NEKOMPLIKOVANE INFEKCIJE MOKRAĆNIH PUTEVA KOD STARIH OSOBA

UNCOMPLICATED URINARY TRACT INFECTIONS IN THE ELDERLY

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Sažetak

Zdrav urinarni trakt nije sterilna sredina već je nastanjen raznorodnim mikroorganizmima koji se menjaju shodno faktorima sredine i bolesnika. Stari bolesnici su predisponirani za nastanak infekcija mokraćnih puteva i asimptomatske bakteriurije, a razlikovanje ova dva stanja je otežano. Oni su specifični po nizu pitanja: patogenezi infekcije i uzročnicima, dijagnostičkim postupcima, primenjenoj terapiji i preventivnim merama. Od velike je važnosti pravilno tumačenje simptoma, uzorkovanje materijala za analizu i interpretacija rezultata. Pravilni postupci omogućavaju poštedu bolesnika od nesvrsishodnog lečenja i komplikacija antibiotske terapije, ali i smanjenu rezistenciju bakterijskih vrsta.

Ključne reči: infekcije mokraćnih puteva, stare osobe, terapija

Uvod

Infekcije mokraćnih puteva (*Urinary tract infections,* UTI) odgovorne su za oko 15,5% hospitalizacija zbog infektivnih bolesti kod osoba starijih od 65 godina (odmah posle upale pluća) i uzrok su smrti kod oko 6% bolesnika[1]. UTI se mogu podeliti, kao i kod mlađih osoba, na osnovu više kriterijuma: na osnovu lokacije (cistitis, pijelonefritis), tendencije ponavljanja (povremene, recidivirajuće), simptomatologije (asimptomatske, simptomatske) i na osnovu prisutne komplikacije (komplikovane i nekomplikovane). Kod osoba sa normalnim genitourinarnim traktom ove infekcije se nazivaju nekomplikovane UTI, dok strukturne i funkcionalne abnormalnosti urinarnog trakta dovode do komplikovanih UTI. Zlatni standard za dijagnozu UTI je nalaz patogena u urinu uz prisustvo simptoma od strane bolesnika. Međutim, granična vrednost bakteriurije nije jasno definisana niti standardizovana od strane mikrobioloških laboratorija. Mnoge laboratorije definišu vrednost od 10^5 CFU/mL (jedinice formiranja kolonija bakterija) kao graničnu, međutim na taj način je moguće propustiti neke infekcije, te se savetuje niža granična vrednost (10^3 CFU/mL). Prema kriterijumima Američkog udruženja za infektivne bolesti (*Infectious Disease Society of America,* IDSA), asimptomatska bakteriurija (*Asymptomatic Bacteriuria*, ASB) definiše se ukoliko bolesnici imaju u urinu ≥ 10^5 CFU/mL ili više od jedne bakterijske vrste u dva uzastopna uzorka urina kod žena i jednom uzorku kod muškaraca u odsustvu kliničkih znakova i simptoma karakterističnih za UTI[2].

Epidemiologija

Incidenca ASB raste sa godinama starosti i dostiže 20% kod osoba ženskog pola starijih od 80 godina. Kod zdravih muškaraca, ASB nije tipična pre 60. godine, dok je incidenca od 5 do 10% kod muškaraca starijih od 80 godina[3]. Simptomatske infekcije nisu u direktnoj korelaciji sa ASB kao ni incidentna bubrežna slabost i hipertenzija[2]. Starije žene imaju veću učestalost UTI u odnosu na muškarce, ali ta razlika nije toliko izražena kao kod mlađih osoba.

Osobe koje su smeštene u ustanovama za zbrinjavanje starih lica imaju višu incidencu ASB (25-50% kod žena i 15-40% kod muškaraca) u odnosu na ambulantno lečene stare osobe[2]. Bakteriurija je dinamična pojava: kod osoba sa dijagnostikovanom ASB jedna trećina će u periodu od 3 do 6 meseci imati negativnu urinokulturu, dok će trećina bolesnika sa inicijalno negativnom kulturom razviti bakteriuriju. ASB kod osoba koje se nalaze u smeštajnim ustanovama nije udružena sa lošim preživljavanjem, ali je često uzrok nepotrebne upotrebe antibiotika što vodi povećanoj incidenci infekcija uzrokovanih *Clostridium difficile* i drugim negativnim efektima antibiotske terapije.

Simptomatska UTI jeste druga infekcija po učestalosti svih infekcija kod ovih osoba sa podacima o učestalosti od 0,5 na 1.000 bolničkih dana[4]. Kod starih osoba koje su u stanju da daju validne podatke o svojim simptomima, razlikovanje UTI od ASB je relativno lako. Međutim, kod onih koji imaju kognitivno oštećenje, ASB je teško razlikovati od UTI. Oko 45-56% svih bakterijemija kod osoba iz smeštajnih

ustanova se objašnjava urinarnim poreklom, ali se to u najvećoj meri odnosi na osobe sa trajnim kateterom.

Hospitalizacije usled akutnog pijelonefritisa su češće sa godinama starosti, a rekurentne UTI su češće uglavnom kod osoba sa komplikovanim infekcijama. Mortalitet usled UTI je neuobičajen[5]. Analiza 270 osoba prosečne starosti 83,7 godina koje su hospitalizovane zbog UTI (od toga 14% iz doma za smeštaj starih lica), pokazala je da je bolnički mortalitet bio 8,9%, a faktori rizika za mortalitet su bili neadekvatna antimikrobna terapija, APACHE II na prijemu ≥ 15, demencija i solidne neoplazme[6]. Izraelska studija koja je obuhvatila 191 osobu (od toga 35% iz smeštajnih ustanova) starosti od 75 do 105 godina, a koje su hospitalizovane u gerijatrijskoj bolnici, pokazala je da je intrahospitalni mortalitet bio 33%, a faktori rizika su bili hospitalizacija (duža od 20 dana), demencija i komorbiditet, a ne pol i starosno doba[7]. Očigledno, mortalitet bolesnika sa UTI zavisi od više faktora.

Patogeneza

Kod nehospitalizovanih starijih osoba, faktori rizika su slični za ASB i UTI i uključuju menopauzu, hipertrofiju prostate, dijabetes melitus, funkcionalno i kognitivno oštećenje, inkontinenciju.

