

# MEDICUS

ISSN 1409-6366 UDC 61 Vol · 27 (1) · 2022

## Original scientific paper

- 7 EFFICACY OF TRICHLOROACETIC ACID IN TREATMENT OF HPV RELATED INFECTIONS OF THE UTERINE CERVIX**  
Anita Morarcalieva Chochkova<sup>1</sup>, Nevenka Velickova<sup>2</sup>, SimonidaKotlarova Poposka<sup>3</sup>, Gligor Dimitrov<sup>3</sup>, Marina Nakova<sup>1</sup>
- 14 LEISHMANIASIS IN REPUBLIC OF NORTH MACEDONIA, 1975-2020**  
Dejan Filipovikj<sup>1</sup>, Maja Dimova<sup>1</sup>, Julija Mitrova Telenta<sup>1</sup>, Ivana Dochcheva Karajovanov<sup>1</sup>, Nevzat Elezi<sup>2</sup>
- 18 QT SEGMENT INTERVAL INDICES AT ADULTS WITH UNCOMPLICATED OBESITY**  
Atilla J Rexhepi<sup>1</sup>, Valon N Asani<sup>1</sup>, Hysni I Ismaili<sup>1</sup>, Fisnik F Demiri<sup>2</sup>, Vlora Ibrahimij<sup>2</sup>
- 23 ИНСУЛИН-ЛАЈК ГРОУТ ФАКТОР-1 И ВАСКУЛАРНО ЕНДОТЕЛИЈАЛЕН ГРОУТ ФАКТОР – РАНИ ПРЕДИКТИВНИ БИОМАРКЕРИ ЗА РЕТИНОПАТИЈА НА ПРЕМАТУРИТЕТ**  
Елизабета Петковска<sup>1</sup>, Никола Оровчанец<sup>2</sup>, Викторија Јовановска<sup>1</sup>, Стојка Нацева Фуштиќ<sup>3</sup>

## Professional paper

- 32 ASST AND AUTOIMMUNITY IN PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA**  
Trajkova Vesna<sup>1</sup>, Velichkova Nevenka<sup>2</sup>, Breshkovska Hristina<sup>3</sup>
- 39 LIFE THREATENING UROLOGY CONDITIONS AS COMPLICATIONS OF SARS COV2 INFECTION – SYMPTOMS, DIAGNOSE, CONSERVATIVE, OPERATIVE AND POST-OPERATIVE TREATMENT**  
Ivchev J<sup>1,2</sup>, Gjorevski A<sup>2,3</sup>
- 47 INDEX OF THE OSTEOPOROTIC RISK IN THE EVALUATION OF THE DENOSUMAB TREATMENT**  
Slavica Shubeska Stratrova<sup>1,5</sup>, Snezana Markovik Temelkova<sup>1,5</sup>, Irfan Ahmeti<sup>1,5</sup>, Jasmina Meceska Jovcevska<sup>2</sup>, Dejan Spasovski<sup>3,5</sup>
- 54 HEARING RECOVERY IN PATIENTS WITH IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS**  
Lidija Ristovska<sup>1</sup>, Zora Jachova<sup>2</sup>
- 60 ПРОМЕНИ НА ВНАТРЕШНА ЛИМИТНА МЕМБРАНА КАЈ ПАЦИЕНТИ СО ОКЛУЗИЈА НА ЦЕНТРАЛНА РЕТИНАЛНА ВЕНА**  
Петрушевска Андријана, Голубовиќ Милена, Ѓошевска Даштевска Емилија, Нивичка Каева Јана
- 65 DHURIMI I GJAKUT NË KOMUNËN E TETOVËS NË PERIUdhËN 2018 - 2021**  
Ekrem Ismani<sup>1</sup>, Sani Bajrami<sup>2</sup>, Mazllum Belegu<sup>2</sup>
- 70 IMPLEMENTATION OF SHEAR WAVE ELASTOGRAPHY AS A NEW METHOD IN THE CLINIC OF GASTROENTEROHEPATOLOGY – SKOPJE**  
Arzana Hasani Jusufi, Meri Trajkovska, Atip Ramadani, Arta Bina, Xhem Adem, Georgi Janevski.
- 77 MATERNAL PLASMA BIOMARKERS (ANTITHROMBIN 3, PLASMOINOGEN ACTIVATOR INHIBITOR 1, SOLUBLE TIE 2, VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR2) AS INDICATORS FOR PLACENTA ACCRETA SPECTRUM (PAS) IN THE THIRD TRIMESTER OF PREGNANCY**  
Iva Malahova Gjoreska<sup>1</sup>, Vesna Antovska<sup>1</sup>, Goran Kochoski<sup>1</sup>, Katerina Nikoloska<sup>1</sup>, Josif Gjoreski<sup>1</sup>

## Review

- 81 МЕХАНИЧКИ ПОВРЕДИ НА ОЧИТЕ – МОЖНОСТИ ЗА НИВНА ПРЕВЕНЦИЈА И РЕХАБИЛИТАЦИЈА**  
Ѓошевска Даштевска Емилија, Петрушевска Андријана, Голубовиќ Милена
- 87 EVALUIMI DHE MENAXHIMI I DHIMBYES SKROTALE**  
Ilbert Ademi<sup>1</sup>, Majlinda Ademi<sup>2</sup>
- 92 МОЖНИ КОМПЛИКАЦИИ ОД ФАКОЕМУЛЗИФИКАЦИОНА ХИРУРГИЈА НА КАТАРАКТА**  
Велковска Б<sup>1</sup>, Трпевска Шекеринов Н<sup>1,2</sup>, Петрушевска А<sup>1</sup>, Нивичка Каева Ј<sup>1,2</sup>, Шекеринов Д<sup>3</sup>
- 100 EMBRYOLOGY, MORPHOLOGY, CLASSIFICATION AND SURGERY OF SYNDACTYLY**  
Ermira Hamzai<sup>1</sup>, Djordje Dzokic<sup>2</sup>, Elizabeta Mircevskaja Zogovska<sup>2</sup>
- 106 SOME CONSIDERATIONS ABOUT POSTOPERATIVE NAUSEA AND VOMITING.**  
Anna Mandi<sup>1</sup>, Estela Muho<sup>1</sup>, Majlinda Naço<sup>1, 2</sup>, Haxhire Gani<sup>1</sup>, Agron Dogjani<sup>3</sup>

