Vol 2, No 2 (2021) ISSN 2637-3408

Symposium of anesthesiologists and reanimatologists in FB&H with international participation

Proceedings

What we learned during the COVID-19 pandemic

03rd – 05th December, 2021

Hotel "Zenica", Zenica, Bosnia and Herzegovina

PROCEEDINGS
December, 03rd – 05th, 2021
Zenica, Bosnia and Herzegovina

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What we learned during the COVID-19 pandemic

Editor

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Publisher
Association of medical doctors Anesthesiologists Reanimatologists in the Federation of Bosnia and Herzegovina

Technical editor
Eldar Sehic

ORGANIZER

Association of medical doctors Anesthesiologists-Reanimatologists in the Federation of Bosnia and Herzegovina

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LECTURERS

Prof Seda Banu Akinci, MD.

Dr. Seda Banu Akinci earned her M.D. from the Hacettepe University, Ankara, Turkey. She trained in Anesthesiology in the same university after which, she completed a fellowship in Critical Care Medicine in Johns Hopkins University, Baltimore, USA. She has served on the Medical Faculty at Hacettepe University since 2001. She has spent many years for the education of medical students, residents and intensive care fellows. She believes the standardization of anesthesia and ICU education across different programs both within and between countries is very important and cooperation between different countries can help to improve this standardization. During her management of different ICU's (postoperative, mixed medical and surgical, and COVID Unit, lately), she has spent years to improve communication, well-being and team work between different professionals including physicians, nurses, pharmacists, dietitians, and other health care personnel. As the director of the largest multidisciplinary critical care medicine fellowship education program of Turkey, she has worked with fellows from many different backgrounds (Anesthesiology, Surgery, Chest diseases, Infectious diseases, Internal medicine, Neurology) and observers from many different countries. She organized many courses regarding ultrasonography, mechanical ventilation, airway management, sedation and analgesia in the ICU. She currently is a member of the Intensive & Critical Care Medicine (ICCM) Committee of World Federation of Societies of Anesthesiologists (WFSA) and serves on the editorial boards of many national and international scientific journals. She has actively worked for the scientific preparation of national /international symposiums and congresses. She is especially interested in experimental research in sepsis. She is also actively engaged in clinical trials on critically ill patients with COVID-19

Senita Beharic, MD, primarius

Senita Beharic, prim., MD, employee of KCUS, at the Clinic for Anesthesia, Resuscitation and Intensive Medicine (KAR) as a specialist in anesthesiology with resuscitation, subspecialist in intensive care medicine. Works together with colleagues anesthesiologists, infectologists and specialists in other fields with patients with COVID-19 infection from April 2020 until now (in JIT Izolatorija Podhrastovi, JIT Infectious Diseases Clinic, Special Respiratory Center - from 19.04. to 04.06. as the person responsible for RC, JIT KAR), facing a number of demands and challenges during the hospitalization of these patients. From September 2021. Acting Head of the Department of Intensive Care with Post-Intensive Care for Patients with COVID-19 Infection of the Clinic for Infectious Diseases.

Asst Prof Vesna Cengic, MD, PhD, primarius

Vesna Čengić was born in Tuzla in 1955 where she finished her elementary education. In 1980, she graduated from Medical Faculty of University of Sarajevo and afterwards, in 1984, started anaesthesiology residency. Four years later, in 1988, she completed her board exam at VMA (Military Medical Academy) in Belgrade. After that, the General hospital "Prim. dr Abdulah Nakas" permanently employed her as a certified anaesthesiologist at Department of anaesthesia and ICU. During the period between 2002 and 2015, she was chief of Emergency medicine department in the same hospital. Dr Cengic engaged in several education programmes in university hospitals in Paris, where she made the pioneer steps for international collaboration among SFAR (French Society of anaesthesia and ICU) and Association of Medical Doctors Anaesthesiologists-Reanimatologist FB&H. Her work was published in local and international journals several times. Alongside being a presenter at congresses, she was also guest presenter for international meetings in France and England. She completed her doctoral dissertation at Medical Faculty of University of Sarajevo in 2017. She was also declared and honoured as primarius of medicine in 1997. Dr Cengic is a mentor for residents of anaesthesia and has been one for a significant period of time in the past. From 2001 to 2006, she had a role of an educator in emergency medicine for family medicine teams in Project Hope-Partnership for Health. Furthermore, she was also engaged in reforms and multiple projects organised by Ministry of Health FB&H in Canton Sarajevo and B&H. Dr Cengic is fluent in English and French. Vesna Cengic is a member of Chamber of doctors of medicine FB&H, Association of Medical Doctors Anaesthesiologists-Reanimatologist FB&H and European Association of Anaesthesia.

