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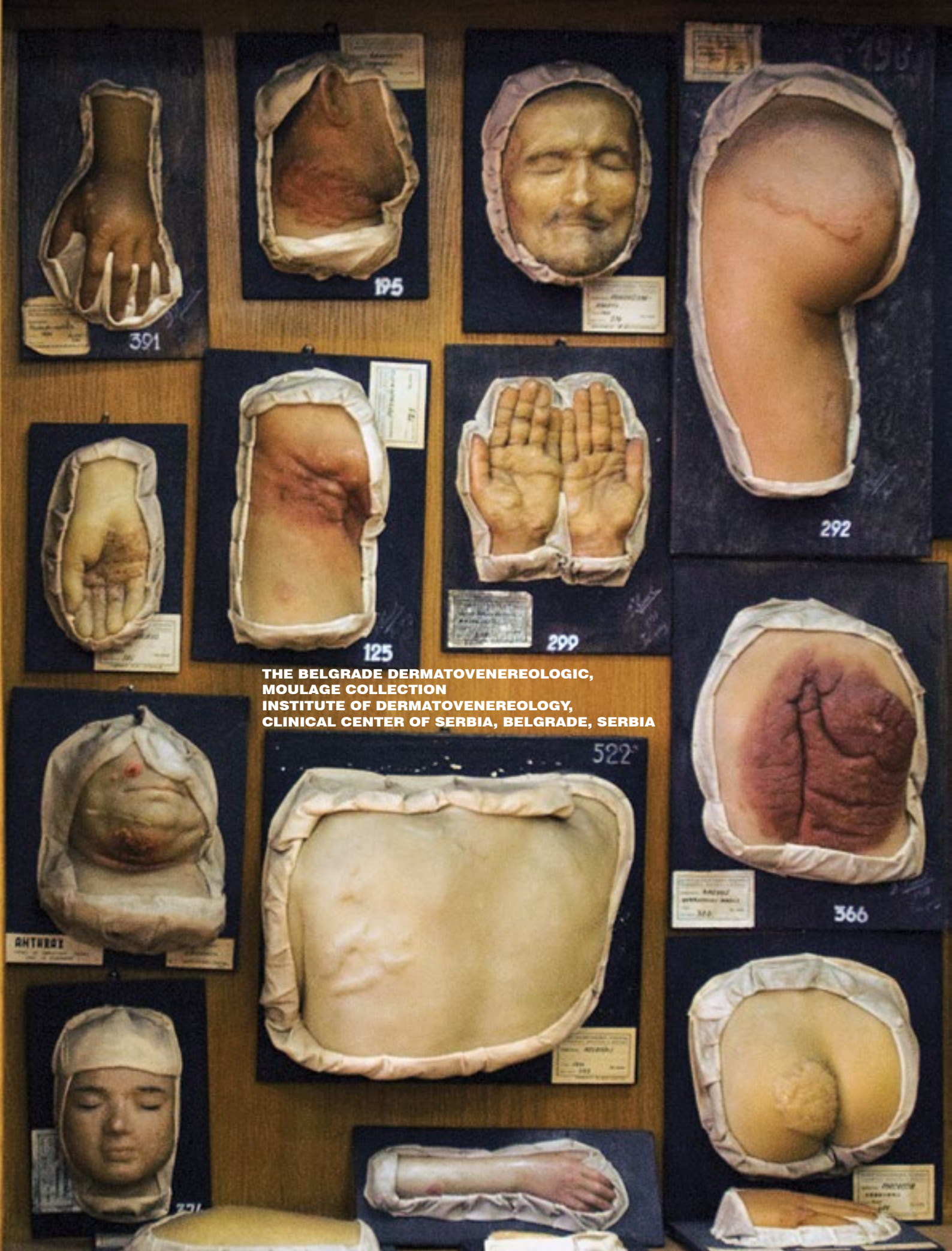

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Urethritis and antimicrobial resistance

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Abstract

Urethritis is a clinical syndrome which is characterized by mucopurulent or purulent urethral discharge with or without dysuria, due to an increased number of polymorphonuclear leukocytes in the anterior urethra. Antimicrobial therapy and preventive measures are essential in the management of bacterial urethritis. However, these drugs may cause antimicrobial resistance, resulting in unsuccessful treatment and complications of urethritis. Resistance of Neisseria gonorrhoeae to antibiotics is well known for decades, and in recent years there are more cases of resistance of Chlamydia trachomatis and Mycoplasma genitalium to different antibiotics. There is a danger that in the future certain strains of N. gonorrhoeae will be resistant to all available antimicrobial agents, unless new antibiotics to which resistance will not develop rapidly or an effective vaccine are developed.

Key words

Urethritis + etiology + classification + prevention and control + therapy; Drug Resistance, Microbial

Urethritis is a clinical syndrome which is characterized by mucopurulent or purulent (Figures 1 and 2) urethral discharge with or without dysuria, due to an increased number of polymorphonuclear leukocytes in the anterior urethra. There are two types of urethritis. The first type is not sexually transmitted and occurs due to urinary tract infections, phimosis, bacterial prostatitis, chemical or mechanical irritation. Urethritis which is directly related to sexually transmitted diseases may be classified as: gonococcal and nongonococcal. Regarding its course, urethritis can be acute or chronic.

Neisseria gonorrhoeae is the most common cause of urethritis in Africa and South East Asia, while *Chlamydia trachomatis* is predominant in other geographic areas, especially in Europe and North America (1, 2). Table 1 shows the etiologic agents of nongonococcal urethritis (3).

When considering the etiology of nongonococcal urethritis, one should take into account microorganisms of partner's oropharyngeal flora and vaginal secretions during unprotected intercourse. Recently discovered bacteria should also be considered, for example *Atopobium vaginae*, an anarerobic bacterium, discovered in 1999, often found in the vagina causing bacterial vaginosis (4).

Antimicrobial drugs and preventive measures are essential in the treatment of bacterial urethritis. However, these drugs may cause antimicrobial resistance, resulting in unsuccessful treatment and complications such as: epididymo-orchitis, prostatitis, SARA (Sexually acquired reactive arthritis), pelvic inflammatory disease, ectopic pregnancy, perihepatitis and sterility.

Resistance of *Neisseria gonorrhoeae* to antibiotics is well known for decades, and in recent years there is an increasing number of reports on resistance of *Chlamydia trachomatis* and *Mycoplasma genitalium* to different antibiotics. In cases of persistent dysuria, sometimes it is difficult to assess whether there is resistance, and there are diagnostic and therapeutic shortcomings when indentifying the source of infection, reinfection or compliance.

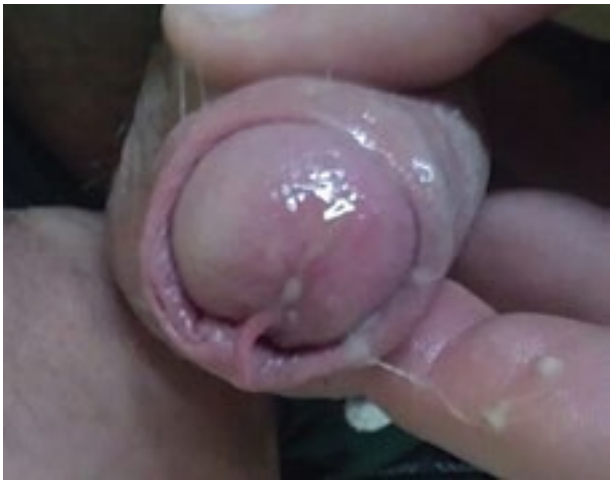

Figure 1a. Pus-like discharge from the penis: a diagnostic and therapeutic challenge

Neisseria gonorrhoeae

Treatment of gonorrhea has changed through history in many ways, from the old procedures (urethral adstringens, mechanical and chemical substances applied into the urethra), until the appearance of antibiotics. The first antibacterial drugs were sulfonamides, that appeared in 1936, while penicillin appeared seven years later (5, 6).

Penicillin was the standard treatment for gonorrhea, but decreased sensitivity to penicillin in the 1950s to 1970s required a change and a combination of penicillin and probenecid was recommended (7). In 1976, ß-lactamase encoding plasmids caused a high level of penicillin resistance, and in 1989, there was a significant level of resistance in U.S., and the drug was removed from the list of recommended therapy for gonorrhea (8, 9). A similar thing happened with tetracyclines which ceased to be the recommended treatment for gonorrhea in the U.S. and Western Europe in the late 1980s (10). Quinolones have been the first-line therapy since the mid 1980s to the early 90 in many countries. Except for urogenital, they were effective in the eradication of oropharyngeal and anorectal gonorrhea with a single oral dose of 500 mg of ciprofloxacin. Resistance was first observed in South East Asia, and later in other parts of the world, contributing to its exclusion as a first-line treatment of gonorrhea in the early and mid 2000s (11, 12).

Azithromycin, a relatively new macrolide, has shown significant efficacy in the treatment of gonorrhea. Cure rates of urethral and endocervical gonorrhea were 96.5% for 1 g azithromycin to 99% for 2 g azithromycin (13). However, some studies have

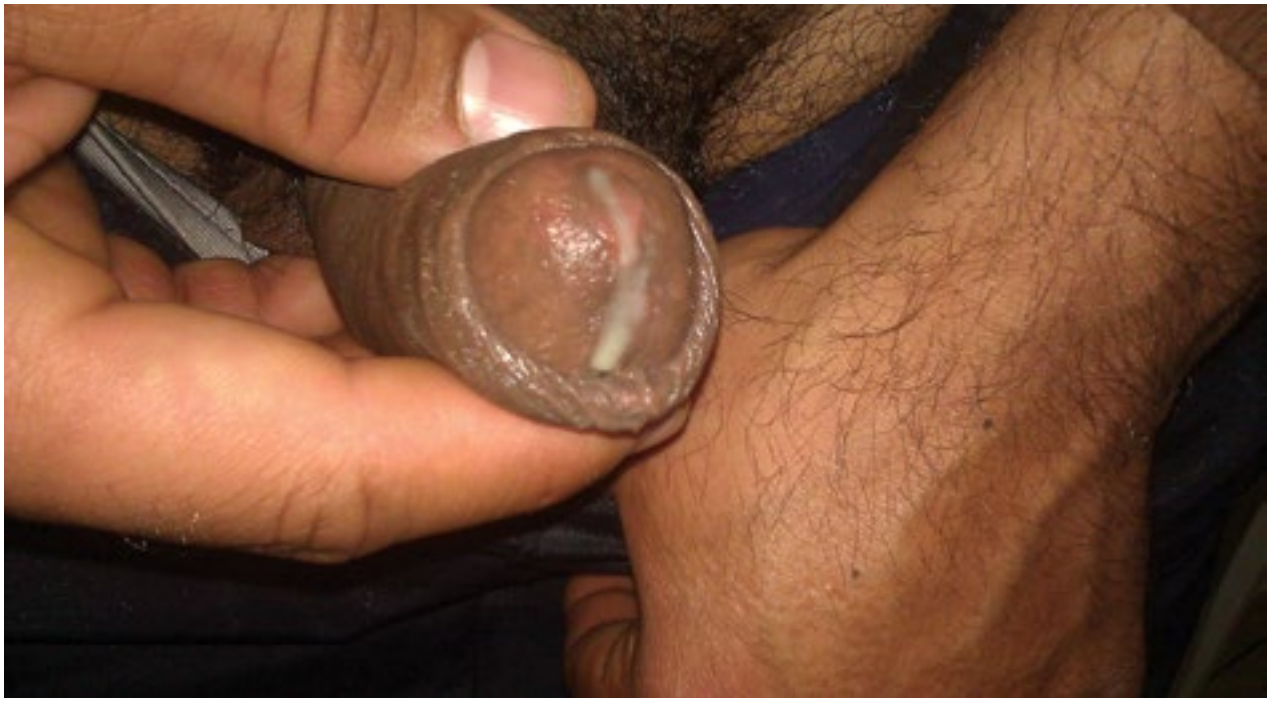

Figure 1b. Pus-like discharge from the penis

Table 1. Causative agents of non-gonococcal urethritis

Causative agents	Frequency (%)
Chlamydia trachomatis	11-43%
Mycoplasma and Ureaplasma	9-25%
Trichomonas vaginalis	1-20%
Adenoviruses	2-4%
Herpes Simplex virus type 1 and type 2	2-3%

shown a failure of treatment with 1 g of azithromycin, suggesting that the resistance can quickly develop if this dose is used (14). Due to rapid development of resistance, azithromycin has never been a first-line treatment in self-medication. It was used in combination with cephalosporins in the treatment of associated infections *Neisseria gonorrhoeae* and *Chlamydia trachomatis* infections.

Today, cephalosporins are the first line treatment of gonorrhea, showing high efficacy for urogenital, anorectal, and pharyngeal gonorrhea for years and decades. Cefriaxone has a long half-life of 6-9h and is suitable for a single dose (10). Clinical trials, including pregnant women and children, have shown that cefriaxone at a dose of 250 mg IM is suitable for the treatment of gonorrhea regardles of areas, with an efficiency of 99.2% for uncomplicated urogenital and anorectal cases of gonorrhea. Cefixime, an oral cephalosporin, showed similar efficacy as intramuscular ceftriaxone in the treatment of complicated gonorrhea. A single dose of 400 mg of cefixime showed an efficacy of 95% of urogenital and anorectal gonorrhea (13, 15, 16).

However, the high efficiency of cephalosporins is compromised by data from certain parts of the world about resistant strains of gonococci. The first data of gonorrhea treatment failure with third-generation cephalosporins were published in Japan in 2000 (17). Data on resistance to cephalosporins in other countries were published in the following years, and the first two cases of treatment failure with cefixime in Europe took place in Norway in 2010 (18). In Japan, high-level resistance to ceftriaxone of *N. gonorrhoeae* strain (strain H041) has recently been published (19). In Europe, the first case of genital infection with *N. gonorrhoeae* highly resistant to ceftriaxone was published in France in 2011 (20). The mechanisms of resistance to previously used agents are both plasmid and chromosome mediated (21). The question is how long cephalosporins will remain the first line treatment for gonorrhea. In the United Kingdom, the national guidelines have already been changed and recommend ceftriaxone as the first-line therapy with cefixime as an alternative (22). Due to the increase in the minimum inhibitory concentration of cefixime and ceftriaxone, there are recommendations to increase the dosage. However, the current dosage of 400 mg cefixime is the highest single dose licensed for gonorrhea and so any increase would require multiple doses. The dilemma with ceftriaxone is that it is administered intramuscularly and this is not so palatable for adverse reactions. The recommendation of increasing the dose from 250 to 500 mg and additionally adding 1 g azithromycin for all patients in order to delay any resistant mutants has been met with some skepticism and some believe that this is an over-reaction to a potential situation (23).

The recommended therapy for uncomplicated *N. gonorrhoeae* infections of the urethra, cervix and rectum in adults and adolescents, when the antimicrobial sensitivity of the infection is unknown, includes a single dose of 500 mg ceftriaxone together with 2 g of azithromycin as a single oral dose. Alternative regimens are as follows: 1) a single dose of 400 mg oral cefixime as together with a single oral dose of 2 g azithromycin; 2) a single dose of 500 mg

ceftriaxone IM; 3) a single dose of 2 g spectinomycin IM together with a single oral dose of 2 g azithromycin (24).

