ORIGINAL STUDY
YARROW OINTMENTS AND VENOUS ULCERS

REVIEW ARTICLE
GENITAL WARTS

CASE REPORT
ERYTHRODERMIC CUTANEOUS T-CELL LYMPHOMA

HISTORY OF MEDICINE
HISTORY OF DERMATOVENEREOLOGY IN SERBIA FROM 1881 – 1918

IN MEMORIAM
REPORT

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ORIGINAL STUDY

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TO THE FACULTY OF MEDICINE IN NOVI SAD, BELGRADE, 1964
Treatment of venous leg ulcers with an ointment containing yarrow (Achillea millefolium) extract

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Abstract

Traditional medicine credits yarrow (Achillea millefolium) with the ability to accelerate wound healing. The purpose of this research was to determine the effects of yarrow on the epithelization of the lower leg venous ulcers. The study included 39 patients with venous leg ulcers. They were divided into two groups: the first (experimental) group of patients were treated with an ointment containing 7.5% of yarrow extract. In the second (control) group, saline solution dressings were applied to ulcers, within the period of three weeks. In the experimental group, at the beginning of the therapy, the total surface of all the ulcers was 44736 mm². After three weeks, the total surface of all the ulcers was 27000 mm² (a decrease of 39.64%). In the control group, at the beginning of the therapy, the total surface of all the ulcers was 46116 mm². At the end of the study (21 days) the total surface of all the ulcers was 39153 mm² (a decrease of 15.1%). Herbal preparations are suitable for application in the therapy of venous ulcers, but their efficiency in wound healing is still to be investigated.

According to the World Health Organization statistics, disorders of the venous circulation are among the most frequent diseases affecting the world population. It is estimated that 15% of the whole adult population has some type of chronic venous insufficiency (1, 2, 3). According to various epidemiological studies, it is evaluated that the prevalence of lower leg ulcers in adult population is about 2%. The etiological factor of the vast majority (70-90%) of these ulcers is chronic venous insufficiency (4, 5).

Any topical preparation that accelerates wound healing is of great help. Because of this, modern medicine is frequently using traditional methods.

Yarrow (Achillea millefolium L., Asteraceae) is a widely distributed medicinal plant. The herbal drug (Millefollii herba) is believed to possess antiinflammatory, spasmylytic, stomachic, carminative and cholagogue activities. Topically, it is used in the treatment of skin disorders, especially inflammation of skin and mucous membranes, as well as a trophic protective agent (6). Recent investigations also point to the antimicrobial (7, 8, 9) and antioxidant activities (8) of yarrow. Yarrow is also well known for its wound healing properties, particularly in staunching blood flow. An infusion of the leaf, stems, and flowers will speed the healing of rashes, hemorrhoids, and skin ulcers (10).

Its pharmacological activity is attributed to particular plant constituents. A. millefolium contains essential oil which, depending on the origin, contains no, or up to 50% of chamazulene (produced during the distillation process of proazulene). The presence of prochamazulene is correlated with the chromosome number in the plant. Only tetraploid plants contain prochamazulene and blue sesquiterpene (chamazulene) in essential oil. Most
common oil compounds are camphor, sabinene, 1,8-cineole, etc. The plant contains several classes of sesquiterpene lactones: guaianolides, germacranoles, dihydroparthenolides. These substances have been proven to take part in the antiseptic and antiphlogistic action of yarrow. However, although Millefolii herba is widely used in phytotherapy, its use is sometimes restricted, because it may cause allergic contact dermatitis (11, 12). Guaianolide peroxides and sesquiterpene lactones, and with azulenes in the essential oil, are believed to be responsible for itching and inflammatory skin changes with formation of vesicles (11). Beside terpenoids, yarrow contains considerable amount of plant phenolic compounds, of which the most important are flavonoids: apigenin, luteolin and their 7-O-glycosides, 6-methoxylated or di- and trimethylated flavonols (pectolinarigenin, 3-methylbutelutol, etc). Flavonoids are presumed to be responsible for the well-known anti-inflammatory effects of yarrow’s herbal medicines (13).

Purpose
The aim of this research was to determine the therapeutic efficiency of yarrow (Achillea millefolium) extract on the epithelization of the lower leg venous ulcers.

Material and methods
The experiment was carried out on 39 patients with venous leg ulcers. All patients were treated at the Clinic of Dermatovenereology Diseases of the Clinical Center of Vojvodine in Novi Sad, Serbia. All patients were randomly assigned into the investigation in regard with their arrival to the Clinic. Arterial etiology of ulcers was excluded by measuring the ankle-brachial pressure index (ABPI). The average value of ABPI was 0.98. Prior to being included into the study, all patients were tested with originally made 1%, 3% or 10% ether extract of yarrow, in order to exclude contact sensitivity due to previous sensitization to compositae-containing herbal remedies and cosmetics (14). Patch tests were performed according to international guidelines (15). They were applied to the patients’ back using Curates® (Lohmann-Rauscher, Neuwied, Germany). All patients were divided into two groups.

Potential adverse effects of the therapy were explained to all patients in detail, and all signed a written consent form for participation in the research.

Experimental group
In the first group, patients were treated with an ointment with yarrow extract.

Plant material
The herbaceous part of the cultivated Achillea millefolium L. (Asteraceae) was collected in June of 2003, in the Province of Vojvodina. Voucher specimens were confirmed and deposited at the Herbarium of the Botany Department, Faculty of Sciences, University of Novi Sad.

Plant extract preparation
Sixty-five grams of dry plant material was subjected to the Soxhlet extraction with absolute ethanol for 3 hrs. After that, the solvent was evaporated under vacuum, and the obtained dry residue (4 g) was subsequently dissolved in propylene glycol. A 7.5% concentration of yarrow extract was added to a neutral basis, Galsana® (Galenika, Belgrade, Serbia).

Treatment protocol
The first group, included a total of 20 patients: 6 males and 14 females, of an average age of 63.05, with a total number of 32 venous ulcers. Local therapy was applied twice a day, for three weeks.

Control group
The second group was the control group. It included 19 patients, 15 females and 4 males, of an average age of 68.35, with a total number of 31 venous ulcers. This group was treated with saline solution dressings which were applied to ulcers, for the period of three weeks.

Results
At the beginning of the therapy the total surface of all ulcers in the experimental group (treated with ointment containing yarrow extract) was 44736 mm², that is 1398 mm² on average. After the first week there was a 14.07% decrease of ulcer size, 26.80% after the
second and after the third week the total surface of all ulcers was 27000 mm² (a decrease by 39.64%) (Figure 1). In 3 cases a complete epithelization was achieved (Figure 2, Figure 3).

All of the registered semi-quantitative parameters (granulation, epithelization and dermatitis) were significantly improved when compared to the beginning of the treatment. During the experiment, there were no systemic or local side effects.

In the control group, at the beginning of the therapy the total surface of all ulcers was 46116 mm², 1487 mm² on average. After 7 days, a 3.93% decrease was established, 10.11% after 14 days, and at the end of the experiment (21 days) the total surface of all

Figure 1. Decrease in total ulcer surface in patients treated with topical preparation with yarrow extract

Figure 2. Before treatment

Figure 3. After treatment
ulcers was $39153 \text{ mm}^2$ (a 15.10% decrease) (Figure 4). In 4 cases a complete epithelization was achieved.

After statistical evaluation (student t-test) of results between the experimental and control groups, the group treated with ointment containing yarrow extract showed no statistically significant acceleration of wound healing ($p>0.05$) (Figure 5).

**Discussion**

In contemporary literature, no previous researches concerning the effects of yarrow preparation on venous ulcers healing were found. In general, there are very few controlled clinical studies concerning the effects of medicinal plants on wound healing.

The obtained results of the study point to a faster epithelization of venous ulcers after the application of the cream with yarrow extract, in comparison with the control group (decrease of ulcer surface by 39.64% in comparison with 16.75%), although without statistical significance.