Moreover, she is also a president of Scientific board in General hospital "Prim. dr Abdulah Nakas". Dr Cengić is a certified physician for French embassy in B&H and medical correspondent for insurance company AXA Assistance France for B&H.

Prof Ömür Erçelen, MD

Prof. Ömür Erçelen, M.D., was born in Ankara in 1964 and completed his primary, secondary and high school education at TED Ankara High School. He graduated from Hacettepe University School of Medicine in 1987, and went on to conclude his residency at the Department of Anesthesiology and Reanimation of the same university in 1992. He attained the title of associate professor in 1997 and obtained his subspecialty degree in algology in 2011. He began practicing his specialty of Anesthesiology and Reanimation at VKV American Hospital in 1998, and was later named Deputy Chief Physician in 2008 and Medical Director/Chief Physician in 2010 also at VKV American Hospital, respectively. In 2011, he was assigned as a Faculty Member of Koç University School of Medicine. He attained professorship in 2013. In addition to his faculty membership, he served as Head of Anesthesiology and Reanimation at Koç University School of Medicine from 2017 to 2019.

Prof. Ömür Erçelen, M.D., has been serving as the Chief Medical Officer of VKV Healthcare Institutions since 2015 and as Head of Anesthesiology and Pain Clinic since 2020. His fields of specialization include algology, orthopedics and obstetrical anesthesia.

Ognjen Gajic, MD MSc FCCM FCCP.

Dr. Gajic practices and teaches critical care medicine at Mayo Clinic in Rochester, Minnesota. Dr Gajic has published more than 350 peer-reviewed articles and book chapters related to critical care medicine. He has served as a chair of the Discovery Research Network of the Society of Critical Care Medicine. He pioneered the concepts of improving critical care and outcomes with intelligent ICU environments.

Dr Gajic and his group designed and implemented one of the largest international quality improvement projects in critical care: CERTAIN (Checklist for Early Recognition and Treatment of Acute Illness & iNjury)

Prof Radmilo Jankovic, MD, PhD

Radmilo Janković is a professor at the Faculty of Medicine in Niš and the director of the Clinic for Anesthesia and Intensive Care, the largest in Serbia, and the deputy director of the Clinical Center Niš. He is also the secretary of the European Association of Anesthesiologists and Intensivists, which is the second most important place in that European association. Among other things, he is a member of the Presidency of Anesthesiologists of Serbia and the President of the Scientific Committee and a member of the Expert Commission for Anesthesia and Intensive Care at the Ministry of Health.

He has over 130 published papers in the country, but more abroad, which have been reviewed, and about fifty in the world's top scientific journals, viewed through a database of scientific papers such as: Science Citation Index, Web of Science or Scopus and PubMed. It also has its chapters in 12 home textbooks in anesthesia, surgery, and intensive care, including a major textbook on anesthesiology. In 2009, they organized the first International Congress, as a small regional meeting in Nis. So far, it has been held 10 times in a row and has gained a great reputation in the world.

Assoc Prof Gordana Jovanovic, MD, PhD

Dr Gordana Jovanovic is Attending Anaesthesiologist and Intensivist and Associate Professor of Anesthesia and Intensive Care at Clinical Centre of Vovodina, Novi Sad Serbia. For the most of her working career she was dedicated to intensive care and her special professional interest is anesthesia education and simulation. She is Diplomate of the Walden University in College Teaching and Learning. Dr Jovanovic has been involved in WFSA and ESA TTT (Teach the Teacher) courses since 2006 and currently is a member of senior faculty of the ESA TTT Masterclass.

She represent her country in the ESAIC Council. She is also board member in SAAI (Serbian Associatin of Anaesthesiologists and Intensivists).

Assoc Prof Dafina Karadzova, MD, PhD.

Dr. Dafina Karadzova was born 1972, graduated in 1997 on the Medical Faculty in Skopje. She has worked in primary health care as physician and also as an educator on a project regarding continuous medical education. As of 2002 she works at the University Clinic for Gynecology and Obstetrics in Skopje. She finished her specialization in Anesthesia, reanimation and intensive care in 2007. She enrolled in the School of doctorate studies in 2012 and defended her doctorate dissertation with the title “Patient-controlled analgesia with remifentanyl for painless birth: Efficiency and effects on the mother and child” in 2018. She was elected Assistant Professor at the Department for Anesthesia, Reanimation, and Intensive Care in 2019. She is active in her teaching-scientific activity for students and as a mentor and educator of anesthesia residents at the Department for anesthesia and reanimation. During the course of her carrier, she has been dedicated to increasing the percentage of painless births, as well as the development of new techniques in obstetric anesthesia. She has held lectures at scientific-expert gatherings, National Congresses. She is author and coauthor of over 30 papers, published in journals with international editorial boards, and over 80 abstracts.