## Case report

- 111 ХИРУРШКИ ТРЕТМАН НА DIGITUS QUINTUS VARUS BILATERALIS**  
Андријана Ѓорѓеска<sup>1</sup>, Ѓорѓе Џокиќ<sup>1</sup>, Томислав Јованоски<sup>1</sup>, Маргарита Пенева<sup>1</sup>, Христина Брешковска
- 119 LARGE OVARIAN CYST PRESENTING AS WEIGHT GAIN IN AN ADOLESCENT GIRL: A CASE REPORT**  
Milica Pashoska<sup>1</sup>, Elizabeta Stojovska Jovanovska<sup>2</sup>, Zlatica Jovanovska<sup>2</sup>, Marta Kamcheva<sup>2</sup>, Marija Dukovska<sup>2</sup>
- 123 PERIRENAL URINOMA IN A YOUNG WOMAN AFTER CHILDBIRTH.**  
Eva Shagla<sup>1</sup>, Liri Cuko<sup>2</sup>, Arlinda Hysenj<sup>1</sup>, Ariola Fida<sup>1</sup>, Agron Dogjani<sup>2</sup>
- 126 БИЛАТЕРАЛНО ЗГОЛЕМУВАЊЕ НА СУБМАНДИБУЛАРНИТЕ И ПАРОТИДНИ ЖЛЕЗДИ, ИНИЦИЈАЛЕН СИМПТОМ НА АКУТНА МИЕЛОИДНА ЛЕУКЕМИЈА**  
Поповски В<sup>1</sup>, Бранко А<sup>2</sup>
- 134 BROWN СИНДРОМ КАКО ПОСЛЕДИЦА НА РОДИЛНА ТРАУМА ВО ПРЕДЕЛ НА ДЕСНА ОРБИТА**  
Беким Татеш<sup>1</sup>, Сузана Кленкоски<sup>1</sup>, Стефан Пандилов<sup>1</sup>
- 139 CASES OF GUILLAIN-BARRÉ SYNDROME ASSOCIATED WITH COVID-19**  
Teuta Dalipi<sup>1</sup>, Ivan Barbov<sup>1</sup>, Frosina Stojkovska<sup>1</sup>, Jasmina Mitrevska Velkov<sup>1</sup>, Marija Babunovska<sup>1</sup>
- 143 POST-COVID-19 POLYRADICULONEURITIS WITH SEVERE RESPIRATORY INSUFFICIENTION. A CASE REPORT.**  
Vanja Trajkovska<sup>1,2</sup>, Biljana Andonovska<sup>1,2</sup>, Maja Mojsova Mijovska<sup>1</sup>, Saso Popovski<sup>1</sup>, Amela Mumunovik<sup>1</sup>
- 147 POST COVID-19 AUTOIMMUNE THYROID DISEASE IN 21 YEAR OLD MAN**  
Daniela Misoska Pendova





# MEDICUS

## Original scientific paper

- 7 EFFICACY OF TRICHLOROACETIC ACID IN TREATMENT OF HPV RELATED INFECTIONS OF THE UTERINE CERVIX**  
Anita Morarcalieva Chochkova<sup>1</sup>, Nevenka Velickova<sup>2</sup>, SimonidaKotlarova Poposka<sup>3</sup>, Gligor Dimitrov<sup>3</sup>, Marina Nakova<sup>1</sup>
- 14 LEISHMANIASIS IN REPUBLIC OF NORTH MACEDONIA, 1975-2020**  
Dejan Filipovikj<sup>1</sup>, Maja Dimova<sup>1</sup>, Julija Mitrova Telenta<sup>1</sup>, Ivana Dohcheva Karajovanov<sup>1</sup>, Nevzat Elezi<sup>2</sup>
- 18 QT SEGMENT INTERVAL INDICES AT ADULTS WITH UNCOMPLICATED OBESITY**  
Atilla J Rexhepi<sup>1</sup>, Valon N Asani<sup>1</sup>, Hysni I Ismaili<sup>1</sup>, Fisnik F Demiri<sup>2</sup>, Vlora Ibrahim<sup>2</sup>
- 23 ИНСУЛИН-ЛАЈК ГРОУТ ФАКТОР-1 И ВАСКУЛАРНО ЕНДОТЕЛИЈАЛЕН ГРОУТ ФАКТОР – РАНИ ПРЕДИКТИВНИ БИОМАРКЕРИ ЗА РЕТИНОПАТИЈА НА ПРЕМАТУРИТЕТ**  
Елизабета Петковска<sup>1</sup>, Никола Оровчанец<sup>2</sup>, Викторија Јовановска<sup>1</sup>, Стојка Нацева Фуштиќ<sup>3</sup>

## Profesional paper

- 32 ASST AND AUTOIMMUNITY IN PATIENTS WITH CHRONIC SPONTANEOUS URTICARIA**  
Trajkova Vesna<sup>1</sup>, Velichkova Nevenka<sup>2</sup>, Breshkovska Hristina<sup>3</sup>
- 39 LIFE THREATENING UROLOGY CONDITIONS AS COMPLICATIONS OF SARS COV2 INFECTION – SYMPTOMS, DIAGNOSE, CONSERVATIVE, OPERATIVE AND POST-OPERATIVE TREATMENT**  
Ivchev J<sup>1,2</sup>, Gjorevski A<sup>2,3</sup>
- 47 INDEX OF THE OSTEOPOROTIC RISK IN THE EVALUATION OF THE DENOSUMAB TREATMENT**  
Slavica Shubeska Stratrova<sup>1,5</sup>, Snezana Markovik Temelkova<sup>1,5</sup>, Irfan Ahmeti<sup>1,5</sup>, Jasmina Meceska Jovcevska<sup>2</sup>, Dejan Spasovski<sup>1,3</sup>
- 54 HEARING RECOVERY IN PATIENTS WITH IDIOPATHIC SUDDEN SENSORINEURAL HEARING LOSS**  
Lidija Ristovska<sup>1</sup>, Zora Jachova<sup>2</sup>
- 60 ПРОМЕНИ НА ВНАТРЕШНА ЛИМИТНА МЕМБРАНА КАЈ ПАЦИЕНТИ СО ОКЛУЗИЈА НА ЦЕНТРАЛНА РЕТИНАЛНА ВЕНА**  
Петрушевска Андријана, Голубовиќ Милена, Ѓошевска Даштевска Емилија, Нивичка Каева Јана
- 65 DHURIMI I GJAKUT NË KOMUNËN E TETOVËS NË PERIUHDËN 2018 - 2021**  
Ekrem Ismani<sup>1</sup>, Sani Bajrami<sup>2</sup>, Mazllum Belegu<sup>2</sup>
- 70 IMPLEMENTATION OF SHEAR WAVE ELASTOGRAPHY AS A NEW METHOD IN THE CLINIC OF GASTROENTEROHEPATOLOGY – SKOPJE**  
Arzana Hasani Jusufi, Meri Trajkovska, Atip Ramadani, Arta Bina, Xhem Adem, Georgi Janevski.
- 77 MATERNAL PLASMA BIOMARKERS (ANTITHROMBIN 3, PLASMOINOGEN ACTIVATOR INHIBITOR 1, SOLUBLE TIE 2, VASCULAR ENDOTHELIAL GROWTH FACTOR RECEPTOR2) AS INDICATORS FOR PLACENTA ACCRETA SPECTRUM (PAS) IN THE THIRD TRIMESTER OF PREGNANCY**  
Iva Malahova Gjoreska<sup>1</sup>, Vesna Antovska<sup>1</sup>, Goran Kochoski<sup>1</sup>, Katerina Nikoloska<sup>1</sup>, Josif Gjoreski<sup>1</sup>