Kod žena u postmenopauzi rekurentne infekcije su udružene sa učestalim infekcijama u mladosti i nesekretovanjem antigena krvnih grupa[8]. Žene sa dijabetesom, starosti 55-75 godina imaju duplo veću učestalost UTI u odnosu na žene bez dijabetesa[9]. Usled nedostatka estrogena, u postmenopauznom periodu smanjuje se kolonizacija sa *Lactobacilli spp* koji održavaju kiseli pH vagine. Viši pH omogućava kolonizaciju uropatogenima (*E. Coli i Enterococcus spp*) što povećava incidencu UTI kod žena u postmenopauzi[10]. Smatra se da terapija sa nadomeštanjem estrogena može oporaviti vaginalnu floru i pH, mada povezanost infekcija i estrogena nije u potpunosti razjašnjena.

Hipertrofija prostate zauzima posebno mesto kod patogeneze UTI kod starijih muškaraca. Ona uzrokuje opstrukciju i turbulentni protok urina što olakšava prodor bakterija u zid mokraćne bešike. Bakterije mogu ostati u prostati trajno zbog teškog prodora antibiotika u žlezdu. Inkontinencija pre pogoduje bakteriuriji, ali može biti uzrok infekcija kod starijih muškaraca i žena. Rezidualna zapremina urina je čest nalaz kod ženskih osoba između 62. i 90. godine[11]. Kod muškaraca, medijane starosti od 62 godine, prosečna rezidualna zapremina urina je bila 257 mL u slučaju pozitivne bakteriurije i 133 mL bez bakteriurije[12]. Međutim, prospektivna studija nije potvrdila korelaciju između UTI i rezidualne zapremine urina kod žena starosti 55-75 godina što ukazuje na kompleksnu povezanost ove dva klinička stanja[13].

Poseban osvrt zaslužuju veoma stare osobe, sa više od 80 godina. Švedska studija je potvrdila da su faktori rizika bakteriurije kod veoma starih žena nepokretnost, inkontinencija i terapija estrogenima, a kod muškaraca bolesti prostate, podatak o moždanom udaru i zavisnost od drugog lica[3]. Podaci iz Holandije za starije osobe (od 80 do 90 godina) pokazali su kao faktore rizika kognitivno oštećenje, nesamostalnost u svakodnevnom životu i inkontinenciju mokraće. Pol i prebivalište nisu bili faktori rizika za nastanak UTI[14].

Kod osoba koje su smeštene u ustanovama za zbrinjavanje starih lica, ASB je udružena sa poremećajem u mokrenju usled neuroloških oboljenja (cerebrovaskularne bolesti, Parkinsonova bolest, demencija) koje su i razlog za smeštaj osobe u specijalizovanu ustanovu[15]. Zapremina rezidualne mokraće ne korelira sa nastankom simptomatske ili asimptomatske infekcije. Muškarci koji koriste eksterni urinarni kateter u obliku kondoma imaju veću učestalost bakteriurije i simptomatske infekcije u odnosu na inkontinentne muškarce koji ih ne koriste[16].

Izazivači infekcije

U slučaju simptomatskih infekcija, najčešće se kao uzročnici izoluju *E. coli*, ali i *Enterobacteriaceae*, *Enterococcus spp* i *Pseudomonas aeruginosa*. Koagulaza negativne stafilokoke se mogu izolovati kod asimptomatskih infekcija kod muškaraca. Kandida se može otkriti kod osoba sa dodatnim faktorima rizika kao što je dijabetes, urološka pomagala i primena antibiotika širokog spektra. Kod starih izolati su češće multirezistentni na antibiotike u odnosu na mlađe osobe što se dovodi u vezu sa prethodnom (zlo)upotrebom antibiotika i urološkim procedurama kod bolesnika sa komplikovanim infekcijama. Španska studija potvrdila je da su kod ambulantnih bolesnika sa urinarnom infekcijom godine starosti bile značajno udružene sa izolovanjem *E. coli* koja je rezistentna na fluorohinolone, a nezavisni faktor rizika ove rezistencije je bila upotreba antibiotika tokom prethodnog meseca[17]. Slično, podaci iz američke studije su pokazali tigeciklin neosetljivu, karbapenem rezistentnu *Klebsiella pneumoniae,* a faktor rizika je bila hospitalizacija iz domova za smeštaj starih lica[18]. Takođe, *E. coli* je najčešći uzročnik infekcija u domovima za smeštaj starih lica, ali je zastupljenost drugih enterobakterija češća nego kod ambulantnih bolesnika. Kod osoba u ustanovama češća je i polimikrobna infekcija (10-25%), čak i bez prisustva trajnog katetera, a češća je i rezistencija na antimikrobnu terapiju, što otežava lečenje.

Dijagnoza

Klinička dijagnoza se bazira na spektru simptoma, počevši od iritacije donjih mokraćnih puteva do septičnog šoka. Kod ambulantnih bolesnika se najčešće javlja učestalo mokrenje, dizurija, nokturija, suprapubični bol i ponekad hematurija. Kod simptoma pijelonefritisa nastaje i bol u kostovertebralnoj regiji, groznica i povišena temperatura, sa ili bez dizurije. Međutim, kliničku dijagnozu je teže postaviti kod osoba koje su smeštene u ustanovama za stara lica

usled otežane komunikacije i prisustva simptoma hroničnih bolesti. Kliničko pogoršanje stanja bolesnika bez lokalizovanih genitourinarnih simptoma najverovatnije nije posledica UTI kod osoba sa bakteriurijom[16]. Međutim, netipični simptomi i promene u kliničkom statusu bolesnika, kao što su padovi, smanjena funkcionalnost i promena u mentalnom statusu se često pripisuju UTI kod starih. Promene u mirisu, boji i zamućenosti urina koreliraju sa bakteriurijom, ali su češće u vezi sa pogoršanjem inkontinencije ili sa dehidracijom, nego simptomatskom infekcijom, te nisu dovoljne za postavljanje dijagnoze UTI[18-20]. Prepoznavanje simptoma je veoma važno jer su oni osnovni kriterijum za započinjanje terapije kod sumnje na UTI: akutna dizurija ili visoka temperatura, akutna konfuzija ili groznica sa pogoršanjem jednog od genitourinarnih simptoma (hitno mokrenje, učestalo mokrenje, suprapubični bol, hematurija, bol u kostovertebralnom predelu, inkontinencija urina)[21, 22]. Na taj način se značajno smanjuje primena antibiotika u odnosu na standardni pristup. Tamo gde je dijagnoza nepouzdana, savetuje se praćenje bolesnika i, ukoliko se ne pojave lokalni simptomi u predelu genitourinarnog trakta, bolesnika bi trebalo lečiti pre kao stanje sepse nepoznatog uzroka, nego kao UTI[22].