Assoc Prof Andrijan Kartalov, MD, PhD

Born 1968 year at Skopje, Macedonia. Employed at Clinic for Anesthesia and Intensive care, University “St Cyril and Methodius”,Skopje, Republic of North Macedonia. In the period of 1983-1996th he was attending Medical High School, Medical Faculty, St Cyril and Methodius University, Skopje, Macedonia. Since 1997 until 2001 he had Anesthesiology and Reanimatology - specialisation, Medical Faculty, St Cyril and Methodius University, Skopje, Macedonia (4 years)

2008 MSc, Medical Scienes, St Cyril and Methodius University, Skopje, Macedonia. He is member of Macedonian Medical Association, Member of Macedonian Chamber of Medicine and was President of Macedonian Society of Anesthesia (MSA)in the period of 2012-2019.

In 2001 he did a Fellowship - Cardiac Anesthesia, organized at Soroka Medical Center, Beer Sheva - Israel (6 months). In the year of 2011 he was part of WHO Workshop for Blood and Blood Products, Astana, Kazakhstan, and in the following 2012. He received his PhD - Medical Scienes, St Cyril and Methodius University, Skopje, Macedonia.

His accomplishments are following : The effect of the small-dose of ketamine on postoperative analgesia and cytokine changes after laparoscopic cholecystectomy35 Publications in Medical , and Scientific Journals, 85 Poster and oral ppresentation at International and National Conferences, National anesthesiology meetings - MSA , Senior anesthesiologist at the department of abdominal surgery, ESAIC counsel representative from R. North Macedonia

Mirza Kovacevic, MD

Born on October 31, 1988. in Tuzla, Bosnia and Herzegovina. Primary and secondary school finished in Gračanica, Bosnia and Herzegovina. I obtained my medical degree at Faculty of Medicine at the University of Tuzla, and graduated at the same University in 2013. Employed at the Cantonal Hospital Zenica in the Department of Anesthesiology, Resuscitation and Intensive Care since 2013. Anesthesiology residency training started in 2015. Final year of my residency training finished at the Clinic for Anesthesiology, Resuscitation at University Medical Center Tuzla. Specialist exam passed in 2020. in Tuzla and acquired the title of specialist of anesthesiology, resuscitation and intensive care. My postgraduate (doctoral) studies began in 2019 year at the University of Tuzla. Since then, I have been actively involved in scientific research. As the author and co-author of several published scientific and professional papers. Before and during my doctoral studies, I was a lecturer at numerous domestic and international symposia and congresses, with membership of the Association of Anesthesiologists of the Federation of BiH.

Assoc professor Pedja Kovacevic, MD, PhD, FCCP, primarius

2014 – 2016: Critical Care fellowship, awarded on September 2016.2002 – 2006: Training from the filed of Pulmonology, awarded on December 22, 2006. (Resident in University hospital and Clinic for lung diseases in Banja Luka, Address of hospital: Zdrave Korde 1., Banja Luka 78000, Bosnia - Herzegovina). 2002 – 2006: Postgraduates studies (Ph.D.); from the field of respiratory physiology, awarded December 2, 2006; finished at Medical school University in Banja Luka, Address of Medical School: Save Mrkalja 14. Banja Luka, Bosnia - Herzegovina. 1999 – 2002: Postgraduates studies (M.Sc.); from the field of respiratory physiology, awarded Jun 15, 2002; finished at Medical school University in Banja Luka, Address of Medical School: Save Mrkalja 14. Banja Luka, Bosnia - Herzegovina. 1992 – 1999: Studies of Medicine (Medical doctor), awarded Jun 20, 1999; finished at Medical school University of Nis, Serbia: Address Medical school: Bulevar Dr Zorana Djindjic 81, Nis, Serbia.