## Review

- 81 МЕХАНИЧКИ ПОВРЕДИ НА ОЧИТЕ – МОЖНОСТИ ЗА НИВНА ПРЕВЕНЦИЈА И РЕХАБИЛИТАЦИЈА**  
Ѓошевска Даштевска Емилија, Петрушевска Андријана, Голубовиќ Милена
- 87 EVALUIMI DHE MENAXHIMI I DHIMBJES SKROTALE**  
Ilbert Ademi<sup>1</sup>, Majlinda Ademi<sup>2</sup>
- 92 МОЖНИ КОМПЛИКАЦИИ ОД ФАКОЕМУЛЗИФИКАЦИОНА ХИРУРГИЈА НА КАТАРАКТА**  
Велковска Б<sup>1</sup>, Трпеска Шекеринов Н<sup>1,2</sup>, Петрушевска А<sup>1</sup>, Нивичка Каева Ј<sup>1,2</sup>, Шекеринов Д<sup>3</sup>
- 100 EMBRYOLOGY, MORPHOLOGY, CLASSIFICATION AND SURGERY OF SYNDACTYLY**  
Ermira Hamzai<sup>1</sup>, Djordje Dzokic<sup>2</sup>, Elizabeta Mircevska Zogovska<sup>2</sup>
- 106 SOME CONSIDERATIONS ABOUT POSTOPERATIVE NAUSEA AND VOMITING.**  
Anna Mandi<sup>1</sup>, Estela Muho<sup>1</sup>, Majlinda Naço<sup>1, 2</sup>, Haxhire Gani<sup>1</sup>, Agron Dogjani<sup>3\*</sup>

## Case report

- 111 ХИРУРШКИ ТРЕТМАН НА DIGITUS QUINTUS VARUS BILATERALIS**  
Андријана Ѓорѓеска; Ѓорѓе Џокиќ; Томислав Јованоски; Маргарита Пенева; Христина Брешковска
- 119 LARGE OVARIAN CYST PRESENTING AS WEIGHT GAIN IN AN ADOLESCENT GIRL: A CASE REPORT**  
Milka Pashoska<sup>1</sup>, Elizabeta Stojovska Jovanovska<sup>2</sup>, Zlatica Jovanovska<sup>2</sup>, Marta Kamcheva<sup>2</sup>, Marija Dukovska<sup>2</sup>
- 123 PERIRENAL URINOMA IN A YOUNG WOMAN AFTER CHILDBIRTH.**  
Eva Shagla<sup>1</sup>, Liri Çuko<sup>2</sup>, Arlinda Hysen<sup>1</sup>, Ariola Fida<sup>1</sup>, Agron Dogjani<sup>2</sup>
- 126 БИЛАТЕРАЛНО ЗГОЛЕМУВАЊЕ НА СУБМАНДИБУЛАРНИТЕ И ПАРОТИДНИ ЖЛЕЗДИ, ИНИЦИЈАЛЕН СИМПТОМ НА АКУТНА МИЕЛОИДНА ЛЕУКЕМИЈА**  
Поповски В<sup>1</sup>, Бранко А<sup>2</sup>
- 134 BROWN СИНДРОМ КАКО ПОСЛЕДИЦА НА РОДИЛНА ТРАУМА ВО ПРЕДЕЛ НА ДЕСНА ОРБИТА**  
Беким Татеш<sup>1</sup>, Сузана Кленкоски<sup>1</sup>, Стефан Пандилов<sup>1</sup>
- 139 CASES OF GUILLAIN-BARRÉ SYNDROME ASSOCIATED WITH COVID-19**  
Teuta Dalipi<sup>1</sup>, Ivan Barbov<sup>1</sup>, Frosina Stojkovska<sup>1</sup>, Jasmina Mitrevska Velkov<sup>1</sup>, Marija Babunovska<sup>1</sup>
- 143 POST- COVID-19 POLYRADICULONEURITIS WITH SEVERE RESPIRATORY INSUFFITIENTION. A CASE REPORT.**  
Vanja Trajkovska<sup>1,2</sup>, Biljana Andonovska<sup>1,2</sup>, Maja Mojsova Mijovska<sup>1</sup>, Saso Popovski<sup>1</sup>, Amela Mununovik<sup>1</sup>
- 147 POST COVID-19 AUTOIMMUNE THYROID DISEASE IN 21 YEAR OLD MAN**  
Daniela Misoska Pendova

## **Betimi i Hipokratit**

*Në çastin kur po hy në radhët e anëtarëve të profesionit mjekësor premtoj solemnisht se jetën time do ta vë në shërbim të humanitetit. Ndaj mësuesve do ta ruaj mirënjohjen dhe respektin e duhur.*

*Profesionin tim do ta ushtroj me ndërgjegje e me dinjitet. Shëndeti i pacientit tim do të jetë brenga ime më e madhe. Do t'i respektoj e do t'i ruaj fshehtësitë e atij që do të më rrëfëhet. Do ta ruaj me të gjitha forcat e mia nderin e traditës fisnike të profesionit të mjekësisë.*

*Kolegët e mi do t'i konsideroj si vëllezër të mi.*

*Në ushtrimin e profesionit ndaj të sëmurit tek unë nuk do të ndikojë përkatësia e besimit, e nacionalitetit, e racës, e politikës, apo përkatësia klasore. Që nga fillimi do ta ruaj jetën e njeriut në mënyrë absolute. As në kushtet e kërcënimit nuk do të lejoj të keqpërdoren njohuritë e mia mjekësore që do të ishin në kundërshtim me ligjet e humanitetit. Këtë premtim po e jap në mënyrë solemne e të lirë, duke u mbështetur në nderin tim personal.*

## **The Oath of Hippocrates**

*Upon having conferred on me the high calling of physician and entering medical practice, I do solemnly pledge myself to consecrate my life to the service of humanity. I will give my teachers the respect and gratitude which is their due. I will practice my profession with conscience and dignity. The health of my patient will be my first consideration. I will respect the secrets which are confided in me, even after the patient has died. I will maintain by all the means in my power, the honor and the noble traditions of the medical profession.*

*My colleagues will be my brothers.*

*I will not permit considerations of religion, nationality, race, party politics or social standing to intervene between my duty and my patient. I will maintain the utmost respect for human life from its beginning even under threat and I will not use my medical knowledge contrary to the laws of humanity. I make these promises solemnly, freely and upon my honor*

Medical Journal

# MEDICUS

ISSN 1409-6366 UDC 61 Vol · 27 (1) · 2022

Revistë Shkencore Nderkombëtare e Shoqatës së Mjekëve Shqiptarë të Maqedonisë  
International Journal of Medical Sciences of the Association of the Albanian Doctors from Macedonia

Botues/ Publisher: **SHMSHM / AAMD**

Tel. i Kryeredaktorit / Contact: **+389 (0) 71 240 927**

Zhiro llogaria / drawing account: **200-000031528193**

Numri tatimor / tax number: **4028999123208**

Adresa e Redaksisë-Editorial Board Address: **Mehmed Pashë Deralla nr. 16, Tetovë**  
e-mail: **shmshm@live.com**