However, the previous investigation, in which we analyzed the influence of the cream with 7.5% marigold extract on the healing of venous ulcers, a statistically significant acceleration of the healing process ($p<0.05$) was established (16).

Nevertheless, the evaluation of semi-quantitative parameters (granulation, epithelization and dermatitis) showed better results in the group treated
with yarrow extract, especially concerning reduction of dermatitis. On the basis of these findings, one can conclude that, even though both of these plants are known for their capacity to accelerate wound healing, their effects are achieved at different levels. Therefore, a combination of several medicinal plants probably exerts a synergistic effect. This is in accordance with yet another of our previous investigations, in which a preparation containing 4 different medicinal herbs (Calendula officinalis, Achillea millefolium, Symphytum officinale, Salvia officinalis) showed the best results (17). In this investigation we treated 40 patients with a total number of 66 venous ulcers. After a 3-week therapy, a 58.55% decrease of ulcer surface was established. A complete epithelization was recorded in 22 ulcers.

**Conclusion**

Our investigation showed no significant acceleration of wound healing after application of cream with yarrow extract. However, based on this research and our previous investigations, we can conclude that herbal preparations are safe and suitable for application in the therapy of venous ulcers. Better results may be achieved by appropriate combination of different medicinal herbs and by utilization of their synergistic effect. Yet, this calls for good knowledge of herbal medicines and venous pathology.

**Acknowledgement**

This study was conducted as part of the Republic Project entitled "Contact and Photocontact Sensitization to Allergens of Ubiquitous Weeds".

**References:**

Primena preparata sa ekstraktom hajdučke trave (*Achillea millefolium*) u lečenju venskih ulkusa potkolenice

Sažetak

Uvod: U Tradicionalnoj medicini hajdučka trava (*Achillea millefolium*) je dobro poznata po svojoj sposobnosti da ubrzava zarastanje rana.

Cilj: Cilj ovog istraživanja bio je da ispitamo uticaj hajdučke trave na zarastanje venskih ulkusa potkolenice.


Rezultati: Na početku ispitivanja u eksperimentalnoj grupi ukupna površina ulkusa iznosila je 44 736 mm². Posle tri nedelje terapije ukupna površina ulkusa bila je 27 000 mm² (smanjenje za 39,64%). U kontrolnoj grupi ukupna površina ulkusa na početku eksperimenta je bila 46116 mm². Na kraju ispitivanja (21 dan) ukupna površina ulkusa bila je 39 153 mm² (smanjenje za 15,1%).

Zaključak: Primena biljnih preparata pogodna u terapiji venskih ulkusa, ali efikasnost njihovog dejstva na zarastanje ulkusa tek treba da bude detaljnije ispitana.
Abstract

Genital warts are one of the most common sexually transmitted infections caused by the human papilloma virus. Persons with genital warts may be infected by several types of human papilloma viruses: various types may have antagonistic or synergistic interactions, causing regression or recurrence of the existing lesions. No specific antiviral therapy is currently available. The treatment includes removal of symptomatic lesions on the skin and mucous surfaces. Apart from classical surgical procedures, local destruction of lesions is performed using various chemical and physical agents, whereas systemic therapy includes administration of agents promoting the immune system. The efficacy of treatment is not identical in all cases, and relapses are still inevitable. Combination therapy is often an alternative to monotherapy, while vaccine has an important role in prevention of genital warts.

Etiology and immunology

Genital warts (GWs) (lat. Condylomata acuminata) are visual manifestations of genital human papilloma virus (HPV) infection, and they are among the most common sexually transmitted diseases (STDs) in developed countries. Due to their high prevalence, viral etiopathogenesis and still inefficient therapy, GWs represent a complex clinical problem in dermatology and venereology.

Epidemiology

Genital warts are a clinical manifestation of HPV infection in 1% of the sexually active population. The incidence of GWs is around 2.4 per 1000 inhabitants of Western Europe, and 8 per 1000 females in North America. The incidence is ten times higher among HIV (eng. Human Immunodeficiency Virus) positive individuals (1, 2). Genital warts are the most common viral sexually transmitted infection in the Great Britain (3). The highest prevalence of GWs is established among people from 20 – 24 years of age, and it is around 0.6 to 1.2% in both sexes (1, 4). In 2000, it was estimated that in the US, 6.2 million people, aged 15 – 44 years, are infected with GWs (5). The infection affects men and women equally, but it is also seen in the pediatric population. Vertical transmission and sexual transmission are the main routes of acquisition at an early age (6).
adolescents each year and that every fourth sexually active adolescent gets a STI before the age of 18 (11). Taking into consideration the threatening results of the research performed among high-risk teenagers in the United States, revealing a significant immune deficiency even in HIV-negative persons, it is obvious that immune deficiency is directly associated with high prevalence of STI in this age group (12).

Patients with GWs may be infected with various types of HPV at the same time (13). It has been established that during infection different types of viruses may have antagonistic or synergistic effects on other types of HPV, which can be an explanation for frequent spontaneous regression and recurrence of skin and mucous lesions (14). Spontaneous regression of GWs occurs in up to 30% of affected patients during a 4-month period (9).

**Clinical manifestations**

Genital warts are the most common clinical manifestation of genital HPV infection. They are warty, flat, dome-shaped, papillomatous, filiform, keratotic growths of normal skin color; rarely they are inflamed or hyperpigmented, and may affect any part of the skin or exposed mucous surfaces. Genital warts are most frequently found inside the preputium and frenulum, glans and coronary sulcus, on scrotum, inguinal folds, vulva, perineum, perianal and intraanal region, the vagina, cervix and urethra. More than 50% of women with GWs on the external genitalia have the same lesions in the vagina, whereas 20% of men with external lesions have intraurethral warts. Genital warts are frequently multifocal, especially in the intertriginous areas (madidation and maceration) (25, 26). A study of recent literature indicates a special entity - flat condyloma (lat. Condylomata plana), which used to be described as a clinical form of genital warts. They are commonly caused by HPV types 16, 18, 31, and 33. They are considered as an entity due to their higher oncogenic potential in regard to GWs (27, 28). Giant condyloma, or Buschke-Lowenstein tumor, is a massive timorous lesion of the anogenital region, the size of a fist. Despite the impressive clinical picture, malignant transformations are rare. They are commonly caused by HPV types 6 and 11. It is believed that immunosuppression plays an important role in the pathogenesis of giant condylomas. In cases of clinical and histological malignancy, HPV types 16 and 18 were identified (29, 30, 31).

Another clinical manifestation of genital HPV infection also includes Bowenoid papulosis. This disease manifests as multiple hyperpigmented or hypopigmented papules, with histological signs of cellular atypia (similar to: Morbus Bowen; spinocellular carcinoma in situ). Lesions commonly contain HPV type 16 (29, 30, 31). Although usually asymptomatic, due to their location and size, GWs may cause pain, itching, urethral and vaginal bleeding, as well as urinary obstruction (25).

**Diagnosis and differential diagnosis**

The diagnosis of GWs is based on the clinical presentation. A biopsy may be indicated if genital warts cannot be easily identified, in immunosuppressed patients, when response to therapy is unsatisfactory,
in cases when warts are pigmented, indurated, fixed, and ulcerated, but also in cases of high risk of malignancy (chronic GWs or positive Pap test) (32, 33). HPV infection is determined only by HPV DNA detection. The diagnosis is also made by polymerase chain reaction (PCR) and hybrid capture test (HC2). Serological tests with low sensitivity are useless (34). Application of 3-5% acetic acid is not recommended any more (false positive results) (9).

The differential diagnosis includes the following diseases and conditions: condylomata lata, seborrheic keratosis, dysplastic and benign nevi, molluscum contagiosum, papillae coronae glandis, Crohn's disease, lichen planus, lichen nitidus and malignant skin diseases (35).