2021. Fundamental Critical Care Support (FCCS) instructor, (Society of Critical Care Medicine)

2012. Education in the field of intensive care at Mayo Clinic Jacksonville, under supervision of Prof Emir Festic MD.

2009. Fundamental Critical Care Support (FCCS) instructor, (Society of Critical Care Medicine)

2007 (September, fifth weeks) Education in the field of intensive care with main topic of non-invasive ventilation at Mayo Clinic (St Mary's hospital), under supervision of Prof Ognjen Gajic MD. M.Sc. FCCP. 2005. and 2007. Education in the field of intensive care and pulmonology at University hospital in Heidelberg (Im Neuneheimerfel 410), under supervision of Prof. F.J. Meyer MD FCCP. (Coimbra group project). At 2006 Education in the field of bronchoscopy (especially rigid) at University hospital in Heidelberg – Rorbach "Thoraxklinik" (Amalienstr. 5), under supervision of Prof. Heinrich D. Becker MD FCCP (UICC – ICRETT project).

2014 - present: Head of Medical Intensive Care Unit in University Clinical Centre of Republika Srpska (Banja Luka)

2007 – present: associate professor from the field of physiology and medicine, Medical School, Universities of Banja Luka and East Sarajevo, Bosnia. He is also the editor-in-chief of several books and the Respiratio medical journal, and has confirmed his scientific work by publishing more than 120 scientific papers.

Fellow of American College of Chest Physicians in 2019.

Assoc Prof Biljana Kuzmanovska, MD, PhD

Was born 1972 in Skopje, Macedonia. Dr Biljana Kuzmanovska is anesthesiologist who obtained her medical degree and specialization in Anesthesiology from Ss Cyril and Methodius University in Skopje, N. Macedonia. She defended Master and PhD Thesis in the field of Anesthesiology at the same university. Dr Kuzmanovska is author of several scientific publications, coauthor of three books in the field of anesthesiology and reanimation, and participant in several international multi centric scientific clinical trials as Principal Investigator for her clinical center. The results of some of the trials are published, and others are ongoing. She is contributor to the following published clinical trials: Effect of Intraoperative High Positive End-Expiratory Pressure (PEEP) With Recruitment Maneuvers vs Low PEEP on Postoperative Pulmonary Complications in Obese Patients: A Randomized Clinical Trial Writing Committee for the PROBESE Collaborative Group of the PROtective VEntilation Network (PROVEnet) for the Clinical Trial Network of the European Society of Anaesthesiology et al. JAMA. 2019. Post-anaesthesia Pulmonary Complications After Use of Muscle Relaxants (POPULAR): A Multicentre, Prospective Observational Study Eva Kirmeier et al. Lancet Respir Med. 2019 Feb. Rivaroxaban for Thromboprophylaxis After Hospitalization for Medical Illness Alex C Spyropoulos et al. N Engl J Med. 2018. Dr Kuzmanovska was invited speaker to several international scientific conferences and congresses in the field of anesthesiology and intensive care. She currently holds the position of Associate Professor of Anesthesiology at Medical Faculty, Ss Cyril and Methodius University, Skopje, N.Macedonia.

Asmira Ljuca, MD.

Education-Medical faculty Sarajevo, July, 2005.

Anesthesiologist, anaesthesiology dept of Cantonal hospital Zenica, BiH, 2012- present

Intensivist, ICU subspecialist, ICU dept., Cantonal hospital of Zenica , RBiH, 2017-present

Head of department of Anesthesiology and ICU Cantonal hospital Zenica since april 2021

Assoc Prof Sanja Maric, MD, PhD

Professor Sanja Maric was born in 1967 in Foca, where she finished primary and secondary school. She graduated from Faculty of Medicine in Sarajevo, in 1991. Since then, she has been working in Regional Hospital Foca, wich is now called University Hospital Foca.

She specialized in anesthesiology with reanimatology in 1999 at Military Medical Academy in Belgrade. In the same year, she was elected as a teaching assistant at Faculty of Medicine in Foca. She started postgraduate studies of Experimental physiology and clinical pathology in 1999 at Faculty of Medicine in Belgrade, where she earned a master's degree in 2006. She completed her PhD program in Foca, in 2012.

She was promoted to senior teaching assistant in 2006; assistant professor in 2013 and associate professor in 2018. She passed the oral exam of her subspecialisation in Pain Medicine in 2017, in Belgrade and defended her thesis in 2021. She has been practising pain therapy since 2000. She took the initiative to open The Ambulant for pain therapy in University Hospital Foca.

She published over 100 articles as an author and coauthor. She was a part of 3 projects of international relevance. She successfully completed Pain School under the patronage of ESRA, in Klangefurt (2011) and Montescano (2012). She is a member of ESA, IASP, ESRA and Association for Pain Therapy of BiH.

