*/respirations/ min
Leukocitoza/Leukocytosis	> 12000

SIRS – Systematic Systemic Inflammatory Response Syndrome 2 i više kriterijuma definišu SIRS
SIRS – Systematic Systemic Inflammatory Response Syndrome Two or more criteria define SIRS

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*Postoje brojna stanja koja mogu ličiti na celulitis, kako prema lokalnom nalazu, tako i po propratnim simptomima – temperatura i leukocitoza, tzv. pseudocelulitisi [6, 18]. Smatra se da kod čak 33% pacijenata bude pogrešno dijagnostikovan celulitis [6]. Kada su promene bilateralne lokalizacije svakako treba razmotriti drugu dijagnozu [18] (**Dijagram 3, Tabela 5).***

Laboratorijska ispitivanja (dijagnostika i praćenje)

*Laboratorijska ispitivanja koja se sprovode kod pacijenata sa celulitisom prikazana su u **tabelama 6 i 7.***

Često se dešava da se bakteriološkim brisom određeni uzročnik celulitisa ne može potvrditi. Pojedini autori naglašavaju da treba izbegavati briseve sa otvorenih rana u okviru celulitisa (ulceracija, erozija) budući da postoji rizik rasta komensalnih bakterija, obično je prisutno više patogena, česta je kolonizacija rana rezistentnim sojevima bakterija, i samim tim je onemogućeno odrediti pravi uzrok celulitisa, a dovodi i do bespotrebne upotrebe antibiotika [6, 17]. Bakteriološku kulturu (iz bioptata tkiva ili aspiracija sadržaja) treba sprovesti kod pacijenata sa rizikom razvoja komplikovanih i purulentnih celulitisa [6]. Stoga je dijagnoza bazirana kao što je prethodno navedeno na osnovu kliničke prezentacije, toka bolesti i anamnestičkih podataka.

Kod skoro svih pacijenata prisutni su ubrzana sedimentacija, leukocitoza i povišen CRP. Kod pacijenata sa normalnim vrednostima, malo je verovatno da je dijagnoza celulitisa, ali je ne isključuju [28]. Kod pacijenata sa nekomplikovanim apscesima, iako se retko koristi u dijagnostičke svrhe [13].

cular abscesses, although it is seldom used for diagnostic purposes [13].

There are numerous conditions that can mimic cellulitis in terms of local findings and associated symptoms such as elevated temperature and leukocytosis, a phenomenon known as pseudo-cellulitis [6, 18]. It is estimated that up to 33% of patients are misdiagnosed with cellulitis [6]. When changes are bilaterally localized, another diagnosis should certainly be considered (**Diagram 3, Table 5)** [18].

Laboratory *investigations (diagnostics and monitoring)*

Laboratory tests conducted on patients with cellulitis are outlined in **Tables 6 and 7.**

It is common for the causative agent of cellulitis to remain unidentified despite bacterial swab testing.

Some authors advise against swabbing open wounds within cellulitis (ulcerations, erosions) due to the risk of detecting commensal bacteria, the frequent presence of multiple pathogens, and colonization with resistant bacterial strains. This can lead to unnecessary use of antibiotics as the true cause of cellulitis cannot be accurately determined [6, 17]. Bacterial culture should be performed on tissue biopsy or aspirate samples from patients at risk of developing complicated or purulent cellulitis [6]. Therefore, diagnosis is primarily based on clinical presentation, disease progression, and medical history.

In nearly all cases, patients with cellulitis exhibit an elevated sedimentation rate, leukocytosis, and increased CRP levels. However, normal

***Dijagram 3.** Diferencijalna dijagnoza celulitisa (modifikovano, po Goldenbergu, 2021)*
Diagram 3. Differential diagnosis of cellulitis (modified, according to Goldenberg, 2021)

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Tabela 5. *Celulitis – diferencijalna dijagnoza*
Table 5. Cellulitis – differential diagnosis