**Therapy**

There is no specific antiviral therapy for GWs. The therapy primarily involves the removal of visible lesions on the skin and mucous areas. If untreated, genital warts may grow larger and multiply, and about 95% of patients wish to undergo therapy. It is believed that therapy may induce natural regression of GWs. It remains unclear to what extent immunologic response affects and modifies the treatment, so it is impossible to predict relapses in treated patients. There is still no evidence that the treatment of GWs decreases the contagiousness of treated patients (36, 37). The matter of contagiousness opens another question: if subclinical infections should be treated or not. Clinical studies have shown that after laser therapy of subclinical infections, in women diagnosed by colposcopy, relapses occur in 88% of cases (38). It is still unclear whether patients with subclinical infections are as contagious as patients with clinical infections, but there is evidence that in many cases transmission to the partner occurs when there are no clinical signs or symptoms. According to the traditional clinical approach, treatment of genital warts in one partner does not affect the treatment outcome in the other (37).

Treatment of genital warts mostly includes medications and procedures targeting lesions and the immune system: 1) chemical agents (podophyllin, podophyllotoxin, imiquimod, trichloroacetic acid, 5-fluorouracil, interferon, cidofovir); 2) cryotherapy (liquid nitrogen or carbon dioxide snow); 3) CO₂ laser; 4) photodynamic therapy; 5) surgical treatment (curettage, excision, electrocauterization, circumcision); 6) systemic and intralesional interferon therapy.

**Topical chemical agents**

**Podophyllin**

Podophyllin is a crude plant extract prepared by extracting the resin from the rhizome of Indian Podophyllum emodi or American Podophyllum pelatum. It induces tissue necrosis by blocking the cell mitosis. It is applied to genital warts as a 10-25% suspension in tincture, and it is removed by washing after 1 - 4 hours. It is usually applied once a week for at least 6 weeks. Due to its potential systemic toxicity causing bone marrow depression, its application is limited to less than 0.5 ml per less than 10 cm². Podophyllin has teratogenic effects, whereas relapses occur in 40% of treated patients. It is least effective on the frenulum, scrotum and labia major in women (39). Studies also show that podophyllotoxin, a crude alcohol extract and a biologically active component in the podophyllum resin, is more effective than podophyllin and that it is taking its place in the treatment of GWs.

**Podophyllotoxin**

Podophyllotoxin causes both epidermal and dermal necrosis by binding to cellular microtubules and by blocking mitotic activity in the metaphase. Podophyllotoxin is contraindicated in pregnancy. It is applied twice a day, three times a week, during 2 – 6 weeks. It is available in a 0.5% solution, cream or gel. In clinical practice, podophyllotoxin solution is used for penile lesions, while cream is used in women and for anal lesions. The maximum treatable surface area should not exceed 10 cm². A complete remission is reported in 75% of cases treated with podophyllotoxin solution, and in 64.6% of cases treated with cream (8). Relapses occur in one third of patients after one month. Topical application of podophyllin and podophyllotoxin is associated with possible local adverse effects such as itching, pain, inflammation, edema and ulcerations (37, 39).

**Imiquimod**

Imiquimod modifies the immune response and increases cellular indirect antiviral activity. However, imiquimod has no direct antiviral effects. Its effects proved better in women than in men, with complete...
remission in 72% of treated women. Imiquimod 5% cream is used three times per week, during a 16 week period. The most frequent local adverse reaction is erythema (40). The reported relapse rate is lowest after three months – 9%, and highest after six months – 23% (41).

**Trichloroacetic acid**
Trichloroacetic acid is used in an 80 – 90% solution. It has no systemic effect and it is safe for use during pregnancy. It is applied once a week. Its remission rate after six applications is 70%, while relapses occur in 36% of patients (42).

**5-Fluorouracil**
5-Fluorouracil inhibits the nucleic acids synthesis. Due to its teratogenic effects, it is contraindicated during pregnancy. It is applied as a 5% cream on vulvar, perianal, penile and intrameatal genital warts. It is used 1 – 3 times a week, during 3 – 10 hours. It often causes local irritation (36, 39). Complete remission is reported in 41% of patients after 3 months, while relapses occur in 50% (43).

**Interferon**
Interferon is a proinflammatory cytokine with antiviral effects. When combined with surgical or laser therapy, it causes complete remission of GWs in 54 – 62% of treated patients (44).

**Cidofovir**
Cidofovir is a medication which was used for the treatment of cytomegalovirus and herpes virus infections, and later for GWs in HIV-positive patients. 1% cidofovir gel is applied once a day, for 5 days, during 6 two-week cycles. In immunocompetent patients complete remission is reported in 47% (44).

**Cryotherapy**
Cryotherapy is a procedure in which a chemical, usually nitrous oxide or liquid nitrogen is used to freeze off genital warts. It causes both epidermal and dermal cellular necrosis, consequently leading to cessation of circulation in the tissues and edema. Cryotherapy is an effective and inexpensive method which is safe for use during pregnancy. Cryotherapy with liquid nitrogen is the most widely used method and it is applied with a cryo-spray. Another method includes application of liquid nitrogen or carbon dioxide snow using a cryo-probe for 10 – 20 seconds, freezing a wart and a margin of healthy skin. Generally, three sessions are required, at intervals of 1 to 2 weeks. Anesthesia is rarely required for cryotherapy. Complete wart removal occurs in 79 – 88% of cases, while relapses occur in 25 – 39% (37, 39).

**Laser therapy**
CO₂ laser therapy provides precision preserving the healthy tissue, especially in the treatment of extensive genital warts. It is used in the treatment of penile, anorectal and urethral GWs in men, and flat vaginal condylomas in women. It is safe to use during pregnancy. However, anesthesia is necessary. Complete wart clearance after CO₂ laser surgery has been reported in 23 – 52% of patients, while relapses occur in 60 – 77% of cases (36, 37, 39).

**Photodynamic therapy**
By photodynamic (photochemical) therapy, 5-aminolevulinic acid is selectively accumulated in neoplastic and HPV-infected tissues and then activated by a red laser light. The result is tissue destruction (37).

**Surgical treatment**
Surgical removal of GWs can be performed with a scalpel, scissors (scissor excision was first used for perianal and anal condylomas in 1978), or a curette in local anesthesia. It can be used during pregnancy, but there is a risk of infection. Regression occurs in 35 – 93% of patients, while relapses are reported in 19 – 29% (36, 37, 39). Electrosurgery is associated with a regression of 61 – 94%, whereas relapses occur in 14 – 22% of patients (45). In extensive and long-term GWs on the preputium, circumcision may be performed (45).

**Systemic and intralesional interferon therapy**
Due to its high cost, bone marrow suppression, anaphylaxis, bronchospasm, fever, headache and myalgia, systemic use of interferon (3 million U sc or im 3 times/wk for 6 weeks) is neither primary, nor adjuvant therapy for GWs. Its efficacy varies from 7 – 82%, while relapses occur in 23% of treated patients (36, 39). Administration of intralesional interferon is associated with pain, because interferon is injected directly into the wart. Regression occurs in 35 – 53% of treated patients, whereas relapses occur in 21 – 25% of cases (39). Spontaneous resolution of genital warts in children is reported in more than 50% of cases. Drugs of choice are podophyllotoxin and imiquimod (46, 47).
Combination therapy
High recurrence rate reported for monotherapy led to use of combination therapy (simultaneous or sequential application of two or more methods) with: CO₂ laser surgery and intralesional interferon therapy or imiquimod cream (48); intralesional interferon alpha 2b and podophyllin (49); electrocoagulation and 1% cidofovir gel (49); trichloroacetic acid and podophyllin; trichloroacetic acid and cryotherapy; cryotherapy and podophyllotoxin; cryotherapy and imiquimod; surgical and imiquimod; podophyllin and imiquimod; trichloroacetic acid and podophyllin and cryotherapy; trichloroacetic acid and podophyllin and podophyllotoxin; trichloroacetic acid and podophyllin and imiquimod (3).