Assoc Prof Vojislava Neskovic, MD, PhD, DEAA

Dr Vojislava Neskovic is currently working at the Military Medical Academy in Belgrade, Serbia, as the staff anaesthetist and Associate Professor in Anesthesia and Intensive Care at the Medical Faculty of the Military Medical Academy.

Her special interest is mostly focused on cardiac, thoracic and vascular anaesthesia, including intensive care. She has been invited speaker on many national and international events, but also involved in organization of the international educational courses, symposia and congresses.

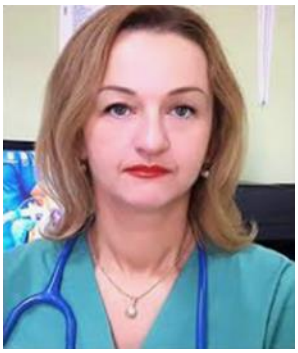
Currently Dr Neskovic is a member of the EACTA Thoracic Subcommittee, the Chair of the ESAIC Gender Equity Committee and past president of the Serbian Association of Anesthesiologists and Intensivists. Also, she is a member of the ESAIC Teach the Teachers Masterclass Faculty and Committee, and examiner for the EDAIC (the European Diploma of Anesthesia and Intensive Care) examination.

Denis Odobasic, MD, primarius

Dr Denis Odobasic works at University Clinical Center Tuzla since 1992. He is a member of the Medical Chamber of Canton of Tuzla since 1998 and also a member of the Society of Anesthesiologists and Reanimatologists of Federation of Bosnia and Herzegovina since 1997.He received his title of Primarius Doctor in 2011. Dr. Denis Odobasic works in the medical field for the past 21 years, is primarily engaged in practical application and education of new procedures in the field of regional obstetric anesthesia. After a successful completion of several Training schools in "Obstetric Anesthesia" in organization of the Clinical Center of Vojvodina in Novi Sad and the Kybele Organization from the USA, he started successfully applying the learnt protocols in the Clinical Center Tuzla. He is one of the lading organizers and active educators in the School of Obstetric Anesthesia in the UKC Tuzla, Bosnia and Herzegovina which was initiated in cooperation with the Kybele, USA. Finished post-graduate Studies – Hopitaux Universitaires De Strasbourg, Sept. 2003, Strasbourg, France. From 2002 until 2004 Post-graduate Studies in "Regional Obstetric Anesthesia" at Regional Center of Republic of Croatia, F.E.E.A – 6 modules At Feb. 2012 Post-graduate Studies in "Anesthesia & Intensive Care in Pregnancy" The Hospital of "Saint Spirt" - Zagreb, Croatia. From February 2015 until present Posta-graduate Studies in "Regional (Lumber) Obstetric Anesthesia and The Introduction of New Procedures & Protocols in Obstetric Anesthesia" In the Organization of Clinical Center of Vojvodina, Novi Sad, Serbia and Kybele Program, USA. At Second Congress of Anesthesiologists and Reanimatologists of Federation of Bosnia & Herzegovina Work Presentation "Thrombocytopenia in Childbirth". International Congress of Anesthesia & Intensive Care, HYPNOS 2017, Banja Luka, Republika Srpska, 22.9 – 24.9.2017. Work Presentation "Regional Obstetric Anesthesia & Analgesia in JZU in the UKC Tuzla". First Symposium of Anesthesiologists of Federation of Bosnia & Herzegovina Tuzla, 1.11 – 2.11.2019 Work Presentation "Pain-free Childbirth – Introduction of the Project in the UKC Tuzla.

Asst Prof Meldijana Omerbegovic, MD, PhD

Dr Meldijana Omerbegovic was born on in Sarajevo, Bosnia and Herzegovina. After secondary school she finished Study of medicine and graduated at Medical faculty of University of Sarajevo in Sarajevo in 1984.Between 1984 to 1993 she was practicing as general practitioner in the Policlinic of Sarajevo. In the period from 1989 to 1990 Dr Meldijana Omerbegovic attended and finished postgraduate study in the Experimental medicine at Medical Faculty University of Sarajevo. In the period from 1993 to 1997 she had practicing and specialization in the field of Anesthesiology and Resuscitation at University Clinical Centre Sarajevo and after certification in Anesthesia and Resuscitation she continued working as a specialist in anesthesiology and reanimation in the Clinic of Anesthesia and Resuscitation of University Clinical Centre Sarajevo. She got a degree of the master of science in medicine at Medical Faculty of University of Sarajevo in 2004 on the topic of „Preoperative administration of ketoprofen in patients who had cholecystectomy“and later on the degree of PhD in medical science at Medical Faculty of University of Sarajevo on the topic „Perioperative heart rate variability in the period of induction and maintenance of general anaesthesia“. During her work as anaesthesiologist at University Clinical Centre Sarajevo, she had participated in the educational process in the field of Anesthesia and Resuscitation for the Medical Faculty and Faculty of Dentistry of University of Sarajevo in last twenty years. Dr Meldijana Omerbegović is the author and coauthor of professional and scientific papers in the field of anaesthesia, intensive care and resuscitation, and she has participated at many professional and scientific meetings: national, regional and international meetings and congresses.