To reduce the risk of treatment failure (gonococcal treatment failure) there are recommendations to increase the dose of oral cefixime to 800 mg for persons 9 years of age and older (25).

Because of this, there is a danger that in the future certain strains of *N. gonorrhoeae* will be resistant to all available antimicrobial agents, unless new antibiotics to which resistance will not develop rapidly, or an effective vaccine are developed.

New research suggests that treatment of gonococcal infections may include gentamicin, solithromycin and ertapenem.

In the African country of Malawi, a single dose of 240 mg IM gentamicin was used as first-line treatment of gonorrhea. Limited surveys showed that apparently gonorrhea has not mutated and developed resistance to gentamicin in that country over the past two decades. Because of the necessary new research on the effectiveness of gentamicin, the American National Institutes of Allergy and Infectious Diseases (NIAID) is conducting a randomized clinical trial of the following interventions in cases of gonorrhea: 1) gentamicin 240 mg (intramuscular injection) + azithromycin 2 g (orally); 2) gemifloxacin 320 mg + azithromycin 2 g, both drugs taken orally (26).

A new fluoroketolide, solithromycin, is a potential treatment option for gonorrhea. Solithromycin was tested in laboratory experiments, and strains of gonorrhea were resistant to at least one of the following antibiotics: azithromycin, ampicillin, cefixime, ceftriaxone, ciprofloxacin, spectinomycin, tetracycline and gentamicin. In all cases, solithromycin showed powerful antibacterial activity. Results from phase I and II studies suggest that solithromycin is well absorbed when taken orally and it accumulates inside cells. This drug has anti-inflammatory activity, which makes it useful for treating infections. At doses between 200 and 600 mg, it is well tolerated and safe (27, 28).

In vitro results suggest that ertapenem may be an effective treatment option against *N. gonorrhoeae* isolates particularly for the currently identified extended-spectrum cephalosporins resistant cases and possibly in a dual antimicrobial therapy regimen (29). Ertapenem is a broad spectrum carbapenem antibiotic used primarily in the treatment of aerobic gram-negative bacterial infections.

Mycoplasma

Two mycoplasma species most commonly detected in the urethra are *Mycoplasma hominis* and *Mycoplasma genitalium*. The colonisation rate with Mycoplasma increases proportionally with the number of different sexual partners (30). There is no evidence supporting the role of *M. hominis* as a cause of urethritis. It is often isolated from the genital tract of healthy individuals (31).

M. genitalium has been strongly and uniformly associated with urethritis in more than 30 studies. It probably accounts for 15 to 20% of nongonococcal urethritis cases and it is the second most common cause of nongonococcal urethritis after *C. trachomatis* (32).

The main antibiotic classes used in the treatment of mycoplasmas are tetracyclines, macrolides, quinolones and clindamycin. *M. hominis* infections are treated with tetracyclines, quinolones and clindamycin, whereas M. hominis is intrinsically resistant to macrolides. *M. genitalium* is generally susceptible to tetracyclines, macrolides and quinolones in vitro, although tetracyclines are clinically ineffective (33).

Target alterations are the only acquired resistance mechanisms that have been described in vivo for *M. genitalium*. Mutations of the ribosome target, in the central loop of the 23S rRNA domain V, are major *M. genitalium* resistance mechanisms to macrolides. In 85% of patients infected with mutant strains and unsuccessfully treated with 1g azithromycin, there is a resistance to macrolides, which speaks in favor of azithromycin-induced resistance (34). Therefore, as previously noted for resistance to antibiotics, today there is no generally accepted standard treatment for *M. genitalium*.

Comparative therapeutic studies of infection with M. genitalium deal with the most commonly used medications: azithromycin and doxycycline. A Scandinavian study showed that the eradication rate of *M. genitalium* after 9 days of treatment with doxycycline (200 mg day one, then 100 mg the following eight days) was 22%, and with a single dose

of 1 g of azithromycin it was 86% (35). In the study of Mena et al., azithromycin was also more efficient: a single dose of 1 g led to a cure rate of 87% of treated patients compared to 45% treated with doxycycline (200 mg for seven days). In an American study, azithromycin (1g single dose) resulted in a cure in 66.7%, and doxycycline (200 mg/d for seven days) in 30.8% of treated patients (36). Azithromycin is superior to doxycycline, but the dose and duration of therapy remain to be considered. In studies where azithromycin was used for five days (day one 500 mg, 250 mg from day 2 to day 5) eradication rates were 100% (37). Establishment of acquired resistance to macrolides prior therapy would reduce the number of unsuccessful treatment trials.

However, one study showed that azithromycin has a proarrhythmic effect. Although several macrolides are proarrhythmic and associated with an increased risk for sudden cardiac death, published reports of arrhythmias suggest that azithromycin may increase the risk of cardiovascular death (38).

From other antibiotics, moxifloxacin has proven effective (seven to ten days treatment) in patients who were unsuccessfully treated with macrolides and tetracyclines (39).

Despite acquired resistance to macrolides, the first-line treatment of urethritis caused by *M. genitalium* is 1 g single dose of azithromycin with PCR test of cure and microbiological eradication at least 3 weeks later. If this therapy fails, and M. genitalium persists, moxifloxacin 400 mg a day for 7 to 10 days is recommended. Five-day azitromycin or moxifloxacin should be used as first-line treatment for upper genital tract *M. genitalium* infection and post-treatment bacterial eradication should always be checked to prevent long-term complications (40).

Ureaplasma

In contrast to the consistency of studies associating *M. genitalium* with urethritis, the role of ureaplasma in this disease has been more controversial. The results of studies support a causal role of ureaplasma in non-gonococcal urethritis, particularly in its chronic form (41). *Ureaplasma urealitycum* has been reported as a causal agent of acute urethral syndrome in women with reproductive failure (42). This bacterium may also be an etiological factor for urethritis in men (43). Other species of human ureplasmas, like *Ureaplasma parvum*, were isolated more often in control groups, indicating that this species has a lower pathogenic potential. Some patients with hypogammaglobulinemia may develop a prolonged urethritis with persistent ureaplasmal infection (44).

Ureaplasmas are susceptible to tetracyclines, quinolones and macrolides, whereas clindamycin is mostly ineffective.

Reports of macrolide resistance in ureaplasmas go back to the 1980s. The first description of high-level macrolide resistance in human ureaplasmas accompanied characterization of the mechanism involved. Macrolide influx and accumulation, as well as binding affinity to the ribosomes, were reduced in macrolide-resistant isolates (45). Mechanisms of resistance in *U. parvum* were characterized by sequencing portions of genes encoding 23S rRNA and ribosomal protein L4 and L22. Mutants with significantly increased minimum inhibitory concentrations could be selected with many antibiotics, except different macrolides and related antibiotics. Most of the mutations were associated with complete loss of macrolide and ketolide activity, whereas streptogramin combinations were less affected (46). Resistance of ureaplasmas to erythromycin is still a matter of debate. Some authors found a great proportion of erythromycin-resistant strains, whilst others did not (47). Authors from China reported target site methylation and active efflux mechanisms in clinical isolates of macrolide-resistant ureaplasmas (48).

Treatment of urethritis caused by ureaplasma is performed according to recommendations for treatment of chronic urethritis due to the association of this agent with persistent and recurrent urethritis. Persistent urethritis after doxycycline treatment may be caused by doxycycline resistant *U. urealyticum*. A single dose of 1 g oral azithromycin should be administered, and if the infection is associated with *T. vaginalis*, single oral dose of 2 g metronidazole should be added (49).

Chlamydia trachomatis

First-line treatment of uncomplicated urogenital chlamydial infections should be a single dose of 1 g azithromycin. Azithromycin is still an option in

pregnancy and in women who are breastfeeding. Doxycycline, 100 mg two times daily for 7 days, is a suitable alternative (50). Another alternative treatment is josamycin, 500 - 1000 mg two times daily for 7 days. Josamycin is used with success in some countries (51).

Earlier trials indicate that the first-line treatment is more than 95% effective. However, recent evidence suggests that treatment failure may occur in more than 5% of patients. Studies in women, not at risk of reinfection, showed treatment failure rates of approximately 8%, while in men treated with a single dose azitrhromycin it was 23% (52).

An American study showed a higher cure rate when using doxycycline than azithromycin. Cure rate in patients treated with doxycycline (100 mg twice daily for 7 days) was 94.8%, while in patients treated with azithromycin (single dose of 1 g) it was 77.4%. Reasons for lower cure rates may be high incidence of *C. trachomatis* infection and lower observed efficacy of azithromycin therapy in this study, as well as potential reinfections in high-risk population (36).

Resistance, although infrequently reported to date, may occur in *C. trachomatis* and is associated with treatment failure. The incidence of resistance is unknown, but it is estimated to be very low (53). In experiments with multiple cultivation passages, resistant mutants of *C. trachomatis* to sparfloxacin, ofloxacin, ciprofloxacin, rifampin and azithromycin were found. In one in vitro experiment, doxycycline showed the least activity against C. trachomatis compared with azithromycin or fluoroquinolones. Ofloxacin activity was found to be almost similar to azithromycin (54). Thus, therapy of C. trachomatis is initiated empirically.

Conclusion

Antimicrobial therapy and prevention are essential elements in the management of bacterial urethritis. The increase in bacterial resistance to existing antimicrobial agents indicates that timely revision of treatment guidelines is necessary, as well as development of new antimicrobial compounds and vaccines that are a real challenge for researchers due to the antigenic variations of bacteria.

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Uretritis i antimikrobna rezistencija

Sažetak

Uvod. Uretritis je klinički sindrom za koji je karakteristična pojava mukopurulentnog ili purulentnog uretralnog sekreta, sa dizurijom ili bez nje, zbog povećanog broja polimorfonuklearnih leukocita u prednjoj uretri. Antimikrobna terapija i mere prevencije su osnova u borbi protiv bakterijskih uretritisa. Ovu borbu remeti antimikrobna rezistencija te je i terapija neuspešna, a postoji i mogućnost komplikacija uretritisa.

Neisseria gonorrhoeae. Tokom proteklih decenija mnogi antibiotici kojima su lečeni pacijenti oboleli od gonoreje, kao što su penicillin, tetraciklini, hinoloni i makrolidi, više nisu lekovi izbora. Danas su terapija izbora cefalosporini treće generacije. Prvi podaci o rezistenciji na cefalosporine objavljeni su u Japanu 2000. godine, što ukazuje na to da bi lečenje ove infekcije moglo da predstavlja veliki problem u budućnosti.

Mycoplasma i ureaplasma. U terapiji se primenjuju azitromicin i doksiciklin. Istraživanja pokazuju da je azitromicin superiorniji od doksiciklina, ali sa rizikom od razvoja azitromicin-indikovane rezistencije. Zbog toga danas nema opšteprihvaćene standardne terapije.

Chlamydia trachomatis. Prva linija terapije je primena azitromicina. Istraživanja pokazuju da je neuspeh terapije veći od ranije objavljenih 5% lečenih.

Ključne reči

Uretritis + etiologija + terapija + klasifikacija + prevencija i kontrola; Antimikrobna rezistencija

Treatment of Severe Atopic Dermatitis with Cyclosporine: A Review of Eight Patients

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Abstract

Atopic dermatitis is most frequently well controlled with topical therapeutic agents, but based on several studies, 10-20% of patients need systemic therapy. The most common systemic treatment for atopic dermatitis in everyday practice includes systemic corticosteroids, although there are insufficient valid data to support this. Cyclosporine is the treatment of choice for severe atopic dermatitis resistant to other commonly used treatment options, since its favorable therapeutic risk/benefit ratio is well documented in randomized placebo controlled trials, and also in uncontrolled trials. However, approximately 10% of patients with atopic dermatitis with indication for cyclosporine treatment are actually treated with this modality in Serbia, and there are no published case series on its use in this region so far. In this article, we evaluated the treatment efficacy and safety of cyclosporine microemulsion in patients with severe atopic dermatitis hospitalized at the Military Medical Academy in Belgrade from 2009 to 2012. This restrospective analysis included patients with severe forms of atopic dermatitis treated at the Department of Dermatology of the Military Medical Academy from 2009 - 2012. The hospital database was used to retrieve patients' medical records. Approximately 200 patients were treated for atopic dermatitis and 20 patients were admitted to the hospital, 17 due to severe forms of disease. In total, 8 of 17 (47.05%) hospitalized patients with severe forms or erythroderma due to atopic dermatitis were treated with cyclosporine microemulsion with an initial dose of 4-5 mg/kg. Laboratory tests were done before treatment, 7 days later, and/or at the end of hospitalization. Therapeutic efficacy was evaluated based on the percentage of reduction of skin lesions from baseline to the end of hospital treatment (early efficacy), and at the end of follow-up (late efficacy). Duration of therapy, adverse events, treatment efficacy and reasons for treatment cessation were recorded during the follow-up period. There were five male and 3 female patients, with an average age of 36.8 years (15 - 60 years). Previous treatment modalities in all patients included emollients, topical and systemic corticosteroids and PUVA therapy. The average dose of cyclosporine was 4.5±0,5 mg/kg. Median reduction of skin lesions at discharge was 60%. There was no need for further hospitalization after an average of 10±3.2 days. Mean duration of treatment was 16 months (3 - 24), with an average reduction of skin lesions of 75% during follow-up. Arterial blood pressure increased in 3/8 (37.5%) patients, regardless of their age, with and average increase of systolic blood pressure of 11.9±11.6 mm Hg (median 7.5, 0-30 mm Hg) and diastolic blood pressure of 5.6±12.9 mm Hg (median 0, -10-20). Mean increase in urea concentration was 0.3 mmol/L (11.8%) and creatinine increased only in three patients by 4.2% (median increase 4 mmol/L). Hypertension was found in three patients during follow-up, and there were no other adverse events. In conclusion, based on previous studies and this small case series of hospitalized patients with severe forms of atopic dermatitis including erythroderma, cyclosporine can be regarded as a safe and effective treatment modality and it can be recommended as first line therapy in severe forms of atopic dermatitis refractory to topical therapy and phototherapy. Long term therapy, however, should be avoided and a maximum 1-2 year therapy is recommended.

Key words

Dermatitis, Atopic; Cyclosporine; Treatment Outcome; Immunosuppressive Agents

Atopic dermatitis (AD) is a chronic inflammatory immune-mediated skin disease, that affects 20% of children and up to 10% od adults in developed countries. Most frequently it is well controlled with topical therapeutic modalities. Emollients, topical corticosteroids of mild to moderate potency, and topical calcineurin inhibitors are quite efficient in controlling symptoms and signs in the majority of cases (1). However, based on several studies, 10-20% of patients need systemic therapy (2). Systemic immunosuppressive treatment is an option reserved for severe cases. The most common systemic treatment for atopic dermatitis in everyday practice includes systemic corticosteroids, although there are insufficient valid data to support this (1, 2). Their unfavorable risk/benefit ratio is evident in long term use in AD patients. The most commonly used adjuvant modalities include ultra violet (UV) phototherapy, evaluated in detail in the treatment of AD. This is especially true for narow band (nb) UVB phototherapy, which is considered to be the first line phototherapy option for relieving pruritus in chronic pruritic lichenified forms of the disease (1-3).

