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SINUSITISA: PRIKAZ SLUČAJA I PREGLED LITERATURE

Završni specijalistički rad

Zagreb, rujan, 2023.

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Case Report

Alloiococcus otitidis—Cause of Nonspecific Acute Sinusitis: First Case Report and Review of Literature

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Abstract: Although most sinus infections are viral, potential bacterial pathogens such as *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* can migrate during a viral respiratory infection from the nasopharynx into the sinus cavity causing sinusitis. *Alloiococcus otitidis* is a commensal of the external auditory canal and is considered one of the potential middle ear pathogens. Unlike most otopathogens, *A. otitidis* is rarely found in the nasopharynx of healthy individuals. This difficult-to-culture organism has not previously been described as a causative agent of sinusitis. Here we describe one case of acute sinusitis due to *A. otitidis* and review previous knowledge of this controversial organism based on recent literature.

Keywords: acute sinusitis; *Alloiococcus otitidis*; nasopharyngeal microbiota



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1. Introduction

The nasopharyngeal microbiota is very diverse and varies from person to person. The upper respiratory tract, including the nasopharynx, serves as a reservoir for pathogens that can cause respiratory infections, including sinusitis [1]. Although most sinus infections in children are viral in nature, potential bacterial pathogens can migrate from the nasopharynx into the sinuses during a viral respiratory infection and cause sinusitis [2]. The most common bacteria isolated in pediatric patients with acute sinusitis are *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Streptococcus pyogenes* [3].

Alloiococcus otitidis was first isolated from the middle ear fluid (MEF) of children with acute otitis media (OM) by Faden and Dray in 1989 [4]. Since then, it has been frequently detected in MEF specimens and suspected as a cause of OM. However, more than three decades later, its possible role in this disease remains controversial. There is still insufficient evidence to clarify whether *A. otitidis* is a commensal or a true pathogen, or perhaps indirectly contributes to the pathogenesis of OM by supporting important pathogens in some way [5,6].

Acute bacterial sinusitis and OM have identical pathogenesis: an antecedent viral infection and nasopharyngeal colonization by bacterial pathogens. Although frequently detected in MEFs in recent decades, *A. otitidis* has very rarely, if ever, been detected in nasopharyngeal cultures from healthy individuals or patients with respiratory infections [6,7]. However, with recent advances in culture-independent techniques such as 16S rRNA gene sequencing, *Alloiococcus* has been detected as a common genus in the microbiota of the healthy nasopharynx [8]. The same study also revealed that the microbiota of the healthy nasopharynx is most similar to the microbiota of the external auditory canal [8]. However, *Alloiococcus* is most closely related to *Dolosigranulum* by 16S rRNA sequence homology [6]. *Dolosigranulum* is a nasopharyngeal commensal of relevance to OM, and its similarity leads

to misclassification in 16S rRNA gene studies using older taxonomic databases [6]. This must be taken into account when using 16S rRNA analysis.

To our knowledge, this difficult-to-culture organism has not been described in the literature as a causative agent of acute sinusitis in children or adults. We describe here a case of acute sinusitis attributable to *A. otitidis* and review previous knowledge of this organism based on the current literature.

2. Case Report

A 9-year-old boy with no significant past medical history (allergic rhinitis only) was brought to the Department of Otolaryngology-Head and Neck Surgery in February 2020 complaining of a headache in the frontal area above the frontal sinus that had been present for 10 days. The patient had previously received intranasal Maxitrol[®] drops containing neomycin, polymyxin B, and dexamethasone (Novartis Pharmaceuticals, Basel, Switzerland) for two weeks, after which he experienced relief of symptoms. For his allergy, he received Nisita[®] (physiological saline nasal spray; Engelhard Arzneimittel GmbH & Co. KG., Niederdorfelden, Germany), Auerius[®] (desloratadine; Schering-Plough Central East Ag, Zürich, Switzerland), and Melarth[®] (montelukast sodium; Pliva d.o.o., Zagreb, Croatia). We assume these medications minimized other sinusitis symptoms such as mucopurulent discharge and more severe inflammation with obstruction. On examination, the boy was afebrile, otoscopically normal, rhinoscopically with edematous and inflamed mucosa without pathologic mucopurulent discharge, and oropharyngoscopically with the present catarrh and visible tonsils occupying 50% of the pharynx. Sinus aspiration was performed according to the Proetz method and the sinus aspirate was sent to the microbiology laboratory for culture. The patient was instructed to take Maxitrol[®] drops (3 × 2 drops per day for 5 days) until the results of the microbiological analysis were available, and to take the amoxicillin prescribed by the general practitioner in case of fever.

The aspirate was cultured on 5% sheep blood agar, chocolate agar and Columbia agar (BD Difco[™], Le Pont-de-Claix, France) at 35 °C for 48 h aerobically with 5% CO₂ and anaerobically. Small, moist, weakly catalase-positive, alpha-hemolytic colonies grew in pure culture after 48 h aerobically. It should be noted that colonies were too small to see without a magnifying glass. Gram staining revealed small Gram-positive cocci. *A. otitidis* was identified using the VITEK 2 microbial identification system (bioMérieux, Marcy l'Etoile, France). Antimicrobial susceptibility testing was performed by disk diffusion on Müller-Hinton agar (Oxoid, Basingstoke, UK) spiked with 5% sheep blood. Since breakpoints are not defined for *A. otitidis*, the EUCAST standard for *S. pneumoniae* was used to interpret the results [9]. The isolate showed sensitivity to ampicillin, amoxicillin, cefuroxime, ceftriaxone, sulfamethoxazole-trimethoprim, vancomycin, teicoplanin, and tetracycline, and resistance to erythromycin, azithromycin, clarithromycin, and clindamycin.