Asst Prof Nermina Rizvanovic, MD, PhD

Rizvanovic dr Nermina was born on May 24, 1972. in Konjic, Bosnia and Herzegovina. Primary and secondary school she finished in Zenica, while she graduated at the Faculty of Medicine, University of Sarajevo, in 2001. From 2001.–2003., she was working in the Public Institution Health Center, in Zenica and performing primary health care activities as a general practitioner. In December 2003., started a period of specialized medical training in anesthesiology and resuscitation in Cantonal Hospital Zenica. In March 2008., she completed a specialization in anesthesiology and resuscitation in University Clinical Center in Sarajevo. She is employed as an anesthesiologist with 13 years experience at the Cantonal Hospital in Zenica, Department of Anesthesiology and Intensive Care Unit. In the field of anesthesia, qualified in preoperative care and anesthesia procedures for general and laparoscopic surgery, gynecology & obstetrics, otolaryngology, ophthalmology, pediatric surgery, plastic surgery, vascular surgery, neurosurgery, trauma and orthopedic surgery considering general, spinal, anesthesia and caudal blocks. In the field of intensive care, she is trained in the treatment of adult surgical, non-surgical and trauma patients. For six years she has been acting as the transplant coordinator. She performs procedures in identification of possible organ donors, determination of brain death and management of the potential donors after brain death. In January 2020., she completed PhD at Faculty of Medicine Tuzla, University of Tuzla. In November 2021., she was appointed Assistant Professor of Anesthesiology and resuscitation at the Faculty of Medicine, University of Zenica. She is interested in research work and has published several papers.

Prof Fatma Saricaoğlu, MD.

Born in 1969 Ankara. Married-2 children (twins). She is Prof at Hacettepe University Dep. of Anesthesiology and Reanimation, ANKARA

Graduated at Gazi University Medical Faculty ANKARA at 1993. Worked at Hacettepe University Dep. of Anesthesiology and Reanimation, ANKARA 1994-1999. She has been profesor since 2011.

She has been to Germany Giessen University and Zurich University in 2006 for 4 months.

She became Pain Therapy subspecialist since 2012. and get Acupuncture Training Certificate at 2014.

Since 2021 she is General secretary of Turkish Anesthesiology and Reanimation society and Turkey Council Member at European Society of Regional Anesthesia since 2017.

In the period from 2010. until 2016. she was General Secretary at Anesthesiology and Reanimation Specialist Society and later she was General Secretary Of Society of Regional Anesthesia in the period between 2016-2019.

Prof Mirjana Shosholcheva, MD, PHD

Prof. Mirjana Shosholcheva is employed in the University Clinic of Surgery “Ss. Naum Ohridski” in Skopje, Macedonia. Its current position is director of Department of Anaesthesia and Intensive care from 2001. She is also Head of Cathedra of Anaesthesia and Reanimation, at Faculty of Medicine, “Ss. Cyril and Methodius” in Skopje, Macedonia from 2013. Her scientific fields of expertise are critically ill patients in intensive care unit, mechanical ventilation, brain death as well as organ donor management. She presents her long-term scientific research work in 140 scientific research and professional papers reviewed so far, published in domestic and foreign reference journals. She is the author of 4 textbooks in the field of anesthesiology as well as author and co-author of books and manuals for CME in the field of anesthesiology, resuscitation and intensive care. She is a participant in international scientific projects and chief researcher of domestic projects. She organizes and teaches at accredited schools, symposia, courses and professional meetings. She participates in both domestic and international congresses and symposia, with oral and poster presentations and introductory lectures. She is also a member of international professional associations, a member of ESAIC, ESICM and the founding committee of the Balkan Anesthesiology Forum (BAF). Since 2010 she is a member of the European Board of Anesthesiologists (EBA), a section of UEMS, where she has been actively working throughout this period in preparing European curricula for the specialization in anesthesia. In this body she works from 2012 as an accreditor of European symposia, congresses in the fields of anesthesia and intensive care. As a representative of EBA, she accredits hospitals and training centers in European countries for specialists in anesthesia and intensive care from 2013. She has been ESAIC Council member from 2016-2020.