Laboratorijska dijagnoza je neophodna i za definitivnu dijagnozu i za lečenje UTI kod starih, s obzirom na visok procenat rezistencije mikroorganizama[15]. Izuzetak čine zdrave žene koje u ambulantnim uslovima imaju ponavljane akutne cistitise kod kojih je obično kratkotrajna primena antibiotika efikasna. Međutim, i kod njih treba raditi urinokulturu ukoliko izostane željeni efekat na empirijsku terapiju, ako su simptomi atipični ili dođe do brzog povratka simptoma posle sprovedene terapije, što sve ukazuje na rezistentnog uzročnika.

Jedna od osnovnih prepreka u dijagnostici UTI jeste neophodnost pravilnog uzorkovanja urina za analizu u cilju prevencije kontaminacije uzorka. Kod žena koje nisu u stanju da prate uputstva, radi se jednokratna kateterizacija, a kod muškaraca se primenjuje čist kondom-kateter. Dijagnostički kriterijum podrazumeva nalaz više od 10^5 CFU/mL pojedinačnog mikroorganizma u uzorku urina. Kada se izoluje manji broj klica ili multipli mikroorganizmi, nalaz urinokulture se tumači u skladu sa kliničkim simptomima. Manji broj kolonija se sreće kod oko 10% zdravih žena u postmenopauzi sa akutnom nekomplikovanom UTI[13]. Takođe, kod UTI može da se izoluje manji broj kolonija ako učestalo mokrenje ometa inkubaciono vreme bakterija u bešici usled čestog pražnjenja. Zato je za muškarce dijagnoza UTI prisutna ako se izoluju patogeni u broju 10^3 CFU/mL ili više od toga u pravilno uzetom uzorku urina (sem u slučaju postojanja trajnog urinarnog katetera kada je kriterijum 10^5 CFU/mL)[15]. Ako se sumnja na pijelonefritis, nalaz pojedinačnog mikroorganizma u broju 10^4 CFU/mL ili iznad je preporučeni dijagnostički kriterijum. Nalaz mikroorganizama u broju od 10^2 CFU/mL ili iznad toga je indikativan za infekciju ukoliko se uzorak dobije jednokratnom kateterizacijom mokraćne bešike[23].

Piurija je nespecifičan laboratorijski nalaz kod starih[15]. Često je pozitivna i bez bakteriurije, a kod osoba sa bakteriurijom ne razdvaja simptomatsku UTI od ASB. Sa druge strane, odsustvo piurije ima visoku negativnu prediktivnu vrednost za isključivanje UTI[24]. Kod sumnje na UTI, kod osoba u domovima za starija lica treba prvo ispitati prisustvo piurije, pa ako je nalaz negativan ne treba raditi urinokulturu[24]. Kod žena starijih od 80 godina povišena vrednost leukocitne esteraze, interleukina IL-8 i IL-6 može da ukaže na razliku između ASB i akutnog cistitisa. Ipak, određivanje ovih biomarkera nema veći klinički značaj[25]. U slučaju sumnje na urosepsu, nalaz istih bakterija u krvi i u urinu ukazuje na poreklo infekcije.

Antimikrobna terapija

Kod starijih osoba se ne preporučuje lečenje ASB s obzirom na to da se time ne smanjuje nastanak i učestalost narednih UTI, niti otklanjaju simptomi, a može dovesti do pojave neželjenih efekata terapije[2]. Stoga i skrining starih osoba za ASB nije indikovan.

U odabiru antimikrobne terapije treba se rukovoditi efikasnošću leka, tolerisanjem od strane bolesnika, kliničkom prezentacijom bolesti, bubrežnom funkcijom, potrebom za parenteralnim putevima primene i cenom lečenja. Ukoliko to klinička slika dozvoljava, savetuje se čekanje rezultata urinokulture. Iako se sa godinama smanjuje klirens kreatinina, nije indikovano smanjenje doze lekova samo na osnovu godina bolesnika. Prva linija peroralne terapije za akutni

Tabela 1. Izbor i doziranje antimikrobnih lekova u terapiji infekcije mokraćnih puteva kod starih osoba sa normalnom funkcijom bubrega

	Peroralna terapija	Parenteralna terapija
Prva linija	Trimetoprim/Sulfametoksazol 2 x 160/800 mg Nitrofurantoin 2 x 100 mg Ciprofloksacin 2 x 250-500 mg Norfloksacin 2 x 400 mg Levofloksacin 1 x 250-500 mg	Ampicilin 4 x 500 mg ± gentamicin ili tobramicin 5-7 mg/kg/24 h Ceftriakson 1-2 g/24 h Cefotaksim 3 x 1 g Ciprofloksacin 2 x 400 mg Levofloksacin 500-750 mg/24 h
Druga linija	Amoksicilin 3 x 500 mg Amoksicilin/klavulonska kiselina 2 x 875 mg ili 3 x 500 mg Cefaleksin 4 x 500 mg Cefuroksim 2 x 500 mg Cefiksim 1 x 400 mg Doksiciklin 2 x 100 mg Fosfomicin 3 g Trimetoprim 2 x 100 mg	Amikacin 2 x 7,5 mg/kg ili 1 x 15 mg/kg Cefazolin 3 x 1 g Ceftazidim 3 x 1 g Ceftazidim/Avibaktam 3 x 2,5 g Doripenem 4 x 500 mg Ertapenem 1 x 1 g Meropenem 4 x 500 mg ili 3 x 1 g Piperacilin/Tazobaktam 3 x 3,375 g Vankomicin (za Gram+) 2 x 1 g

cistitis su trimetoprim/sulfametoksazol i nitrofurantoin (tabela 1), sa time da nitrofurantoin nije efikasan kod infekcije prostate i bubrega, nego samo infekcije donjih mokraćnih puteva.