Although there are no sufficient data to make any conclusions, a combination therapy with podophyllin and cryotherapy induces complete clearance of GWs in 72.5% of patients after two treatment cycles, while after the same period of time combination of trichloroacetic acid and podophyllin shows regression of GWs in 62.3% of patients (Table 1) (50-53).

According to a recent cross-sectional survey, only 11% of all treatments involved a combination of two or more agents. However, the following combinations proved to be the most frequent initial choice of treatment: trichloroacetic acid and podophyllin, trichloroacetic acid and cryotherapy, cryotherapy and podophyllotoxin, cryotherapy and imiquimod (3).

Prevention of HPV infections is of great importance, not only to avoid transmission, but also to prevent HPV associated diseases, primarily cervical cancer. Considering the fact that prevention strategies are still not available, sexual abstinence is believed to be the only absolute primary prevention. Taking into account the above-mentioned HPV susceptibility to latent infection, secondary preventive strategies, such as treatment of GWs and cervical displasias, have not been found to be helpful. Complete protection from HPV infection is not possible, because infections may occur on sites not covered by the condom (54).

The quadrivalent prophylactic vaccine against HPV types 6, 11, 16 and 18 is the first successfully applied vaccine (55). Vaccination of children of both sexes, aged 10 – 13, would directly protect the immunized individuals, and indirectly protect their partners (56). Although this vaccine is not intended for treatment of GWs, the therapeutic vaccine HspE7, which consists of a fusion of the well known stimulator of cellular immunity, heat shock protein from Mycobacterium bovis and HPV 16E7 oncoprotein, given to patients with anal dysplasia, showed complete remission of GWs in 73% of patients 18 months after the first injection (57).

Conclusions
Genital warts infection commonly occurs early in the sexual life of men and women. There is a strong relationship between GW infection and development of glandular and squamous cervical intraepithelial lesions, and HPV-16 associated invasive cervical cancer. Early detection of HPV infections is of great importance. Combination therapy

### Table 1. Summary of reported results of combination therapy of genital warts

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Wart clearance</th>
<th>Recurrence</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Trichloroacetic acid and podophyllin</td>
<td>53/85 (62.3%)</td>
<td>Not reported</td>
<td>Sherrard et al 50</td>
</tr>
<tr>
<td>Podophyllin and cryotherapy</td>
<td>55/76 (72.5%)</td>
<td>Not reported</td>
<td>Sherrard et al 50</td>
</tr>
<tr>
<td>Intraleisonal interferon and podophyllin</td>
<td>25/41 (61%)</td>
<td>67%</td>
<td>Douglas et al 51</td>
</tr>
<tr>
<td>Systemic interferon and isotretinoin</td>
<td>40/44 (90.9%)</td>
<td>0%</td>
<td>Cardamakis et al 52</td>
</tr>
<tr>
<td>Electrocauterization and cidofovir gel</td>
<td>19/19 (100%)</td>
<td>27%</td>
<td>Orlando et al 53</td>
</tr>
</tbody>
</table>
of precancerous and cancerous lesions. There is no consensus about the treatment of GWs and there are many therapeutic options, but unfortunately no cure yet exists to prevent relapses. Vaccine has an important role in the prevention, and its application provides encouraging results in developing immunization strategies worldwide. A systematic and effective use of HPV vaccine should facilitate the implementation of universal immunization of persons of both sexes at the earliest age, not only of groups at risk. Until then, our task is to determine and apply the most effective methods of prophylactic treatment.

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Genitalne bradavice - novi pristupi u lečenju

Sažetak

Epidemiologija: Genitalne bradavice su klinička manifestacija infekcije humanim papilomavirusima sa prevalencijom od 1% kod seksualno aktivne populacije.

Etiologija i imunologija: Humani papilomavirusi su epitelo-epidermotropni. Čelijski imunološki sistem ima glavnu ulogu u regresiji oboljenja uzrokovanih ovim virusima.

Kliničke manifestacije: Najčešća klinička manifestacija genitalne infekcije humanim papilomavirusima su genitalne bradavice. Ispoljavaju se u vidu bradavičastih formacija koje mogu biti: šiljaste (condylomata acuminata) i bradavičaste (condylomata plana). Ove formacije često se nalaze na genitalnom organu, a u nekim slučajevima i na drugim tijelovitim površinama. U zavisnosti od lokacije, genitalne bradavice mogu izazvati iznemogućenja seksualne živote.

Epidemiologija: Genitalne bradavice su klinička manifestacija infekcije humanim papilomavirusima sa prevalencijom od 1% kod seksualno aktivne populacije. Ova infekcija se često upravo pruža kroz seksualnu aktivnost i može reperićirati u putnu populaciju.

Tehnologije: Sada je razvit broj lako pružljivih tehnologija za liječenje genitalnih bradavic. Međutim, ne postoji jednoznačno definisana tehnologija koja bi bila najbolja i najefikasnija za ovakvo liječenje.

Risorijski papilomavirus (HPV) je virus koji se često iskorišćava u liječenju genitalnih bradavic. Ovaj virus može uzrokovati i više operativnih formacija u tijelu, ima mešovito-aktivni status i ima veoma složenu strukturu.


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acuminata), karfiolaste (eng. coulifower-shaped), kupaste (eng. dome-shaped), zaravnjene (condylomata plana) ili viseće (eng. peduculated).

Dijagnoza i diferencijalna dijagnoza: Dijagnoza se najčešće postavlja na osnovu kliničke slike. Neposredno prisustvo virusa može da se dokaze jedino detekcijom HPV DNK.

Terapija: Za sada ne postoji specifično antivirusno lečenje. Terapija podrazumeva uklanjanje vidljivih promena sa kože i sluznica. U lokalnoj destrukciji lezija, pored klasičnih hirurških metoda, primenjuju se različiti hemijski i fizički agensi, a u sistemskoj terapiji agensi koji deluju na imunološki sistem. Lečenje nije u svim slučajevima jednako efikasno i recidivi su za sada neizbježni. Alternativu monoterapiji čini, sve češće, kombinovana terapija. Važnu ulogu u prevenciji ima vakcina.
Samokvalitetan proizvod pruža sigurnost primene i očekivano dejstvo

Čim vreme ostavi svoj trag

Eluage Anti-age

RAL
Retinaldehid je direktni prekursor retinoičke kiseline
+ H.A.F.
Fragmenti hijaluronske kiseline srednje molekulske mase

Povećavaju koncentraciju hijaluronske kiseline u koži

DUBOKE BORE
OPUŠTENA KOŽA

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Erythrodermic cutaneous T-cell lymphoma: Two case reports

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Abstract

Primary cutaneous T-cell lymphomas (CTCLs) are Non-Hodgkin lymphomas where skin may be the only involved organ for a long time. The erythrodermic form of CTCL, including Sezary syndrome, with increased IgE concentration, eosinophilia and intense pruritus, may suggest atopic dermatitis, in the lack of evidence for diagnosis of T-cell lymphoproliferative disorder. After vigorous research, two patients with erythroderma, increased IgE and eosinophilia, were not diagnosed with CTCL. Adult atopic dermatitis was diagnosed, based on clinical examination and histopathologic analysis of the skin sample. Therapy with oral cyclosporin A (CsA) and systemic corticosteroids were initiated, but the improvement was minimal and short-lived. Disease progression was noted in both patients, after a month of cyclosporine therapy: malaise, subfebrile and febrile temperatures, and development of generalized skin nodules were evident. In the first patient (aged 30) repeated examinations confirmed presence of Sezary cells in peripheral blood samples, dominant T-cell clone in the skin, peripheral blood and bone marrow, whereas the last repeated histopathologic analysis revealed T-lymphoproliferative skin disorder. In the second patient, (aged 44) primary cutaneous CD30+ T-cell lymphoma was diagnosed, based on histopathologic analysis of the newly appearing skin nodule. Differential diagnosis of erythroderma is always difficult, since clinical, histopathologic and immunophenotypic findings are frequently insufficient to differentiate between inflammatory and lymphomatous erythroderma. Treatment with cyclosporin A always demands careful evaluation of the course of the disorder.