Asst Prof Selma Sijercic, MD, PhD, primarius

Selma Sijercic was born on April 26, 1975 in Tuzla. She finished elementary school, high school and medical school in Tuzla and received the title of doctor of medicine. After passing the professional exam, she was employed in January 2003. at the Clinic of Anesthesiology and Reanimatology of University Clinic Center Tuzla. The specialization in the field of "Anesthesiology with Reanimatology" began in 2004. and passed the specialist exam in 2008. in Sarajevo, thus gaining the title of specialist in Anesthesiology with Reanimatology. At the Medical Faculty of the University of Tuzla on 2008. she successfully defended her master's thesis entitled "Effects of postoperative analgesia on the acute phase of response in thoracic surgery" and obtained the title of master of medical sciences. She acquired the title of senior assistant in 2009. She successfully defended her doctoral dissertation entitled "Initial treatment of patients with subarachnoid hemorrhage of aneurysmal origin" at the Medical Faculty of the University of Tuzla on 2014. and thus acquired the title of Doctor of Medical Sciences. She acquired the title of assistant professor in 2014. For long-term and successful work and achieved special results in the protection of public health, as well as the development of health, the decision on the name Primarius in Sarajevo was awarded on April 7, 2019. He is the author and co-author of scientific papers and a participant and invited lecturer at several professional meetings, workshops, symposias and congresses in the field of anesthesiology, reanimatology and intensive care. He is the author of the book "Anesthesia in Neurosurgery". He is a member of the World and European Association of Anesthesiologists as well as the Association of Anesthesiologists of the Federation of BiH. Actively speaks English.

Assoc Prof Jasmina Smajic, MD, PD, primarius

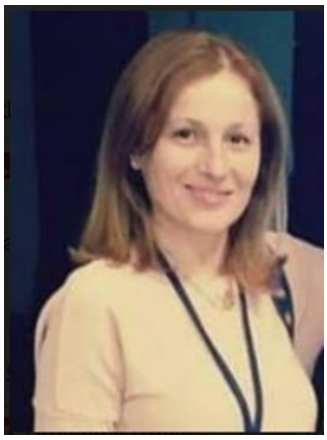
Jasmina Smajić, born on December 14, 1972. in Dortmund, Germany. Primary and secondary school ended in Tuzla. Graduated from the Medical Faculty of the University of Tuzla in 2001. Worked as an intern at the Tuzla Health Center, passing the professional exam in November 2002. Since January 2003. an employee of the University Clinical Center Tuzla, at the Clinic for Anesthesiology and Intensive Care. The specialist exam was passed in September 2008, and works as a specialist in anesthesiology with resuscitation. Areas of professional interest are adequate depth of anesthesia, transplant medicine, pain treatment, infection control, polytrauma treatment, intensive care. Received master's degree in "Assessment of the depth of anesthesia" in November 2009 and defended her doctoral dissertation on "Clinical significance of coagulation parameters in the process of systemic inflammatory response in the surgical patients" in February 2014. Associate professor at the Department of Anesthesiology, Resuscitation and Intensive Care. Leads the subjects "Emergency Medicine and" Pain Medicine "at the Medical Faculty of the University of Tuzla, and" Palliative Health Care "at the University" Džemal Bijedić "Mostar. Since 2019 the primarius. From 2016 to 2020 the head of the Intensive Care Unit, after which became the head of the Clinic for Anesthesiology and Resuscitation. The President of the Association of Doctors of Medicine Anesthesiologists-Reanimatologists in the Federation of Bosnia and Herzegovina, a member of the European Association of Anesthesiologists and Intensive Care in which was a member of the Council in the period 2016-2021. As the president of the organizing committee, participated in the organization of several professional and scientific conferences, domestic and international workshops, seminars, symposia and congresses. Participates as an invited lecturer at domestic and international professional and scientific gatherings. The author and co-author of several papers published in indexed journals, professional journals, collections, author of 3 chapters in books, editor of two handbooks. Member of the editorial board in two, peer-reviewed in several journals. Participated as a coordinator or team member in several domestic or international scientific research projects. Member of the commission for taking the specialist exam as well as the defense of the master's thesis and doctoral dissertation.

Prof Predrag D. Stevanovic, MD, PhD

During his career, Prof Predrag Stevanovic expressed a special interest and talent to chose from an abundance of the latest scientific achievements and knowledge which appear on daily basis in the medical science, the appropriate method to be developed in practice .