Cyclosporine is the treatment of choice for severe atopic dermatitis resistant to other commonly used treatment options. Its favorable therapeutic risk/benefit ratio is well documented in randomized placebo controlled trials, and also in uncontrolled trials (4-6). According to recent therapeutic guidelines for atopic dermatitis published in 2012 by the European Academy of Dermatology and Venereology, cyclosporine should be used in severe chronic forms of atopic dermatitis in a maximum daily dose of 5 mg/kg in two single doses (3). A slow dosage tapering of 0.5-1 mg/kg/day every 2 weeks, depending on treatment effects, is advised after achieving desirable therapeutic efficacy. Long term treatment, however, is not advised and treatment should be ceased after 2 years (3).

In Serbia, cyclosporine is indicated in: solid organ transplant recepients, patients with bone marrow transplantation, nephrotic syndrome, rheumatoid arthritis, endogenous uveitis, psoriasis and atopic dermatitis, and is reimbursed for organ transplant recepients and severe autoimmune diseases. However, approximately only 10% of AD patients are actually treated with this modality and there are no published case series on its use in this region so far. In this article, we evaluated the treatment efficacy and safety of cyclosporine microemulsion in patients with severe atopic dermatitis hospitalized at the Military Medical Academy (MMA) in Belgrade from 2009 to 2012.

Patients and methods

This retrospective analysis included patients with severe forms of atopic dermatitis treated at the Department of Dermatology of the Military Medical Academy in Belgrade from January 1, 2009 to January 1, 2012. The hospital database was used to retrieve patinets' medical records. Atopic dermatitis was diagnosed based on clinical criteria proposed by Hanifin and Rajka (7).

In the period from 2009 to 2012, two hundred patients were treated for atopic dermatitis at the Military Medical Academy in Belgrade. During this period, 20 patients were admitted to the hospital, 17 due to a severe form of the disease. Erythroderma due to atopic dermatitis was defined as involvement of more then 90% of skin surface, while the severe form of AD was defined as involvement of more then 70% of skin surface (suberythroderma), or involvement of more than 50% of skin surface with resistance to other treatment options. In total, 8 of 17 (47.05%) hospitalized patients with severe forms of AD were treated with cyclosporine microemulsion with an initial dose of 4-5 mg/kg. Laboratory tests were done before treatment, 7 days later and/or at the end of hospitalization. Early therapeutic efficacy was evaluated on the last day of hospitalization based on the percentage of skin lesion reduction related to the percentage before treatment. Intensive local treatment with emollients and topical corticosteroids was used as concomitant therapy, as well as oral antihistamines in 7/8 (87.5%) patients. Duration of therapy, adverse events, treatment efficacy and reasons for treatment cessation were recorded during the follow-up of patients.

Results

Baseline disease characteristics of AD patients treated with cyclosporine microemulsion are presented in Table 1.

There were 5 male and 3 female patients, with an average age of 36.8 years (15 - 60 years). In five patients the disease started in childhood, while in three it was adult-onset atopic dermatitis. On admission, three

Table 1. Baseline disease characteristics of atopic dermatitis patients (before treatment)

Patient	Sex	Age	Age of onset	Clinical manifestation	Manifested allergic rhinitis or asthma	Prick tests*	IgE** (IU/ml)	Eosinophilia***	Previous treatment modalities
1.	F	60	55	erythroderma	no	no	539	no	tCS, sCS
2.	M	30	24	erythroderma	no	no	24700	no	tCS, sCS, PUVA
3.	M	27	14	erythroderma	yes	yes	6750	no	tCS, sCS
4.	M	52	32	severe AD	yes	yes	19300	yes	tCS, sCS
5.	F	30	20	severe AD	no	yes	530	no	tCS, sCS
6.	F	15	7	severe AD	no	yes	171	yes	tCS
7.	M	25	7	severe AD	yes	yes	969	no	tCS
8.	M	56	53	severe AD	no	no	80	no	tCS

*, positive prick tests to common inhalatory allergens; ** serum IgE level; *** blood eosinophilia; tCS - topical corticosteroids; sCS - systemic corticosteroids; PUVA - psoralen ultraviolet A irradiation

patients also had manifestations of allergic rhinitis and bronchial asthma. The mean IgE concentration was 754 IU/ml (80-24700), 7/8 (87.5%) patients had serum immunoglobulin E (IgE) levels above 100 IU/ml, and in 3 patients IgE was above 1000 IU/ml. Eosinophilia was noted in 2/8 (25%) patients. Previous treatment modalities in all patients included emollients, topical and systemic corticosteroids, while one patient was also treated with psoralen plus ultra violet A (PUVA) therapy (Table 1).

The initial dose of cyclosporine was 4 mg/kg/day in four patients and 5 mg/kg/day in another four patients, with the average dose of 4.5±0,5 mg/kg/day. The first therapeutic effects were evaluated at discharge showing 60% mean reduction of skin lesions. There was no need for further hospitalization after an verage of 10±3.2 days. Finally, taking into account further follow-up, mean duration of treatment was 16 months (3 - 24), with an average reduction of 75% of skin lesions. In 3 patients the treatment was discontinued when satisfying clinical response was achieved, and in 5 when the maximum recommended length of treatment was over with a reduction of 75% of skin lesions. Cyclosporine was tapered to a minimum average dose of 1.45 mg/kg/day at the end of treatment. The treatment parameters are presented in Table 2.

Blood pressure and serum levels of urea and creatinine, measured at baseline and at discharge, as well as adverse events during the follow-up period are presented in Table 3. Arterial blood pressure increased in 3/8 (37.5%) patients, regardless of age, with and average increase of systolic blood pressure of 11.9±11.6 mm Hg (median 7.5, range 0 - 30 mm Hg) and diastolic blood pressure of 5.6±12.9 mm Hg (median 0, range -10 - 20). Mean increase in urea concentration was 0.3 mmol/L (11.8%) and creatinine increased only in three patients by 4.2% (mean increase 4 mmol/L). Hypertension was recorded in three patients during follow-up, and there were no other adverse events.

Discussion

Atopic dermatisis, or atopic eczema is a chronic, relapsing inflammatory skin disease commonly

Table 2. Treatment parameters of AD patients treated with cyclosporine

Patient	Initial dose (mg/kg)	Duration of hospitalization (days)	Treatment efficacy at discharge (% of skin lesion regression)	Duration of treatment (months)	Treatment efficacy at the end of follow-up (% of skin lesion regression)	Dose of cyclosporine before withdrawal (mg/kg)	Reasons for withdrawal of treament
1.	5	12	70	14	75	0.4	satisfying efficacy
2.	4	7	50	12	75	1.5	duration of treatment
3.	4	14	50	3	75	1.5	satisfying efficacy
4.	5	15	90	6	100	2	complete regression
5.	5	9	70	18	75	1.4	duration of treatment
6.	4	8	70	24	100	NA	duration of treatment
7.	4	8	50	24	100	1.25	duration of treatment
8.	5	7	50	24	75	NA	duration of treatment
Mean±SD	4.5±0.5	10±3.2	62.5±14.8	15.6±8.3	84.3±12.9	1.34±0.5	-
Mean min-max	4.5 4-5	8.5 7-15	60 50-90	16 3-24	75 75-100	1.45 0.4-2	-

affecting persons with personal and family history of atopy, as well as bronchial asthma, and allergic rhinoconjunctivitis. It is one of the most common dermatoses, affecting up to 20% of children and 5-10% of adult persons in developed countries (1-4).

In up to 80% of patients the disease is mild, and it can be contolled with topical treatment. Based on European Guidelines, basic treatment for all stages of AD is emollient therapy and proper skin care with steroid sparing effects. Addition of topical corticosteroids of mild to moderate potency can efficiently control flare-ups. In patients with frequent relapses, topical calcineurin inhibitors can provide long-term control of the disease with steroid-sparing effects and prevention of flares (2).

However, up to 10-20% of patients with moderate or severe AD fail to control flare-ups with topical treatment. They need to use either adjuvant photoherapy or systemic immunosuppressants such as systemic corticosteroids which are most commonly used, and cyclosporine which is considered to be the first line option based on current guidelines (3). Azathioprine, methotrexate and mycophenolate mofetil are used in patients refractory to cyclosporine treatment. In recent years, biologic therapy with infliximab, anti tumor necrosisis factor–alpha (TNF-α), rituximab (anti CD-20) and omalizumab (anti-IgE antibody) were evaluated in small case series with variable results, and may be considered in the treatment of patients refractory to any other treatment modality including cyclosporine and other forms of immunosuppressive agents (3).

Cyclosporine was evaluated in the treatment of atopic dermatitis in more than 20 clinical trials (24 based on PubMed search), including 10 randomized

Table 3. Blood pressure and serum levels of urea and creatinine during cyclosporine therapy

Patient	Systolic blood pressure (mmHg)			Diastolic blood pressure (mmHg)			Urea serum level			Creatinine serum level			Adverse events during follow-up
	Before*	After**	Increase	Before*	After**	Increase	Before*	After**	Increase	Before*	After**	Increase	
1.	120	125	5	80	85	5	3.3	4.1	0.8	85	75	-	hypertension
2.	120	150	30	80	100	20	2.8	3	0.2	74	70	-	hypertension
3.	120	130	10	80	80	0	5.9	5.9	0	93	103	10	none
4.	110	140	30	80	90	10	6.7	7.1	0.4	105	109	4	hypertension
5.	120	125	15	80	80	0	3.3	4.8	1.5	82	76	-	none
6.	120	120	0	80	70	-10	7.2	5.4	-1.8	73	49	-	none
7.	120	125	5	70	70	0	4	4	0	97	101	4	none
8.	130	140	10	80	80	0	4.4	5.9	1.5	73	59	-	none
Mean ±SD	120 ±5.3	131.8 ±10.3	13.1 ±1.3	76 ±7.4	81.9 ±10	3.12 ±8.8	4.7 ±1.7	5.0 ±1.3	0.32 ±1.05	85.3 ±12.1	80.3 ±21.9	6 ±3.46	-
Mean min-max	120 110-130	127.5 120-150	10 0-30	80 60-80	80 70-100	0 -10-20	4.2 2.8-7.2	5.1 3-5.9	0.3 -1.8-1.5	83.5 73-105	75.5 70-109	4 4-10	-

* - before treatment; **- after hospitalization

controlled trials. A placebo controlled trial design was used in 3 studies; 3 studies were on cyclosporine efficacy in relation to two different doses, different formulations and intermittent vs. continuous treatment, respectively, and the remaining 4 studies compared cyclosporine to topical tacrolimus, systemic corticosteroids and enteric coated mycophenolate mofetil, respectively (5, 6, 8-15). Based on these studies and given the fact that there are no available trials evaluating systemic corticosteroids with unfavorable benefit/risk ratio, cyclosporine is nowadays regarded to be the first line therapy for severe forms of atopic dermatitis refractory to topical therapy and phototherapy. Microemulsions of cyclosporine show an earlier onset of peak values of efficacy compared to enteric coated mycophenolate mofetil, while in the maintenance phase both drugs are equally effective. In the study comparing cyclosporine therapy with systemic corticosteroids, a 6-week therapy with cyclosporine was more effective than 2-week therapy with systemic corticosteroids, but the duration of treatment was significantly shorter in the group of patients treated with corticosteroids with fast dose tapering (15). Interestingly, in one randomized study that compared effects of topical treatment with tacrolimus ointment 0.1% and oral cyclosporine in adult patients affected by atopic dermatitis, tacrolimus ointment was more effective than oral cyclosporine 3 mg/kg/day after 14-35 days of treatment (12).

The initial dose of cyclosporine in our study was 4.5 mg/kg/day on average, close to the maximum recommended dose for AD, since this group of patients was considered to have severe AD refractory to other treatments. The usual recommended initial dose in moderate-to-severe atopic dermatitis is 2.5-3.5 mg/kg/day and should be increased to a maximum of

5 mg/kg/day. Microemulsions of cyclosporine show an earlier onset (usually after 14 days) of peak efficacy compared to traditional formulations. In our patients, a significant partial regression of atopic dermatitis (when there was no further need for hospitalization), was achieved after 10 days on average. Higher initial dose and more intensive local therapy with emollients and topical corticosteroids contributed to the observed efficacy. After hospitalization, cyclosporine was tapered by 0.5-1 mg/kg/day every 2-4 weeks after clinical efficacy was achieved.

In our study, the safety of cyclosporine was confirmed by clinically insignificant increase of urea and creatinine serum levels, which were not above the reference values. The average increase in systolic blood pressure was 10 mm Hg and of diastolic blood pressure 5 mm Hg, which did not compromise the treatment. During the follow-up period, hypertension was found in three patinets, but did not compromise the treatment. The duration of treatment was 3-24 months. Long term therapy, however, should be avoided and a maximum 1-2 year therapy is recommended in order to avoid potential side effects. Since continuous oral administration of the calcineurin inhibitor - cyclosporine is associated with an increased photocarcinogenicity risk in solid organ transplant patients, UV protection with sunscreens is advised. In regard to the lymphoma risk, diagnosis of AD is associated with an increased risk for lymphoma. Moreover, risk-adjusted analysis showed that severity of AD was associated with a 3-fold increase in the risk of lymphoma (16). It is possible that misclassification of cases is partially responsible for the increased risk of lymphoma found in patients with severe AD. High incidence of mycosis fungoides (MF) among cases makes misdiagnosis a plausible hypothesis. MF and Sezary syndrome may present with cutaneous manifestations that resemble chronic severe adult AD and it is possible that some cases were in fact MF cases that had been misdiagnosed as AD (17, 18). In our study, atopic dermatitis was diagnosed based on clinical criteria by Hanifin and Rajka (7). The main limitation of our study was its retrospective character. Since Hanifin and Rajka published their diagnostic criteria, clinical features are critically evaluated, and it is suggested that in addition to the presence of at least 2 of 3 principal criteria (pruritus, typical morphology and distribution, chronic or chronically relapsing course), the presence of allergen-specific IgE, should be mandatory for diagnosis. In patients who fulfill the principal criteria, but in whom allergen-specific IgE cannot be detected, even on repeated occasions, a number of diagnoses in which atopic dermatitis-like symptoms may occur should be excluded: Wiskott–Aldrich syndrome, hyper-IgE syndrome, phenylketonuria, Netherton's syndrome, Job's syndrome, agammaglobulinemia, IgA defficiency, ataxia telangiectasia and so on (19).

In conclusion, based on this small case series of hospitalized patients with severe forms of atopic dermatitis including erythroderma, cyclosporine may be regarded as a safe and effective treatment modality and it can be recommended as the first line therapy in severe forms of atopic dermatitis refractory to topical therapy and phototherapy.