After completion of microbiological analysis and antimicrobial susceptibility testing, the patient underwent endoscopic examination, which revealed hypertrophic and livid turbinates, enlarged adenoids, and increased nonpurulent nasal discharge.

The patient was administered amoxicillin 1000 mg orally twice daily for 10 days. At follow-up two weeks later, the patient recovered (subjective improvement with otoscopic and oropharyngoscopic normal findings and rhinoscopic pre-existing signs of allergic and vasomotor rhinitis) with no recurrence at follow-up two months later. No additional microbiological control examinations were performed.

3. Discussion and Literature Review

A thorough literature search was performed in the MEDLINE database for case reports and reviews published in English-language peer-reviewed journals using MeSH terms. A search for "*Aleiococcus otitidis*" as a keyword yielded 66 articles, whereas the keywords "*Aleiococcus otitidis*" and "otitis media" yielded 55 articles. In addition, Table 1 summarizes all studies in which *Alloiococcus otitidis* was detected in nasopharyngeal specimens. Searching for the keywords "*Aleiococcus otitidis*" and "sinusitis" yielded only one article,

published in 2003 by Kalcioğlu et al. [5]. The authors reported the detection of *A. otitidis* by polymerase chain reaction (PCR) in two specimens with chronic sinusitis and suggested that this organism could cause chronic sinusitis. However, no case of acute sinusitis caused by *A. otitidis* has been reported to date.

A. otitidis is the only species of the genus *Alloiococcus*. This difficult-to-culture Gram-positive coccus is an aerobic, slow-growing bacterium that was originally isolated from MEF by microbiological culture and considered to be the cause of OM [10]. In the last two decades, it has been frequently detected in the middle ear of children with OM, along with other common otitis-associated bacteria or alone [7,10–13]. Since its discovery, it has been highly controversial as to whether *A. otitidis* is truly a pathogen or merely a commensal of the external auditory canal [6]. This is mainly because the organism could be found in the external auditory canal (EAC) of apparently healthy individuals [14]. In a recent study, Sjøvall et al., reported that EAC samples with a high relative abundance of *Staphylococcus* typically had a low abundance of *Alloiococcus* and vice versa. The authors hypothesized that these two genera should be considered competing members of the microbial community.

Moreover, *A. otitidis* was rarely detected in the nasopharynx of healthy individuals, where the major otopathogens (*S. pneumoniae*, *H. influenzae*, and *M. catarrhalis*) mainly colonize. Nasopharyngeal colonization is a necessary first step in the pathogenesis of acute OM. However, the reason for the rarity of *A. otitidis* in clinical specimens may simply be the failure to culture this fastidious organism. The organism is difficult to isolate using conventional culture methods, and the use of culture-independent methods has greatly improved the detection rate of this bacterium in respiratory specimens. Recently, the high prevalence of the genus *Alloiococcus* in the nasopharyngeal microbiota of otitis-prone children compared with healthy controls was demonstrated by 16S rRNA analysis [13].

In the previously cited article by Kalcioğlu et al., the detection of *A. otitidis* DNA in sinus aspirates from two patients with chronic sinusitis was confirmed [5]. Also, in another study using the PCR method, the presence of *A. otitidis* in effusions from OM correlated with persistent inflammation of the tympanic mucosa [10]. This may suggest that the bacterium is less important in acute infections and more associated with chronicity [5].

However, it cannot be ruled out that *A. otitidis* is present in the acute phase of these two diseases but is overlooked by conventional culture-based methods because of its slow growth (see Table 1). Although its pathogenicity has not yet been proven, Chan et al. have shown that *A. otitidis* can form a biofilm through bacterial interaction with *H. influenzae*, thus indirectly contributing to pathogenicity [15]. *A. otitidis* forms a biofilm with both *H. influenzae* and other species. In addition, *A. otitidis* in a polymicrobial biofilm can promote the growth and survival of *H. influenzae* by increasing biofilm production under unfavorable growth conditions and altering antimicrobial resistance. This study of bacterial interference by biofilm showed an inverse ratio of the relative abundance of *A. otitidis* and *H. influenzae*, suggesting a possible bacterial interaction in patients with sinusitis or OM. Accordingly, chronic sinusitis can be considered as a disease caused by biofilm [15]. Namely, the bacteria may cause subacute inflammation during biofilm formation, thus promoting sinusitis. Moreover, biofilm gives bacteria a survival advantage and makes them resistant to antibiotics, phagocytosis, and humoral immunity [15–18]. Thus, we can assume that one of the most important hypotheses for the etiology of chronic rhinosinusitis is bacterial biofilm formation, which includes *A. otitidis* among other bacteria.