Infektivne bolesti/Infectious diseases	
Uobičajene Common	*Erythema migrans*/Erythema migrans *Herpes simplex, Herpes zoster*/Herpes simplex, Herpes zoster *Kutani apscesi*/Cutaneous abscesses
Retke Rare	*Bakterijske (erisipeliod, nekrozantni fasciitis)*/Bacterial (erysipeliod, necrotizing fasciitis) *Virusne (parvo v. B 19)*/Viral (parvovirus B19) *Gljivične (Cryptococcus neoformans, Sporothrix schenckii, mucormycosis);* Fungal (Cryptococcus neoformans, Sporothrix schenckii, mucormycosis) *Parazitarne (Trypanosoma cruzi, Dermatobia hominis [myiasis]); osteomyelitis* Parasitic (Trypanosoma cruzi, Dermatobia hominis [myiasis]); osteomyelitis);
Inflamatorne/Inflammatory	
Uobičajene Common	*Neželjene reakcije kože na lekove, Erythema nodosum, kontaktni dermatitis, angioedema, Sweet sindrom, giht, burzitis*/Cutaneous drug reactions, Erythema nodosum, contact dermatitis, angioedema, Sweet's syndrome, gout, bursitis
Retke Rare	*Pyoderma gangrenosum; sarcoidosis; eozinofilni celulitis (syndroma Wells); polychondritis; polyarteritis nodosa; panniculitis, autoinflamatorni sindromi (familijarna mediteranska groznica)* Pyoderma gangrenosum; sarcoidosis; eosinophilic cellulitis (Wells syndrome); polychondritis; polyarteritis nodosa; panniculitis, autoinflammatory syndromes (familial Mediterranean fever)
Vaskularne/Vascular	
Uobičajene Common	*Stazni dermatitis, limfedem, duboka venska tromboza, superficijelni tromboflebitis, hematomi* Stasis dermatitis, lymphedema, deep vein thrombosis, superficial thrombophlebitis, hematomas
Retke/Rare	*Eritromelalgija, kalcifilaksa*/Erythromelalgia, calciphylaxis
Neoplazijske/Neoplastic	
	Carcinoma erysipeloides; mamarni i ekstramamarni Mb Paget; limfomi, leukemije Carcinoma erysipeloides; mammary and extramammary Paget's disease; lymphomas, leukemias
Ostale bolesti/Other diseases	
	Ubodi insekata, reakcije oko stranog tela (implanti i sl) Insect bites, foreign body reactions (implants, etc.)

vanim celulitisom ***(klasa I i II, Tabela 4)*** *obično nije potrebno raditi ni laboratorijske analize.*

Preporuke su da se kod svih pacijenata sa infekcijama kože i potkožnog tkiva koji imaju sistemske manifestacije (klasa III i IV, ***Tabela 4****) rade laboratorijske analize (kompletna krvna slika, kreatin kinaza, elektroliti, CRP i laktat). O analizi i praćenju prokalcitonina, nema dovoljno podataka za pacijente sa celulitisom. Obično ga treba pratiti kod komplikovanih celulitisa, sa rizikom razvoja sistemskih manifestacija. U odnosu na kliničku klasifikaciju, u* ***Tabeli 7*** *prikazana je potrebna laboratorijska evaluacija pacijenata sa celulitisom.*

Hemokulture se rade kod komplikovanih celulitisa, kod kojih postoje znaci sistemkih

laboratory values do not definitely rule out cellulitis but may lower suspicion [28]. Laboratory tests are usually not necessary in patients with uncomplicated cellulitis (class I and II, **Table 4**).

Laboratory tests like complete blood count, creatine kinase, electrolytes, CRP, and lactate are typically recommended for patients with skin and soft tissue infections exhibiting systemic symptoms **(**class III and IV, **Table 4)**. There is limited data on procalcitonin monitoring in cellulitis cases. It is usually reserved for complicated cellulitis with a systemic risk. **Table 7** outlines the necessary laboratory evaluation of cellulitis cases based on clinical classification.

Blood cultures are indicated for complicated cellulitis cases with signs of systemic

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simptoma. Mogu se raditi eventualno kod imunokompromitovanih pacijenata (malignitet, neutropenija, hemioterapija…). Očekuje se da su pozitivne u manje od 10% slučajeva [1].

Terapija celulitisa

Budući da se etiološki faktor često ne otkrije, većinom se terapija zasniva na empirijskom iskustvu. Nekomplikovani celulitisi obično zahtevaju samo oralnu primenu antibiotika.

Ne postoje jasno definisani vodiči. Terapija nije standardizovana. Kako je većina nekomplikovanih celulitisa uzrokovana beta hemolitičkim streptokokom, blaži oblici se tretiraju penicilinskim peroralnim preparatima (amoksicilin). Iako su penicilinski preparati više decenija u širokoj upotrebi, streptokok grupe A i dalje je osetljiv na ovu grupu antibiotika, te se i dalje preporučuje. Ukoliko nakon 24−48 h, odnosno 48−72 h ne dođe do inicijalnog poboljšanja, ili pak dolazi do progresije i pojave udruženih simptoma, pacijenta je potrebno prevesti na parenteralnu terapiju [1, 6, 9]. Treba znati da, zbog upotrebe antibiotika širokog spektra, inicijalno može doći do izraženijeg eritema i edema, kao i febrilnosti, a koja se javlja zbog dejstva antibiotika, i bržeg uništavanja patogena i oslobađanja njihovih toksina i enzima. To ne treba shvatiti kao neadekvatan terapijskii odgovor.