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Abbreviations

AD - atopic dermatitis
UV - ultra violet
IgE - immunoglobuline E
PUVA - psoralen plus ultraviolet A
TNF-α - tumor necrosis factor-alpha

Lečenje teškog oblika atopijskog dermatitisa sa ciklosporinom: prikaz serije od osam pacijenata

Sažetak

Uvod. Atopijski dermatitis je hronično inflamatorno oboljenje kože koje se kod većine pacijenata leči lokalnom primenom emolijenasa, koritkosteroida i kalcineurinskih inhibitora. Međutim, kod 10–20% bolesnika neophodna je sistemska terapija, a najčešće korišćeni modalitet sistemske terapije u svakodnevnoj praksi su sistemski kortikosteroidi, iako nema dovoljno proverenih podataka koji podržavaju njegovu upotrebu. S druge strane, efikasnost i neželjeni efekti ciklosporina dobro su definisani u randomizovanim kontrolisanim studijama i prema savremenim vodičima on je preporučen kao modalitet prvog izbora za teške oblike atopijskog dermatitisa, koji nemaju dobar terapijski odgovor na lokalnu terapiju i fototerapiju. Međutim, svega oko 10% pacijenata sa atopijskim dermatitisom, koji imaju indikaciju za lečenje ciklosporinom, zaista se i leči ciklosporinom. Nema objavljenih serija slučajeva o njegovoj upotrebi u ovom regionu. U ovom članku, mi smo analizirali efikasnost i bezbednost lečenja ciklosporinom kod pacijenata sa teškim oblikom atopijskog dermatitisa, lečenih na Vojnomedicinskoj akademiji u Beogradu od 2009. do 2012. godine.

Ispitanici i metode. Učinjena je restrospektivna analiza bolesnika sa teškim oblikom atopijskog dermatitisa lečenih na Klinici za kožne i polne bolesti VMA u periodu 2009–2012. godine a podaci su dobijeni iz bolničke baze podataka i medicinske dokumentacije. U navedenom periodu, približno 200 pacijenata lečeno je od atopijskog dermatitisa, 20 pacijenata je primljeno na bolničko lečenje, a 17 sa teškim oblikom bolesti. Ukupno 8 od 17 (47,05%) hospitalizovanih pacijenata sa težim oblikom bolesti ili eritrodermijom izazvanom atopijskim dermatitisom lečeni su ciklosporinom sa prosečnom dozom od 4,5 mg/kg TT. Laboratorijske analize su uzete pre tretmana, posle 7 dana i/ili na kraju hospitalizacije. Terapijska efikasnost je ocenjena na osnovu procenta redukcije kožnih lezija

od početka terapije do poslednjeg dana hospitalizacije (rana efikasnost) i do poslednjeg dana praćenja (kasna efikasnost). Trajanje terapije, neželjeni efekti tokom terapije, efikasnost lečenja i razlog za prekid lečenja beleženi su na kontrolnim pregledima pacijenata.

Rezultati. Ukupno je lečeno osam pacijenata, pet muškaraca i tri žene, prosečne starosti 36,8 godina (15–60 godina). Prethodni modaliteti lečenja kod svih bolesnika bili su topikalni i sistemski kortikosteroidi, PUVA terapija i emolijensi. Prosečna doza ciklosporina je bila 4,5 ± 0,5 mg/kg. Srednja vrednost redukcije promena na koži poslednjeg dana hospitalizacije iznosila je 60%, posle prosečno vremena hospitalizacije od 10 ± 3,2 dana. Medijana trajanja terapije bila je 16 meseci (3–24), sa srednjom vrednošću redukcije promena na koži tokom praćenja od 75%. Arterijski krvni pritisak je bio povećan kod 3 od 8 (37,5%) bolesnika, bez obzira na starost, sa prosečnim porastom sistolnog krvnog pritiska od 11,9 ± 11,6 mm Hg (prosečno 7,5, 0/30 mm Hg) i dijastolnog krvnog pritisaka 12,9 ± 5,6 mm Hg (prosečno 0, -10–20). Srednje povećanje vrednosti uree u serumu iznosilo je 0,3 mmol/l (11,8%), dok su vrednosti kreatinina bile povećane kod tri bolesnika (prosečno 4 mmol/l). Tokom praćenja, hipertenzija je zabeležena kod tri bolesnika, dok ostali neželjeni efekti nisu evidentirani.

Zaključak. Na osnovu prethodnih studija i ove serije malog broja slučaja kod hospitalizovanih bolesnika sa teškim oblikom atopijskog dermatitisa, uključujući eritrodermiju, ciklosporin se može smatrati bezbednom i efikasnom terapijom i može se preporučiti kao prva linija terapije kod obolelih od teških oblika atopijskog dermatitisa koji ne reaguju na lokalnu terapiju i fototerapiju. Dugotrajnu terapiju, međutim, treba izbegavati, a preporučuje se maksimalno jedna do dve godine terapije.

Ključne reči

Atopijski dermatitis; Ciklosporin; Ishod lečenja; Imunosupresivni lekovi

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La Roche-Posay. Posvećen dermatologiji.

Keratitis, Ichthyosis and Deafness (KID) Syndrome – a Case Report

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Abstract

Keratitis, ichthyosis and deafness (KID) syndrome is a rare congenital ectodermal dysplasia characterized by ichthyosiform hyperkeratosis of the skin, neurosensory hearing loss and vascularizing keratitis. It is inherited as an autosomal dominant trait, now known to be due to mutations in the connexin gene.

This paper presents a case of a 20-year-old male patient with erythrokeratodermia and mild scaling since birth. He presented mild hearing impairment at the age of two and often suffered from eye inflammations. On admission, his clinical picture was typical of KID syndrome with erythrokeratodermia, neurosensory deafness, vascularizing keratitis, alopecia, palmoplantar keratosis, and nail dystrophy. The patient also had a history of recurrent infections, especially bacterial and candidal infections of the skin, auditory canals and eyes. Despite extensive skin, ocular, ear and hair manifestations, his physical and psychomotor growth and development were normal.

Adjuvant balneotherapy in Prolom Spa, along with emollient creams, significantly reduced cutaneous manifestations in our patient.

Key words

Keratitis; Ichtyosis; Deafness; Syndrome; Balneology; Baths; Treatment Outcome; Connexins

Keratitis, ichthyosis and deafness (KID) syndrome is a rare congenital disorder which is included in the broad category of ectodermal dysplasias. The acronym was made in order to highlight the main features of the syndrome, skin lesions, neurosensory hearing loss and vascularizing keratitis (1, 2). Burns first described a disorder with these symptoms in 1915 (3), and Skinner et al, proposed KID as the term for this syndrome in 1981 (4). However, taking into consideration that keratitis is not present in all cases, and that the syndrome actually presents features of a hystrix-like ichthyosis combined with erythrokeratoderma, a new hystrix-like ichthyosis with deafness (HID) and KED (keratodermic ectodermal dysplasia) syndrome were proposed (5), but not accepted (1, 6). HID syndrome is now regarded as an allelic variant of KID (6).

Case report

A 20-year-old male patient was referred to Prolom Spa accompanied by his father.

The patient's history revealed erythrokeratodermia and mild scaling since birth. With time, erythematous hyperkeratotic plaques developed on elbows, knees, dorsal sides of hands and feet, with marked thickening (leather-like consistency) of palms and soles. Lesions spread to the face and the concha of the ears. Since the age of two, the patient frequently developed whole body erythema. At the same time, his parents observed hearing impairment as well. He often suffered from eye inflammations. The patient was treated by a dermatologist, ophtalmologist, otorinolaryngologist and visited a psychiatrist on a regular basis. His personal history revealed presence of documented

bilateral keratopathy with corneal neovascularization, neurosensory hypoacusis and inguinal hernia for which he underwent surgery in childhood, as well as recurrent infections, especially bacterial and candidal infections of the skin, auditory canals and eyes. No other diseases were diagnosed. Family history showed no consanguinity, or similar disorders. The patient complained of itching, and had speech, hearing and vision problems. He suffered from insomnia in the past several months.

On admission, the patinet's whole body skin was diffusely thickened showing follicular keratosis. Prominent erythema affected the face and furrowing erythematous plaques were present around the mouth. Bilateral keratoconjunctivitis and corneal vascularization were also present (Figure 1). The patient presented with scalp hypotrichosis and scarring alopecia, with thick crusty squamous plaqes with rhagades showing sanguinolent exudation (Figure 2). The scalp hair was sparse, fine, brittle, pale in colour and slow growing. The eyebrows and eyelashes were thin or absent. Body, pubic and axillary hair was also affected.

Rough hyperkeratotic plaqes were found on the elbows, knees, dorsal aspects of the hands, and feet (Figures 3, 4, 5, 6). Diffuse palmoplantar hyperkeratosis was reticular in pattern and yellowish in color. All nail plates were short, thick, slow growing and yellowish.

Routine blood tests and urine analysis were within the range of reference values. The patient was examined by a psychiatrist and neurologist. The scores on the psychomotor development scale were within the normal range.

The therapy included direct topical application of peloid combined with bland emollient creams, mineral water baths and drinking of mineral water.

After 15 days of balneotherapy in Prolom Spa, the patient's skin has improved substantially (Figures 7-12). The erythema was less intense, hyperkeratosis has substantially reduced, keratodermic plaques on the scalp and rhagades have disappeared, and exudation has ceased. The itching was considerably reduced, and sleep restored.

Discussion

KID syndrome is a complex disorder of the ectodermal cell layer. In the developing embryo, this layer gives rise to a variety of tissues, thus, in addition to the skin, other ectodermal tissues are also affected, including corneal and inner ear epithelium (6). KID syndrome is a rare disorder. Most often it occurs sporadically in both sexes (7). According to literature data, during the period from its first description by Burns up to 2006 and 2012, over 90 and 100 cases of KID syndrome were reported, respectively (8, 9).

The main diagnostic criteria for KID syndrome include erythrokeratodermia, neurosensory deafness, vascularizing keratitis, palmoplantar keratosis and alopecia. The two latter are reminiscent of Clouston syndrome. According to the literature review of Caceres-Rios and associates (5), neurosensory deafness occurs in 90% cases, erythrokeratodermia in 89%, vascularizing keratitis in 79%, alopecia in 79%, and reticular hyperkeratosis of palms and soles in 41%. KID syndrome may also be associated with follicular keratosis, hypohidrosis, mental retardation, cryptorchidism, breast hypoplasia, short stature, oral ulcerations and dental anomalies, which emphasize the complexity and diversity of phenotypes caused by dominant-acting connexin mutations and the overlap in genotype/phenotype correlation in the connexin disorders (10).

Acneiform eruptions and cysts on the upper trunk are common, while chronic abscesses and discharging sinuses may present late complications in some patients such as in the case report on KID syndrome with follicular occlusion triad consisting of hidradenitis suppurativa, acne conglobata, and dissecting folliculitis of the scalp (perifolliculitis capitis abscedens et suffodiens) (11). Zhang and Li described a case of KID syndrome with the Dandy–Walker syndrome malformations of the posterior fossa eg., bilateral cerebral atrophy, left more prominent than right, and dysplasia of cerebellar vermis (12). One patient presented with tumors originating from hair follicle stem cells: specifically trichilemmal cysts in early lesions, proliferating trichilemmal tumors in moderate duration lesions, and malignant proliferating tumors in advanced lesions (13). Patients with KID syndrome present with a higher predisposition to develop cutaneous neoplasms (squamous cell carcinoma of the skin and tongue have been described in more than 10% of patients, and may occur during childhood) (5, 7, 10,

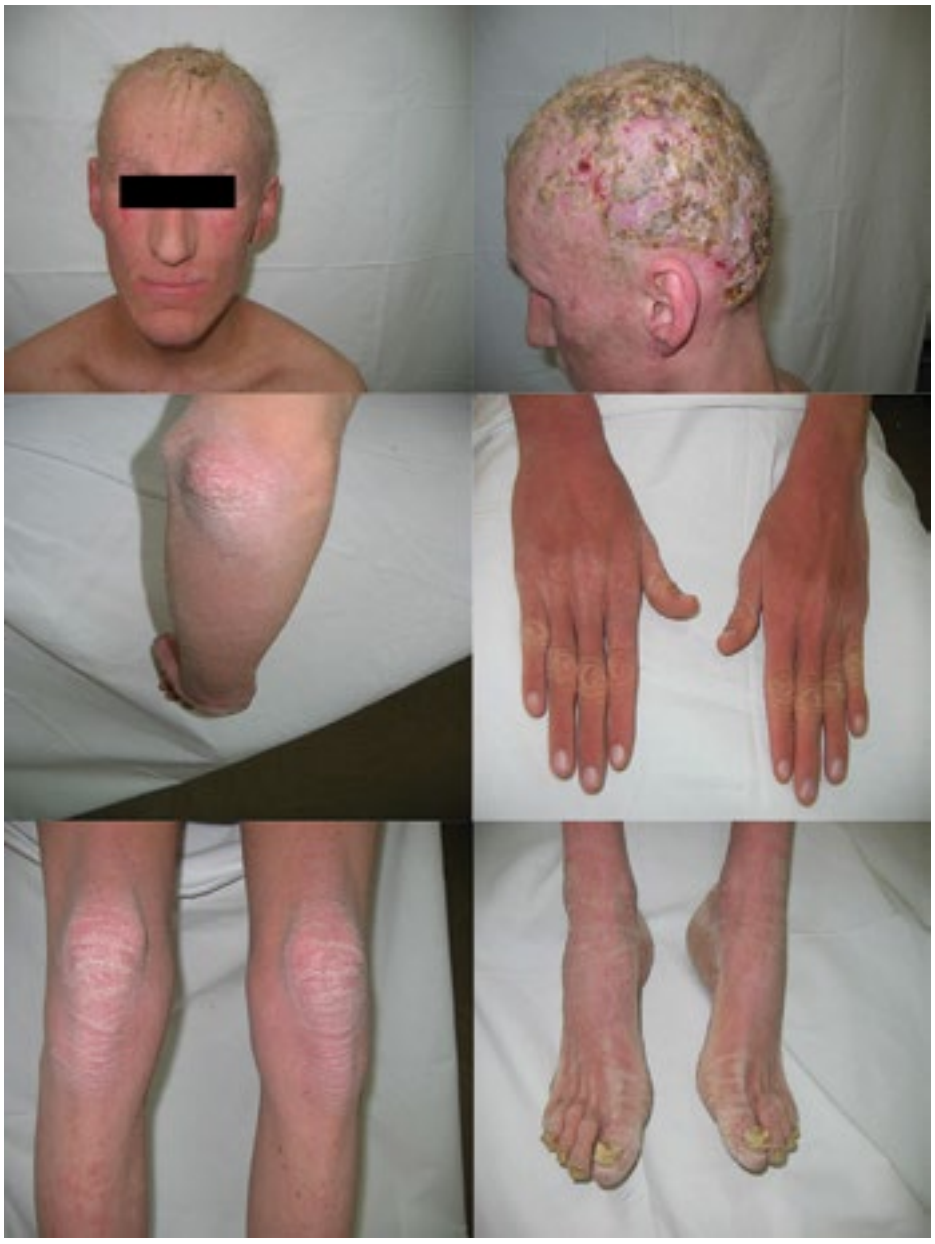

Figure 1. The patient before balneotherapy

14, 15), as well as infections (bacterial, fungal, and viral) (10, 16).

Histopathological and electron-microscopic findings of the skin are non-specific (17). Ortho-hyperkeratosis was reported, and hyperkeratotic plugs occluding the follicular and sudoriferous gland openings were described (7). The diagnosis is established by genetic tests or, after infancy, based on physical features (supported by audiological and ophthalmological evidence of neurosensory deafness and vascularizing keratitis in early childhood), just like in the majoity of other syndromes of ectodermal dysplasia (18).