## Kryeredaktori

Prof. Dr. Nevzat Elezi

## Editor-in-Chief

Nevzat Elezi, MD, PhD

## Redaktorët

Prof. Dr. Omer Xhemaili, Zurich, Zvicër

Prof. Dr. Florin Ramadani, Wels, Austri

Prof. Dr. Atilla Rexhepi, Tetovë, Maqedoni

Prof. Dr. Lul Raka, Prishtinë, Kosovë

Prof. Dr. Nevzat Elezi, Tetovë Maqedoni - Ud. Dekan i

Fakultetit të Shkencave Mjekësore - Tetovë

Doc. Dr Rexhep Selmani, Shkup, Maqedoni

## Editors

Omer Dzemaili, MD, PhD, Zurich, Switzerland

Florin Ramadani, MD, PhD, Wels, Austria

Atilla Rexhepi, MD, PhD, Tetovo, Macedonia

Lul Raka, MD, PhD, Prishtina, Kosova

Nevzat Elezi, MD, PhD, Tetovo, Macedonia - Dean of

Faculty of Medical Sciences - Tetovo

Rexhep Selmani, MD, PhD, Skopje, Macedonia

## Këshilli Redaktues

Nobelisti Prof. Dr. Ferid Murad, Hjuston, SHBA

Prof. Dr. Rifat Latifi, Arizona, SHBA

Prof. Dr. Alex Leventa, Jerusalem, Izrael

Prof. Dr. Sedat Üstündağ, Edirne, Turqi

Prof. asoc. dr. Avdyl Krasniqi, Prishtinë, Kosovë

Prof. dr. sci. Kirk Milhoan, Texas, SHBA

Dr. sci. Minir Hasani, Gjermani

Prof. dr sci. Alfred Priftanji, Tiranë, Shqipëri

Prof. dr. sci. Naser Ramadani, Prishtinë, Kosovë

Prof. dr Yovcho Yovchev, Stara Zagora, Bullgari

Doc. Dr. Skender Saiti, Shkup, Maqedoni

Prof. Dr. Milka Zdravkovska, Shkup, Maqedoni

Prof. dr Gentian Vyshka, Tiranë, Shqipëri

Prim. dr Gani Karamanaga, Ulqin, Mali Zi

Prof. dr Ramush Bejiqi, Prishtinë, Kosovë

Dr. Sc. Spec. Meral Rexhepi, Tetovë, Maqedoni

Dr. Sc. Irfan Ahmeti, Shkup, Maqedoni

## Editorial Board

Nobel Laureate Ferid Murad, MD, PhD, Houston, USA

Rifat Latifi, MD, PhD, Arizona, USA

Alex Leventa, MD, PhD Jerusalem, Israel

Sedat Ustündağ, Edirne, Turkiye

Avdyl Krasniqi, MD, PhD, Prishtina, Kosova

Kirk Milhoan, MD, PhD, Texas, USA

Minir Hasani, MD, PhD, Germany

Alfred Priftanji, MD, PhD, Tirana, Albania

Naser Ramadani, MD, PhD, Prishtina, Kosova

Yovcho Yovchev, MD, PhD, Stara Zagora, Bulgaria

Skender Saiti, MD, PhD, Skopje, Macedonia

Milka Zdravkovska, MD, PhD, Skopje, Macedonia

Gentian Vyshka, MD, PhD, Tirana, Albania

Gani Karamanaga, MD, Ulcinj, Montenegro

Ramush Bejiqi, MD, PhD, Prishtina, Kosova

Meral Rexhepi, MD, PhD, Tetovo, Macedonia

Irfan Ahmeti, MD, PhD, Skopje, Macedonia

### **Bordi Këshillëdhënës**

Prof. dr. Shpëtim Telegrafi, Nju Jork, SHBA  
Prof. dr. Gëzim Boçari, Tiranë, Shqipëri  
Prof. dr. Donço Donev, Shkup, Maqedoni  
Prof. Dr. Isuf Dedushaj, Prishtinë, Kosovë  
Prof. Dr. Ramadan Jashari, Belgjikë  
Prof. Dr. Holger Tietzt, Gjermani  
Prof. Dr. Vjollca Meka-Sahatçiu  
Prof. Dr. Milena Petrovska, Shkup, Maqedoni  
Prof. Dr. Sonja Bojaxhieva, Shkup, Maqedoni  
Dr. Spec. Ylbert Ademi, Gostivar, Maqedoni  
Doc. Dr. Naser Durmishi, Shkup, Maqedoni

### **Sekretariati i redaksisë**

Dr. Bekim Ismaili, Maqedoni  
Dr. Sead Zeynel, Maqedoni  
Dr. Rihan Saiti, Maqedoni

### **Këshilli Botues**

Prim. Dr. Ali Dalipi  
Prim. Dr. Ferit Muça  
Prim. Dr. Lavdërim Sela  
Prim. Dr. Shenasi Jusufi  
Dr. Nadi Rustemi  
Dr. Bedri Veliu  
Dr. Gafur Polisi  
Dr. Baki Alili  
Dr. Ilber Besimi  
Dr. Gazi Mustafa  
Dr. Edip Sheji  
Dr. Murat Murati  
Dr. Dukagjin Osmani  
Dr. Bari Abazi  
Dr. Fadil Murati  
Dr. Fadil Maliqi  
Dr. Besa Pocesta-Islami  
Dr. Jakup Jakupi  
Dr. Muharem Saliu  
Dr. Sufjan Belcista-Ferati  
Dr. Xhabir Bajrami  
Dr. Sc. Majlinda Ademi

### **Dizajni & Pamja**

Aleksandar Kostadinovski

### **Shtypur në**

Shtypshkronjen "Pruf Print", Shkup

Medicus shtypet në tirazh: 600 ekzemplarë  
Revista shperndahet falas

### **Advisory Board**

Shpetim Telegrafi, MD, PhD, New York, USA  
Gezim Bocari, MD, PhD, Tirana, Albania  
Donco Donev, MD, PhD, Skopje, Macedonia  
Isuf Dedushaj, MD, PhD, Prishtina, Kosova  
Ramadan Jashari, MD, PhD, Belgjum  
Holger Tietzt, MD, PhD, Germany  
Vjollca Meka-Sahatciu, MD, PhD  
Milena Petrovska, MD, PhD, Skopje, Macedonia  
Sonja Bojadzieva, MD, PhD, Skopje, Macedonia  
Ylbert Ademi, MD, Gostivar, Macedonia  
Naser Durmishi, MD, PhD, Skopje, Macedonia

### **Editorial Secretariat**

Bekim Ismaili, MD, Macedonia  
Sead Zeynel, MD, Macedonia  
Rihan Saiti, MD, Macedonia

### **Editorial Council**

Ali Dalipi, MD  
Ferit Muça, MD  
Lavderim Sela, MD  
Shenasi Jusufi, MD  
Nadi Rustemi, MD  
Bedri Veliu, MD  
Gafur Polisi, MD  
Baki Alili, MD  
Ilber Besimi, MD  
Gazi Mustafa, MD  
Edip Sheji, MD  
Murat Murati, MD  
Dukagjin Osmani, MD  
Bari Abazi, MD  
Fadil Murati, MD  
Fadil Maliqi, MD  
Besa Pocesta-Islami, MD  
Jakup Jakupi, MD  
Muharem Saliu, MD  
Sufjan Belcista-Ferati, MD  
Xhabir Bajrami, MD  
Majlinda Ademi, MD, PhD

### **Design & Layout**

Aleksandar Kostadinovski

### **Printed in:**

Print House "Pruf Print", Skopje

The Journal Medicus is printed and distributed free of charge with a circulation of 600 copies.