Što se tiče izazivača infekcije, *Klebsiella pneumoniae, Proteus mirabilis* i *Pseudomonas aeruginosa* su rezistentni na nitrofurantoin, dok su na njega senzitivni beta-laktamaza produkujuća *E. coli* i vankomicin-rezistentan *Enterococcus*. Iako su fluorohinoloni (norfloksacin, ciprofloksacin i levofloksacin) efikasni u lečenju UTI, njihova upotreba je često ograničena rezistencijom bakterijskih vrsta[26]. Upotrebu ove vrste lekova treba čuvati za slučajeve empirijske terapije bolesnika sa slikom pijelonefritisa, kada postoji rezistencija na druge lekove ili kada bolesnici ne tolerišu drugu terapiju. Peroralna terapija cefalosporinom, fosfomicinom, doksiciklinom, amoksicilinom i amoksicilin/klavulonskom kiselinom je druga terapijska linija shodno antimikrobnoj osetljivosti i toleranciji od strane bolesnika.

Parenteralna terapija je indikovana ukoliko kod bolesnika postoji hemodinamska nestabilnost, ako ne tolerišu peroralnu terapiju i/ili imaju nesigurnu apsorpciju iz gastrointestinalnog trakta ili ukoliko se radi o infekciji koja je neosetljiva na spektar peroralne terapije. Parenteralna terapija se daje tokom prvih 48-72 sata, nakon čega se radi reevaluacija stanja bolesnika, a lečenje eventualno nastavlja peroralnom terapijom. Ukoliko se aminoglikozidi daju duže od 7 dana neophodno je pratiti nivo leka u krvi i funkciju bubrega.

Pokazano je da su kod žena prosečne starosti od 78,5 godina rezultati lečenja isti ako se ciprofloksacin primeni u trajanju od tri i pet dana[26]. Takođe, primena trimetoprim/sulfametoksazola u trajanju od tri dana i nitrofurantoina u trajanju od pet dana ima povoljne rezultate.

Prevencija

Dugotrajna antimikrobna profilaksa može da spreči nastanak akutnih nekomplikovanih infekcija kod starijih žena u uslovima ambulantnog lečenja. Prva terapijska linija je nitrofurantoin 50 ili 100 mg na dan ili trimetoprim/sulfametoksazol pola tablete dnevno ili na drugi dan. Inicijalno trajanje profilakse je 6 do 12 meseci. Iako postoje podaci da lokalno davanje estrogena može da smanji učestalost UTI kod žena, ova prevencija je imala manje uspeha od profilakse nitrofurantoinom[27].

Prospektivna kohortna studija nije potvrdila pozitivan efekat primene preparata na bazi brusnice kod žena starosti 55-75 godina[13]. Primena soka od brusnice je bila manje efikasna od trimetoprima i u odnosu na placebo. *Lactobacilus* je takođe bio značajno manje efikasan nego trimetoprim/sulfametoksazol u prevenciji UTI kod žena u postmenopauzi sa nekomplikovanim UTI i pored nalaza mikroorganizama rezistentnih na ovaj lek[28].

Prevencija UTI kod osoba smeštenih u specijalizovanim ustanovama nije opisana. Sistemska primena estrogena i preparata brusnice nije se pokazala kao efikasna preventivna strategija. Najvažnija je korekcija eventualnih genitourinarnih abnormalnosti u slučajevima komplikovane UTI. Profilaktička primena antimikrobne terapije nije štitila od narednih epizoda komplikovanih UTI. Kod bolesnika sa ASB koji se pripremaju za genitourinarne procedure koje su praćene krvarenjem postoji povećan rizik od bakterijemije i sepse posle procedure, te se savetuje profilaktična antimikrobna terapija neposredno pre intervencije[2].

Dovoljan unos tečnosti u prevenciji i u lečenju UTI kod starih veoma je važan. Stari izbegavaju tečnost da bi ređe mokrili, te im treba objasniti posledice takve navike. Ostale preventivne mere koje se odnose na mlađe osobe važe i za stare, a pre svega hitno mokrenje odmah posle nagona na mokrenje.

Specifičnosti infekcije mokraćnih puteva u vezi sa trajnim kateterom

Podaci iz literature ukazuju na visoku učestalost trajnih urinarnih katetera kod stanovnika domova za smeštaj starih lica[29]. Prema podacima iz Amerike oko 13% osoba na prijemu u domove ima trajni kateter, kao i 16% muškaraca i 3% žena - korisnika 67 domova za stare u Švedskoj[30]. Ovi bolesnici uvek imaju bakteriuriju, a simptomatska UTI nastaje 2,2 puta češće, dok je bakterijemija i do 39 puta češća nego kod osoba bez katetera[23, 31]. Takođe, autopsijski nalaz akutnog pijelonefritisa je osam puta češći kod kateterizovanih osoba. Ipak, povećan mortalitet osoba u domovima za smeštaj starih lica je pre posledica funkcionalnog oštećenja i komorbiditeta nego infekcije urinarnog porekla.

Najvažniji patogenetski mehanizam u nastanku bakteriurije i UTI kod osoba sa keteterom jeste formiranje biofilma ubrzo po plasiranju katetera[32]. Mikroorganizmi odmah adheriraju na površinu katetera i umnožavaju se na spoljašnjoj i unutrašnjoj strani stvarajući polisaharide. Stvaranju biofilma doprinose i sastojci urina (*Tamm-Horsfallov* protein, joni kalcijuma i magnezijuma) koji se inkorporiraju u biofilm. Mikrokolonije su zaštićene u biofilmu gde teško prodiru i antibiotici i lokalni faktori odbrane (leukociti i imunoglobulini)[33]. Alkalizacija urina od strane ureaza-produkujućih bakterija pospešuje taloženje soli kalcijuma i magnezijuma, što ima za posledicu stvaranje kristalnog biofilma. Kristalni biofilm može da pravi inkrustaciju i opstrukciju katetera.

Osobe sa kateterom imaju najčešće *E. coli, Enterococcus faecalis* i *Proteus mirabilis*. Takođe, čest nalaz je ureaza-produkujućih bakterija - *Proteus mirabilis*, *Morganella morganii*, *Klebsiela pneumonia* i *Providencia stuartii*[34]. *Proteus mirabilis* je posebno aktivan u formiranju biofilma i kristalnog biofilma i u oko 80% slučajeva odgovoran je za sve opstrukcije katetera[35].