In addition, there are many studies describing the ability of *A. otitidis* to stimulate an immune response. These results indicate its pathogenic potential and preliminary evidence that the immune system responds to it. Thus, *A. otitidis* was able to stimulate the production of IL-8 and IL-12 to a similar extent as *M. catarrhalis*, *S. pneumoniae*, and *H. influenzae* (important otopathogens) [19,20]. The elicitation of an inflammatory response suggests that *A. otitidis* may be a pathogen. Moreover, MEFs positive for *A. otitidis* contained similar levels of proinflammatory cytokines as MEFs positive for *S. pneumoniae* (in the absence of other otopathogens) [21,22]. However, it should be noted that these studies did not involve

replication in a nasopharyngeal epithelial environment and the results were not compared with non-pathogenic bacteria [6].

To date, *A. otitidis* has been associated almost exclusively with MEF as a putative pathogen. There are few reports of *A. otitidis* as a causative agent of unrelated diseases. For example, *A. otitidis* has been described as the causative agent of endophthalmitis following intravitreal injection in two clinical cases [23], and endocarditis [24] developed as a complication of chronic OM. However, in both cases, the source of infection remained unclear. Recently, *A. otitidis* was isolated from a blood culture of a septic patient who had recently suffered an ear infection [25].

Because *A. otitidis* is a potential pathogen of the paranasal sinuses, the advent of molecular methods has significantly changed our understanding of the paranasal sinus microbiota. The culture-independent approaches have clearly demonstrated that healthy paranasal sinuses are not sterile and furthermore harbor complex polymicrobial communities [5,26,27]. Abreu et al. showed that the health of the paranasal sinus mucosa is highly dependent on the composition of its resident microbiota [26]. In a 2016 systematic literature review, Lee et al. reported greater species diversity in paranasal sinus aspirates from healthy individuals compared with diseased individuals and selective abundance of certain microbes in patients [27]. Reduced bacterial diversity and dysbiosis are now considered critical for disease occurrence. However, *A. otitidis* has not yet been described as part of the normal microbiota of the paranasal sinuses. In addition, common respiratory pathogens (*S. pneumoniae*, *H. influenzae*, *M. catarrhalis*, and *S. pyogenes*) and anaerobic bacteria are mentioned as causative agents in all the literature reviewed on acute sinusitis [3]. Sinusitis can be caused by multiple pathogens; polymicrobial infection is described in about one-third of reported cases. Sometimes the pathogen could not be isolated and grown in cultures at all. Brook found that pathogens could be isolated from sinus aspirates in only two-thirds of patients with acute sinusitis [3].

We now know that laboratory detection of organisms associated with sinusitis and OM can be unreliable if only culture-based methods are used. However, not all diagnostic laboratories have the equipment and expertise needed for non-culture-based methods.

Isolation of *A. otitidis* using standard culture methods is difficult because its growth rate is slow. Therefore, its small colonies on blood agar plates may be overlooked or mistaken for slow-growing viridans group streptococci. Since the initial growth of isolates often starts after 72 h, it would be better to extend the aerobic incubation to 3–4 days for middle ear/sinus samples. In addition to direct cultures, the use of enrichment culture media, such as brain heart infusion (BHI) broth, can improve cultivation efficiency [28]. The aerobic growth characteristics of *A. otitidis* may help distinguish the genus from other facultatively anaerobic Gram-positive cocci.

Published data suggest that a combination of culture-based and culture-independent methods can improve the detection rate of *A. otitidis*. Culture-independent methods can be used selectively to detect this largely overlooked organism in culture-sterile clinical specimens. There are no guidelines for antimicrobial susceptibility testing for this species. Our sensitivity results are consistent with those of Ashhurst-Smith et al. Our isolate was sensitive to beta-lactams, tetracycline, vancomycin, and co-trimoxazole [28].

Although the isolate described here was sensitive to amoxicillin, the drug of choice for acute sinusitis, the observed macrolide and clindamycin resistance may complicate treatment of patients with penicillin allergy.

Our literature search revealed no other reports of *A. otitidis* associated with acute sinusitis. This case report is unique because it reports the growth of the organism in pure culture on a conventional culture medium from a sinus aspirate. We believe that the detection of *A. otitidis* in sinus aspirate in pure culture may have clinical significance. This finding allowed us to assume that no other interfering bacteria were present and that *A. otitidis* indeed has its own pathogenicity. Further studies are needed to better define its role in the pathogenesis of sinusitis.

Table 1. Review of literature on detection of *A. otitidis* from nasopharyngeal specimens.

Specimen	Diagnosis	Culture <i>n</i> (%)	PCR <i>n</i> (%)	Reference
SA	chronic sinusitis	0/27	2/27 (7)	[5]
NPS	OME	0/56	6/56 (11)	[11]
NPS	upper RTI	0/129	9/129 (7)	[29]
NPS	healthy children	NP	2/386 (0.5)	[30]
NPS	OME	0/34	0/34	[31]
NPS	healthy children	NP	4/50 (8)	[32]
NPS	healthy young adults	0/10	0/70	[33]

SA, sinus aspirate; NPS, nasopharyngeal swab; RTI, respiratory tract infection; OME, otitis media with effusion; NP, not performed.

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Data Availability Statement: Data supporting this case report are available from the corresponding author on reasonable request.