Pojedini lekari empirijski, a kako bi pokrili i stafilokok osetljiv na meticilin − MSSA (engl. Methicillin susceptibile Staphylococcus aureus, MSSA), u terapiju uključe penicillin sa klavulonskom kiselinom, cefalosporine, klindamicin (iako je poslednjih godina zabeležena rezistencija na klindamicin i stafilokoka i streptokoka) [1]. Antibiotici koji bi pokrili MRSA kao što su doksiciklin ili trimetroprim sulfametoksazol po pravilu se ne koriste u terapiji blagog, nekomplikovanog celulitisa [1, 2].

Na osnovu SIRS kriterijuma, gde je blagi celulitis okarakterisan bez znakova sistemske infekcije, umeren celulitis koji sadrži jedan ili dva od četiri SIRS kriterijuma i teška forma celulitisa dva i više SIRS kriterijuma, zasniva se i izbor terapije i predloženi su terapijski algoritmi [9]. Umereni i teški celulitisi se uglavnom leče parenteralnom antibiotskom terapijom.

Pacijentima u hospitalnim uslovima sa umerenim i teškim formama celulitisa, posebno infekcije S. aureusom, treba pretpostaviti da su u pitanju rezistentni sojevi, s obzirom na visoku prevalenciju CA MRSA i dati antibiotike

symptoms or in immunocompromised individuals (malignancy, neutropenia, chemotherapy). Positive results are anticipated in less than 10% of cases [1].

Treatment for cellulitis

Cellulitis treatment is largely empirical due to the often unidentified causative agent. Uncomplicated cellulitis typically requires only oral administration of antibiotics.

There are no universally standardized guidelines for cellulitis therapy. Given that beta-hemolytic streptococcus is a common cause of uncomplicated cellulitis, milder cases are treated with oral penicillin preparations (amoxicillin). Despite their long use, prenicillin remains effective against group A streptococcus and is still recommended as first-line therapy. If there is no improvement within 24-48 hours or symptoms worsen, the patient should be switched to parenteral therapy [1, 6, 9]. It is important to note that broad-spectrum antibiotics can initially exacerbate symptoms like erythema, edema, and fever due to rapid bacterial destruction and toxin release, which should not be mistaken for inadequate therapeutic response.

Some physicians empirically add penicillin with clavulanic acid, cephalosporins, or clindamycin to cover methicillin-susceptible Staphylococcus aureus (MSSA), although resistance to clindamycin by staphylococci and streptococci has been observed recently [1]. Antibiotics like doxycycline or trimethoprim-sulfamethoxazole, which target MRSA, are not typically used for mild, uncomplicated cellulitis [1, 2].

Therapeutic choices are guided by the SIRS criteria, where mild cellulitis lacks signs of systemic infection, moderate cellulitis meets 1 or 2 SIRS criteria, and severe cellulitis meets 2 or more SIRS criteria [9]. Moderate and severe cellulitis are usually treated with parenteral antibiotics.

In hospital settings, especially for moderate to severe cellulitis infections involving S. aureus, assume involvement of resistant strains like CA-MRSA, and administer antibiotics effective against these strains (such as vancomycin or linezolid) [14].

The IDSA recommends starting with oral antibiotics for uncomplicated cellulitis based on suspected etiology [9]. Excessive use of broad-spectrum antibiotics could lead to resistance and adverse effects. Studies have

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Tabela 6. *Laboratorijska i dopunska ispitivanja kod pacijenata sa celulitisom*
Table 6. Laboratory and ancillary tests in patients with cellulitis