Klinička slika simptomatske infekcije osoba sa kateterom se najčešće odlikuje visokom temperaturom bez lokalnih genitourinarnih simptoma[23]. Kod nekih bolesnika može se javiti bol i napetost kostovertebralnog predela, opstrukcija katetera ili hematurija. Konsenzus po pitanju otpočinjanja empirijske antibiotske terapije podrazumeva prisustvo jednog od simptoma: visoka temperatura, nova zategnutost kostovertebralnog ugla, novonastali delirijum, odsustvo alternativnog izvora infekcije[36].

Savetuje se uzimanje uzorka sa novim kateterom kada je nalaz isključivo iz urina, a ne i iz biofilma, a broj viši od 10 CFU/mL se smatra relevantnim za definiciju bakteriurije. Takođe, savetuje se započinjanje terapije tek posle zamene katetera ako je postavljen pre više od dve nedelje[38].

Lečenje ASB se ne preporučuje jer to ne smanjuje učestalost UTI, a vodi reinfekcijama rezistentnim klicama[37]. Optimalni izbor terapije se ne razlikuje u odnosu na bolesnike bez katetera (tabela 1). Poželjno je da lečenje traje sedam dana ukoliko postoji brz odgovor na terapiju. Duže lečenje vodi češćim neželjenim efektima terapije. Korist uklanjanja katetera pre započinjanja terapije ogleda se u smanjenim relapsima i smanjenju broja klica koje zaostaju u biofilmu.

Prevencija infekcija udruženih sa trajnim kateterom nalazi svoje mesto u postojećim preporukama[38, 39]. Najbitnije je smanjiti upotrebu katetera ili ih koristiti što jer kraće moguće. Takođe, neki autori savetuju spoljne, kondom-katetere koji nose manji rizik od infekcija[40]. Posebnu pažnju treba obratiti na netraumatsko plasiranje katetera da ne bi došlo do krvarenja koje pogoduje infekciji. Važno je blagovremeno prepoznati opstrukciju i zameniti kateter. Posebni kateteri koji su impregnirani antimikrobnim sredstvima ili drenažne kese sa antisepticima izgleda da nisu opravdali očekivanja u smislu smanjenja učestalosti infekcije[41]. Tokom zamene katetera može doći do tranzitorne bakterijemije koja nema ozbiljnije posledice, te se antimikrobna profilaksa ne savetuje tokom zamene katetera.

Zaključak

Kod starih osoba se registruje visoka učestalost asimptomatske bakteriurije i urinarne infekcije. Asimptomatska bakteriurija ne zahteva lečenje, sem pre uroloških hirurških procedura. Dijagnoza simptomatskih infekcija se češće postavlja nego što je to opravdano, što ima za posledicu zloupotrebu antibiotika i reinfekciju rezistentnim mikroorganizmima.

Kod osoba koje se nalaze u smeštajnim ustanovama razlikovanje ASB i UTI nije lako s obzirom na nepouzdanost i nespecifičnost simptoma. Osobe sa trajnim urinarnim kateterom imaju povišen rizik za UTI i kod njih se primenjuju posebne dijagnostičke, terapijske i preventivne strategije.

Abstract

A healthy urinary tract is not a sterile environment but is inhabited by diverse microorganisms that change according to environmental factors and the patient's condition. Elderly patients are predisposed to urinary tract infections and asymptomatic bacteriuria, and distinguishing between these two conditions is challenging. They are specific in several issues: the pathogenesis of infection and causative agents, diagnostic procedures, applied therapy, and preventive measures. Proper interpretation of symptoms, sampling of materials for analysis, and interpretation of results are of great importance. Correct procedures allow sparing patients from unnecessary treatment and complications of antibiotic therapy, as well as reducing bacterial resistance.

Keywords: urinary tract infections, elderly individuals, therapy

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UNCOMPLICATED URINARY TRACT INFECTIONS IN THE ELDERLY

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Abstract

A healthy urinary tract is not a sterile environment but is inhabited by diverse microorganisms that change according to environmental factors and the patient's condition. Elderly patients are predisposed to urinary tract infections and asymptomatic bacteriuria, and distinguishing between these two conditions is challenging. They are specific in several issues: the pathogenesis of infection and causative agents, diagnostic procedures, applied therapy, and preventive measures. Proper interpretation of symptoms, sampling of materials for analysis, and interpretation of results are of great importance. Correct procedures allow sparing patients from unnecessary treatment and complications of antibiotic therapy, as well as reducing bacterial resistance.

Keywords: urinary tract infections, elderly individuals, therapy

Introduction

Urinary tract infections (UTIs) are responsible for approximately 15.5% of hospitalizations due to infectious diseases in individuals over the age of 65 (right after pneumonia) and are the cause of death in about 6% of patients[1]. UTIs can be classified, in younger individuals, based on several criteria: based on location (cystitis, pyelonephritis), recurrence tendency (intermittent, recurrent), symptomatology (asymptomatic, symptomatic), and based on the presence of complications (complicated and uncomplicated). In individuals with a normal genitourinary tract, these infections are termed uncomplicated UTIs, while structural and functional abnormalities of the urinary tract lead to complicated UTIs. The gold standard for diagnosing UTI is the presence of pathogens in the urine along with symptoms reported by the patient. However, the threshold for bacteriuria is not clearly defined or standardized by microbiology laboratories. Many laboratories define a threshold of 10^5 CFU/mL (colony-forming units of bacteria) as the cutoff, but this may lead to missing some infections, so a lower threshold (10^3 CFU/mL) is advised. According to the criteria of the Infectious Disease Society of America (IDSA), asymptomatic bacteriuria (ASB) is defined when patients have $\geq 10^5$ CFU/mL or more than one bacterial species in two consecutive urine samples in women and one sample in men, in the absence of clinical signs and symptoms characteristic of UTI[2].

Epidemiology

The incidence of ASB increases with age and reaches 20% in females older than 80 years. In healthy males, ASB is not typical before the age of 60, while the incidence is between 5 to 10% in males older than 80 years[3]. Symptomatic infections are not directly correlated with ASB, nor are incidental renal impairment and hypertension[2]. Elderly women have a higher frequency of UTIs compared to men, and this difference is more pronounced than in younger individuals.

Individuals residing in long-term care facilities for the elderly have a higher incidence of ASB (25-50% in women and 15-40% in men) compared to older adults treated on an outpatient basis[2]. Bacteriuria is a dynamic phenomenon: among individuals diagnosed with ASB, one-third will have a negative urine culture within 3 to 6 months, while one-third of patients with initially negative cultures will develop bacteriuria. ASB in individuals residing in long-term care facilities is not associated with poor survival, but it is often the cause of unnecessary antibiotic use, leading to increased incidence of infections caused by *Clostridium difficile* and other negative effects of antibiotic therapy.