# EFFICACY OF TRICHLOROACETIC ACID IN TREATMENT OF HPV RELATED INFECTIONS OF THE UTERINE CERVIX

Anita Morarcalieva Chochkova<sup>1</sup>, Nevenka Velickova<sup>2</sup>, SimonidaKotlarova Poposka<sup>3</sup>, Gligor Dimitrov<sup>3</sup>, Marina Nakova<sup>1</sup>

<sup>1</sup>PHI General Hospital, Gevgelija, N. Macedonia

<sup>2</sup>Faculty of medical sciences, University GoceDelcev, Stip, N. Macedonia

<sup>3</sup>Private Hospital Remedika, Skopje, N. Macedonia

Corresponding author:

Anita Morarcalieva Chochkova, MD, PHI General Hospital Gevgelija, Republic of North Macedonia, Slobodan Mitrov Danko No.38, Gevgelija, RN Macedonia,  
cell: +389 70 346 468,  
e-mail: dr.anita\_morarcalieva@hotmail.com;

Medicus 2022, Vol. 27 (1): 7-13

## ABSTRACT

**Objective:** To establish the efficacy of single topical 85% trichloroacetic acid (TCA) treatment of the subclinical Human papillomavirus (HPV) infections of the uterine cervix.

**Methods:** This is a retrospective study including patients with HPV infection of the uterine cervix established by HPV DNA PCR assay. All the patients were treated with 85% TCA, applied topical and treatment response was followed up by HPV DNA PCR assay in various groups of patients, two, three, four, six and twelve months after the treatment with TCA. Remission was defined as complete clearance of HPV.

**Results:** In total, 173 patients with HPV specific type were included in the study. Unfortunately 70 patients didn't return for following check up after the treatment and in 103 patients follow up HPV DNA PCR was made, which showed that 70 of them had complete HPV clearance. In addition, 68% and 33 patients were confirmed as positive, 32% and 10 of the HPV positive group still had the same type of HPV, 30% and 23 of them were typed with new type of HPV, 70%.

**Conclusion:** A single treatment of topical TCA for subclinical HPV infections is associated with high HPV clearance, especially two, three and four months after the treatment. The HPV clearance six and twelve months after the treatment, decreases progressively. This gives us the right to think of TCA as an effective agent for subclinical HPV infection treatment.

**Key words:** #human papillomavirus #trichloroacetic acid #cervical intraepithelial neoplasia #cervical cancer

## INTRODUCTION

Cervical cancer remains the third most common cancer in women worldwide. There are 604 237 new diagnosed cases, representing 6.5% of all female cancers and 341843 deaths in 2020 year, 90% of whom were in less developed countries. Incidences of cervical cancer are disproportionally distributed between developed

and less developed countries. Developed countries have progressively declined the incidence of cervical cancer by providing cancer screening programs and HPV vaccination programs. According to Global Cancer Observatory, our country, North Macedonia is among the countries with middle high age standardized rate of 7,5 (1).Statistical evaluation or annual review of Institute of public health of North Macedonia, showed that in average

there are 150 new diagnosed cases of cervical cancer per year in our country, and one third of them died (2).

HPV is the cause of almost all cervical cancers and is responsible for a substantial fraction of other anogenital cancers and oropharyngeal cancers (3). It is one of the most common causes of sexually transmitted disease in men and women worldwide. Papillomaviruses are ubiquitous and more than 200 types were recognized by DNA sequence data, showing genomic differences. 40 of them show anogenital tropism. Based on their association with cervical cancer and precursor lesions, HPVs can also be grouped to high risk and low risk HPV types. Low risk types include types 6, 11, 42, 43 and 44. High risk HPV types include types 16, 18, 31, 33, 34, 35, 39, 45, 51, 52, 56, 58, 59, 66, 68 and 70 (4).

The HPV genome encodes DNA sequences for six early (E) proteins associated with viral gene regulation and cell transformation, two late (L) proteins which form the shell of the virus and a region of regulatory DNA sequences. Most important HPV proteins in the pathogenesis of malignant disease are E6 and E7 (5). They act in a cooperative manner to immortalize epithelial cells through binding with two intracellular proteins p53 and retinoblastoma (Rb). In normal cells p53 protein is a negative regulator of cell growth and also functions as a tumor suppressor protein by halting cell growth after chromosomal damage and allowing DNA repair enzymes to function. Binding of E6 to p53 allows unregulated cellular cycling, promoting the antiapoptotic effect, permitting accumulation of chromosomal mutations without DNA repair. This leads to chromosomal instability in the HPV containing cells. The Rb protein inhibits the effect of positive growth regulation and induces cell apoptosis in response to DNA damage (6,7,8,9). E7 interacts with Rb protein via an E2F/Rb protein complex which allows cyclin A to promote cell cycling. This results with unchecked cell growth in the presence of genomic instability that may lead to malignant change (10, 11, 12, 13). Cooperative interaction between E6 and E7 enhances immortalization efficiency. High risk HPV E6 and E7 expressing cells have a decreased ability to maintain genomic integrity as they act as mitotic mutators and induce mitotic abnormalities, including anaphase bridges, unaligned or lagging chromosomes and multipolar mitoses, which are histopathological hallmark of high risk HPV associated cervical lesions and cervical cancer (5,14).

The infectious cycle of HPV is tailored to the differentiation program of the target cells, keratinocytes, from basal

cell to terminally differentiated superficial squames. The time from infection to virus release takes about 3 weeks, the time needed for the basal keratinocytes to migrate through the epithelium and undergo complete differentiation and desquamation. The period between infection and appearance of lesion ranges from weeks to months, suggesting that the virus effectively evades host defenses. There is no cytolysis or cytopathic death as a consequence of virus replication and therefore no inflammation. There appears to be little or no release of proinflammatory cytokines. As an exclusively intracellular pathogen, HPV doesn't induce blood born viremic phase of the life cycle and only minimal amount of virus is exposed to immune defenses, so the virus is practically invisible to the host defense (15, 16). Its invisibility is due to limiting expression of viral protein until later stages of epithelial differentiation, infecting only cells of basal layer of the cervical epithelium and virally mediated suppression of the proinflammatory proteins that activate cytotoxic T lymphocytes, which assist in killing infected cells. Although most women clear the infection within a few months, those who do not are at risk for development of cervical precancer and cancer (16, 17).

Factors that contribute to development of cervical dysplasia are age older than 55, as 50% of high risk infections persist in women older than 55. Duration of infection is well known as predisposing factor for appearance of cervical precancerous lesion and high oncogenic HPV DNA types are more related to cervical lesions. If the HPV remains in an episomal nonintegrated state, it results with low grade lesion and if virus becomes integrated into the human genome, high grade lesions and cancer may develop (18). Low grade lesion is cervical intraepithelial neoplasia 1 (CIN1) and it refers to mildly atypical cellular changes in the lower third of the epithelium. High grade cervical lesions are cervical intraepithelial dysplasia 2 (CIN2) and 3 (CIN3). CIN 2 refers to moderately atypical cellular changes confined at the basal two thirds of the epithelium and CIN 3 refers to severely atypical cellular changes encompassing greater than two thirds of the epithelial thickness. If the lesion breaks through the basal membrane than microinvasive carcinoma is diagnosed (19).