Laboratorijske analize/Laboratory tests	
KKS, rutinske biohemijske analize, CRP/ESR, CBC, routine biochemical analyses, CRP	*Ubrzana sedimentacija, leukocitoza, povišen CRP* Accelerated sedimentation rate, leukocytosis, elevated CRP
Kreatin kinaza Creatine kinase	*Može biti od pomoći da se utvrdi ili ne evl. zahvaćenost mišića (koji se viđa kod nekrotišućeg fasciitisa i bakterijskog miozitisa).*/May be helpful to determining muscle involvement (seen in necrotizing fasciitis and bacterial myositis). *Često povišena kod infekcije Vibrio vulnificus* Often elevated in Vibrio vulnificus infection
Laktat Lactate	*Povišene vrednosti ukazuju na sniženu perfuziju i/ ili moguću nekrozu tkiva.* Elevated levels indicate reduced tissue/perfusion and/or possible tissue necrosis.
Dijagnostičke procedure/Diagnostic procedures	
Rentgen/X-ray	*Prisustvo gasa (nekrotišuća infekcija)*/The presence of gas (necrotizing infection)
Ultrazvuk Ultrasound	*Procedura izbora ako se sumnja na prisustvo apscesa.* Procedure of choice if abscess is suspected.
Kompjuterizovana tomografija Computed tomography	*Moguća uloga u otkrivanju nekrozantne infekcije (gas u mekom tkivu, zadebljanje fascije i duboki apscesi)*/Possible role in detecting necrotizing infection (gas in soft tissue, fascial thickening and deep abscesses)
Magnetna rezonanca Magnetic resonance imaging	*Moguća uloga u otkrivanju nekrozantne infekcije ili osteomijelitisa (zahvaćenost duboke fascije, gas, kolekcije tečnosti)*/Possible role in the detection of necrotizing infection or osteomyelitis (deep fascia involvement, gas, fluid collections)
Bakteriološka dijagnostika/Bacteriological diagnostics	
Bakteriološki bris postojeće bule Bacterial swab of the existing bulla	*Pouzdan, lako se izvodi.* Reliable, easy to perform.
Hemokultura Blood culture	*Od malog značaja, evl. kod hospitalizovanih pacijenata.* Of little importance, possibly in hospitalized patients.
Bris postojeće rane/ulceracije Swab of existing wounds/ulcerations	*Od značaja ali ako je pravilno uzet (debridirani ulkus, uzorak se uzima kiretiranjem ili biopsijom baze ulceracije).*/Significant if properly taken (debrided ulcer, sample taken by curettage or biopsy of the base of the ulceration).
Aspiracija sadržaja (igla) i/ ili kultura bioptata/Aspiration of content (needle) and/or culture of biopsy	*Razmotriti kod imunokompromitovanih pacijenata i kod onih gde nema terapijskog odgovora (empirijska terapija). Kultura bioptata – potencijalno ožiljavanje* Consider in immunocompromised patients and in those with no therapeutic response (empirical therapy). Culture of biopsy – potential scaring
Kultura sadržaja (dreniranog) Culture of content (drained)	*Rizik od kontaminacije. Prethodni debridman.* Risk of contamination. Previous debridement.

SE – sedimentacija, CRP – C-reaktivni protein, KKS – kompletna krvna slika
ESR – sedimentation, CRP – C-reactive protein, CBC – complete blood count

koji će delovati na ove sojeve (vankomicin, linezolid) [14].

Preporuka IDSA jeste započinjanje tretmana oralnim antibioticima za nekomplikovane celulitise pretpostavljajući etiološki faktor (i na osnovu kliničke prezentacije i iskustva) [9]. Preterana shown similar outcomes for uncomplicated cellulitis treated with oral cephalexin alone (covering streptococci and MSSA) compared to combination therapy with cephalexin and trimethoprim-sulfamethoxazole for potential MRSA [9, 28]. Empirical treatment for CA-

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Tabela 7. *Laboratorijska evaluacija pacijenata sa celulitisom*
Table 7. Laboratory evaluation of patients with cellulitis

Pacijenti klasa II, III i IV Patients of Class II, III and IV	*Samo u pojedinačnim slučajevima* Only in individual cases
	Hemokultura (samo pacijenti klasa III ili IV)/Blood culture (class III or IV patients only)
SE/ESR *CRP*/CRP *KKS*/CBC *Urea*/Urea *Elektroliti*/Electrolytes	*ASTO ili Antideoxyribonuclease-B titar (AND B, serološki marker, kvantitativna količina antistreptokonih antitela)*/ASO or Antideoxyribonuclease-B titer (AND-B, serological marker, quantitative amount of anti-streptococcal antibodies)
	Biopsija promene (isključivanje drugih inflamatornih bolesti neifektivne etiologije) Biopsy of the lesion (to exclude other inflammatory diseases of non-infectious etiology)

SE – sedimentacija, CRP – C-reaktivni protein, KKS – kompletna krvna slika, ASTO – antistreptolizinski test
ESR – sedimentation, CRP – C-reactive protein, CBC – complete blood count, ASO – antistreptolysin test

upotreba antibiotika (inicijalno pokrivanje više mogućih sojeva) može dovesti do stvaranja rezistentnih sojeva a i neželjenih efekata lečenja. Rezultati različitih istraživanja su pokazali da su vrlo slični ishodi kod pacijenata sa nekomplikovanim celulitisom lečenih samo oralnim cefaleksinom (pokriva spektar streptokoka i MSSA) u odnosu na one lečene kombinacijom cefaleksina i trimetoprim sulfametoksazola (u cilju pokrivanja evl. MRSA) [9, 28], odnosno autori su stava da empirijski davanje antibiotika kod blagog, nekomplikovanog celulitisa za CA MRSA ne utiče na krajnji ishod.