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Datum rođenja: 04/02/1983 | **Državljanstvo:** hrvatsko | **Spol:** Žensko | **Telefonski broj:**

(+385) 0917550647 (Mobilni telefon) | **E-adresa:** tanja.grubic@medri.uniri.hr |

Adresa: Braće Branchetta 20, 51000, Rijeka, Hrvatska (Službena)

RADNO ISKUSTVO

2023 – TRENUTAČNO Rijeka, Hrvatska

IZVANREDNI PROFESOR SVEUČILIŠTE U RIJECI MEDICINSKI FAKULTET - ZAVOD ZA FIZIOLOGIJU, IMUNOLOGIJU I PATOFIZIOLOGIJU

04/11/2019 – TRENUTAČNO

SPECIJALIZANT KLINIČKE MIKROBIOLOGIJE KLINIČKI BOLNIČKI CENTAR RIJEKA- KLINIČKI ZAVOD ZA KLINIČKU MIKROBIOLOGIJU

Adresa Rijeka, Hrvatska

2017 – 2022

DOCENT SVEUČILIŠTE U RIJECI MEDICINSKI FAKULTET - ZAVOD ZA FIZIOLOGIJU, IMUNOLOGIJU I PATOFIZIOLOGIJU

Adresa Rijeka, Hrvatska

2015 – 2017

POSLIJEDOKTORAND (POSTDOC) SVEUČILIŠTE U RIJECI MEDICINSKI FAKULTET - ZAVOD ZA FIZIOLOGIJU, IMUNOLOGIJU I PATOFIZIOLOGIJU

Adresa Rijeka, Hrvatska

2008 – 2015

ZNANSTVENI NOVAK-ASISTENT SVEUČILIŠTE U RIJECI MEDICINSKI FAKULTET - ZAVOD ZA FIZIOLOGIJU, IMUNOLOGIJU I PATOFIZIOLOGIJA

Adresa Rijeka, Hrvatska

2007 – 2008

PRIPRAVNIČKI STAŽ KLINIČKI BOLNIČKI CENTAR RIJEKA

Adresa Rijeka, Hrvatska

OBRAZOVANJE I OSPOSOBLJAVANJE

2021 – 2023 Zagreb, Hrvatska

POSLIJEDIPLOMSKI SPECIJALISTIČKI STUDIJ KLINIČKA MIKROBIOLOGIJA Sveučilište u Zagrebu, Medicinski fakultet

Adresa Zagreb, Hrvatska

2015 Rijeka, Hrvatska

DOKTOR ZNANOSTI - ZNANSTVENI SURADNIK Sveučilište u Rijeci, Medicinski fakultet

Adresa Rijeka, Hrvatska

2008 – 2011 Rijeka, Hrvatska

POSLIJEDIPLOMSKI DOKTORSKI STUDIJ BIOMEDICINE - SVEUČILIŠTE U RIJECI

Adresa Rijeka, Hrvatska

2008 Zagreb, Hrvatska

ODOBRENJE ZA SAMOSTALAN RAD - LICENCA (DRŽAVNI ISPIT) Ministarstvo zdravstva

Adresa Zagreb, Hrvatska

2007 – 2008 Rijeka, Hrvatska

PRIPRAVNIČKI STAŽ - LIJEČNIK PRIPRAVNIK Klinički bolnički centar Rijeka

Adresa Rijeka, Hrvatska

2007 Rijeka, Hrvatska

DOKTOR MEDICINE Sveučilište u Rijeci Medicinski fakultet

Adresa Rijeka, Hrvatska

2001 – 2007 Rijeka, Hrvatska

STUDIJ OPĆE MEDICINE Sveučilište u Rijeci, Medicinski fakultet

Adresa Rijeka, Hrvatska

JEZIČNE VJEŠTINE

Materinski jezik/jezici: **HRVATSKI**

Drugi jezici:

	RAZUMIJEVANJE		GOVOR		PISANJE
	Slušanje	Čitanje	Govorna produkcija	Govorna interakcija	
ENGLESKI	C1	C1	C1	C1	C1
NJEMAČKI	B2	B2	B1	B2	B1

Razine: A1 i A2: temeljni korisnik; B1 i B2: samostalni korisnik; C1 i C2: iskusni korisnik

DODATNE INFORMACIJE

MREŽE I ČLANSTVA

Članstva

1. Hrvatsko društvo za kliničku mikrobiologiju od 2022.
2. Hrvatski liječnički zbor - HLZ od 2022.
3. CroLASA - Hrvatsko društvo za znanost o laboratorijskim životinjama od 2022.
4. Hrvatsko društvo za biokemiju i molekularnu biologiju od 2019.-2020.
5. Hrvatsko imunološko društvo od 2014.-2018.
6. Hrvatska liječnička komora od 2008.
7. Hrvatsko društvo fiziologa od 2008.

ORGANIZACIJSKE VJEŠTINE

Organizacijske vještine 2014. - 2019. Voditelj demonstratora
2018. Ovlaštenik za provedbu sigurnosti rada djelatnika

OSTALE VJEŠTINE

Ostale vještine

- Tehničke vještine: grafički dizajn, uređivanje radova, priručnika i knjiga

- Laboratorijske vještine: real time PCR (Q-PCR), mikroskopiranje (slikanje, softverska obrada i kvantificiranje podataka), imunološke metode na tkivnim rezovima, parafinska obrada tkiva i rezova, eksperimentalan rad sa životinjama (certifikat), Western blot, mikrobiološke metode