Erythroderma (erythema of at least 90% of the body skin surface) is a rare, but severe skin manifestation of several cutaneous disorders including psoriasis, atopic dermatitis, pityriasis rubra pilaris and cutaneous T-cell lymphoma (CTCL). CTCLs are Non-Hodgkin lymphomas where skin may be the only involved organ for a long time. Erythrodermic CTCLs most often include erythrodermic mycosis fungoides and Sezary syndrome. The erythrodermic form of CTCL, including Sezary syndrome, with increased IgE concentration, eosinophilia and intense pruritus, may be mistaken for atopic dermatitis in the lack of evidence for diagnosis of T-cell lymphoproliferative disorder. We report two patients with erythroderma, increased IgE and eosinophilia in whom, after vigorous research, the diagnosis of CTCL was not established, and adult atopic dermatitis was diagnosed. The therapy with cyclosporine A was initiated and after a month of therapy, which showed to be ineffective, repeated clinical examination and histopathological, immunohistochemical and gene rearrangement analyses, revealed existence of T-cell cutaneous lymphoma in both patients.

Case 1

A male patient, aged 30 years, was admitted to our Department with extremely itchy erythroderma with generalized peripheral lymphadenopathy and hyperkeratosis of the palms and soles, that lasted for two months (Figure 1). During the previous year he received therapy for dry, red and scaly erythematous macules in the skin folds, with topical and systemic corticosteroids and topical pimecrolimus, without improvement. A short course of P-UVA phototherapy led to minimal improvement.

Laboratory analyses revealed leukocytosis 16.65×10⁹/L, and eosinophilia 8.5%, as well as elevated lactate dehydrogenase (LDH) of 559 U/L
and increased IgE concentration - 5650 IU/L. Other complete blood count (CBC) parameters, electrolytes, urea, creatinine, total bilirubine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), gamma glutamyl transpeptidase (yGT), IgG, IgA, IgM, were within normal range. ELISA HIV test was negative. Increased number of leukocytes was evident (14x10^9/L), in the peripheral blood smear, but Sezary cells were not found. Chest X-ray findings and abdominal and pelvic ultrasounds were normal. Histopathologic analysis of the skin sample specimens revealed immune inflammatory response and secondary neutrophilic spongiosis consistent with non-specific inflammatory dermatosis. Cytologic analysis of the left supraclavicular enlarged lymph node smear revealed a non-specific lymphoid hyperplasia. T-cell receptor-y gene rearrangement analysis of skin and blood specimens showed polyclonal T-cell population. Due to lack of evidence for the diagnosis of T-cell lymphoproliferative disorder, the diagnosis of adult atopic dermatitis was established, and therapy with cyclosporin A (CsA) oral solution (5 mg/kg/bw), and methylprednisolone 40 mg/d i.v. was initiated, with chloropyramine i.m. and topical corticosteroid therapy.

Three weeks later, the patient referred for check-up with signs of disease progression: malaise, more enlarged peripheral lymph nodes, fever (39.1°C) and generalized erythemolivid nodules, with more intense erythroderma. Repeated peripheral blood smear revealed younger lymphatic cells (5% were suspicious for Sezary cells). In the peripheral blood and skin, a dominant T-cell clone was detected by T-cell receptor-y gene rearrangement analysis. A dominant T-cell clone was also detected in the bone marrow. CD4/CD8 ratio was increased to 7.8. Chest and abdominal multi-slice computed tomography (MSCT) revealed axillary lymphadenopathy up to 3.5 cm in diameter, while chest and retroperitoneal lymph nodes were not enlarged. Repeated skin biopsy was performed, and histopathological analysis was consistent with T-lymphoproliferative disorder - Sezary syndrome (Figure 2.). Based on repeated hemoculture test, staphylococcal sepsis was also diagnosed, so intravenous sulfamethoxazol trimetoprim was administred. Based on these findings, diagnosis of Sezary syndrome was established in stage III B: T4 (confluence of erythema covering ≥80% body surface area) N1 (clinically abnormal peripheral lymph nodes; histopathology Dutch grade 1) M0 (no visceral organ involvement) B2 (high blood tumor burden: positive clone, increased CD4/CD8), according to revised classification of mycosis fungoides/Sezary syndrome (1). The patient was referred to a hematologist for...
marrow specimens, immunophenotypization of peripheral blood lymphocytes were done, but the nature of the presenting erythroderma was not elucidated. Due to the lack of evidence for diagnosis of T-cell lymphoproliferative disorder, it was concluded that the diagnosis could be an adult form of atopic dermatitis, so a trial of CsA oral solution (5 mg/kg/bw) with methylprednisolone (40 mg/d) i.v. was commenced, with systemic antihistamine and topical corticosteroids and emollients.

Three weeks later, the patient became febrile (38°C), with worsened peripheral lymphadenopathy (enlarged lymph nodes in the right groin were evident). Also, disseminated livid papules up to 5 mm in diameter, some with necrotic surface appeared, while erythroderma aggravated during the second admission (Figures 3a and 3b). Leukocytosis (14.51x10^9/L) and eosinophilia (9%), with platelets count of 590x10^9/L and ESR 67 mm/h were also present. The chemocultures remained sterile. The repeated peripheral blood smear confirmed leukocytosis and eosinophilia, while on flow-cytometry, CD4/CD8 index was within normal range. Histopathologic analysis of the enlarged lymph node specimen was consistent with dermatopathic lymphadenopathy. Examinations to establish a lymphoproliferative disease, including bone marrow biopsy, histopathological analysis, peripheral blood smear, T-cell receptor-γ gene rearrangement analysis of the skin, peripheral blood and bone

**Case 2**

A male patient, aged 44, was admitted to our Department with generalized dry, scaly and itchy livid skin, and lichenification on the elbows, knees and ankles. At the age of 26, his skin turned dry, scaly and itchy, and at the age of 39 his skin condition worsened, with pronounced livid erythema and scaling of over 95% of the skin surface. He was treated by several dermatologists for generalized ichthyosis of unknown cause. Repeated histopathologic findings, in the last 15 years, were non-specific and inconclusive. There was no other evidence of atopy in personal and family history. Topical corticosteroid therapy and emollients showed no benefit. The patient turned chronically subfebrile 4 months before admission, and generalized peripheral lymphadenopathy occurred.

On admission, increased erythrocyte sedimentation rate (ESR) 38 mm/h, leukocytosis 13.91x10^9/L, eosinophilia 8.9%, thrombocytosis 604x10^9/L, and increased concentration of IgE (3200 IU/L) were established. Other parameters of CBC, blood biochemistry, AST, ALT, γGT, LDH, carcinoembryonic antigens (CEA), alpha fetoprotein antigens (AFP), amylase and immunoglobulins (G, A, M) were within normal range. ELISA tests for anti-HIV and anti-Borrelia burgdorferi antibodies were negative. Chest X-ray and abdominal and pelvic ultrasound findings were normal. Histopathologic analysis of skin specimens and hyperkeratotic skin specimens revealed chronic inflammation and reparative changes suggestive of hypersensitive reaction. Histopathological analysis of the enlarged right axillary lymph node specimen was consistent with dermatopathic lymphadenopathy. Examinations to establish a lymphoproliferative disease, including bone marrow biopsy, histopathological analysis, peripheral blood smear, T-cell receptor-γ gene rearrangement analysis of the skin, peripheral blood and bone

**Figure 3.a. Erythemolivid skin color of the back and upper arms, with numerous necrotic papules in the second patient.**
Figure 3.b. Close-up view at livid, scaly skin of the abdomen, with erosions at places of previous necrotic papules to the following diagnosis: primary cutaneous CD30+ T-cell lymphoma (Figures 4a and 4b). The patient was referred to a hematologist who prescribed bleomycin, cyclophosphamide, doxorubicine, vincristine, prednisolone (B-CHOP) polychemotherapy. After six cycles of (B-CHOP) polychemotherapy, the skin lesions regressed, as well as lymphadenopathy, but the peculiar livid color of the skin was still evident on the last follow-up (Figure 5).