Umerene i teške forme celulitisa leče se parenteralnom terapijom, za teške forme se savetuju antibiotici širokog spektra kao što su vankomicin i piperacilin tazobaktam [9].

Uzimajući u obzir da je većina purulentnih celulitisa uzrokovana Staphylococcus aureusom, izbor antibiotika zavisi od sumnje na MRSA. Terapiju je potrebno odmah empirijski započeti, budući da se bakteriološke kulture čekaju do pet dana [1, 2, 25].

Treba naglasiti da se preporuke za antibiotsku terapiju razlikuju u odnosu na ispitivanu populaciju, a i u odnosu na dostupne antibiotike. Rezervni antibiotici se preporučuju u slučajevima komplikovanih celulitisa, odnosno pojave sistemskih simptoma, bakterijemije i sepse.

Preporuke za terapiju IDSA su prikazane u ***Tabeli 8.***

Kada se odlučiti za zamenu terapije (parenteralna u oralnu)

Malobrojna istraživanja i velika klinička praksa ukazuju da kod većine pacijenata sa nekomplikovanim celulitisom, moguće prevesti pacijenta na oralnu terapiju nakon 3-4 dana [29]. Potre-

MRSA in mild, uncomplicated cellulitis does significantly impact outcomes.

Moderate and severe cellulitis requires parenteral therapy, with broad-spectrum antibiotics like vancomycin and piperacillin-tazobactam recommended for severe cases [9].

Given that Staphylococcus aureus is a common cause of purulent cellulitis, initial antibiotic choice depends on MRSA suspicion, with immediate empirical therapy as bacterial cultures can take up to 5 days [1, 2, 25].

It should be emphasized that antibiotic therapy recommendations should be tailored to specific populations and available antibiotic options. Reserve antibiotics are advised for complicated cellulitis with systemic symptoms, bacteremia, and sepsis.

IDSA therapy recommendations are presented in **Table 8.**

Deciding when to transition from parenteral to oral therapy

While research is limited, extensive clinical experience suggests that for most patients with uncomplicated cellulitis, transitioning to oral therapy is feasible after 3-4 days [29]. The duration required depends on the patient's response to previous therapy, including clinical improvement, laboratory tests, systemic symptoms, and bacteriological culture findings. The duration of treatment also varies based on therapeutic response, typically ranging from 5-7 days for uncomplicated cases, 7-10 days for complicated cases, and up to 14 days for immunocompromised patients [2, 9, 22, 24].

In addition to antibiotics, some authors recommend non-steroidal anti-inflammatory

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ban period zavisi od odgovora pacijenta na prethodnu terapiju – kliničkog nalaza, laboratorijskih analiza i sistemskih simptoma, bakteriološke kulture. Što se tiče same dužine lečenja, i ona zavisi od terapijskog odgovora. Za nekomplikovane celulitise, obično je dovoljno 5–7 dana, za komplikovane 7–10 dana, za imunokompromitovane pacijente do 14 dana [2, 9, 22, 24].

Pored antibiotika pojedini autori savetuju i nesteroidne antiinflamatorne lekove [2, 30], (ibuprofen 400 mg na 4–6 sati) u cilju bržeg smanjenja inflamacije i bržeg terapijskog odgovora, dok prema drugim autorima se ne savetuje [31] jer nisu uočene razlike kod pacijenata sa NSAIL ili bez na tok celulitisa. Treba imati na umu da upotreba NSAIL može da zamaskira simptome nekrozantne infekcije. Slično je i sa sistemskom kortikosteroidnom terapijom, kao antiinflamatornim agensom, iako ima jako malo podataka [32].

Komplikacije

Nelečeni ili neadekvatno lečeni celulitis može dovesti do brojnih komplikacija – bakterijemija, septikemija i sepsa, i bakterijski endokarditis ukoliko se bakterijemija/septikemija ne leči. Kao krajnji ishod nelečenog/neadekvatno lečenog celulitisa može doći do letalnog ishoda.

Druge komplikacije jesu mogući recidivi celulitisa, u cilju njegove prevencije potrebno je sprovoditi adekvatnu negu i lečenje, posebno lokalnih faktora rizika ***(Tabela 2)****.*

Prema definiciji, prethodna epizoda celulitisa predstavlja faktor rizika razvoja recidiva, čak je prema istraživanjima jedne grupe autora bila jedini značajni prognostički faktor recidiva [12].