Symptomatic UTI is the second most common infection among these individuals, with a reported frequency ranging from 0.5 to 1 per 1.000 hospital days[4]. In elderly individuals capable of providing valid symptom data, distinguishing between UTI and ASB is relatively easy. However, in those with cognitive impairment, distinguishing ASB from UTI is challenging. Approximately 45-56% of all bacteremias in individuals from long-term care facilities are attributed to urinary origin, but this mostly pertains to individuals with indwelling catheters.

Hospitalizations due to acute pyelonephritis are more common with increasing age, while recurrent UTIs are more frequent mainly in individuals with complicated infections. Mortality due to UTI is uncommon[5]. An analysis of

270 individuals with an average age of 83.7 years who were hospitalized due to UTI (including 14% from nursing homes) showed that hospital mortality was 8.9%. Risk factors for mortality included inadequate antimicrobial therapy, APACHE II score on admission $\geq$ 15, dementia, and solid neoplasms[6]. An Israeli study involving 191 individuals (of whom 35% were from nursing homes) aged 75 to 105 years, hospitalized in a geriatric hospital, showed an in-hospital mortality of 33%. Risk factors included hospitalization (lasting longer than 20 days), dementia, and comorbidities, rather than gender and age[7]. The mortality of patients with UTI depends on multiple factors.

Pathogenesis

In non-hospitalized older adults, risk factors are similar for ASB and UTI and include menopause, prostate hypertrophy, diabetes mellitus, functional and cognitive impairment, and incontinence. In postmenopausal women, recurrent infections are associated with frequent infections in youth and non-secretion of blood group antigens[8]. Women with diabetes, aged 55-75 years, have twice the frequency of UTIs compared to women without diabetes[9]. Due to estrogen deficiency, colonization with *Lactobacilli spp*, which maintains the acidic pH of the vagina, decreases in the postmenopausal period. A higher pH allows colonization by uropathogens (*E. coli* and *Enterococcus spp*), increasing the incidence of UTIs in postmenopausal women[10]. It is believed that estrogen replacement therapy can restore vaginal flora and pH, although the association between infections and estrogen is not fully understood.

Prostatic hypertrophy plays a significant role in the pathogenesis of UTIs in older men. It causes obstruction and turbulent urine flow, facilitating bacterial penetration into the bladder wall. Bacteria may remain in the prostate permanently due to poor penetration of antibiotics into the gland. Incontinence predisposes to bacteriuria, but it can also be a cause of infections in older men and women. Residual urine volume is a common finding in female individuals between the ages of 62 and 90[11]. In men with a median age of 62 years, the average residual urine volume was 257 mL in cases of positive bacteriuria and 133 mL without bacteriuria[12]. However, a prospective study did not confirm a correlation between UTI and residual urine volume in women aged 55-75 years, indicating a complex relationship between these two clinical conditions[13].

A special focus is warranted on very elderly individuals, aged over 80 years. A Swedish study confirmed that risk factors for bacteriuria in very elderly women include immobility, incontinence, and estrogen therapy, while in men, risk factors include prostate issues, history of stroke, and dependency on others[3]. Data from the Netherlands for older individuals (aged 80 to 90 years) showed that risk factors for UTI include cognitive impairment, dependence on daily activities, and urinary incontinence. Gender and place of residence were not risk factors for UTI[14].

In individuals residing in long-term care facilities for the elderly, ASB is associated with urinary dysfunction due to neurological disorders (cerebrovascular diseases, Parkinson's disease, dementia), which are also the reasons for placement in specialized facilities[15]. Residual urine volume does not correlate with the occurrence of symptomatic or asymptomatic infection. Men who use external urinary catheters in the form of condoms have a higher frequency of bacteriuria and symptomatic infections compared to incontinent men who do not use them[16].

Infection causing agents

In the case of symptomatic infections, the most common causative agents isolated are *E. coli*, but also *Enterobacteriaceae*, *Enterococcus spp*, and *Pseudomonas aeruginosa*. Coagulase-negative *staphylococci* can be isolated in asymptomatic infections in men. Candida can be detected in individuals with additional risk factors such as diabetes, urological aids, and the use of broad-spectrum antibiotics. In the elderly, isolates are more likely to be multidrug-resistant compared to younger individuals, which is associated with previous (mis)use of antibiotics and urological procedures in patients with complicated infections. A Spanish study confirmed that in ambulatory patients with urinary tract infections, older age was significantly associated with the isolation of fluoroquinolone-resistant *E. coli*, and an independent risk factor for this resistance was the use of antibiotics during the previous month[17]. Similarly, data from an American study showed tigecycline-resistant, carbapenem-resistant *Klebsiella pneumoniae*, and the risk factor was hospitalization from nursing homes[18]. Additionally, *E. coli* is the most common pathogen in nursing homes, but the prevalence of other enterobacteria is higher compared to ambulatory patients. In institutionalized individuals, polymicrobial infections are more common (10-25%), even without the presence of an indwelling catheter, and antimicrobial resistance is also more prevalent, making treatment more challenging.

Diagnosis

Clinical diagnosis is based on a spectrum of symptoms, ranging from irritation of the lower urinary tract to septic shock. In ambulatory patients, common symptoms include frequent urination, dysuria, nocturia, suprapubic pain, and sometimes hematuria. Symptoms of pyelonephritis also include pain in the costovertebral region, fever, and elevated temperature, with or without dysuria. However, clinical diagnosis is more challenging in individuals residing in nursing homes due to impaired communication and the presence of symptoms of chronic diseases. Clinical deterioration in patients without localized genitourinary symptoms is unlikely

to be due to UTI in individuals with bacteriuria[16]. However, atypical symptoms and changes in the patient's clinical status, such as falls, reduced functionality, and changes in mental status, are often attributed to UTIs in the elderly. Changes in the odor, color, and cloudiness of urine correlate with bacteriuria but are more commonly associated with worsening incontinence or dehydration rather than symptomatic infection, so they are not sufficient for diagnosing UTI[18-20]. Recognizing symptoms is very important because they are the primary criteria for initiating therapy when UTI is suspected: acute dysuria or high temperature, acute confusion or fever with worsening of one of the genitourinary symptoms (urgent urination, frequent urination, suprapubic pain, hematuria, pain in the costovertebral region, urinary incontinence)[21, 22]. This significantly reduces antibiotic use compared to the standard approach. In cases where the diagnosis is unreliable, it is advisable to monitor the patient and, if local symptoms in the genitourinary tract area do not appear, the patient should be treated more as a condition of sepsis of unknown origin rather than as UTI[22].