A great number of sporadic cases were reported due to high rates of new mutations (8). Most reported cases of KID syndrome have been sporadic, but inheritance was evident in several families (2, 19, 20). Although autosomal recessive inheritance was proposed (21), more recent literature shows evidence of spontaneous mutation inherited as an autosomal

dominant trait (22). Mutation in gap junction proteins, namely connexins, has been considered a primary cause of the disorder and occurs in the GJB2 gene inconding connexin 26 (Cx26) (23). Cx26 is a gap junction protein which participates in the intra-cellular communication and controls cellular differentiation of ectoderm-derived epithelial layers of the cochlea, cornea, palmoplantar epidermis, sweat glands and ductal epithelium (8). Cx26 is also strongly expressed in the hair follicles (24). The commonest GJB2 mutation found in KID syndrome is the *p.Asp50Asn* mutation, which occurs in 80% of patients and accounts for most of the familial cases (2, 20). Patients with *p.Ser17Phe* mutation may present with serious forms of the disorder, with a higher risk for tongue cancer (2).

To emphasize the overlap in genotype–phenotype correlation in the connexin disorders,

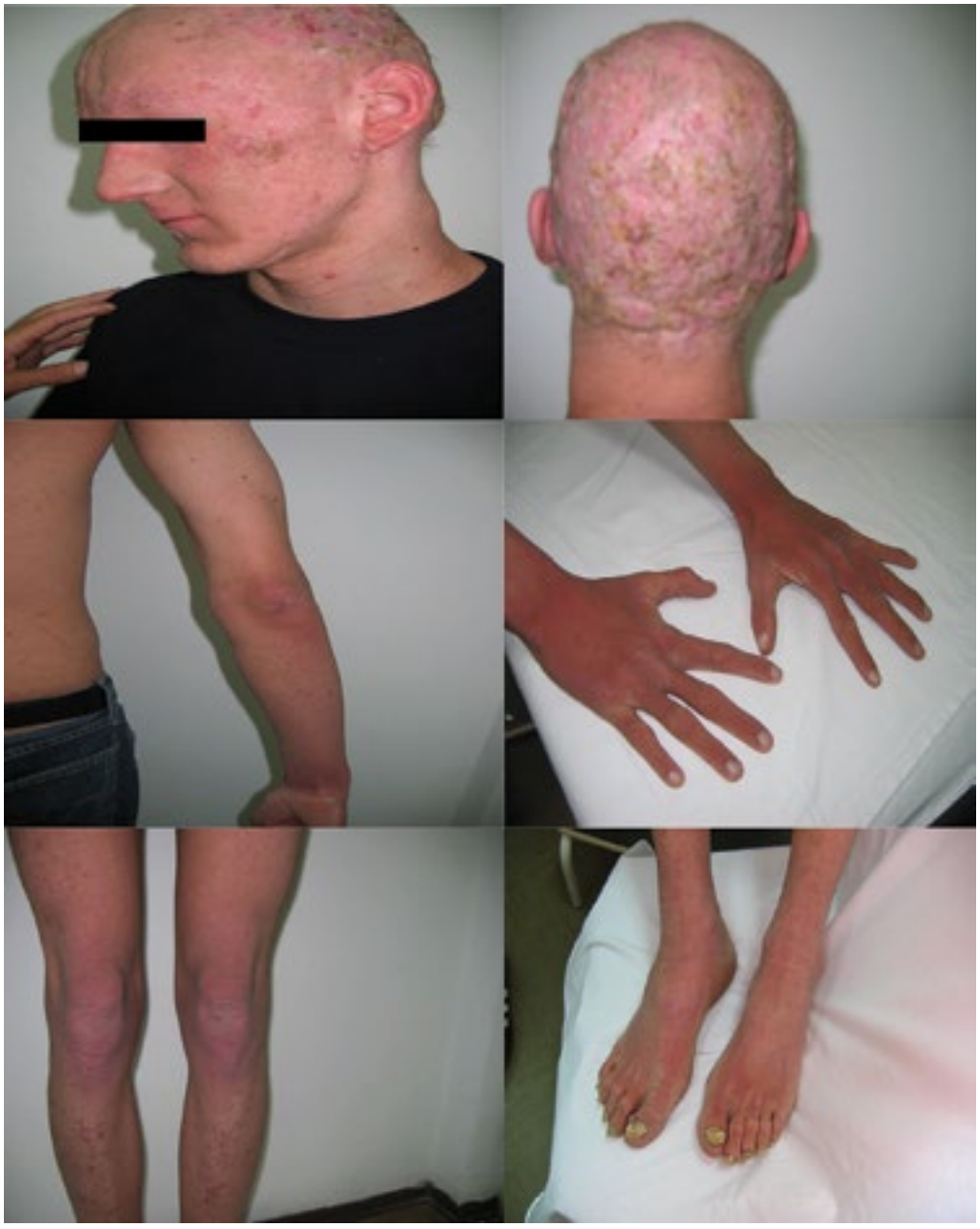

Figure 2. The patient after balneotherapy

patients carrying identical mutations in Cx30 (V37E) have been shown to have classical Clouston syndrome (autosomal dominant hidrotic ectodermal dysplasia) and a KID syndrome-like phenotype (24). Jan and associates identified the mutation of GJB6 gene inconding Cx30 in a patient with KID syndrome and congenital atrichia (25). These support the genetic heterogeneity of the KID syndrome since mutation in Cx26 and Cx30 can cause overlapped phenotypes (25). Fozza and associates described a patient with KID syndrome and peripheral T-cell lymphoma, with a dilemma whether this was random association (26). Natsuga et al. examined the possibility of modifying effects (modifier genes are defined as genes that affect the phenotypic expression of another gene) of mutation in the keratin 17 gene on KID syndrome (27). However, due to the limited scope of this study (single case report) authors could not determine the clinical significance of the obtained findings (27).

Treatment of patients with KID syndrome requires a multidisciplinary approach. It is necessary to ensure cooperation among a dermatologist, ophthalmologist, otorhinolaryngologist, psychiatrist, speech therapist and other specialists if required. Skin changes should be treated with keratolytics and emollients administered topically, and antibiotics and antimycotics in case of secondary infections. Systemic administration of retinoids failed to yield satisfactory results (28). However, Zhang and associates reported good results when treating children with ichthyosis, though the exact risk/benefit ratio has not been fully established (29).

As far as the literature data available to us are concerned, there are no reports in the world literature on using balneotherapy in KID syndrome. Taking into consideration our treatment results, we believe that it would be useful to point out some features of the mineral water, peloids and mechanisms of action of balneotherapy in Prolom Spa.

In recent decades, balneotherapy has been rediscovered and there is an increased interest in studying effects of natural resources on human health. The main therapeutical factor of balneotherapy is the mineral water – natural solution formed under the effect of specific geological ingredients and "chemical-physical dynamics", without microorganisms and with a great therapeutical potential. Fundamental and clinical investigations carried out in spas worldwide, showed therapeutical potentials for a great number of skin diseases, with a minimum risk of adverse effects (30 - 39). Bathing in mineral water is safe, efficient and has beneficial effects on health and recovery. The therapeutical effect originates from local interactions between mineral water, peloids and skin surface.

Prolom water belongs to the category of sodium-hydrocarbonate, alkaline, oligomineral and hypothermal waters (40), and in terms of hydromorphology, it belongs to mineral waters of the "Serbian Crystal Core", coming from the depth of about 200 m (41). The water temperature is 26 - 31.5^{0}C, and pH ranges from 8.7 to 9.2. It contains the following cations: Na, K, Ca, Mg, Sr, Fe, Al, Li, a weak electrolyte of metasilicic acid and free hydrogen sulphide gas.

Mineral water has mechanical, thermal and chemical effects (42). Mechanical effect is realized through hydrostatic pressure and thrust through mechanoreceptors and modified thermal and chemical effect, manifesting in increased skin permeability, increased penetration of minerals, keratolysis, increased muscle tonus and reduced pain intensity. Thermal effects include increased enzyme activity, accelerated catalytical biochemical processes, increased local metabolic processes, redistribution of blood, and sedation of the vegetative nervous system. Chemical matters from mineral waters and peloids may have indirect or direct effects on different organs and systems and modify the effects of thermal and mechanical factors (42). Chemical components of mineral waters and peloids cause morphological changes in the skin and its structures. The effects of balneotherapy on the skin include: skin softening, increased permeability, regulation of the skin surface layers (anti-proliferative effect), reduction of inflammation and irritation, increased resistance to microorganisms, anti-allergic effect, fast epithelialization, and improved microcirculation.

All these effects were manifested in our patient.

Conclusion

This paper presents a case of a patient suffering from a typical KID syndrome: erythrokeratodermia,

neurosensory deafness, vascularizing keratitis, alopecia, palmoplantar hyperkeratosis, onychodystrophy and recurrent chronic skin infections.

Adjuvant balneotherapy, along with emollient creams, significantly reduced cutaneous manifestations in our patient.

Abbrevations

KID - Keratitis, ichthyosis and deafness
HID - Hystrix-like ichthyosis with deafness
KED - Keratodermic ectodermal dysplasia)

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KID sindrom - prikaz slučaja

Sažetak

Uvod. KID sindrom (eng. *keratitis, ichthyosis, deafness*) kongenitalni je nasledni epidermalni poremećaj koji se manifestuje kožnim lezijama, neurosenzornim gubitkom sluha i vaskularizujućim keratitisom. Uzrok oboljenja su mutacije u genu GJB2 koji kodira sintezu koneksina 26 (Cx26); koneksini (eng. *connexin*) jesu proteini koji učestvuju u unutarćelijskoj komunikaciji (eng. *gap junction*); Cx26 kontroliše ćelijsku diferencijaciju u tkivima poreklom iz ektoderma kao što su epitel unutrašnjeg uva i rožnjače, epidermis u palmoplantarnoj koži, folikulima dlake i znojnim žlezdama. Opisani su sporadični slučajevi obolelih do kojih dolazi zbog pojave novih spontanih mutacija, ali i slučajevi sa porodičnim javljanjem i autozomno dominantnim nasleđivanjem.

Prikaz slučaja. Osoba muškog pola stara 20 godina upućena je na banjsko lečenje u Prolom banju u pratnji oca. Iz anamneze se saznaje da od rođenja ima promene na koži u vidu crvenila i ljuspanja. Vremenom se crvenilo smanjilo, ali su se javila zadebljanja na laktovima, kolenima, šakama i stopalima, na čelu i ušnim školjkama. Od druge godine života često se dešavalo da mu se zacrveni koža čitavog tela, njegovi roditelji su primetili da on slabije čuje, a često je imao i „zapaljenje očiju". Lečili su ga: dermatolog, oftalmolog, otorinolaringolog i psihijatar. Od ranijih bolesti navodi da je operisan zbog ingvinalne kile. Iz porodične anamneze se saznaje da nije bilo obolelih srodnika ni konsangviniteta.

Dermatološki status na prijemu. Koža celog

tela bila je difuzno zadebljala sa folikularnom keratozom dok su na licu dominirali eritem i izbrazdane eritematozne ploče oko usta; obostrano sklere su bile injicirane; na kosmatom delu glave bila je prisutna hipotrihoza sa ožiljnom alopecijom, naslagama debelih krustoskvama, ragadama i secerniranjem sukrvičavog sadržaja; obrve su bile znatno proređene, trepavice su nedostajale, kao i dlake na telu u aksilarnoj i pubičnoj regiji; na laktovima i kolenima dominirali su grubi hiperkeratotični plakovi; difuzna palmoplantarna hiperkeratoza imala je mrežast izgled sa žućkastim koloritom; nokatne ploče su bile zadebljale, žućkasto prebojene; na dorzumima šaka i stopala i prstima ruku i nogu bili su prisutni keratotični plakovi. Od subjektivnih tegoba pacijent je naveo osećaj svraba, postojao je poremećaj sna, govora, sluha i vida.

Laboratorijski nalazi. Rezultati rutinskih anliza uključujući i osnovne biohemijske parametre bili su u granicama referentnih vrednosti.

Konsultativni pregledi. Izveštaji konsultovanih specijalista (prema priloženoj pismenoj dokumentaciji), govorili su o prisustvu keratopatije s neovaskularizacijom kornee, neurosenzornom smanjenju sluha i očuvanom psihomotornom razvoju.

Terapija. U toku 15 dana boravka u Prolom banji, primenjeni su peloid direktno na kožu, emolijentne kreme, podvodna masaža i pitke kure sa mineralnom vodom.

Efekti terapije. Nakon petnaestodnevnog lečenja, stanje na koži je značajno poboljšano: eritem i hiperkeratoza su značajno smanjeni, sa kože poglavine su uklonjene keratodermijske ploče, ragade su epitelizovale, eksudacija je sanirana; svrab je postao znatno manji; vratio se san.

Diskusija. KID sindrom predstavlja kompleksni poremećaj ektoderma, u kome su pored epidermisa zahvaćena i druga ektodermalna tkiva, epitel rožnjače i unutrašnjeg uva. Glavni dijagnostički kriterijumi su: eritrokeratodermija, neurosenzorna gluvoća, vaskularizujući keratitis, alopecija i palmoplantarna keratoza, dva poslednja prisutna su i u Cloustonovom sindromu (hidrotska ektodermalna displazija). Oboleli od KID sindroma takođe mogu ispoljiti folikularnu keratozu, hipohidrozu, mentalnu retardaciju, kriptorhizam, hipoplaziju dojki, nizak rast, oralne ulceracije i anomalije zuba, što govori o složenosti i mogućim preklapanjima između raličitih genotipova/fenotipova izazvanih mutacijama u koneksin genima. Najčešća GJB2 mutacija u KID sindromu je, *p.Asp50Asn* mutacija: ona je prisutna kod oko 80% obolelih, i odgovorna je za najveći broj porodičnog javljanja sindroma. Kod osoba koje imaju *p.Ser17Phe* mutaciju može se razviti teža manifestacija bolesti sa povišenim rizikom od dobijanja karcinoma jezika. O prisustvu preklapanja između različitih genotipova i fenotipova kod osoba kod kojih postoje poremećaji koneksina govori i prisustvo identične *V37E* mutacije u Cx30 (GJB2) genu kod osoba koje imaju znake klasičnog Cloustonovog sindroma i osoba sa KID fenotipom. Takođe, dokazana je mutacija na GJB6 genu koji kodira sintezu Cx30 kod osobe sa KID sindromom i kongenitalnom atrihijom. Genetska heterogenost KID sindroma ogleda se znači u preklapanju fenotipova koje izazivaju mutacije na dva različita gena koji kodiraju sintezu Cx26 (GJB2) i Cx30 (GJB6) koneksina.

Oboleli imaju povišen rizik za nastanak karcinoma skvamoznih ćelija kože i jezika i za razvoj infekcija (bakterijskih, gljivičnih, virusnih).

Za lečenje kožnih promena lokalno se primenjuju: keratolitici i emolijensi, u slučajevima sekundarne infekcije antibiotici i antimikotici; sistemska primena retinoida nije dala očekivane terapijske efekte.

U nama dostupnoj literaturi nismo našli podatke o primeni balneoterapije kod KID sindroma. S obzirom na naše rezultate lečenja smatramo da je korisno da obrazložimo osobine mineralne vode i peloida i mehanizme dejstva primenjene terapije u Prolom banji.