NAGRADE, PRIZNANJA, POPULARIZACIJA ZNANOSTI

Nagrade, priznanja, popularizacija znanosti

2012.-2013. Priznanje velikog doprinosa projektu Hrvatske zaklade za znanost pod nazivom „Hrvatsko anatomsko i fiziološko nazivlje – HRANAFINA“ (<http://hranafina.sfzg.hr/> : voditelj Doc.dr.sc. Marin Vodanović, dr. stom. uz financiranje Hrvatske zaklade za znanost) iz područja fiziologije i anatomije za formiranje on-line baze naziva (e-STRUNA) sa prvim mjestom ukupno obrađenih naziva (614: uglavnom fizioloških, ali i anatomskih)

2004.-2007. Studentski stipendist grada Crikvenice

1999.-2001. Učenički stipendist grada Crikvenice

SURADNIK NA PROJEKTIMA - AKTIVNI

Suradnik na projektima - aktivni

Suradnik na istraživačkom projektu:

2019.-2022. "Fenolni spojevi promiču translokaciju prijenosnika glukoze 4 (GLUT4) i poboljšavaju potrošnju glukoze u tkivima"; uniri-prirod-18-46; voditelj prof. dr. sc. Jasminka Giacometti.

2014.-2018. „Citoprotektivna i imunoregulacijska svojstva glikoproteina i metalotioneina“; 13.06.1.1.16.; voditelj prof. dr. sc. Biserka Radošević-Stašić.

2014.-2018. „Funkcije metalotioneina u demijelinizaciji uzrokovanoj kuprizonom“; 13.06.2.2.58.; voditelj doc. dr. sc. Hrvoje Jakovac.

2012.-2014. volonter na projektu „Hrvatsko anatomsko i fiziološko nazivlje-HRANAFINA“; 07.01/46; voditelj doc. dr. sc. Marin Vodanović.

2008.-2014. „Morfofenetska svojstva stresnih proteina gp96 i metalotioneina“; 062- 0621341-1337; voditelj prof. dr. sc. Biserka Radošević-Stašić.

VODITELJ ZNANSTVENIH PROJEKATA

Voditelj znanstvenih projekata

2019.-2022. - Kvaliteta života u oboljelih od autoimunih i neautoimunih bolesti lokomotornog sustava; Voditelj; UNIRI Sveučilište u Rijeci; (uniri-biomed-18-41)

2018. - Volonter voditelj projekta "Impact of Exercise on "Invisible" Symptoms and Quality of Life in Multiple Sclerosis Individuals" (<https://clinicaltrials.gov/ct2/show/NCT03768830>)

2017. - Volonter voditelj projekta "The Impact of Exercise Training on Living Quality in Multiple Sclerosis Individuals" (<https://clinicaltrials.gov/ct2/show/NCT03222596>)

TEČAJEVI

Stručni tečajevi

2023. X. tečaj o testiranju osjetljivosti bakterija na antibiotike – uloga upravljanja dijagnostikom i antimikrobnom terapijom

2014. Tečaj za osposobljavanje osoba koje rade s pokusnim životinjama, kategorija 3

2008. Tečaj ALS-a - naprednih mjera održavanja života

2008. Tečaju HLK „Liječenje i prevencija bolesti putnika“

AKTIVNOSTI I KONFERENCIJE TIJEKOM ŠKOLOVANJA

Aktivnosti tijekom školovanja - Studij opće medicine

2006. Međunarodna razmjena studenata u Austriji na Klinici u Innsbruck-u, Odjel ginekologije i porodništva

2003.-2007. Demonstrator na Zavodu za fiziologiju i imunologiju, zamjenik voditelja demonstratora - zadnja godina demonstrature

KNJIGE

Knjige - znanstvene knjige, udžbenici i priručnici

Autorske knjige:

1. Udžbenik "Medicinska fiziologija Guyton" 14to izdanje, Medicinska naklada, 2022.
2. Priručnik za vježbe iz Neurofiziologije; Rijeka, WELT d.o.o., 2019.
3. Handbook for practicals in Neurophysiology; Rijeka, WELT d.o.o., 2019.
4. Tanja Grubić Kezele. Chapter "Iron" (In the book: Trace Elements and Minerals in Health and Longevity. Editors: Marco Malavolta; Eugenio Mocchegiani Springer International Publishing Springer Nature Switzerland AG - 2018. <https://www.springer.com/us/book>. DOI: 10.1007/978-3-030-03742-0
5. Udžbenik na hrvatskom i engleskom: "Physiology and Pathophysiology II"; Rijeka, Tiskara Sušak, 2018.
6. Fiziološki pojmovnik s hrvatsko-engleskim rječnikom. Zagreb: Naklada Slap, 2015.
7. Anatomski pojmovnik s hrvatsko-englesko-latinskim rječnikom (Priručnik Medicinskog fakulteta Sveučilišta u Zagrebu.) Zagreb : Naklada Slap, 2015.