Discussion

Erythroderma is defined as an erythematous dermatitis involving of at least 90% of the cutaneous surface. It is a severe skin manifestation of several cutaneous disorders, including cutaneous T-cell lymphoma (CTCL). If the

Figure 4. b. At least 20% of cells are CD30+ large cells with polymorphic nuclei and small nucleoli (immunoperoxidase staining, DAB chromogen, contrastained with hematoxylin, x100)

Figure 5. Regression of papulonecrotic lesions, with remaining of livid color of the skin in the second patient
diagnosis of a preexisted skin disorder was previously established, such as psoriasis, atopic dermatitis and pityriasis rubra pilaris, there are no doubts about the nature of erythroderma or its treatment. Considering the fact that CTCL is a slow-developing disorder, evolving skin changes and, often repeated, histopathologic findings of erythrodermic skin may lead to the diagnosis. In some cases, there are difficulties to differentiate between inflammatory dermatosis and skin lymphoma by clinical and histopathological features. Thus correlation of clinical appearance, immunohistochemistry and T-cell receptor-γ gene rearrangement analyses are needed (2). Sometimes, even that is not enough, so regular follow-ups and repeated analyses are necessary to detect the true nature of erythroderma and other skin changes of CTCL. It can be said that the final diagnosis of CTCL is possible during the course of the disease, when the tumor load is sufficient to be detected by vigorous research.

In the first patient, the diagnosis of Sezary syndrome, the most frequent form of erythrodermic CTCL, was diagnosed only after repeated analyses to identify the cause of erythroderma, one month after the initiation of cyclosporine treatment. The other patient was diagnosed with primary cutaneous CD30+ T-cell lymphoma which manifested with erythroderma and necrotic skin nodules that appeared late during the course of the disease. Primary CD30+ CTCL are most frequently manifested as primary cutaneous CD30+ anaplastic large cell lymphoma (ALCL), lymphomatoid papulosis, or borderline cases. Primary cutaneous CD30+ ALCL is manifested with multiple, often ulcerating, skin papules and nodules, like in our patient. On histopathological analysis, the majority of cells have anaplastic appearance, but in 20-25% cases non-anaplastic cells are present, which was the case in our patient (3). Erythroderma is not a typical feature of primary cutaneous CD30+ CTCL. In our patient, the preexisting, long-lasting erythroderma may be considered as secondary to the slowly developing T-cell dyscrasia, that could not be detected earlier by repeated histopathological analyses. Previously published cases of primary cutaneous ALCL with prolonged erythrodermic prodrome support this observation (4, 5).

Administration of CsA, used for the treatment of erythrodermic adult atopic dermatitis, caused lymphoproliferative disorders in these two cases, because the therapy lasted only a few weeks. According to previous reports, in adult atopic dermatitis patients, lymphoproliferative disease developed after at least 6 months of cyclosporine A treatment (6, 7). Also, in a large study, CTCL was not found to be more frequent in patients with atopic dermatitis, although in another study increased prevalence of lymphoma (especially cutaneous lymphoma) was found among patients with atopic dermatitis treated with topical corticosteroids (8, 9). Published case reports suggest that in rare cases CTCL may develop in atopic dermatitis patients who never received cyclosporine A therapy (10).

In conclusion, correlation of the clinical appearance, and, often repeated, histopathologic analysis of the skin, enlarged peripheral lymph nodes and bone marrow, together with peripheral blood smears, T-cell receptor-γ gene rearrangement analysis of the skin, peripheral blood and bone marrow specimens and immunophenotypization of peripheral blood lymphocytes, are useful in the diagnosis of patients with erythroderma without previously existing dermatosis, because the lymphomatous nature of presenting erythroderma may be elucidated (2).

References:
Eritrodermalni kutani limfom T-ćelija - prikaz dva slučaja

Sažetak
Uvod: Primarni kutani limfomi T-ćelija su Non-Hočkinovi limfomi kod kojih koža može biti dugo jedini zahvaćeni organ. U nedostatku nalaza koji bi potvrdili limfoproliferativno oboljenje T-ćelija, eritrodermijski oblik ovih limfoma (uključujući i Sezarijev sindrom), uz visoke koncentracije IgE, eozinofliju i izrazit svrab može da podseća na atopijski dermatitis.


Zaključak: Diferencijalna dijagnoza između inflamatorne dermatoze i eritrodermijskog primarnog T-ćelijskog limfoma uvek je teška i zahteva ponovljena ispitivanja sa ciljem dokazivanja mogućeg limfoma. Primena ciklosporina u terapiji uvek zahteva pažljivo praćenje toka bolesti.
THE NOVI SAD DERMATOVENERELOGIC MOULAGE COLLECTION,
CLINIC OF DERMATOVENERELOGY, CLINICAL CENTER OF VOJVODINA,
NOVI SAD, SERBIA
VOJISLAV ŠIKOPARIJA, SCULPTOR DONATES HIS MOULAGES TO THE FACULTY OF MEDICINE IN NOVI SAD, BELGRADE, 1964
This paper deals with the period from 1881 to 1918, when the following Sanitary Laws were passed: *Law on the Organization of the Sanitary Profession and Public Health Care* (1881), which implemented measures for protection from venereal diseases, as well as restriction of prostitution; *Public Sanitary Fund* (1881), with independent budget for health care; *Announcement on Free of Charge Treatment of Syphilis* (1887). Dermatovenereological Departments were also founded: in the General Public Hospital in Belgrade (1881), and in the General Military Hospital (1909). The Hospital in Knjaževac for Syphilis was reopened (1881), as well as mobile and temporary hospitals for syphilis, and a network of County and Municipality hospitals. The first Serbian dermatovenereologist was Dr. Jevrem Žujović (1860 – 1944), and then Dr. Milorad Savičević (1877 – 1915). Skin and venereal diseases were treated by general practitioners, surgeons, internists and neurologists. Although Dr. Laza Lazarević (1851 – 1890) was not a dermatologist, but a physician and a writer, he published three papers on dermatovenereology, whereas Dr. Milorad Godjevac (1860 – 1933) wrote an important study on endemic syphilis. From 1885 to 1912, organization of dermatovenereology service has significantly improved. Considering the fact that archive documents are often missing, only approximate structure of diseases is specified: in certain monthly reports in Zaječar, out of all the diseased persons, 45% had skin or venereal diseases, while in Užice the number was 10.5%, which points to different distribution of these diseases. High percentage of dermatovenereology diseases was caused by high frequency of venereal diseases and syphilis. During the war: 1912 – 1918, the military medical service dominated, and in 1917 *Prince Alexander Serbian Reserve Hospital* was founded in Thessaloniki with a *Department for Skin and Venereal Diseases*. During this period, work of the Civilian Health Care Service was interrupted, consequently leading to a considerable aggravation of public health.

This chapter focuses on the period from 1881, when the health care service was legally regulated, to 1918, when the First World War ended. After the Serbian-Bulgarian War (1885), being on the crossroads of Turkish, Austrian and Russian interests for a long time, Serbia entered a period of peace, which lasted about 25 years. Despite the political turmoil in the country, it contributed to progress in every aspect. After this period, the country entered yet another period of war (1912 – 1918), and the newly established Sanitary Service was shut down. The number of military physicians, insufficient during the peace, became even more apparent during the war, so that civilian doctors were recruited to the army (1), whereas the Sanitary Service was almost completely transformed into a Military Sanitary Service. The consequences were to be distressing and long lasting.