Pod uticajem hemijskih komponenti mineralnih voda i peloida dolazi do morfoloških promena na koži i njenim strukturama. Efekti balneoterapije na koži su: omekšavanje kože, povećanje propustljivosti, regulacija površnih slojeva kože (antiproliferativno dejstvo), redukcija inflamacije, redukcija iritacije, povećanje rezistencije na mikroorganizme, antialergijski efekat, brza epitelizacija, poboljšanje mikrocirkulacije. Svi navedeni efekti su doveli do značajnog poboljšanja kod našeg pacijenta.

Zaključak. Prikazan je bolesnik sa tipičnom slikom KID sindroma: eritrokeratodermija, neurosenzorna gluvoća, vaskularizujući keratitis, alopecija, palmoplantarna hiperkeratoza, onihodistrofija i rekurentne hronične infekcije. Adjuvantna balneoterapija je u kombinaciji sa emolijentnom kremom ublažila kutane manifestacije ovog sindroma.

Ključne reči

Keratitis; Ihtioza; Gluvoća; Sindrom; Balneologija; Kupke; Ishod lečenja; Koneksini

Juvenile Bullous Pemphigoid – a Case Report

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Abstract

Bullous pemphigoid is an autoimmune blistering disease that predominantly affects elderly persons and rarely children. We present a 12-year-old girl with sudden appearance of tense blisters on an erythematous base on the trunk, neck, hands and legs with intense pruritus. Standard laboratory test results were within the normal range except for blood eosinophilia of 12% of the total white cell count. Skin biopsy specimens showed evolving subepidermal blisters with perivascular lymphohistiocytic, eosinophil and neutrophil infiltrations in the papillary dermis. Direct immunofluorescence of perilesional skin showed linear, continuous deposits of IgG and C3 along the dermoepidermal junction. Indirect immunofluorescence showed circulating anti-basement membrane zone IgG autoantibodies at a titer of 1:80. We started treatment with systemic corticosteroids, methylprednisolone 0,5 mg/kg per day and 500 mg erythromycin 4 times a day during 10 days. After 3 days 50 mg dapsone (DDS, 4,4-diaminodiphenylsulphone) per day was added. After a few days, there were no new changes on the skin and pruritus disappeared completely.

Key words

Pemphigoid, Bullous; Autoimmune Diseases; Child; Pruritus; Fluorescent Antibody Technique, Indirect; Dapsone; Treatment Outcome

Bullous pemphigoid (BP) is an autoimmune blistering disease that predominantly affects elderly persons and rarely children. It is an immune-mediated disease that is associated with a humoral and cellular response directed against the two well-characterized self-antigens: bullous pemphigoid antigen 1 (BPAG1) and bullous pemphigoid antigen 2 (BPAG2), both components of hemidesmosome – junctional adhesion complex in the skin and mucosa. The cutaneous manifestations of BP may be extremely polymorphic. In the non-bullous phase of the disease, signs and symptoms are frequently non-specific, from mild to severe intractable pruritus. The bullous stage of BP is characterized by the development of vesicles and bullae on apparently normal or erythematous skin (1).

The first well-documented report of childhood BP was published in 1970 (2). The diagnostic criteria are the same as in adults: appearance of tense bullae, histopathological findings of subepidermal blisters with eosinophilia, direct immunofluorescence (DIF) showing linear deposition of IgG or C3 as the major immunoreactants at the basement membrane zone and presence of circulating IgG anti-basement membrane zone autoantibodies (3). The course of childhood BP is usually indolent with rare relapses (4). Even so, the disease may be life threatening, particularly if appropriate management is delayed (5).

Case report

We present a 12-year-old girl, with sudden appearance of tense blisters on an erythematous base on the trunk, neck, hands and legs (Figure 1, 2) with intense pruritus. Mucous membranes were not involved. The family history showed no evidence of autoimmune diseases. Standard laboratory test results were within the normal range except for blood eosinophilia of 12% of the total white cell count. Histopathological analysis of lesional and perilesional skin samples revealed subepidermal blisters with perivascular

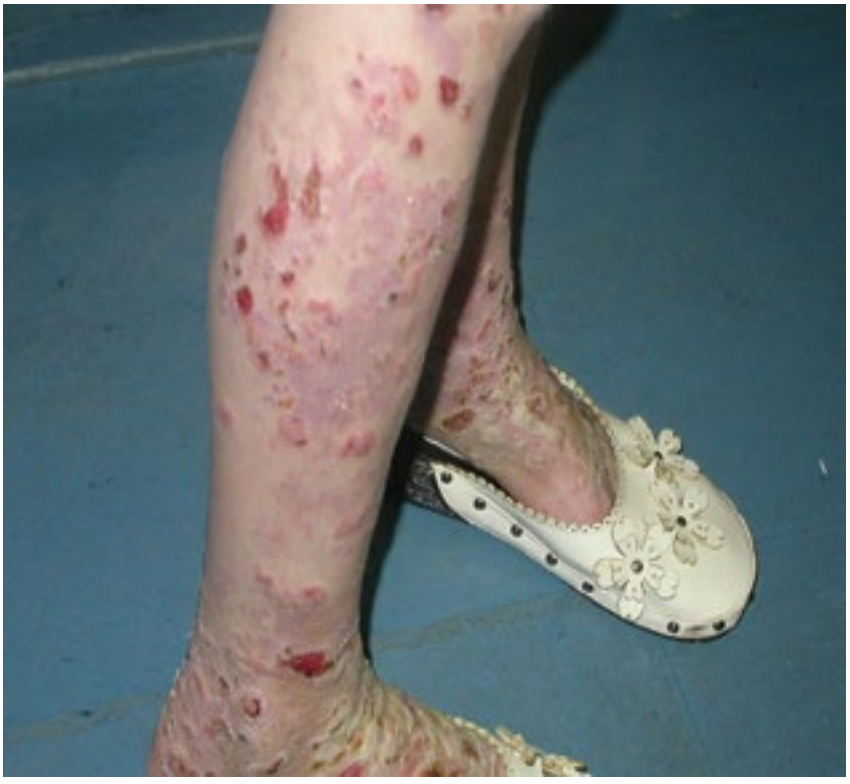

Figure 1. Tense blisters on an erythematous base on the legs

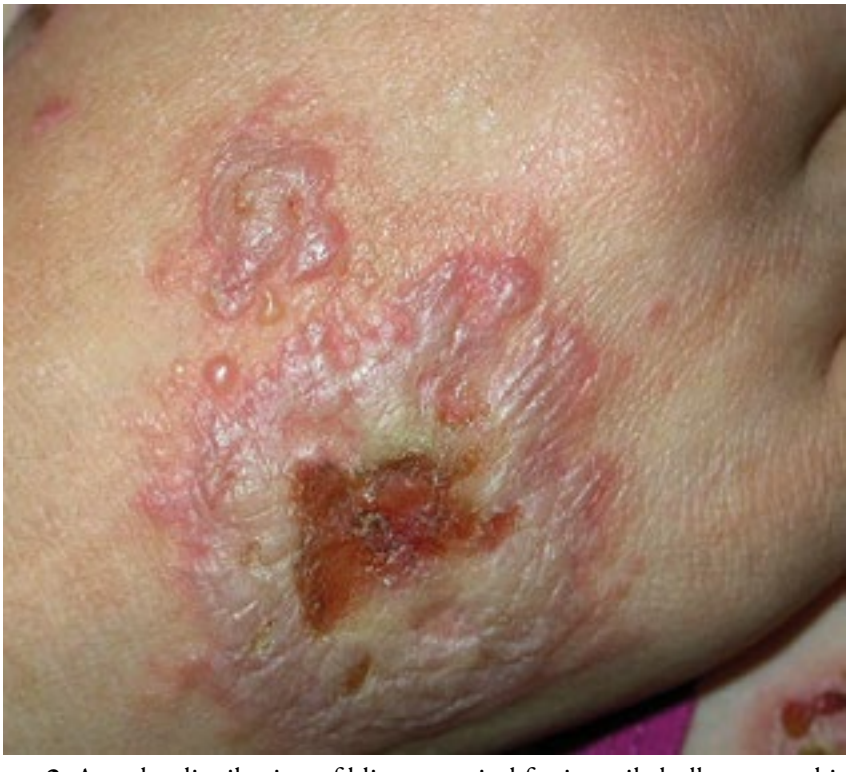

Figure 2. Annular distribution of blisters, typical for juvenile bullous pemphigoid

lymphohistiocytic, eosinophil and neutrophil infiltrations in the papillary dermis (Figure 3). Direct immunofluorescence (DIF) test of perilesional skin demonstrated linear, continuous deposits of IgG and C3 along the dermoepidermal junction (Figure 4). Indirect immunofluorescence (IIF) microscopy demonstrated circulating anti-basement membrane zone IgG autoantibodies at a titer of 1:80.

The diagnosis of juvenile bullous pemphigoid was established based on clinical manifestations (tense bullae on an erythematous base, pruritus), characteristic histopathological findings (subepidermal splits with dominant eosinophils in the cavity and in dermal infiltrations), direct immunofluorescence (DIF) microscopy (linear IgG and C3 deposits along the basement membrane zone) and positive IIF test 1:80.

Treatment with systemic corticosteroids, methylprednisolone 0,5mg/kg per day and 500 mg erythromycin 4 times per day was initiated. However, after 3 days the disease was not under control, so 50 mg dapsone (DDS, 4,4-diaminodiphenylsulphone) per day was added. After a few days, there were no new changes on the skin and pruritus disappeared completely and the therapy with methylprednisolone and dapsone was not discontinued after discharge. The therapy was well tollrated tollerated. Hypertension was not recorded during therapy, while laboratory findings, including glucose as well as arterial blood pressure, were within reference values. Two months later, the disease was in complete remission. During a 6 months follow up, methylprednisolone was tapered to 4 mg per week, until the daily dose of 4 mg was achieved in combination with 50 mg dapsone per day.

Discussion

Autoimmune bullous diseases with subepidermal split are very rare in children. The first case of juvenile bullous pemphigoid (JBP) was published in 1970 (1). In 1993, Fisler and al. analyzed 53 collected cases of juvenile bullous pemphigoid, where the age of onset ranged from 2.5 months to 14 years (4). Female patients accounted for 60% of cases.

The disease most often occurs in children older than 8 years. None of the children had any form of malignancy or any other associated disease (3). We presented a 12 year-old girl, with no evidence of other acute or chronic disease. Sudden appearance of bullous

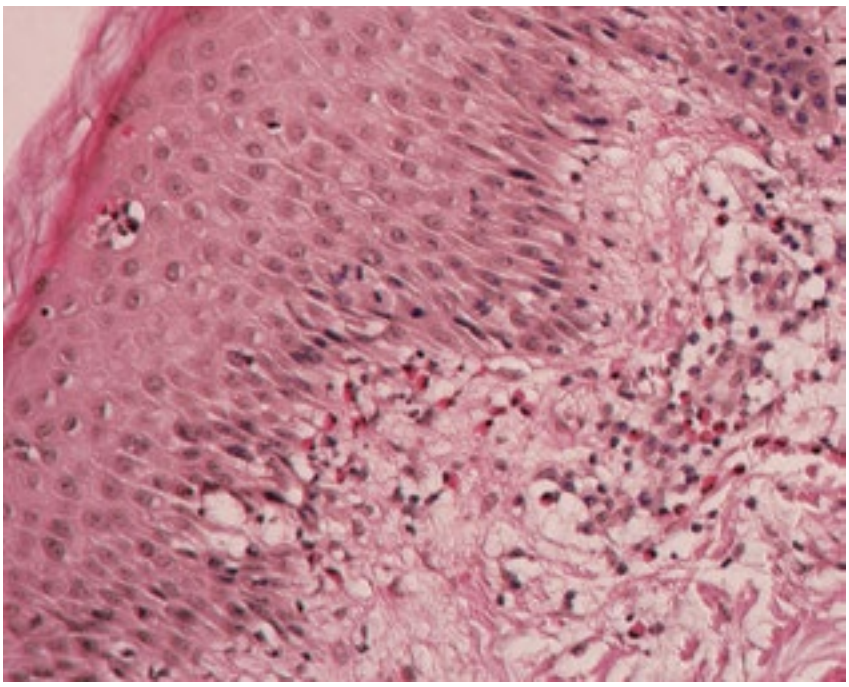

Figure 3. Histopathological analysis of lesional and perilesional skin samples reveales subepidermal blisters with eosinophilic spongiosis and perivascular lymphohistiocytic, eosinophil and neutrophil infiltrations in the papillary dermis (HE, x400)

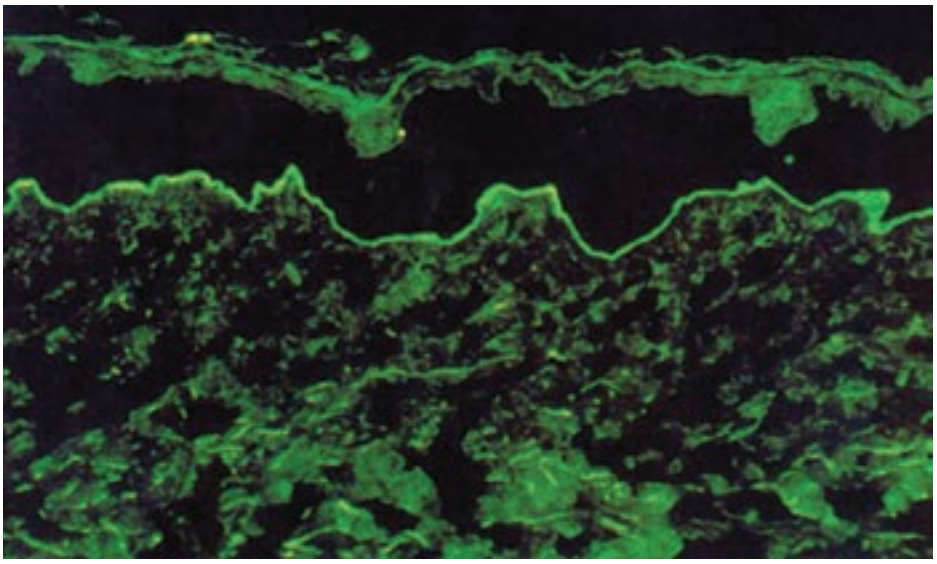

Figure 4. Direct immunofluorescence test of perilesional skin demonstrates linear, continuous deposits of IgG and C3 along the dermoepidermal junction

eruptions was not accompanied by deterioration of the general condition. Skin eruption was generalized, but there was no involvement of mucous membranes. In case series from the Pediatric Dermatology Unit, University Clinic of Dermatology, Belgrade, three of six children with BP had changes on the oral mucosa (6).

In our case, histopathology and DIF analyses were characteristic of BP: subepidermal blistering with perivascular lymphohistiocytic, eosinophil and neutrophil infiltrations in the papillary dermis, while DIF showed linear, continuous deposits of IgG and C3 along the dermoepidermal junction. In a study including six cases with JBP, three showed deposits of IgG, C3 and IgA (6). We did not find deposits of IgA in the perilesional skin. About 60 - 80% of patients present with circulating antibasement membrane IgG autoantibodies, and there is no difference between adults and children considering that matter.