ZNANSTVENI RADovi

2023

Mohar Vitezić B, Štefančić E, Repac Antić D, Grubić Kezele T, Abram M, Bubonja-Šonje M. Borderline SARS-CoV-2 patients: the trace behind

Expert Review of Molecular Diagnostics, Q1, WOS

2023

Human Decidual CD1a+ Dendritic Cells Undergo Functional Maturation Program Mediated by Gp96

IJMS, MDPI, Q1, WOS

2022

Neuroprotective Panel of Olive Polyphenols: Mechanisms of Action, Anti-Demyelination, and Anti-Stroke Properties

Nutrients, MDPI, Q1, WOS

2022

Grubić Kezele T, Abram M, Bubonja-Šonje M. Alloiococcus otitidis— Cause of Nonspecific Acute Sinusitis: First Case Report and Review of Literature

Microorganisms, MDPI, Q1, WOS

2021

H Omrčen, S Zoričić Cvek, L Batičić, S Šućurović, T Grubić Kezele. Gender-Related Differences in BMP Expression and Adult Hippocampal Neurogenesis within Joint-Hippocampal Axis in a Rat Model of Rheumatoid Arthritis

International Journal of Molecular Science, Q1, WOS, Scopus

2021

T Kehler, T Grubić Kezele, A Fužinac Smojver, T Kauzlarić-Živković. Povezanost insuficijencije vitamina D i niske tjelesne aktivnosti s umorom, glavoboljom i psihološkim problemima kod studenata, Sjevernomeditranska Hrvatska-pilot istraživanje

Paediatrica Croatica, Q4, Scopus

2021

Grubić Kezele T, Trope Z, Ahel V, Ružić N, Omrčen H, Đudarić L, Fužinac-Smojver A. Upper-lower limb and breathing exercise program for improving sleep quality and psychological status in multiple sclerosis: a pilot randomized controlled trial

Brain impairment, Q3, Scopus, SCIE

2021

Blagojević Zagorac G, Grubić Kezele T. Ceftriaxone and Doxycycline induced Seroconversion in Previously Seronegative Patient with Clinically Suspected Disseminated Lyme Disease: Case Report

Infection & Chemotherapy, Q2, Scopus

2020

Grubić Kezele T, Babić M, Kauzlarić-Živković T, et al. Combined upper limb and breathing exercise programme for pain management in ambulatory and non-ambulatory multiple sclerosis individuals: part II analyses from feasibility study.

Neurological Sciences, Q2, WOS

2020

Bajek S, Giacometti J, Muhvić D, Grubić-Kezele T, et al. Olive Leaf Polyphenols (OLPs) Stimulate GLUT4 Expression and Translocation in the Skeletal Muscle of Diabetic Rats.

International Journal of Molecular Sciences, Q1, WOS

2020

Giacometti J, Grubić Kezele T. Olive Leaf Polyphenols Attenuate the Clinical Course of Experimental Autoimmune Encephalomyelitis and Provide Neuroprotection by Reducing Oxidative Stress, Regulating Microglia and SIRT1, and Preserving Myelin Integrity

Oxid Med Cell Longev, Q1, WOS

2020

Grubić Kezele T, Ćurko-Cofek B. Age-Related Changes and Sex-Related Differences in Brain Iron Metabolism.

Nutrients, Q1, WOS

2020

Grubić Kezele T, Medjimurec S, Bukarica M, et al. Quality of life and level of physical activity in primary school children with juvenile idiopathic arthritis in Primorje-Gorski Kotar County.

Paediatrica Croatica, Q4, Scopus

2019

Grubić Kezele T, Babić M, Štimac D. Exploring the feasibility of a mild and short 4-week combined upper limb and breathing exercise program as a possible home base program to decrease fatigue and improve quality of life in ambulatory and non-ambulat

Neurological Sciences, Q2, WOS

2019

Grubić Kezele T, Fužinac-Smojver A, Zoretić K, Frank S. Determination of the levels of fatigue, pain, functional independence and quality of life in people with multiple sclerosis (MS) compared to non-MS individuals: use of standard psychometric test

Medicina Fluminensis, Q4, Scopus

2019

Grubić Kezele T. Cryptozoospermia after treatment with clomiphene citrate following long-term use of intramuscular testosterone undecanoate depot injection (Nebido®).

Hormone molecular biology and clinical investigation, Q2, WOS

2018

Jakovac H, Grubić Kezele T, Radošević-Stašić B. Expression Profiles of Metallothionein I/II and Megalin in Cuprizone Model of De- and Remyelination.

Neuroscience, Q1, WOS

2017

Tanja Grubić Kezele, Božena Ćurko-Cofek, Hrvoje Jakovac, Ariana Fužinac-Smojver, Kornelija Turković. Adultna neurogeneza-naglasak na subgranularnu i subventrikularnu zonu u sisavaca.

Medicina fluminensis, Q4, Scopus

2017

Ćurko-Cofek B; Grubić Kezele T; Barac-Latas V. Hepcidin and metallothioneins as molecular base for sex-dependent differences in clinical course of experimental autoimmune encephalomyelitis in chronic iron overload.

Medical Hypotheses, Q3, WOS

2017

Jakovac H; Grubić Kezele T; Šućurović S; et al. Osteopontin-metallothionein I/II interactions in experimental autoimmunune encephalomyelitis.

Neuroscience, Q1, WOS

2016

Ćurko-Cofek B, Grubić Kezele T, Marinić J, et al. Chronic iron overload induces gender-dependent changes in iron homeostasis, lipid peroxidation and clinical course of experimental autoimmune encephalomyelitis.

Neurotoxicology, Q1, WOS

2016

Grubić Kezele T; Blagojević Zagorac G; Jakovac H; et al. Hippocampal expressions of metallothionein I/II and glycoprotein 96 in EAE-prone and EAE-resistant strains of rats. Histology and histopathology.

Histo. Histopathol., Q2, WOS

2013

Jakovac H, Grebić D, Grubić-Kezele T, et al. Endoplasmic reticulum resident heat shock protein-gp96 as morphogenetic and immunoregulatory factor in syngeneic pregnancy.