The detection of HPV is facilitated by advances in molecular biology and molecular detection of HPV DNA is the golden standard for identification of HPV. Many studies showed high sensitivity and specificity for detecting HPV. Three categories of molecular assays



are available for detection of HPV infection in tissue and exfoliated cell samples, all of which are based on the detection of DNA of HPV and include non amplified hybridization, hybrid capture assays and polymerase chain reaction. Detection of HPV E6/E7 mRNA and the presence of oncogenic activity in cervical specimens can be performed by reverse transcriptase PCR or nucleic acid sequence based amplification (NASBA). These tests indicate similar sensitivity as HPV DNA tests with slightly higher specificity for detecting high level lesions. Nowadays three DNA based and one RNA based assay have been approved by the US Food and Drug Administration (FDA). Although there are a lot of tests in development, S5 test is taken for accurate and early detection of HPV. S5 test is a type of a test that measures DNA methylation of the most common high risk HPV DNA types 16, 18, 31, 33 and EPB41L3 gene expression from cervical smear samples and urine samples. Then a score is generated, which is proportional to the risk of cervical lesion. The HPV E7 protein disrupts cell cycling, leading to an increase in cellular p16 protein expression. Studies are in progress to determine the role of p16 as a possible diagnostic marker. Recently, scientists have developed nanoparticle assisted PCR assay for detection of HPV 16 and 18 DNA. More studies are needed to confirm the utility of these tests in clinical practice. None of them is FDA approved yet (20, 21, 22, 23, 24).

According to Sexually transmitted infections treatment guidelines 2021 by CDC, the treatment of HPV is directed to the macroscopic or pathologic precancerous lesions caused by HPV. Subclinical HPV infection typically clears spontaneously, therefore antiviral therapy is not recommended to eradicate HPV infections (26). But in our experience, a huge amount of HPV infections, especially those caused by high risk HPV types, are persistent and high risk for premalignant or malignant lesions development, more often in patients older than 30. It is very important in HPV infected patients to achieve remission. By remission we obtain complete clearance of the virus. This decreases the viral load of the epithelial cells and postpone the possibility of malignant alteration of the cells. Performing a peeling of the cervical transformational zone denudes the cervix from the infected cells and provides the means to reepithelize with new HPV noninfected cells.

The treatment involves using 85% trichloroacetic acid which is traditionally used for medical and cosmetic skin peeling. It is a small molecule, approved by FDA as an

active substance in 2016. It can be found in concentration from 10-90%. It is primarily used in cosmetics as a chemical peeling for acne scars, melasma, xanthelasmas and in treatment of anogenital condylomas and warts. It makes precipitation and denaturation of the cell proteins, so the epithelium desquamates to the basal membrane. There are no registered cases of acute intoxication after topical use. Systemic levels of trichloroacetic acid which are reached after topical administration for clinical indication, cannot reach the systemic levels of TCA needed for mutagenicity. These features make the TCA perfect agent for cervical peeling and lowering the epithelial burden with HPV (27, 28).

## MATERIALS AND METHODS

We have first started practicing 85% TCA as an agent for treatment of HPV related cervical infection since April 2017 in a private general hospital Remedika, Skopje, North Macedonia, associated with Medical Faculty of University Goce Delcev Stip, North Macedonia, as a response to the great results from the Austrian scientists who had applied it as an agent for treatment of cervical intraepithelial neoplasia. The study encompasses 173 patients, from April 2017 to December 2021. All of them confirmed with HPV DNA PCR assay for presence of HPV that persisted for minimum of 6 months. TCA is a clinically applied treatment and it was used in 85% concentration, provided by General Hospital Remedika. Inclusive criteria are: patient with HPV confirmed with HPV DNA PCR assay, persistent at least for 6 months, who voluntarily by signing informed consent, agreed to take part in the study. Exclusive criteria are: known allergy to TCA, patients at an age younger than 21, patients with biopsy confirmed cervical intraepithelial neoplasia, patients with cervical operative procedures and laser procedures for treatment of cervical dysplasia or malignancy and pregnant women. The treatment was provided only by specialist in gynecology and obstetrics.

After reviling the cervix with a speculum, about 2ml of 85% trichloroacetic acid was topically applied to the ectocervix and TZ and a small amount of the solution that was left in the syringe was inserted into the internal os of the cervix to treat the caudal part of the endocervix. Furthermore, the TZ turned white, indicating denaturation and precipitation of proteins. TCA has low viscosity, therefore care was taken because it can easily drop onto normal tissue, which can also become chemically coagulated. Patients were advised not to have

sexual intercourse for 2 weeks, to choose showering instead of bathing for 4 weeks and to use sanitary pads rather than tampons during menstruation. The follow up was scheduled for 8 weeks after the TCA treatment. On the follow up visit we found that reepithelization of the cervical surface was assessed. Moreover, an endocervical and ectocervical smear was taken for HPV DNA PCR assay for confirmation of the HPV infection. We had five groups of patients and in some of them HPV DNA PCR assay was made at the second, third, fourth, sixth and twelfth month, respectively. To asses side effects patients were asked for vaginal bleeding or discharge, signs of pelvic inflammatory disease, postcoital bleeding, need for medical treatment and using pain reliefs and were asked to report for any other treatment related symptoms. Patients with complete HPV clearance were recommended to have their next PAPtest in 12 months and in case of HPV persistence, repeated HPV DNA PCR test was recommended as well.

The material was statistically analyzed using the methods of descriptive statistics.

**RESULTS**

In total 173 patients with HPV specific type were included in the study. The patients were divided in four age groups, 21-30 years old (79 patients), 31-40 years old (65 patients), 41-50 years old (28 patients) and 51 years old, as well as older patients group (1 patient). 28 types of HPV were identified and one group with mixed HPV infection was identified, too. Most common HPV type among young patients in the age group from 21 to 30 years old, was HPV type 16 with 11% and mixed infection with 13%. HPV type 31 was most frequent in the age groups of 31 - 40 and 41-50 years old , 13% and 9% respectively.

| Type of HPV | 21-30 | 31-40 | 41-50 | 51- | Total |
|-------------|-------|-------|-------|-----|-------|
| type 06     | 1     |       |       |     | 1     |
| type 16     | 9     | 6     | 3     |     | 18    |
| type 17     | 2     |       | 1     |     | 3     |
| type 18     | 7     | 2     | 2     |     | 11    |
| type 19     | 1     |       |       |     | 1     |
| type 30     |       | 1     |       |     | 1     |
| type 31     | 6     | 9     | 6     |     | 21    |
| type 32     |       | 1     | 1     |     | 2     |
| type 33     | 1     | 1     | 2     |     | 4     |
| type 34     |       | 2     |       |     | 2     |
| type 35     | 6     | 5     | 2     |     | 13    |

|                 |           |           |           |          |            |
|-----------------|-----------|-----------|-----------|----------|------------|
| type 39         | 3         | 2         | 1         |          | 6          |
| type 40         | 2         | 1         |           |          | 3          |
| type 45         | 4         | 2         | 1         |          | 7          |
| type 46         | 1         |           | 1         |          | 2          |
| type 51         | 2         | 2         | 1         |          | 5          |
| type 52         | 4         | 4         |           | 1        | 9          |
| type 53         | 3         | 4         | 2         |          | 9          |
| type 56         | 2         | 4         | 1         |          | 7          |
| type 58         | 3         | 1         | 1         |          | 5          |
| type 59         | 2         | 3         |           |          | 5          |
| type 62         | 1         | 1         |           |          | 2          |
| type 63         | 1         |           |           |          | 1          |
| type 66         | 4         | 3         | 1         |          | 8          |
| type 68         | 1         | 1         | 1         |          | 3          |
| type 73         | 1         | 1         |           |          | 2          |
| type 82         | 1         | 1         | 1         |          | 3          |
| type 86         |           | 1         |           |          | 1          |
| Mixed infection | 11        | 7         |           |          | 18         |
| <b>Total</b>    | <b>79</b> | <b>65</b> | <b>28</b> | <b>1</b> | <b>173</b> |