Bullous pemphigoid may coexist with lichen planus in both adults and children (7). Immunopathologically, the disease is identical to bullous pemphigoid. However, it is usually possible to differentiate bullous pemphigoid from lichen planus pemphigoides on clinical base alone: in bullous pemphigoid there is no evidence of associated lichen planus (8). In our case, positive direct DIF test helped to exclude bullous lichen planus (9).

Systemic corticosteroids are the best choice for the initial treatment of JBP. In children, as in adults, a minimal dose of drugs that controls the disease is recommended (2, 10). Powell et al. analyzed immunobullous disease in children and its good response to sulfa drugs and macrolides (11). Macrolide antibiotics, including erythromycin, have anti-inflammatory effects similar to those of tetracyclines. It has been shown that they exhibit not only a steroid-sparing effect when used in conjunction with steroids, but also an inhibition of neutrophil chemotaxis (11). All patients responded well to the therapy with dapsone, sulphonamides and systemic erythromycin (11). In our patient, we initiated therapy with a systemic corticosteroid methylprednisolone 0,5 mg/kg daily and oral 500 mg erythromycin 4 times a day. After 3 days the disease was still not under control, so we added dapsone 50 mg per day. Prompt therapeutic effect with reduction of pruritus was obtained, and there were no new blisters. Spontaneous remission of JBP may be achieved within 5 years and it has a good prognosis, although in some children the course is less benign. The average time to achieve control of BP was about 1 month in the study of Gajić-Veljić et al. (6), which was shorther than in the study reported by Weston et al. (12), where remission with systemic corticosteroids and dapsone was achieved after 2

months. Complete remission was achieved in all JBP patients in both studies, as well as in our patient.

Conclusion

In general, children with BP have a good prognosis. Remission is achieved within several weeks to a few months. In most children the response to treatment is rather fast and ranges between a few days to several months, as in our patient. In juvenile bullous pemphigoid relapses are very rare, which is opposite to much slower remission and higher rate of relapses reported in adults suffering from BP.

Abbreviations

BP - Bullous pemphigoid
BPAG1 – Bullous pemphigoid antigen 1
BPAG2 – Bullous pemphigoid antigen 2
IgG – Immunoglobulin G
C3 – Complement component C3
DIF - Direct immunofluorescence
IIF - Indirect immunofluorescence
JBP – Juvenile bullous pemphigoid

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Juvenilni bulozni pemfigoid – prikaz slučaja

Sažetak

Uvod. Bulozni pemfigoid je autoimuna bulozna dermatoza koja se najčešće javlja kod pacijenata starijeg životnog doba; retko se javlja kod dece.

Prikaz slučaja. Prikazujemo slučaj devojčice, uzrasta 12 godina, sa iznenadnom pojavom napetih bula na eritematoznoj koži trupa, vrata, gornjih i donjih ekstremiteta uz intenzivan pruritus. Učinjene su standardne laboratorijske analize. Svi nalazi su bili u redu osim utvrđene eozinofilije u perifernoj krvi koja je iznosila 12% od ukupnog broja leukocita. Histopatološki nalaz bioptirane kože pokazao je subepidermalni rascep sa perivaskularnim infiltratom, dominantno eozinofilnim i neutrofilnim, u papilarnom dermu. Direktnom imunofluorescentnom mikroskopijom perilezione kože viđeni su linearni, kontinuirani depoziti IgG i C3 antitela duž zone bazalne membrane. Indirektnom imunofluorescentnom mikroskopijom detektovana su cirkulišuća IgG autoantitela prema komponenti zone bazalne membrane u titru 1 : 80. Započeta je terapija sistemskim kortikosteroidima, metilprednizolon 0,5 mg/kg dnevno i eritromicinom per os u dozi od 500 mg 4 puta dnevno, a nakon tri dana u terapiju je uključen i dapson (DDS, 4,4-diamino-difenil sulphone) u dozi 50 mg dnevno. Nekoliko dana po započetoj terapiji pruritus se povukao, a nove promene na koži se nisu pojavljivale.

Diskusija. Ukoliko se javi u dečjem uzrastu, bulozni pemfigoid najčešće pogađa decu stariju od 8 godina.

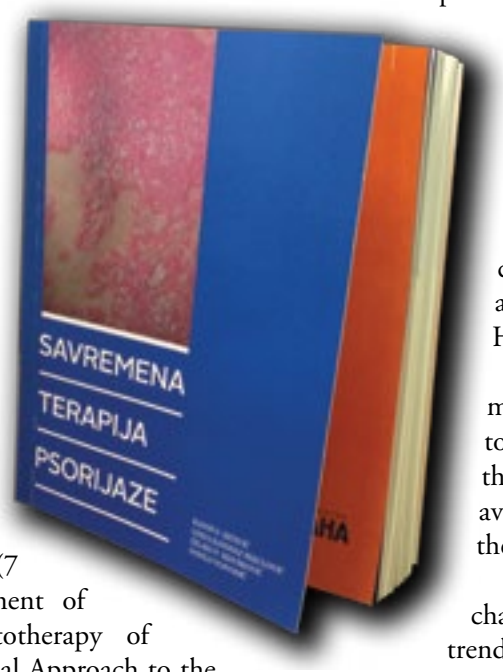
Opšte stanje je obično nepromenjeno, a ni kod jednog deteta do sada nije utvrđen prateći malignitet. Promene mogu da zahvate i vidljive sluzniice, opisani su slučajevi sa promenama na orofaringealnoj sluznici. Presudni dijagnostički značaj ima patohistološki nalaz i direktna imunofluorescencija kojom se duž zone bazalne membrane dokazuje prisustvo kontinuiranih linearnih depozita sastavljenih iz IgG i C3 antitela. Opisani su depoziti sastavljeni i od IgA. Kao i kod odraslih, u 60–80% slučajeva indirektnom imunofluorescencijom potvrđuje se prisustvo u serumu cirkulišućih IgG antitela usmerenih protiv bazalne membrane, koji su bili prisutni i kod našeg pacijenta.

Ključne reči

Bulozni pemfigoid; Autoimune bolesti; Dete; Pruritus; Indirektna imunofluorescentna metoda; Dapson; Ishod lečenja

Current Treatment of Psoriasis

by
Radoš D. Zečević
Lidija Kandolf Sekulović
Željko P. Mijušković
Danilo Vojvodić



Current Treatment of Psoriasis is a book dealing with the nature and mechanisms of action of various therapeutic modalities in current treatment of psoriasis.

The book has 146 pages, without the Content, and it is divided into 11 chapters: 1 – Pathogenesis of Psoriasis (15 references); 2 – Clinical Manifestations and Diagnosis of Psoriasis (21 references); 3 – Extracutaneous Manifestations of Psoriasis and Comorbidity (7 references); 4 – Topical Treatment of Psoriasis (16 references); Phototherapy of Psoriasis (16 references); Individual Approach to the Treatment of Psoriasis (10 references).

References are listed at the end of each chapter, their total number being 83. The book contains 24 figures and 23 tables numbered by chapter.

The chapter 1 deals with current knowledge about the pathogenesis of psoriasis and data are presented in figures.

The 2nd chapter is about clinical manifestations, diagnosis and severity assessment of psoriasis.

The special, chapter 3 reviews clinical manifestations of psoriatic arthritis and diseases associated with psoriasis, predominantly cardiovascular and metabolic diseases and their impact on choosing treatment and treatment efficacy.

The 4th chapter on topical therapy includes current modalities of topical treatment, from classical to biological therapy and emollients which are essential for skin therapy of the diseased.

The chapter 5 reviews data on various modalities of phototherapy.

The 6th chapter is concerned with systemic therapy of psoriasis and it includes indications for systemic therapy of psoriasis and the list of therapeutic agents used in certain countries, where some of them have already been approved, like fumarates.

The chapter 7 shows modalities for biologic therapy of psoriasis.

The chapter 8 deals with possibilities of combination therapy for psoriasis.

The special, chapter 9, reviews special clinical situations and individual groups of patients requiring modified treatment options (psoriasis in pregnancy, childhood psoriasis, psoriasis associated with hepatitis C and HIV infection, and so on).

Considering the fact that many patients with psoriasis turn to complementary and alternative therapies, chapter 10 reviews available scientific evidence on their (in)efficacy.

The last, equally important, chapter 11 deals with current trends in the therapy of psoriasis and experimental modalities of treatment.

This book gives an overview of very useful scientific information on the pathogenesis of psoriasis and mechanisms of action of certain therapeutic modalities. It is also a source of current knowledge in clinical practice for doctors of various profiles, primarily dermatovenereologists, involved in the treatment of psoriasis. *Current Treatment of Psoriasis* is a great textbook and an indispensable source of practical knowledge in the treatment of patients with psoriasis.

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Activities of the Dermatovenereology Section of the Serbian Medical Society in 2012

Four meetings of the *Dermatovenereology Section* (DVS) of the *Serbian Medical Society* were organized in 2012, and all of them were accredited by the *Health Council of the Republic of Serbia.*

The first meeting of the DVS was organized by the *Clinic of Dermatovenereology, Clinical Center of Serbia* on March 9, 2012. The introductory lecture was delivered by Dr. Srđan Tanasilović: Lasers in dermatology. Also, 13 case reports were presented at this meeting:

1. The advisory role of dermatologists in families with genodermatoses, Snežana Minić
2. Epithelioma cuniculatum, Prof. Dr. Ljiljana Medenica
3. Behcet's Disease, Dr. Dubravka Živanović
4. Neglected basal cell carcinoma in a 48-year-old woman from Belgrade, Dr. Biljana Marenović
5. Giant sclerosing basal cell carcinoma, Assist. Prof. Dr. Jelica Vukićević
6. Wells Syndrome, Dr. Mirjana Popadić
7. CD30+ anaplastic lymphoma, Ass. Dr. Dušan Škiljević
8. Genital Aphthosis, Ass. Dr. Svetlana Popadić
9. Collodion baby, Ass. Dr. Mirjana Gajić Veljić
10. Peutz-Jeghers syndrome, Dr. Biljana Arsov
11. Pyoderma gangrenosum, Dr. Vesna Reljić
12. Drug-induced pemphigus, Assist. Prof. Dr. Danijela Dobrosavljević Vukojević

The second meeting of the DVS was organized by the *Department of Dermatology and Venereology, Military Medical Academy* on April 6, 2012. The introductory lecture was presented by Prof. Dr. Radoš Zečević: Contemporary therapy in dermatology - what are our options? Also, 12 case reports were presented at this meeting:

1. Pyoderma gangraenosum and inflammatory bowel disease – a report of three patients, Dr. Miroslav Dinić
2. Systemic vasculitis with nodular vasculitis of the skin – a case report, Dr.Kristina Kostić
3. Granulomatous inflammation induced by an unregistered rejuvenation filler – a case report, Assist. Prof. Dr. Lidija Kandolf Sekulović
4. Sweet Syndrome – a case report, Ass. Dr. Željko Mijušković
5. Bullous Pemphigoid, – a report of two cases, Ass. Dr. Željko Mijušković
6. Scleromyxedema – a case report, Dr. Zorica Perić Hajzler
7. Psoriasis and viral hepatitis – report of two cases, Dr. Dušan Šofranac.

The third meeting of the DVS was organized by the *Clinic of Dermatology and Venereology, Clinical Center Niš* on May 5, 2012 in Prolom Banja. The introductory lecture was delivered by Dr. Slađana Čekić: Contemporary diagnostic and therapeutic approach to lymphedema. Also, 9 case reports were presented at this meeting:

1. Report of two cases with multiple basal cell carcinomas, Prof. Dr. Danica Tiodorović Živković
2. Pityriasis rubra pilaris, Dr. Ljiljana Nikolić
3. Darier Disease and herpetic eczema, Dr. Sci. Med. Viktor Lazarević
4. Giant basal cell carcinoma, Prof. Dr. Dragan Jovanović
5. Adamantiades-Behcet's Disease, Dr. Danijela Popović
6. Hailey-Hailey Disease, Dr. Zorana Zatanović
7. Vulgar psoriasis associated with bullous pemphigoid, Dr. Vesna Karanikolić
8. Papuloeruptive Xanthoma, Dr. Sci. Med. Viktor Lazarević

The fourth meeting of the DVS was organized by the *Clinic of Dermatovenereology, Clinical Center of Vojvodina* on Ocober 5, 2012 in Sremska Kamenica. The introductory lecture was delivered by Prof. Dr. Zlata Janjić: Dermatosurgery – basic principles. Also, 6 more lectures were presented at this meeting:

1. Dermatosurgery – our experience, Dr. Branislava Gajić
2. Histopathological dermoscopic results of suspicious melanocytic lesions from 2008 to 2011 – our experience, Ass. Dr. Milana Ivkov Simić
3. Leiomyoma, Dr. Novak Rajić
4. Photodamaged skin, Prim. Dr. Siniša Tasić
5. Relapsing polychondritis, Assist. Prof. Dr. Zorica Gajinov
6. The role of systemic therapy in chronic venous disease, Assist. Prof. Dr. Milan Matić

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2012 Annual Report on the Activities of the Dermatovenereology Section of the Society of Physicians of Vojvodina of the Serbian Medical Society

Meetings of the Dermatovenereology Section of the Society of Physicians of Vojvodina

During 2012, there were three meetings of the Dermatovenereology Section of the Society of Physicians of Vojvodina.

The first Section meeting was held on March 23, 2012, and its main topic was: *New additional diagnostic and treatment methods at the Dermatovenereology Clinic in Novi Sad.* Lectures were given by doctors of the Dermatovenereology Clinic of the Clinical Center of Vojvodina.

- *Dermoscopy – a new additional diagnostic method* – Teaching Assistants (TA) Dr. Milana Ivkov Simić;
- *Systemic photodynamic therapy,* TA Dr. Milica Subotić;
- *Local photodynamic therapy,* Dr. Ljubinka Matović, MS.

Before the professional part of the meeting, TA Dr. Milica Subotić informed the participants about the jubilee of the Serbian Medical Society. The Serbian Medical Society (SMS) celebrates its 140th anniversary in 2012, while the Society of Physicians of Vojvodina (SPV) was founded in 1947, as the branch society of SMS. The Serbian Medical Society has been recognized as a great professional association, the oldest in the Balkans. Today, SMS has about 25.000 members. This year, on the occasion of its 140th anniversary, SMS was awarded the Sretenje Order of the Second Degree, for special merits in the field of sciences and health promotion. This award was earned for continuous advanced training of physicians, development of medical science, and the study of characteristics and health status of the population. The award was presented by the President of the Republic of Serbia, Mr. Boris Tadić.

The second Section meeting was held on October 5, 2012, in Sremski Karlovci, and it was a joint meeting of Dermatovenereology Sections of SPV and SMS. The main topic of this meeting was: *Dermatosurgery in practice*. Lectures were given by doctors of the Clinical Center of Vojvodina.

- *Basic principles of dermatosurgery,* Prof. Dr. Zlata Janjić (Plastic and Reconstructive Surgery Clinic)
- *Dermatosurgery in practice,* Dr. Branislava Gajić (Clinic of Dermatovenereology Diseases)
- *Histopathological findings of dermoscopically suspected melanocytic lesions in patients of the Clinic of Dermatovenereology Diseases in Novi Sad from 2008 – 2011,* TA Dr. Milana Ivkov Simić (Clinic of Dermatovenereology Diseases)
- *Leiomyoma – a case report*, Prim. Dr. Novak Rajić (Clinic of Dermatovenereology Diseases)
- *Photodamaged skin – a case report,* Prim. Dr. Siniša Tasić (Clinic of Dermatovenereology Diseases)
- *Relapsing polychondritis – a case report,* Assoc. Prof. Zorica Gajinov (Clinic of Dermatovenereology Diseases).