Histol Histopathol., Q2, WOS

2013

Grubić-Kezele T, Blagojević Zagorac G, Jakovac H, et al. Hepatic expression of metallothionein I/II, glycoprotein 96, IL-6, and TGF- β in rat strains with different susceptibilities to experimental autoimmune encephalomyelitis.

Clin. Dev. Immunol., Q1, WOS

2013

Jakovac H, Tota M, Grebic D, Grubic-Kezele T, et al. Barac-Latas V, Mrakovcic-Sutic I, et al. Metallothionein I+II expression as an early sign of chronic relapsing experimental autoimmune encephalomyelitis in rats.

Curr Aging Sci, Q2, WOS

2013

Grubić-Kezele T, Jakovac H, Tota M, et al. Metallothioneins I/II expression in rat strains with genetically different susceptibility to experimental autoimmune encephalomyelitis.

Neuroimmunomodul., Q3, WOS

MENTORSTVA - ZAVRŠNI I DIPLOMSKI RADOVI; DOKTORSKE DISERTACIJE

Mentor doktorandima - Poslijediplomski doktorski studij Biomedicina

1. **Verner Marijančić, mag. rehab.educ.**- Povezanost tjelesne aktivnosti i sjedilačkog načina života sa sastavom tijela, kardiorespiratornim kapacitetom i posturalnom zakrivljenosti kralježnice kod mladih
2. **Hrvoje Omrčen, dr. med.** obranjen doktorat 5. 2. 2023: Spolne razlike u izražaju koštanih morfogenetskih proteina i njihovih inhibitora unutar zglobno-hipokampalne osi u artritisu induciranom pristanom

Mentor diplomskih radova 2022.

1. Ilijana Lončar, UČINKOVITOST LIJEČENJA GLOBALNE RESPIRATORNE INSUFICIJENCIJE TERAPIJOM KLASIČNE PRIMJENE KISIKA I NEINVAZIVNE VENTILACIJE
2. Sestrinstvo-menadžment u sestrinstvu, FZSRI

Mentor diplomskih radova 2021.

1. Antonela Čorapović, *RAZLIKA U FIZIČKOJ AKTIVNOSTI, UMORU I PREHRAMBENIM NAVIKAMA IZMEĐU STUDENATA SVEUČILIŠNIH DIPLOMSKIH STUDIJA FIZIOTERAPIJA I SESTRINSTVO U RIJECI*, Sveučilišni diplomski studij fizioterapija, FZSRI
2. Marcel Bukarica, *USPOREDBA UČESTALOSTI I OBLIKA NASILJA NA RADNOM MJESTU NAD FIZIOTERAPEUTIMA U ODNOSU NA MEDICINSKE SESTRE*, Sveučilišni diplomski studij fizioterapija, FZSRI
3. Marta Turkalj, *POVEZANOST VJEŽBANJA S PSIHIČKIM STATUSOM KOD STUDENATA FIZIOTERAPIJE I SESTRINSTVA*, Sveučilišni diplomski studij fizioterapija, FZSRI
4. Jelena Hagić, *POVEZANOST TJELESNE AKTIVNOSTI S MENTALNIM ZDRAVLJEM OSOBA KOJE ŽIVE NA PODRUČJIMA POGOĐENIM POTRESOM*, Sveučilišni diplomski studij fizioterapija, FZSRI

Mentor završnih i diplomskih radova 2020.

1. Dejan Gvoić, (Diplomski) STAVOVI I ZNANJA FIZIOTERAPEUTA O MANUALNOJ TERAPIJI U PRIVATNIM I DRŽAVNIM INSTITUCIJAMA, Diplomski sveučilišni studij Fizioterapija, FZSRI
2. Petra Vargić, (Završni) The Effect of Olive Leaf Polyphenols on Altered Glutamate Homeostasis in the Rat Brain After Induced Experimental Autoimmune Encephalomyelitis (EAE), Biotehnologija i istraživanje lijekova, Sveučilište u Rijeci-Odjel za biotehnologiju

Mentor završnih i diplomskih radova 2019.

1. Marcel Bukarica - (završni) "Komparativna analiza samoprocjene kvalitete života djece oboljele od juvenilnog idiopatskog artritisa liječenih na Klinici za pedijatriju Kbc-a Rijeka i učenika iste životne dobi OŠ Kantrida"
2. Marija Majetić - (završni) "UTJECAJ SPORTA NA UMOR U ŠKOLSKOJ DOBI"
3. Zrinka Trope - (diplomski) "Utjecaj vježbanja na kvalitetu spavanja i svakodnevnog života kod oboljelih od multiple skleroze"; Sveučilišni diplomski studij fizioterapija
4. Natali Ružić - (diplomski) "Utjecaj vježbanja na fizički bol i glavobolju kod oboljelih od multiple skleroze"; Sveučilišni diplomski studij fizioterapija
5. Valentina Ahel - (diplomski) "Utjecaj vježbanja na umor i anksiozno-depresivnog poremećaja kod oboljelih od multiple skleroze"; Sveučilišni diplomski studij fizioterapija
6. Kristina Klasan - (diplomski) "Educiranost vježbača u teretani o mogućim ozljedama i štetnosti supstanci za povećanje fizičkih sposobnosti"; Sveučilišni diplomski studij fizioterapija
7. Sandro Brnić - (diplomski) "Povezanost fizičke neaktivnosti i vitamina d s anksiozno-depresivnim poremećajem i umorom"; Sveučilišni diplomski studij fizioterapija
8. Diana Khalaf - (diplomski) "Povezanost fizičke neaktivnosti, prehrane i vitamina d s glavoboljama"; Sveučilišni diplomski studij fizioterapija
9. Andrea Ujević - (diplomski) "Translokacija prijenosnika glukoze 4 (GLUT4) u skeletnim mišićima u eksperimentalnom autoimunom encefalomijelitisu"; Sveučilišni diplomski studij biotehnologija

Mentor završnih i diplomskih radova 2016.-2018.