Laboratory diagnosis is necessary for definitive diagnosis and treatment of UTIs in the elderly, given the high percentage of microorganism resistance[15]. An exception is healthy women who have repeated acute cystitis in outpatient settings, where short-term antibiotic therapy is usually effective. However, even in these cases, urine culture should be performed if the desired effect on empirical therapy is not achieved, if symptoms are atypical, or if there is a rapid return of symptoms after treatment, all of which indicate a resistant pathogen.

One of the primary obstacles in UTI diagnosis is the necessity of proper urine sampling for analysis to prevent sample contamination. In women who are unable to follow instructions, a single-use catheterization is performed, while in men, a clean condom catheter is used. The diagnostic criterion involves finding more than 10^5 CFU/mL of a single microorganism in the urine sample. When a smaller number of colonies is isolated or multiple microorganisms are present, the urine culture result is interpreted by clinical symptoms. A lower colony count is encountered in about 10% of healthy postmenopausal women with acute uncomplicated UTI[13]. Additionally, in UTIs, a lower number of colonies may be isolated if frequent urination disrupts the incubation time of bacteria in the bladder due to frequent emptying. Therefore, for men, the diagnosis of UTI is present if pathogens are isolated in a number of 10^3 CFU/mL or more in a properly collected urine sample (except in the case of a permanent urinary catheter, when the criterion is 10^5 CFU/mL)[15]. If pyelonephritis is suspected, finding a single microorganism in a number of 10^4 CFU/mL or above is the recommended diagnostic criterion. Finding microorganisms in a number of 10^2 CFU/mL or above is indicative of infection if the sample is obtained by a single-use catheterization of the bladder[23].

Pyuria is a nonspecific laboratory finding in the elderly[15]. It is often positive even without bacteriuria, and in individuals with bacteriuria, it does not differentiate symptomatic UTI from ASB. On the other hand, the absence of pyuria has a high negative predictive value for excluding UTI[24]. When UTI is suspected in individuals in nursing homes, it is advisable to first examine the presence of pyuria. If the finding is negative, a urine culture should not be performed[24]. In women older than 80 years, elevated levels of leukocyte esterase, interleukin IL-8, and IL-6 may indicate a difference between ASB and acute cystitis. However, determining these biomarkers does not have significant clinical significance[25]. In cases of suspected urosepsis, finding the same bacteria in both blood and urine indicates the source of the infection.

Antimicrobial treatment

In older adults, treatment for asymptomatic bacteriuria (ASB) is not recommended as it does not reduce the occurrence and frequency of subsequent UTIs, nor does it alleviate symptoms, and it may lead to the emergence of unwanted treatment effects[2]. Therefore, screening older adults for ASB is not indicated.

When selecting antimicrobial therapy, one should consider the drug's effectiveness, patient tolerance, clinical presentation of the disease, renal function, need for parenteral administration routes, and treatment cost. If the clinical picture allows, waiting for the results of the urine culture is

Table 1. Selection and dosing of antimicrobial drugs in the treatment of urinary tract infections in elderly individuals with normal kidney function

	Peroral therapy	Parenteral therapy
First line	Trimethoprim/Sulfametoxazol 2 x 160/800 mg Nitrofurantoin 2 x 100 mg Ciprofloxacin 2 x 250-500 mg Norfloxacin 2 x 400 mg Levofloxacin 1 x 250-500 mg	Amoxicillin 4 x 500 mg ± Gentamicin or Tobramycin 5-7 mg/kg/24 h Ceftriaxone 1-2 g/24 h Cefotaxime 3 x 1 g Ciprofloxacin 2 x 400 mg Levofloxacin 500-750 mg/24 h
Second line	Amoxicillin 3 x 500 mg Amoxicillin/clavulanic acid 2 x 875 mg or 3 x 500 mg Cephalexin 4 x 500 mg Cefuroxime 2 x 500 mg Cefixime 1 x 400 mg Doxycycline 2 x 100 mg Fosfomycin 3 g Trimethoprim 2 x 100 mg	Amikacin 2 x 7,5 mg/kg or 1 x 15 mg/kg Cefazolin 3 x 1 g Ceftazidime 3 x 1 g Ceftazidime/Avibactam 3 x 2,5 g Doripenem 4 x 500 mgg Ertapenem 1 x 1 g Meropenem 4 x 500 mg or 3 x 1 g Piperacillin/Tazobactam 3 x 3,375 g Vancomycin (for Gram+) 2 x 1 g

advised. Although creatinine clearance decreases with age, dose reduction of medications based solely on the patient's age is not indicated. First-line treatments for cystitis are trimethoprim/sulfamethoxazole and nitrofurantoin, with the note that nitrofurantoin (Table 1) is not effective against prostate and kidney infections, but only for lower urinary tract infections.

Regarding causative agents of infection, *Klebsiella pneumoniae*, *Proteus mirabilis*, and *Pseudomonas aeruginosa* are resistant to nitrofurantoin, while beta-lactamase-producing *E. coli* and vancomycin-resistant *Enterococcus* are sensitive to it. Although fluoroquinolones (such as norfloxacin, ciprofloxacin, and levofloxacin) are effective in treating UTIs, their use is often limited by bacterial resistance[26]. The use of these types of medications should be reserved for cases of empirical therapy in patients with a picture of pyelonephritis, when there is resistance to other drugs, or when patients do not tolerate other therapies. Oral therapy with cephalosporins, fosfomycin, doxycycline, amoxicillin, and amoxicillin/clavulanic acid is the second-line therapy based on antimicrobial sensitivity and patient tolerance.

Parenteral therapy is indicated if the patient is hemodynamically unstable, if they do not tolerate oral therapy, and/or has uncertain absorption from the gastrointestinal tract, or if the infection is resistant to the spectrum of oral therapy. Parenteral therapy is administered during the first 48-72 hours, after which the patient's condition is reevaluated, and treatment may be continued with oral therapy if appropriate. If aminoglycosides are administered for more than 7 days, it is necessary to monitor the drug levels in the blood and kidney function.