*Pored recidiva, značajna komplikacija jesu rezistencija na antibiotike odnosno odsustvo terapijskog odgovora. Različiti su podaci – odsustvo terapijskog odgovora beleži se u 0–29,5% slučajeva ali ovolike varijacije su uzrok neadekvatno definisanih kriterijuma [33, 34]. Isto se beleže različite učestalosti odsustva terapijskog odgovora u odnosu na put ordiniranja antibiotika (oralna ili parenteralna terapija) [33]. Takođe, neadekvatna antibiotska terapija će u najmanju ruku dovesti do produžetka dužine lečenja [34]. Upravo zbog nepostojanja jasno definisanih terapijskih vodiča i razlike u ordiniranju antibiotika u inicijalnoj fazi kod blagih i umerenih formi celulitisa, dolazi do česte potrebe za zamenom terapije, razlike u rezultatima među istraživačima [35]. U zavisnosti od ispitivane studije, kod bolničkih pacijenata sa celulitisom zabeležen je i smrtni ishod od 2,5% do 5% [36]. Podadrugs (NSAIDs) [2, 30] (such as ibuprofen 400 mg every 4-6 hours) to expedite inflammation reduction and achieve a quicker therapeutic response, while others do not endorse this practice [31] as no differences have been observed in the course of cellulitis with or without NSAIDs. It should be noted that NSAIDs may mask the symptoms of necrotizing infection. Similarly, systemic corticosteroid therapy as an anti-inflammatory agent has limited supporting data [32].

Complications

Untreated or inadequately treated cellulitis can lead to various serious complications, including bacteremia, septicemia, sepsis, and bacterial endocarditis if bacteremia or septicemia remains untreated. Ultimately, untreated or inadequately treated cellulitis can result in a fatal outcome. Recurrence of cellulitis is another significant complication that can be prevented recurrence with appropriate care and treatment, particularly addressing local risk factors **(Table 2).**

A prior episode of cellulitis is a significant risk factor for recurrence according to one group of researchers [12]. In addition to recurrences, a critical complication is the development of antibiotic resistance or failure to respond to treatment. Reported rates of treatment failure range from 0-29.5%, with variations attributed to ambiguously defined criteria [33, 34]. The frequency of treatment failure may also vary based on the route of antibiotic administration (oral or parenteral therapy) [33]. Inadequate antibiotic therapy can lead to prolonged treatment duration at minimum [34].

The lack of clearly defined therapeutic guidelines and variability in antibiotic prescriptions for mild and moderate cellulitis often necessitate therapy adjustments, resulting in differences in outcomes among studies [35]. Hospitalized patients with cellulitis, particularly those with moderate and severe forms, have been reported to have a mortality rate of 2.5% -5% [36]. These outcomes are influenced significantly by comorbidities, patient age, and complications arising from colonization with hospital-acquired strains such as MRSA and Pseudomonas aeruginosa.

Prophylaxis

It is crucial to distinguish recurrent cellulitis from persistent infection (which is not

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Tabela 8. *Preporuke antibiotske terapije za cellulitis, IDSA* (Rrapi, 2021)
Table 8. Recommendations for antibiotic therapy for cellulitis, IDSA *(Rrapy, 2021)*

Uzročnik/Pathogen		*Antibiotik*/Antibiotic	*Doza*/Dose
Streptococcus i *MSSA* Streptococcus and MSSA	*Oralno* Oral	*Amoksicilin-klavulonska kiselina* Amoxicillin-clavulanic acid	2 x 875 mg
		Celaleksin/Cephalexin	4 x 500 mg
		Dicloxacillin/Dicloxacillin	250-500 mg, 4 x *dn*/daily
		Penicilin Vk/Penicillin VK	250-500 mg, 4 x *dn*/daily
	Intravenski Intravenous	*Cefazolin*/Cefazolin	3 x 1 *gr*/g
		Ceftriakson/Ceftriaxone	1-2 gr *dnevno*/daily
		Imipenem/Imipenem	500 mg, 4 x *dn*/daily
		Meropenem/Meropenem	3 x 1 *gr*/g
		Nafcillin Ili oksacilin/Nafcillin or Oxacillin	1-2 *gr na*/every 4 h
		Penicilin G/Penicillin G	2-4 M IU
		Piperacilin Tazobaktam Piperacilin Tazobactam	3,375 *gr*/g, 4 x *dn*/daily
MRSA MRSA	*Oralno* Oral	*Klindamicin*/Clindamycin	300-450 mg, 4 x *dn*/daily
		Doksiciklin/Doxycycline	2 x 100 mg
		Linezolid/Linezolid	2 x 600 mg
		Trimethoprim sulfametoksazol Trimethoprim sulfamethoxazole	1-2 *tbl.*/tablets, 2 x *dn*/daily
	Intravenski Intravenous	*Klindamicin*/Clindamycin	600 mg, 3 x *dn*/daily
		Linezolid/Linezolid	2 x 600 mg
		Tigeciklin/Tigecycline	100 mg, *potom*/then 50 mg, 2 x *dn*/daily
		Vankomicin/Vancomycin	15 mg/kg, 2 x *dn*/daily