The third Section meeting was held on December 14, 2012, at the premises of the SPV in Novi Sad, and its professional part was carried out by doctors of the Clinic of Dermatovenereology Diseases in Novi Sad, Clinical Center of Vojvodina.

- *Urethritis – is it time to change the antibiotic regimen?,* TA Dr. Zoran Golušin
- *CREST syndrome – a case report*, TA Dr. Aleksandra Petrović
- *Pyoderma gangrenosum associated with Crohn's disease,* TA Dr. Ljuba Vujanović
- *Bologna sign in dermoscopy – significance and case series,* TA Dr. Milana Ivkov Simić
- *Planocellular carcinoma of the upper lip – a case report,* Prim. Dr. Bojana Spasić.

Participation of the members of the SPV Dermatovenereology Section at other professional meetings in the country and abroad, advancement and awards

As it has been planned, over the past year our members were actively involved in education, conferences and meetings in our country and abroad.

In collaboration with colleagues from Belgrade and Niš, Prof. Dr. Marina Jovanović has organized a professional meeting of continuing medical education in Belgrade under the heading *Pruritus – what's new?*, where she and TA Dr. Aleksandra Petrović delivered lectures.

A few of our colleagues from the Clinic of Dermatovenereology Diseases of the Clinical Center of Vojvodina, including Assoc. Prof. Milan Matić, TA Dr. Zoran Golušin, and Prim. Dr. Bojana Spasić, have participated in the meeting of the Association of Serbian Cosmetic and Esthetic Dermatology, where Prof. Dr. Marina Jovanović gave a remarkable lecture *Oxidative stress and skin aging*.

Assoc. Prof. Milan Matić, TA Dr. Zoran Golušin, Prim. Dr. Bojana Spasić and Dr. Zoran Nedić took active participation in poster presentations at the 21st Congress of EADV in September 2012, in Prague.

In September 2012, TA Dr. Zoran Golušin had a poster presentation at the 27th European Congress of the International Union Against Sexually Transmitted Infections in Antalya, Turkey.

Many of our members participated in the XVII Belgrade Dermatology Days in November 2012.

a) Lectures by invitation:
   - *Urticaria and contact dermatitis,* Prof. Dr. Marina Jovanović.

b) Case reports:
   - *Multiple seborrheic keratosis – Leser-Trelat sign,* Dr. Svetlana Kovačević Dučić
   - *Squamous dysplasia in patients with malignant hemopathies – a case series,* Dr. Tatjana Roš
   - *An unusual clinical manifestation of pigmented urticaria? – a case report,* Dr. Tatjana Roš
   - *Upper lip planocellular carcinoma – a case report,* Prof. Dr. Slobodan Stojanović
   - *A therapeutic challenge of lipoid necrobiosis – a*

Figure 1. President of the Serbian Medical Society, Academician Radoje Čolović, presents the Annual Award for Scientific Research to Prof. Dr. Marina Jovanović

Figure 2. President of the Serbian Medical Society, Academician Radoje Čolović, and Prof. Dr. Marina Jovanović, the member of the Academy of Medical Sciences

case report, TA Dr. Aleksandra Petrović
- *Erythema induratum of Bazin type – a case report,* TA Dr. Ljuba Vujanović
- *Allergic reaction to a temporary henna tattoo,* Dr. Olga Vlaov Žarkov (Poster presentation).

c) Reports
- *The incidence of recurrent genital warts after monotherapy with Podophyllotoxin and cryotherapy,* TA Dr. Zoran Golušin
- *Dermoscopic diagnosis of skin melanoma at the Clinic of Dermatovenereology Diseases in Novi Sad from 2008 – 2011,* TA Dr. Milana Ivkov Simić.

At the XVII Belgrade Dermatology Days, Dr. Tatjana Roš was awarded the first prize for case series: *Squamous dysplasia in patients with malignant hemopathies*.

Dr. Tatjana Roš was our representative at VIII Congress of the European Association of Dermatooncology. She also delivered a lecture at the Dialysis and Transplant Association in October, 2012. The lecture was intended for dialysis and transplant patients who are at high risk for skin tumors due to immunosuppressive therapy. This was the second lecture on the same topic, whereas the first was given in 2009 by Dr. Milana Ivkov Simić. On this occasion, the Dialysis and Transplant Association printed a guide: *Skin changes in organ transplant patients*, to provide primary and secondary prevention of skin tumors.

TA Dr. Aleksandra Petrović and Dr. Ruža Sante are subspecializing in allergology, and Dr. Siniša Tasić MS in mycology.

TA Dr. Zoran Golušin received a PhD degree on December 10, 2012.

This year, the Serbian Medical Society awarded Prof. Dr. Marina Jovanović for scientific research (Figures 1,2).

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FORTHCOMING EVENTS

Dermatology and Venereology Events 2013

DATE	MEETINGS, CONGRESSES, SYMPOSIA	ABSTRACT SUBMISSION DEADLINE	MORE INFORMATION AT
4-6 April, 2013	11th Anti-Aging Medicine World Congress & Medispa, Monte Carlo, Monaco	No deadline information	www.euromedicom.com
16-18 April, 2013	Dubai World Dermatology & Laser Coference 2013, Dubai, UAE	31 December, 2012	www.dubaiderma.com
19 April, 2013	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Military Medical Academy, Belgrade, Serbia	No abstract submission	www.sld.org.rs
10-12 May, 2013	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Niš, Prolom Banja, Serbia	No abstract submission	www.sld.org.rs
8-11 May, 2013	International Investigative Dermatology, Edinburgh, Scotland	3 January, 2013	www.iid2013.org
23-26 May, 2013	10th EADV Spring Symposium, Krakow, Poland	10 November, 2012	www.eadvcracow2013.org
13-15 June, 2013	2nd/19th Congress of Serbian Association of Dermatovenerologists, Belgrade, Serbia	1 March, 2013	www.udvs.org
22-26 June, 2013	EAACI – WAO World Allergy and Asthma Congress, Milan, Italy	21 January, 2013	www.eaaci-wao2013.com
27-30 June, 2013	9th World Congress of Cosmetic Dermatology, Athens, Greece	1 February, 2013	www.erasmus.gr
4-7 July, 2013	4th International Congress of Psoriasis 2013, Paris, France	15 February, 2013	www.pso2013.com
18-20 July, 2013	8th World Congress of Melanoma, Hamburg, Germany	24 March, 2013	www.worldmelanoma2013.com
21-26 July, 2013	3rd International Summer Academy of Practical Dermatology, Munich, Germany	No abstract submission	www.isa2013.com
25-27 September, 2013	12th World Congress of Pediatric Dermatology, Madrid, Spain	1 May, 2013	www.wcpd2013.com
3-7 October, 2013	22nd EADV Congress, Istanbul, Turkey	10 April, 2013	www.eadv.org
18 October, 2013	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Vojvodina, Novi Sad, Serbia	No abstract submission	www.sld.org.rs
8 November, 2013	Meeting of the Serbian Medical Society's Section of Dermatology and Venereology, Clinical Center of Kragujevac, Serbia	No abstract submission	www.sld.org.rs
4-7 December, 2013	11th International Congress of Dermatology, Delhi, India	31 May, 2013	www.icddelhi2013.com

Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenereology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia

AUTHOR GUIDELINES

Serbian Journal of Dermatology and Venereology is a journal of the *Serbian Association of Dermatologists and Venereologists*. The journal is published in English, but abstracts will also be published in Serbian language. The journal is published quarterly, and intended to provide rapid publication of papers in the field of dermatology and venereology. Manuscripts are welcome from all countries in the following categories: editorials, original studies, review articles, professional articles, case reports, and history of medicine.

Categories of Manuscripts

1. Editorials *(limited to 5 pages) generally provide commentary and analyses concerning topics of current interest in the field of dermatology and venereology. Editorials are commonly written by one author, by invitation.*

2. Original studies *(limited to 12 pages) should contain innovative research, supported by randomized trials, diagnostic tests, outcome studies, cost-effectiveness analysis and surveys with high response rate.*

3. Review articles *(limited to 10 pages) should provide systemic critical assessment of literature and other data sources.*

4. Professional articles *(limited to 8 pages) should provide a link between the theory and practice, as well as detailed discussion or medical research and practice.*

5. Case reports *(limited to 6 pages) should be new, interesting and rare cases with clinical significance.*

6. History of medicine *(limited to 10 pages) articles should be concerned with all aspects of health, illness and medical treatment in the past.*

7. Short Communications *(limited to 3 pages) should disseminate most current results and developments in the shortest possible time. They will be reviewed by expert reviewers and evaluated by the Editor.*

The journal also publishes book reviews, congress reports, as well as reports on local and international activities, editorial board announcements, letters to the editor, novelties in medicine, questions and answers, and "In Memoriam". All submitted manuscripts will undergo review by the editor-in-chief, blind review by members of the manuscript review panel or members of the Editorial Board. Manuscripts submitted to this journal must not be under simultaneous consideration by any other publisher. Any materials submitted will NOT BE RETURNED to the author/s.

All manuscripts should be submitted to the **Editor in Chief: Prof. Dr. Marina Jovanović***, Clinic of Dermatovenereologic Diseases, Clinical Center of Vojvodina, Hajduk Veljkova 1-3, Novi Sad, Serbia, by mail to: serbjdermatol@open.telekom.rs.*

Manuscripts for submission must be prepared according to the guidelines adopted by the International Committee of Medical Journal Editors (www.icmje.org). Please consult the latest version of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

1. Manuscript Preparation Guidelines

The manuscript should be written in English, typed in double spacing throughout on A4 paper, on one side only; Use Times New Roman, font size 12, with 30 lines and 60 characters per line. Articles must be written clearly, concisely and in correct English. Accepted manuscripts in need of editing will be returned after editing to the corresponding author for approval. When preparing their manuscripts, authors should follow the instructions given in the *Categories of Manuscript:* the number of pages is limited (including tables, figures, graphs, pictures and so on to 4 (four)), and all the pages must be numbered at the bottom center of the page.

For manuscript preparation, please follow these instructions:

1.1. Title page

The title page should include the following information:

- The title of the article, which should be informative, without abbreviations and as short as possible;

- A running title (limited to 30 characters);

- Authors' names and institutional affiliations;

- The name, mailing address, telephone and fax numbers, and email of the corresponding author responsible for correspondence about the manuscript. Furthermore, authors may use a footnote for acknowledgements, information and so on.

1.2. Abstracts

A structured abstract in English *(limited to 150 words) should follow the title page. The abstract should*

provide the context or background for the study, as well as the purpose, basic procedures, main findings and principal conclusions. Authors should avoid using abbreviations.

- An **abstract in Serbian language***, (limited to 150 words) should follow the second page. It should contain a briefing on the purpose of the study, methods, results and conclusions, and should not contain abbreviations.*

1.3. A list of abbreviations

Use only standard abbreviations, because use of non-standard abbreviations can be confusing to readers. Avoid abbreviations in the title, abstract and in the conclusion. A list of abbreviations and full terms for which they stand for should be provided on a separate page. All measurements of length, height, weight, and volume should be reported in the metric units of the International System of Units – SI, available at http://www.bipm.fr/en/si/.

1.4. Cover Letter

Manuscripts must be accompanied by a cover letter, which should include a date of submission, statement that the manuscript has been read and approved by all the authors and that the authorship requirements have been met. It should also include the name, address, and telephone number of the corresponding author, who is responsible for communicating with other authors about revisions and final approval of the proofs. The original copy of the cover letter, signed by all authors, should be enclosed with the manuscript.

2. Tables and illustrations

Tables *should capture information concisely and precisely. Including data in tables, rather than in the text, reduces the length of the article itself.*

- Submit tables in separate files, not included in the manuscript. Tables are to be double spaced and numbered sequentially, with Arabic numbers (Table 1, Table 2, etc.), in order of text citation. Each column, including the first, must have a heading. Provide a brief title for each table. Put all explanatory matter in footnotes, including any nonstandard abbreviations used in the table.

- **Figures** should be submitted in a separate file, not included in the manuscript document. Cite figures consecutively, as they appear in the text, with Arabic numbers (Fig. 1, Fig. 2, Fig. 3, etc.). Each figure must be assigned a title, as well as a legend. Legends should appear on a separate page, not with each figure. The **Legend Page** is to be numbered in sequence after the last page of the references list. Figures should be professionally drawn, as sharp black-and-white or color photographs. If photographs of persons are used, either the subjects must not be identifiable, or their pictures must be accompanied by written permission to use them.

3. References

References in the text, tables and legends should be identified by Arabic numerals in parentheses. Number references consecutively in the order in which they are first mentioned in the text. The *Vancouver System* of referencing should be used. List each author's last name and initials; full first names are not included. List all authors, but if the number exceeds six, give the first six followed by „et al." National journals, which are not indexed in *Index Medicus*, should be abbreviated according to the style in the *List of Abbreviated Titles of Yugoslav Serial Publications* available on http://vbsw.vbs.rs. For further information please visit www.ICMJE.org.

4. Additional information

Accepted manuscripts are edited and returned to the corresponding author for approval. Then a final version of the manuscript will be requested in a defined period of time. Authors will be notified of acceptance or rejection by email, within approximately 4 weeks after submission.

- Open access: Every article published in the **Serbian Journal of Dermatology and Venereology** will immediately be accessible on **www.udvs.org** to everyone at no charge.

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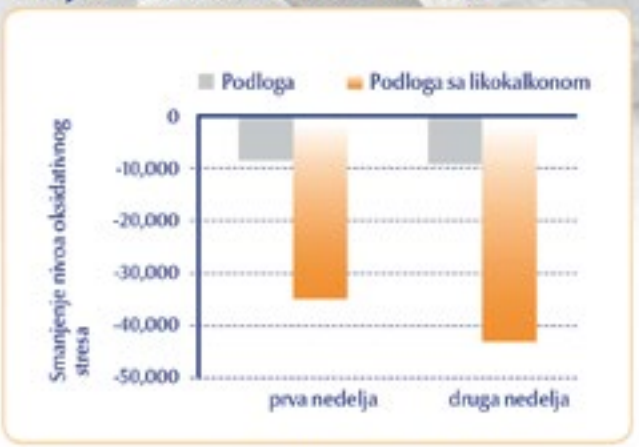

Izvor: Antioksidantska svojstva Likokalkona A iz Glycyrrhiza Inflata na ljudskoj koži in vitro i in vivo, Poster AAD 2006

DNK zaštita sa Gliciretinskom kiselinom

Izvor: Gliciretinska kiselina značajno ubrzava proces reparacije UV indukovanih ciklobutan-pirimidin-dimera (CPD) u ljudskoj koži - Poster EADV 2011

UDRUŽENJE DERMATOVENEROLOGA SRBIJE

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Cover figure: Christ Healing Ten Lepers, Christ's Miracles, 14th century, The monastery Visoki Dečani, Serbia, Kosovo

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