It has been shown that in women with an average age of 78.5 years, the treatment outcomes are the same whether ciprofloxacin is administered for three or five days[26]. Additionally, the use of trimethoprim/sulfamethoxazole for three days and nitrofurantoin for five days has favorable outcomes.

Prevention

Long-term antimicrobial prophylaxis can prevent the onset of acute uncomplicated infections in older women in outpatient settings. The first-line therapy is nitrofurantoin 50 or 100 mg per day or trimethoprim/sulfamethoxazole half a tablet daily or every other day. The initial duration of prophylaxis is 6 to 12 months. Although there is evidence that local estrogen administration can reduce the frequency of UTIs in women, this prevention method has been less successful than nitrofurantoin prophylaxis[27].

A prospective cohort study did not confirm a positive effect of cranberry-based products in women aged 55-75 years[13]. The use of cranberry juice was less effective than trimethoprim and compared to placebo. Additionally, Lactobacillus was also significantly less effective than trimethoprim/

sulfamethoxazole in preventing UTIs in postmenopausal women with uncomplicated UTIs, despite findings of microorganisms resistant to this medication[28].

Preventing UTIs in individuals residing in specialized facilities hasn't been well described. Systemic estrogen administration and cranberry supplements haven't proven effective as preventive strategies. The most important approach is correcting any genitourinary abnormalities in cases of complicated UTIs. Prophylactic antimicrobial therapy hasn't been protective against subsequent episodes of complicated UTIs. For patients with ASB undergoing genitourinary procedures associated with bleeding, there's an increased risk of bacteremia and sepsis post-procedure, so prophylactic antimicrobial therapy is advised immediately before the intervention[2].

Adequate fluid intake is crucial in the prevention and treatment of UTIs in the elderly. Older individuals may avoid fluids to urinate less frequently, so it's important to explain the consequences of such habits. Other preventive measures applicable to younger individuals also apply to the elderly, primarily prompt urination immediately after feeling the urge to urinate.

Specificities of urinary tract infection related to an indwelling catheter

Literature data indicate a high frequency of permanent urinary catheters in residents of homes for the elderly persons[29]. According to data from America, approximately 13% of individuals admitted to nursing homes have an indwelling catheter, with 16% of men and 3% of women being users in 67 nursing homes in Sweden[30]. These patients always have bacteriuria, and symptomatic UTI occurs 2.2 times more frequently, while bacteremia is up to 39 times more common than in individuals without a catheter[23, 31]. Also, autopsy findings of acute pyelonephritis are eight times more common in catheterized individuals. However, increased mortality in nursing home residents is more likely due to functional impairment and comorbidities rather than urinary tract infections.

The most important pathogenetic mechanism in the development of bacteriuria and UTI in individuals with a catheter is the formation of a biofilm shortly after catheter placement[32]. Microorganisms immediately adhere to the surface of the catheter and multiply on both the external and internal sides, creating polysaccharides. Urine components such as Tamm-Horsfall protein, calcium ions, and magnesium ions also contribute to biofilm formation by incorporating them into it. Microcolonies within the biofilm are protected, making it difficult for antibiotics and local defense factors such as leukocytes and immunoglobulins to penetrate[33]. Alkalization of urine by urease-producing bacteria promotes the deposition of calcium and magnesium salts, resulting in the formation of a crystalline biofilm. This crystalline biofilm

can lead to encrustation and obstruction of the catheter[34]. Individuals with catheters most commonly harbor *E. coli*, *Enterococcus faecalis*, and *Proteus mirabilis*. Additionally, urease-producing bacteria such as *Proteus mirabilis*, *Morganella morganii*, *Klebsiella pneumoniae*, and *Providencia stuartii* are frequently encountered[34]. *Proteus mirabi*lis is particularly active in biofilm and crystalline biofilm formation and is responsible for approximately 80% of all catheter obstructions[35].

The clinical presentation of symptomatic infection in individuals with catheters most commonly involves high fever without local genitourinary symptoms[23]. In some patients, pain and tenderness in the costovertebral area, catheter obstruction, or hematuria may occur. The consensus regarding initiating empirical antibiotic therapy implies the presence of one of the following symptoms: high fever, new costovertebral angle tenderness, new-onset delirium, or the absence of an alternative source of infection[36].

It is advisable to take a sample with a new catheter when the finding is exclusively from urine, not from the biofilm, and a count higher than 10 CFU/mL is considered relevant for defining bacteriuria. Additionally, it is recommended to initiate therapy only after replacing the catheter if it has been in place for more than two weeks[38].

Treating ASB is not recommended because it does not reduce the frequency of UTIs and can lead to reinfections with resistant bacteria[37]. The optimal choice of therapy does not differ from patients without catheters (Table 1). Treatment should last for seven days if there is a rapid response to therapy. Prolonged treatment leads to more frequent adverse effects. The benefit of removing the catheter before starting therapy is reflected in reduced relapses and a reduction in the number of bacteria remaining in the biofilm.

Prevention of infections associated with indwelling catheters is included in existing recommendations[38, 39]. The most important thing is to reduce the use of catheters or use them for as short a time as possible. Some authors also recommend external, condom catheters, which carry a lower risk of infection[40]. Special attention should be paid to non-traumatic catheter placement to prevent bleeding, which predisposes to infection. It is important to promptly recognize obstruction and replace the catheter. Special catheters impregnated with antimicrobial agents or drainage bags with antiseptics do not seem to have met expectations in terms of reducing infection rates[41]. During catheter replacement, transient bacteremia may occur, which does not have serious consequences, so antimicrobial prophylaxis is not recommended during catheter replacement.

Conclusion

In elderly individuals, there is a high prevalence of asymptomatic bacteriuria and urinary tract infections. Asymptomatic bacteriuria does not require treatment except before urological surgical procedures. The diagnosis of symptomatic infections is often overdiagnosed, leading to antibiotic overuse and reinfection with resistant microorganisms.

In individuals residing in care facilities, distinguishing between asymptomatic bacteriuria (ASB) and urinary tract infection (UTI) is not easy due to the unreliability and nonspecificity of symptoms. Individuals with indwelling urinary catheters are at increased risk for UTIs, and special diagnostic, therapeutic, and preventive strategies are applied for them.

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