**Legislation and organization of the dermatovenereology service**

After the wars which led to the liberation of Serbia (1876 – 1878), things which happened before, occurred again, like in similar situations in the past: the major health problem was the spread of communicable diseases, while their occurrence was associated with historical ups and downs of the country. Apart from venereal diseases, skin diseases spread as well, due to lack of health care, but also due to low life and hygiene standards. Although syphilis remained a dominant health concern, dermatology gained recognition in the frame of general health care.

This period was characterized by establishment of sanitary laws (2), under the authorization of Dr. Vladan Đorđević, the chief of the Sanitary Department...
II), according to which syphilis was to be treated in hospitals, was extremely important. The new Sanitary Law intended development of a hospital network, as well as reorganization of the existing hospitals, defining eradication of venereal diseases as one of the greatest problems.

By the Sanitary Law, the previous County and Belgrade City Hospital was transformed into the General Public Hospital (GPH), with five departments, one of them being the Department for Skin Diseases and Syphilis. It was the first dermatovenereology department in Serbia, and it had separate sections for male and female patients (5, 6).

A Department for Skin and Venereal Diseases was also founded in the frame of the General Military Hospital (GMH), after a new hospital was built in the western part of Vračar, in 1909. The acting chief of the Department was Captain First Class, Dr. Milutin Pop Jovanović (13).

The Knjaževac Hospital for Syphilis, burnt down in 1876 in the Serbian – Turkish war (see part II), was reopened in 1881, in a private residence. It remained there for ten years to come, but after that it was moved into a restored, old hospital (14).

The County and District General Hospitals also represented important centers for the treatment of skin and venereal diseases. Apart from these, in regions with a great number of patients suffering from syphilis, in 1882 a new way of treatment was organized: two mobile hospitals, which were active till 1885, with some interruptions. The treatment took place at a person’s residence, under the supervision of a doctor, and it lasted for months, even after the end of treatment (12, 14).

For the same reasons, in 1894, three temporary hospitals for syphilis were founded: in Vitkovo, Krupanj and Soko Banja, as well as a Hospital for the Treatment of Syphilis in Boljevac (15).

These kinds of hospitals were possibly organized in other areas with a great number of diseased.

Of the Ministry of Internal Affairs - MIA (1879 – 1884) (3). In 1881, on his initiative, a Public Sanitary Fund was established, which provided an independent sanitary budget (2, 3). Dr. Vladan Đorđević created a Law on the Organization of the Sanitary Profession and Public Health Care (hereinafter: Sanitary Law), which was also adopted in 1881 (4). World experts found it to be one of the best and most contemporary laws in Europe (5).

Of the general Sanitary Law regulations, which applied to all sanitary districts, two were significant for the development of the dermatovenereology service:
- Foundation of district and county hospitals over the whole country during a 10-year-period (6);
- Submission of formal reports on the public health on regular basis (7, 8).

Certain law articles concerned organization and development of the dermatovenereology profession:
- Measures for the prevention of multiplication and spread of venereal diseases (9);
- Suppression of wanton and all that provoked it (8).

In the same year, Prostitution Regulations (10) and Regulations of the Hospital Funds gained for Prostitutes were passed. These funds were used for medical check-ups and hospital treatment of prostitutes (11).

The Announcement dated 1887, was of utmost importance for the dermatovenereology service. According to the Announcement, treatment of syphilis was free of charge for peasants and workers, regardless of their financial status. In 1895, this privilege was exercised by all patients with sexually transmitted diseases, as well as by railway ”guardians” and low-paid railway staff (12).

The main obstacles for the enforcement of these laws included lack of physicians, lack of specialists and hospitals, and that is why special attention was paid to the above mentioned.

Hospitals

The Sultan’s Edict (“Hatiserif”) from 1830 (12), allowed building of hospitals in Serbia, but they were mostly organized in unsuitable buildings for their purpose, whereas their number and equipment were rather deficient. The conclusions of the Medical Board for the investigation of “frenga” in 1846 (see part II), according to which syphilis was to be treated in hospitals, was extremely important. The new Sanitary Law intended development of a hospital network, as well as reorganization of the existing hospitals, defining eradication of venereal diseases as one of the greatest problems.

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These kinds of hospitals were possibly organized in other areas with a great number of diseased.

This extraordinarily long period of peace allowed good organization of an antivenereal service, decreasing the number of patients with syphilis. In 1912, a war period started, and lasted till 1918. At that time, the total number of physicians in Serbia was 370, out of which 296 were recruited into the
army, whereas 57 physicians capable of work were left behind (16). It affected the public health a great deal, causing spread of venereal and skin diseases once again. During the war period, a military sanitary network was reorganized, and on March 16, 1917, the “Prince Alexander Serbian Reserve Hospital” (PASRH) was founded in Thessaloniki. It was the Central Military Hospital of the Serbian Army in exile; it included a Department for Skin and Venereal Diseases, and its chief was Major Dr. Dušan Kopša (17).

In this way, organization of dermatovenereology service gained its position both in peace and in war. However, the discontinuity, which goes hand-in-hand with the Serbian history through centuries, this time, also stopped the progress of the sanitary service.

Physicians

One of the reasons which made enforcement of the Sanitary Law extremely difficult was lack of physicians in Serbia: in 1895 there were 150, in 1900 there were 200, and in 1908 there were 288 physicians. Before the outbreak of the Balkan Wars, in 1912, there were 370 physicians in Serbia. Although the law required medical specialists for some positions, with the exception of surgeons (there were 30 surgeons at the end of the 19th and at the beginning of the 20th century) (3), they were extremely scarce. Until the twentieth years of the 20th century, dermatovenereologists were really rare. That is why implementation of the Sanitary Law took a long time.

Dr. Jevrem Žujović (1860 – 1944) was the first educated Serbian dermatovenereologist (Figure 1). He studied medicine in France, and specialized in dermatovenereology at the St. Louis Hospital in Paris with Professor A. Fournier, a specialist in syphilisology of worldwide reputation (18). He became a Head of the Department of Skin Diseases and Syphilis at the GPH in 1889 (19). He implemented modern dermatology doctrine in the whole country, organized struggle against syphilis and surveillance of prostitution, and also studied leprosy. He introduced arsenic into the treatment of syphilis, while in 1909 he organized a laboratory for the Wassermann reaction test and microscopic detection of Treponema pallidum in skin lesions (20). He translated a book by A. Fournier: “Syphilis and Marriage”. Together with M. Jovanović-Batut, he wrote “Instructions on Syphilis” according to the decision of the Serbian Medical Society (21). He was also the first President of the Yugoslav Dermatology Association.

Dr. Milorad Savičević (1877 – 1915) was a Vienna medical student who specialized in dermatovenereology with Professor Dr. E. Finger. From 1908, he was a secondary physician at the GPH. He died from spotted typhus in 1915 (21). During his short life he had built up an enviable bibliography. Apart from several professional and scientific papers, he wrote the following books: “Venereal Diseases”, “Venereal Diseases and their Effects on Marital Life and on the Offspring”, “Prostitutes”, “Who May get Married”, “Sexual Life and its Consequences”, “Physicians and the Audience”. “The Beauty of the Body, its Care and Cosmetology” is probably our first book in cosmetology. He also translated several books on syphilis (22). His early death was a great loss for Serbian dermatovenereology.

Dr. Filip Tajić, a Sanitary Colonel, was a Vienna student; he specialized in dermatovenereology for 11 months in Paris, but he never practiced it. After his return to the country, he joined the army where he

Figure 1. Jevrem M. Žujović
mostly held leading position in the Military Medicine (21).

The above mentioned doctors, *Mihalin Pop-Jovanović* (GMH) and *Dušan Kopa* (PAH) were educated dermatovenereologists as well. The former one died in 1914, from sepsis (23).