MMSA – stafilokok osetljiv na meticilin; MRSA – stafilokok rezistentan na meticilin; dn – dnevno: M – million; IU – internacionalna jedinica; tbl – tableta
MSSA – methicillin-sensitive staphylococcus aureus; MRSA – methicillin-resistant staphylococcus aureus; M – million; IU – International Unit

ci se uglavnom odnose na pacijente sa umerenim i teškim formama celulitisa, koji su hospitalno lečeni. Komorbiditeti, uzrast pacijenta, komplikacije uzrokovane kolonizacijom bolničkim sojevima kao što su MRSA i Pseudomonas aeruginosa značajno utiču na loš tok bolesti.

Profilaksa

Potrebno je svakako razlikovati recidivantni celulitis od perzistentne infekcije (koja nije izlečena u potpunosti, recidiva i reinfekcije (istim odnosno drugim uzročnikom). Skoro pola veka se sprovodi antibiotska profilaksa kod recidivantnih formi [1, 2].

Kada i kome davati antibiotsku profilaksu? Različite su definicije broja recidiva i različite completely cured), relapses, and reinfections (by the same or different causative agent). Antibiotic prophylaxis has been employed for nearly half a century in cases of recurrent cellulitis [1, 2].

When and for whom should antibiotic prophylaxis be prescribed? Definitions of the number of recurrences and prophylactic treatment regimens vary depending on the population studied. Prophylaxis is strongly recommended for patients with risk factors and multiple recurrences (3-4 annually).

Despite its longstanding use, intramuscular penicillin (and penicillin preparations) are still the first-line antibiotics recommended for recurrent cellulitis prophylaxis [1, 37, 38].

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terapijske šeme profilakse, koje se razlikuju u odnosu na ispitivanu populaciju. Profilaksa se svakako preporučuje kod pacijenata sa faktorima rizika, sa više recidiva (3-4 godišnje).

Iako je u širokoj upotrebi, penicillin i. m. (i penicilinski preparati) i dalje su prvi preporučeni antibiotik u terapiji recidiva (profilaksa) [1, 37, 38]. Rezultati metaanaliza ukazuju da je rizik razvoja nove epizode celulitisa bio smanjen za 69%, kao i da je dužina interval između dve epizode celulitisa produžena [1, 23]. Neadekvatan odgovor na antibiotsku profilaksu je zabeležen kod gojaznih pacijenata, onih sa hroničnim limfedemom i kod pacijenata sa više recidiva [38]. Kod preosetljivosti na penicilin, savetuje se upotreba eritromicina, eventualno. klaritromicina ili doksiciklina [23]. Klindamicin se sve

Meta-analyses have demonstrated a 69% reduction in the risk of developing a new episode of cellulitis with prolonged intervals between episodes [1, 23]. Inadequate response to antibiotic prophylaxis has been observed in obese patients, those with chronic lymphedema, and individuals with multiple recurrences [38]. In cases of penicillin allergy, erythromycin, clarithromycin, or doxycycline are recommended alternatives [23]. Clindamycin is less favored for both therapeutic and prophylactic use due to the risk of developing pseudomembranous colitis. Benzathine penicillin is widely employed for prophylaxis at intervals of 2-4 weeks, with doses ranging from 1.2-2.4 million IU [23]. For patients suspected of being infected with Staphylococ-

Tabela 9. *Predložena antibiotska profilaksa kod recidivantnog celulitisa* (Ong, 2022)
Table 9. Proposed antibiotic prophylaxis for recurrent cellulitis (Ong, 2022)