1. Kornelija Turković - (završni) "Utjecaj vježbanja na adultnu neurogenezu i tijek kliničke slike u eksperimentalnom modelu multiple skleroze"
2. Kristina Klasan - (završni) "Odnos indeksa tjelesne mase i tjelovježbe između studenata stručnog studija fizioterapije i opće medicine u Rijeci"
3. Natali Ružić - (završni) "Usporedba indeksa tjelesne mase i načina prehrane između studenata fizioterapije i opće medicine Sveučilišta u Rijeci"
4. Sara Frank - (završni) "Odnos fizičke ograničenosti i kvalitete života u oboljelih od multiple skleroze"
5. Katarina Zoretić Kanjir - (završni) "Utjecaj umora i tjelesne boli na emocionalno zdravlje u oboljelih od multiple skleroze"
6. Marta Turkalj - (završni) "Kineziterapijski pristup kod oboljelih od osteoporoze"
7. Matea Babić - (diplomski) "Utjecaj vježbanja na kvalitetu života u oboljelih od multiple skleroze"; Sveučilišni diplomski studij fizioterapija
8. Dunja Mršić - (diplomski) "Procjena uspješnosti protetičke rehabilitacije osoba s amputacijom donjeg uda"; Sveučilišni diplomski studij fizioterapija
9. Jan Nemrava - (diplomski) "Učinkovitost liječenja bola terapijom udarnog vala"; Sveučilišni diplomski studij fizioterapija
10. Tomislav Perica - (diplomski) "Uloga dekongestivne terapije u smanjenju limfnog edema kod pacijentica nakon mastektomije"; Sveučilišni diplomski studij fizioterapija

STRUČNA DJELATNOST

Stručna djelatnost

1.6.2018. - Pozvano predavanje na 3. interdisciplinarnom stručnom studentskom simpoziju: Multipla skleroza, vježbanje i neuroplastičnost. Fakultet zdravstvenih studija u Rijeci

2018. - Volonter voditelj projekta "Impact of Exercise on "Invisible" Symptoms and Quality of Life in Multiple Sclerosis Individuals" (<https://clinicaltrials.gov/ct2/show/NCT03768830>)

2017. - Volonter voditelj projekta "The Impact of Exercise Training on Living Quality in Multiple Sclerosis Individuals" (<https://clinicaltrials.gov/ct2/show/NCT03222596>)

NASTAVNA AKTIVNOST

Voditelj kolegija i suradnik

Suradnik: Predavanja, seminari i vježbe za sve stručne i diplomatske smjerove: Fiziologija, Patofiziologija, Neurofiziologija, Imunologija
Studiji na hrvatskom i engleskom jeziku

Voditelj kolegija "Patofiziologija":

2017-2021. Sestrinstvo redovni studij

od 2017. Sestrinstvo izvanredni studij od

OSPOSOBLJAVANJE - U SVRHU ZNANSTVENOG ISTRAŽIVANJA

Osposobljavanje - u svrhu znanstvenog istraživanja

Tečaj za osposobljavanje osoba koje rade s pokusnim životinjama, kategorija 3

RECENZIJE

Recenzije znanstvenih radova

2017-2019. NEUS - Neurological Sciences; AMC - Acta Medica Croatica; JNSK - Journal of Neurology & Stroke; Pathophysiology; MOJ Anatomy & Physiology Journal; Archives of Sports Medicine; Medical Science Monitor

2019-2020. (preko 30 recenzija MDPI: International Journal of Molecular Sciences, Life, International Journal of Sports and Exercise Medicine, Neurological Sciences, Medicina, Brain Sciences, Cells, Biomedicines, itd.)

2021. (preko 30 recenzija MDPI: International Journal of Molecular Sciences, Life, International Journal of Sports and Exercise Medicine, Neurological Sciences, Medicina, Brain Sciences, Cells, Biomedicines, itd.)

2022. (preko 30 recenzija MDPI: International Journal of Molecular Sciences, Life, International Journal of Sports and Exercise Medicine, Neurological Sciences, Medicina, Brain Sciences, Cells, Biomedicines, itd.)

2023. (preko 10 recenzija MDPI: International Journal of Molecular Sciences, Life, International Journal of Environmental and Public Health, Biomedicines, Symmetry, Medicina, itd.)

Recenzija međunarodnog znanstvenog projekta

2018. Medical Research Council (MRC)

UREĐIVAČKI ODBOR ZNANSTVENOG ČASOPISA

Uređivački odbor znanstvenog časopisa

od 2022. - Član uređivačkog odbora za časopis *PLOS ONE*

od 2019. - Član uređivačkog odbora za časopis *International Physical Medicine & Rehabilitation Journal (IPMRJ)*