According to the documents and reports of the Serbian Medical Society, as well as of the Serbian Archive for General Medicine, skin and venereal diseases were mostly treated by general practitioners, surgeons, internists and neurologists. Some of them attracted special attention.

*Dr. Laza Lazarević,* (1851 – 1890), was a writer, creator of the genre of realistic story, “our first clinician, first scientist and first philosopher-physician” (21). During his short life he left his mark in dermatology as well. He graduated from medicine in Berlin in 1879, with a thesis entitled “Effects of Mercury on Rabbit Tissues” (24). He also published the following papers: “A Contribution on Latent Syphilis” (25); “Two Rare Cases of Erythema Nodosum” (26); “Exanthem – Variola – Syphilitic Exanthem” (27).

*Dr. Milorad Godjevac* (1860 – 1933), was a physician in Belgrade municipality (21). He spent three years in Knjaževac (1890 – 1893) on a “special mission” by the order of the MIA, in order to study endemic syphilis and suggest solutions for its eradication. After this mission, he published a monograph which remained a valuable document on all circumstances in the region (28).

In this period, *Vojislav Mihailović* (Graz, 1904), (29), *Ivan Marković* (Vienna, 1914), and *Miloš Đorić* (Nancy, 1914) (30), were among our students of medicine who later became eminent dermatovenereologists.

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8. Zakon o uređenju sanitetske struke i o čuvanju narodnog zdravlja [Law on the organization of the sanitary profession and public health care]. Srp Novine 1881 Apr. 4;49(75).
9. Zakon o uređenju sanitetske struke i o čuvanju narodnog zdravlja [Law on the organization of the sanitary profession and public health care]. Srp Novine 1881 Apr. 9;49(79).
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Abbreviations
MIA: Ministry of Internal Affairs
GPH: General Public Hospital
GMH: General Military Hospital
PASRH: Prince Alexander Serbian Reserve Hospital
Prof. Dr. Mirjana Poljački
1949 – 2009

Professor Dr. Mirjana Poljački was born on August 9, 1949 in Sombor. She received her education in Novi Sad and graduated from the Faculty of Medicine as an excellent student.

Prof. Dr. Mirjana Poljački started her teaching, scientific and professional career in 1976. As a physician specializing in dermatovenereology, she was granted the position of a research assistant in dermatovenereology. Gradually, she passed from one position to another, both at the Faculty of Medicine and Clinic of Dermatovenereology in Novi Sad: from a research assistant to a full professor and a Head of the Department of Dermatovenereology, from a specializing student to the Head of the Clinic of Dermatovenereology. Prof. Dr. Mirjana Poljački acquired a rich teaching, research and professional experience.

After becoming an associate professor in 1997, and a full professor in 2002, Professor Dr. Poljački was included in all the teaching activities at the Department of Dermatovenereology. Apart from taking part in the teaching process for students of medicine and dentistry, for physicians specializing in dermatovenereology, general medicine, occupational medicine and emergency medicine, Prof. Dr. Mirjana Poljački was the Chair of the Commission for Specialist's Exam in Dermatovenereology for years.

As a distinguished educator she contributed to the establishment of higher standards of the teaching process of dermatovenereology. She published and edited “Test Questions in Dermatovenereology”, using tests as a contemporary means for student knowledge assessment. She edited a monograph “Basocellular and Spinocellular Skin Cancers” and was a coauthor of a textbook for students of medicine and dentistry “Selected Chapters in Skin Pathology” and “Dermatovenereology”, which was published in 2000.

She mentored three students writing scientific papers, a few graduate students obtaining their master’s degrees, and one postgraduate student defending his PhD thesis. She published numerous scientific and professional papers, as an author and a coauthor, in international and national journals, and took part in international and national meetings. Prof. Dr. Mirjana Poljački received a great number of awards for her research and professional practice. She participated in three scientific projects, of special value for the development of scientific disciplines, and she was a principal investigator of one research project. She was a member of many associations.

Her main professional interest was in allergology and immunology in the field of dermatovenereology. Apart from these activities, Prof. Dr. Mirjana Poljački founded a Service for Radiation Therapy for Skin Cancer.

Unfortunately, before her full retirement, in December 2008, she fell ill with a severe, incurable illness.

In the end, I should like to point out that using her creative and positive attitude, Prof. Dr. Mirjana Poljački showed an outstanding ability in developing young scientists and professionals, for which we are deeply grateful.

Prof. Dr. Verica DURAN
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A report on the 6th Spring Symposium of the European Academy of Dermatology and Venereology

After Malta, Budapest, Lapland, Sofia and Istanbul, the 6th EADV Spring Symposium was held in Bucharest, Romania, from April 23-26, 2009. The Chair of the Local Organizing Committee was Dan Forsea, and Vice-Chair was Virgil Feier. The Spring Symposium of EADV is a beautiful tradition, bringing together Dermatologists from all parts of Europe and beyond. The concept of the Symposium was “Endless Dermatology”, inspired by the famous work of the world-wide known Romanian sculptor, Constantin Brancusi. His sculpture, “The Endless Column”, stands as the logo of the Symposium, as a symbol of the endless passion to learn, to understand in depth and to strive higher, but also to develop and to perfect our science and our art - Dermatology.

Dermatologists from Serbia were also present in Bucharest. Professor Ljiljana Medenica was the Co-Chair in workshops: “The Burden of Ageing Skin”, and she delivered her lecture “Rejuvenation of the Ageing Skin”. An oral presentation was held by Dr. Javorka Delić and Dr. Milutin Delić: “Ulcus Cruris Venosum - Impact on the Quality of Life” and Dr. Jadranka Krstić and Dr. Spasoje Radovanović: “Nail Plate Dermatoscopy - a Two Year Study”. Eleven posters were exhibited from Serbia.

Six plenary lectures were also presented: Placing Quality of Life in Dermatology Care, Prevention Strategies in Skin Cancer, Advantages and Pitfalls of Biologics in Psoriasis, The Role of Dermato(patho)logy in Composite Tissue (hands and face) Allografts, Kaposi Sarcoma - an Enigma Solved?, and Climate Change and Human Skin Cancer. Seventeen symposia, 17 workshops and 8 focus sessions, along with forums, poster discussions, free communication sessions and satellite symposia, have given the opportunity to physicians and scientists to meet and share their experiences with the skin.

The next EADV Spring Symposium will be held in Cavtat (Croatia) in May, 2010.

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## FORTHCOMING EVENTS

Dermatology and Venereology Events 2009-2010

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<tr>
<th>DATE</th>
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<th>ABSTRACT SUBMISSION DEADLINE</th>
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<tr>
<td>18-19 September, 2009</td>
<td>Photodermatology Meeting &amp; Photopatch Test Course Krakow, Poland</td>
<td>No abstract submission</td>
<td><a href="http://www.photopatch.eu">www.photopatch.eu</a></td>
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<tr>
<td>9-12 November, 2009</td>
<td>11th IUSTI World Congress Spier Wine Estate, Cape Town, South Africa</td>
<td>1 June, 2009</td>
<td><a href="http://www.iusti.co.za">www.iusti.co.za</a></td>
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<td>26-28 March, 2010</td>
<td>Hair and Scalp Diseases in Clinical Practice, Warsaw, Poland</td>
<td>Under construction</td>
<td><a href="http://www.spederm.eu">www.spederm.eu</a></td>
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<tr>
<td>13-16 May, 2010</td>
<td>7th EADV Spring Symposium Cavtat, Croatia</td>
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<tr>
<td>6-10 October, 2010</td>
<td>19th EADV Congress Gothenburg, Sweden</td>
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<td><a href="http://www.eadv.org/eadv-meeting">www.eadv.org/eadv-meeting</a></td>
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Prepared by: Dr. Tatjana Roš, Clinic of Dermatovenerology Diseases, Clinical Center of Vojvodina, Novi Sad, Serbia

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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.

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 authors.

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

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.

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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://vsbw.vs.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.

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