Izvor Source	*Definicija recidivantnog celulitisa*/Definition of recurrent cellulitis	*Profilaksa* Prophylaxis
Američko udruženje za infektivne bolesti (2014) Infectious Diseases Society of America (2014)	*3-4 epizode godišnje* 3-4 episodes per year	*Penicilin ili eritromicin per os, 2 x dnevno tokom Ili benzathine penicilin G, na 2 – 4 nedelje (doza nije definisana)* Oral penicillin or erythromycin, twice daily or benzathine penicillin G, every 2–4 weeks (dose not defined)
Britansko udruženje za limfologiju (2016) British Lymphology Society (2016)	*2 i više epizode godišnje* 2 or more episodes per year	*Eritromicin, 2 x 250 mg ili klaritormicin 250 mg dnevno (do 2 godine)*/Erythromycin, 2 x 250 mg or clarithromycin 250 mg daily (up to 2 years) *Razmotriti i klindamicin 150 mg dnevno ili cefaleksin 125 mg dnevno ili doksiciklin 50 mg dnevno*/Consider also clindamycin 150 mg daily or cephalexin 125 mg daily or doxycycline 50 mg daily
Udruženje Južne Koreje za SSTI (2017)/South Korea's guidelines for SSTI (2017)	*3-4 epizode godišnje* 3-4 episodes per year	*Amoksicilin per os ili benzatin penicilin G, i.m. (doza nije definisana)*/Oral amoxicillin or benzathine penicillin G, IM (dose not defined
Internacionalo udruženje za limfologiju: konsenzus za dijagnozu i lečenje perifernog limfedema (2020) International Society of Lymphology: Consensus for the evaluation and management of peripheral lymphedema (2020)	*Pacijenti sa limfedemom I recidivima celulitisa uprkos adekvatnoj kompresivnoj terapiji* Patients with lymphedema and cellulitis recurrence despite adequate compression therapy	*Penicilin profilaktički (doza nije definisana)* Penicillin prophylaxis (dose not defined)
Australijski terapijski vodič (2021)/Australian Therapeutic Guide (2021)	*Nije definisano* Not defined	*Fenoksimetilpenicilin 250mg, 2x dnevno do 6 meseci, potom praćenje*/Phenoxymethylpenicillin 250mg, twice daily for up to 6 months, then monitoring

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manje savetuje (kako u terapijske, tako i u profilaktičke svrhe zbog čestog razvoja pseudomembranoznog kolitisa). Benzatin penicilin je u širokoj upotrebi, preporučuje se u intervalima 2−4 nedelje, 1,2−2,4 miliona IU [23].

Kod pacijenata kod kojih postoji sumnja da je uzročnik stafilokok, profilaska se sprovodi peroralnim cefalosporinima (I, II i III generacije), kao i trimethoprim sulfametoksazol [9, 25].

Predložena antibiotska profilaksa različitih udruženja prikazana je u ***Tabeli 9.***

Zaključak

Započeti terapiju empirijski, uvek težiti da to budu antibiotici koji deluju na beta hemolitički streptokok i MSSA, kao najčešće uzročnike celulitisa. Lečenju treba pristupiti individualno, uzimajući u obzir lokalne i sistemske faktore rizika, uz detaljnu anamnezu i klinički nalaz. Potrebno je jasno definisati kriterijume − pogoršanje bolesti, odsustvo terapijskog odgovora u cilju adekvatnog ishoda lečenja. Ukoliko je potrebno sprovoditi laboratorijsku i drugu dopunsku dijagnostiku. Nekomplikovane celulitise treba lečiti ambulantno, započeti peroralnu antibiotsku terapiju. Pratiti SISR kriterijume; zamena antibiotika ukoliko je potrebno. Sprovoditi antibiotsku profilaksu kod pacijenata sa recidivima. Potrebno je sprovesti i istraživanje na teritoriji Republike Srbije u cilju eventualnog definisanja terapijskih vodiča.

cus, prophylaxis is conducted using oral cephalosporins (1st, 2nd, and 3rd generations) or trimethoprim-sulfamethoxazole [9, 25].

Table 9 displays proposed antibiotic prophylaxis regimens recommended by different associations**.**

Conclusion

When initiating empiric therapy for cellulitis, always prioritize antibiotics effective against beta-hemolytic streptococci and MSSA, which are the most common causative agents. Approach treatment on an individual basis, taking into account local and systemic risk factors, along with a thorough history and clinical examination. It is essential to clearly establish criteria for treatment response and disease worsening to ensure optimal treatment outcomes. If needed, perform laboratory and other diagnostic tests. For uncomplicated cellulitis, outpatient management with oral antibiotic therapy is appropriate. Monitor SIRS criteria closely and adjust antibiotics if necessary. Administer antibiotic prophylaxis to patients with recurrences. Additionally, conducting research within the Republic of Serbia may help in defining specific therapeutic guidelines.

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