Table 1. Type specific Human papillomavirus by age groups

Unfortunately 70 patients didn't return for follow check up after the treatment and in 103 patients follow up HPV DNA PCR was made and showed that 70 of them had a complete HPV clearance and 33 patients were confirmed as positive, thus 68 % and 32% in the given order.



1. Follow diagram representing Human papillomavirus status

10 of the HPV positive group still had the same type of HPV and 23 of them were diagnosed with a new type of HPV, 30 % and 70% respectively.

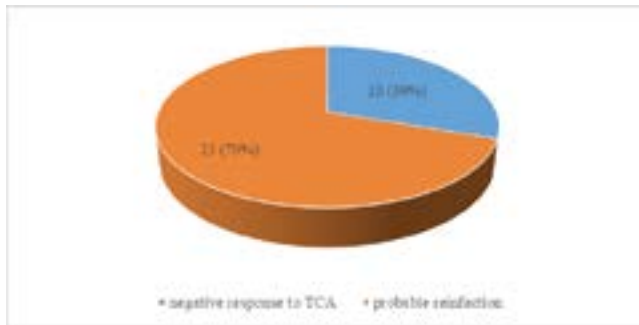


Chart 1. Number of Human papillomavirus positive patients after treatment with TCA

Remission rate among the groups divided by age, 21-30 years (34 %), 31-40 years (21%), 41-50 years old (12%) and patients older than 50 (100%) . HPV infection rate after the treatment, among groups divided by age were 55%, 30% and 15% respectively. Two months after the treatment with TCA, 18 patients were HPV positive (40%), and 27 were negative (60%). After three months, HPV positive were 4 patients (19%) and 17 were negative (81%). Four months after the procedure, HPV negative were 19

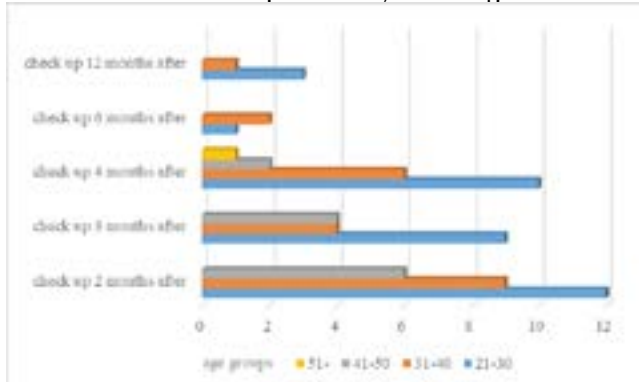


Chart 2. Number of Human papillomavirus negative patients by age groups after the treatment with TCA

This also applies to the HPV infected group.

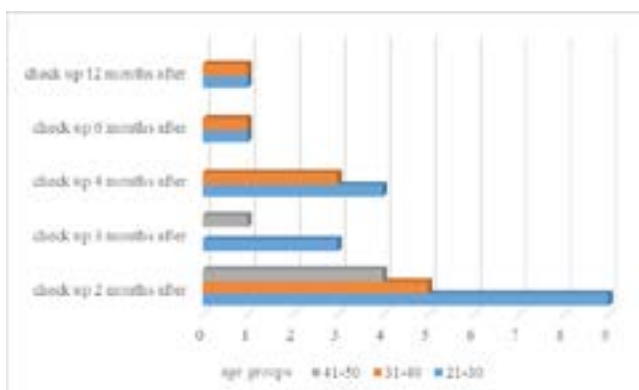


Chart 3. Number of Human papillomavirus positive patients by age groups after the treatment with TCA

There were no side effects observed during the treatment and follow up, such as heavy bleeding, pain, heavy vaginal discharge, postcoital bleeding or pain and vasovagal symptoms. At the follow up visit, reepithelisation of the cervix was complete in all patients.

## DISCUSSION

TCA is a potential treatment for subclinical HPV infections. The acid is cheap, the technique does not require special training to perform, anesthesia is not needed because the treatment causes little or no pain at all. Moreover, it can be performed outpatient without hospitalization and the patient can be discharged home immediately after the treatment, advised not to have sexual intercourse for two weeks, to take showers instead of a bath and to use sanitary towels instead of menstrual tampons (29, 30, 31). In the study of Geisler et al. 2016, the efficacy of TCA after a single topical application was established, with no major differences between high grade and low grade CIN and with remission rates of 80,3% and 82,3% respectively (31). Based on the Suwartono and Andrijono's (2020) study, there is no significant difference between application of 85% TCA compared with cryotherapy for treatment of patients with positive visual inspection with acetic acid (VIA) result. So the TCA treatment should be favored unlike the cryotherapy, which represents an invasive technique requiring special professional and logistic support (32). The ongoing prospective study, TRICIN, which is sponsored by Krankenhaus Barmherzige Schwestern Linz and is planned to end in December 2022, expects high remission and regression rates after single topical use of 85% TCA for CIN I and II, of 70% or even higher (33). Our study demonstrated that by a chemical coagulation of proteins, a single treatment of topical 85% TCA for subclinical HPV infections is associated with high HPV clearance, especially two, three and four months after the treatment. The HPV clearance six and twelve months after the treatment, decreases progressively. This study confirms the future perspective of TCA as an effective agent for subclinical HPV infection treatment. It seemed that the type of HPV does not affect the efficacy of the treatment so it could be applied to all HPV types and mixed infections. The limitation of this study is that it can not answer the question why the efficacy of the treatment decreases progressively six months later. There are three theories according to whom either it comes to a reinfection due to change of sexual partner, it may come to a reinfection due to an infected vaginal epithelium

which is in direct contact with the cervical epithelium, or HPV persists in latent form in some of the basal epithelial cells. Nevertheless, we established that the cervical epithelium is safe from HPV infection at least 6 months and more, so the time necessary for subclinical infection to evolve to cervical lesion is postponed. More studies are needed to establish the long term outcome of the treatment with TCA. It can be considered reapplication of TCA for treatment of reinfections or persistent HPV infection, but further studies are needed to prove the safety of the reuse of TCA, six months after the primer treatment. Therefore, the treatment with TCA indirectly can affect the preterm birth rate, preventing from the invasive surgical techniques, required for treatment of high grade cervical lesions.

## REFERENCE

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F (2021). Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 71(3):209-249. doi: 10.3322/caac.21660
- Rechica V, Tahiri J (2020). Cancer in the Republic of North Macedonia 2010-2019
- Worldwide burden of cancer attributable to HPV by site, country and HPV type Catherine de Martel, 1 Martyn Plummer, 1 Jerome Vignat, 1 and Silvia Franceschi
- Burd EM (2003). Human papillomavirus and cervical cancer. *Clin Microbiol Rev.* 16(1):1-17. doi: 10.1128/CMR.16.1.1-17.2003
- Pinidis P (2016). Human papilloma virus' life cycle and carcinogenesis. *Maedica* 11(1):48-54. PMID: 28465751
- Dupuy C, Buzoni-Gatel D, Touze A, et al. (1997). Cell mediated immunity in mice by HPV 16L1 virus like particles. *Microb Pathog* 22(4):219-25. doi: 10.1006/mpat.1996.0113
- Scheffner M, Huibregtse JM, Vierstra RD, Howley PM (1993). The HPV 16 E6 and E6-AP complex functions as a ubiquitin ligase in the ubiquitination of p53. *Cell* 75(3):495-505. doi: 10.1016/0092-8674(93)90384-3.
- Harve PA, Yuan J, Hedrick L, et al. (1995). P53 inactivation by HPV 16 E6 results in increased mutagenesis in human cells. *Cancer Res.* 55(19):4420-4. PMID: 7671255
- Werness BA, Levine AJ, Howley PM (1990). Association of human papillomavirus types 16 and 18 E6 proteins with p53. *Science* 248(4951):76-9. doi: 10.1126/science.2157286.
- Pagano M, Durst M, Joswing S, et al. (1992). Binding of the human E2F transcription factor to the retinoblastoma protein but not to cyclin A is abolished in HPV 16 immortalized cells. *Oncogene* 7(9):1681-6. PMID: 1323816
- Schwarz E, Freese UK, Gissmann L, et al. (1985). Structure and transcription of human papillomavirus sequences in cervical carcinoma cells. *Nature* 7-13;314(6006):111-4. doi: 10.1038/314111a0
- Tommasino M, Adamczewski JP, Carlotti F, et al. (1993). HPV 16 E7 preprotein associates with the protein kinase p33CDK2 and cyclin A. *Oncogene* 8(1):195-202 PMID: 8380917
- Demers GW, Foster SA, Halbert CL, Galloway DA (1994). Growth arrest by induction of p53 in DNA damaged keratinocytes is bypassed by human papillomavirus 16 E7. *Proc Natl Acad Sci USA* 91(10):4382-4386. doi: 10.1073/pnas.91.10.4382
- McLaughlin-Durbin ME, Munger K (2008). Viruses associated with human cancer. *Biochim Biophys Acta* 1782(3):127-150. doi: 10.1016/j.bbadis.2007.12.005
- Stanley M. (2012). Epithelial cell responses to infection with human papillomavirus. *Clin Microbiol Rev.* 25(2):215-22. doi: 10.1128/CMR.05028-11.
- Stanley M. (2006). Immune responses to human papillomaviruses. *Vaccine* 24(Suppl 1):S16-22. doi: 10.1016/j.vaccine.2005.09.002.
- Einstein MH, Schiller JT, Viscidi RP, et al. (2009). Clinician's guide to human papillomavirus immunology: knowns and unknowns. *Lancet Infect Dis.* 9(6):347-56 doi: 10.1016/S1473-3099(09)70108-2.
- Pett M, Coleman N. Integration of high-risk human papillomavirus: a key event in cervical carcinogenesis? *J Pathol* 2007; 212:356
- DiSaia PJ, Creasman WT (2011). *Clinical Gynecologic Oncology*, 7th edition, Elsevier Inc.
- Schiffman M, Wentzensen N, Wacholder S, et al. Human papillomavirus testing in the prevention of cervical cancer. *J Natl Cancer Inst* 2011; 103:368.
- Lie AK, Kristensen G. Human papillomavirus E6/E7 mRNA testing as a predictive marker for cervical carcinoma. *Expert Rev MolDiagn* 2008;8:405-415.
- Benevolo M, Vocaturo A, Caraceni D, French D, Rosini S, Zappacosta R, Terrenato I, Ciccocioppo L, Frega A and Rossi PG. (2011). Sensitivity, Specificity, and Clinical Value of Human Papillomavirus (HPV) E6/E7 mRNA Assay as a Triage Test for Cervical Cytology and HPV DNA Test. doi:10.1128/JCM.02570-10



23. Cook DA, Kraiden M, Brentnall AR, Gondara L, Chan T, Law JH, Smith LW, Van Niekerk DJ, Ogilvie GS, Coldman AJ, Warman R, Reuter C, Cuzick J, Lorincz AT. (2018). Evaluation of a validated methylation triage signature for human papillomavirus positive women in the HPV FOCAL cervical cancer screening trial. PMID: 30412281 PMCID: PMC6492122 DOI: 10.1002/ijc.31976
24. Ma X, Li Y, Liu R, Wei W, Ding C. (2020). Development of a sensitive and specific nanoparticle-assisted PCR assay for detecting HPV-16 and HPV-18 DNA. *J Med Virol*. Doi: 10.1002/jmv.25962
25. Tsikouras P, Zervoudis S, Manav B, Tomara E, Iatrakis G, Romanidis C, Bothou A, Galazios G. (2016). Cervical cancer: screening, diagnosis and staging. *J BUON* 21(2):320-5. PMID: 27273940
26. CDC. Sexually transmitted guidelines 2021
27. Rajalingam D, Loftis C, Xu JJ, Kumar TKS (2009). Trichloroacetic acid induced protein precipitation involves the reversible association of a stable partially structured intermediate. *Protein science*. 18(5):980-93.
28. FDA briefing information for the November 3, 2016 Meeting of the Pharmacy Compounding Advisory Committee
29. Malviya VK, Deppe G, Pluszczynski R, Boike G. (1987 Jul); 70(1):72-4. Trichloroacetic acid in the treatment of human papillomavirus infection of the cervix without associated dysplasia. PMID: 3037457
30. Menéndez Velázquez JF, González Sánchez JL, Rodríguez de Santiago JD, Muñoz Reyes R, Bailón Uriza R. (1993 Feb); 61:48-51. The treatment of cervical human papillomavirus (HPV) infection with trichloroacetic acid]. PMID: 8406118
31. Boothby RA, Carlson JA, Rubin M, Morgan M, Mikuta JJ. (1990 Aug); 76(2):278-80. Single application treatment of human papillomavirus infection of the cervix and vagina with trichloroacetic acid: a randomized trial. PMID 2164652
32. Geisler S, Speiser S, Speiser L, Heinze G, Rosenthal A, and Speiser P. (2016) 127(2):1. Short-Term Efficacy of Trichloroacetic Acid in the Treatment of Cervical Intraepithelial Neoplasia. DOI:10.1097/AOG.0000000000001244
33. Suwartono H, Andrijono (2020). Efficacy of Trichloroacetic acid (TCA) compared to cryotherapy in treating patients with positive VIA result. *INAJOG*. doi.org/10.32771/inajog.v8i4.1382
34. TRICIN: Prospective study on the efficacy of single topical trichloroacetic acid (TCA) 85% in the treatment of cervical intraepithelial neoplasia (CIN 1/2) (2020). Clinical NCT04400578