This approach of Prof Predrag Stevanovic is highly approved and applied in his Clinic of anaesthesia. Furthermore he shared his work and knowledge with his young colleagues , which is a standard and routine in all highly developed countries. In addition to developing anaesthesiology , Prof Predrag Stevanovic has developed , at the same time, two related , but now independent medical fields - Intensive care and pain management.

Leading the work of his team, as a professional and intellectual leader of a group of over 30 anesthesiologists-intensivists, he has been treating the most difficult, critically ill Covid-19 patients in the red zone of Clinical Hospital Center “Dr Dragisa Misovic-Dedinje” in Belgrade (Serbia) since the beginning of the pandemic.



Adisa Sabanovic, MD

Was born on April 16, 1979 in Novi Pazar, Republic of Serbia. She finished primary and secondary school in Sjenica, Republic of Serbia. She enrolled at the Faculty of Medicine at the University of Belgrade, Republic of Serbia in 1998 and graduated in 2005. In the period 2006-2009. She was employed at the Goražde Health Center, Bosnia and Herzegovina, where she worked as a family medicine doctor. Since 2009, has have been employed at the Cantonal Hospital Zenica in the Department of Anesthesiology, Resuscitation and Intensive Care. She started my specialization in anesthesiology in 2009. She spent the final year of my specialization at the Clinic for Anesthesiology, Reanimatology, University Medical Center Sarajevo. She passed the specialist exam in 2013 in Tuzla and thus acquired the title of specialist in anesthesiology, resuscitation and intensive care. She started the subspecialization of pediatric anesthesiology in 2017 at University Children's Clinic Tirsova in Belgrade, Republic of Serbia. She passed the subspecialist exam in 2019 and thus acquired the title of subspecialist in pediatric anesthesia. She became a member of the organizing committee of the pediatric anesthesia WFSA in 2020. She enrolled in postgraduate (doctoral) studies in 2020 at the University of Banja Luka. She has been a full-time assistant at the Faculty of Health in Zenica since 2014 in the subject Intensive Care, and since 2021 a full-time assistant at the Faculty of Medicine in Zenica, in the subject Anesthesiology and Resuscitation. She is a member of the Association of Anesthesiologists of the Federation BiH. She has participated in several domestic and foreign professional and scientific gatherings. She is the author and co-author of several published scientific and profession.

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Since 2020 she has been a professor at the Medical Faculty, University of Sarajevo, lecturer in the three subjects - First aid, Anesthesiology and resuscitation and Emergency medicine at the National Study of Medicine and also teaching students studying medicine in English.

She is an active member in the ESAIC, EACTAIC, ESICM, and UDMAR. Fluent in English and Italian language.

CONTENTS

RECOMMENDATIONS FOR THE TREATMENT OF COVID-19

Senita Beharic

Introduction

Hospitalized patients with coronavirus disease 2019 (**COVID-19**) as a result of **SARS-CoV-2** (***severe acute respiratory syndrome coronavirus 2***) infection have a high mortality rate and frequently require noninvasive respiratory support or invasive ventilation. Optimizing and standardizing management through evidence-based guidelines may improve quality of care and therefore patient outcomes.

Background

First identified in Wuhan, China in November 2019, the disease rapidly developed into a global pandemic with over 217,2 million infections and more than 4,5 million deaths recorded worldwide, as of the end of November 2021 [1–3]. The case fatality rate of COVID-19 is debated but appears to be lower than Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), with an estimated 5% of those experiencing symptoms requiring hospitalization. The mortality rate in those requiring hospitalization ranges from 5% to 25% [2, 4]. Risk factors for hospitalization and mortality have been defined [2,5].

Predicting risk

In hospitalized patients, **the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) WHO** risk prediction tool incorporates increased age, male sex, number of comorbidities, increased respiratory rate, oxygen saturations, Glasgow coma scale, urea and C-reactive protein as risk factors for mortality [2]. People admitted to hospital with COVID-19 can be divided into four distinct groups, according to data from the world's largest study of patients with the disease. One in every 100 patients in the low-risk group was found to be at risk of dying. That number was 10 in 100 patients in the intermediate-risk group, 31 in 100 in the high-risk group and 62 in 100 in the very high-risk group. The categorizations made new treatment pathways possible, the researchers said. People who fall into low-risk subgroups could be treated at home, while those in the high or very high-risk groups could have more aggressive treatment like early admission to critical care.

The most frequently experienced symptoms

The onset of symptoms occurs around 3–5 days from initial infection, with fever, new continuous cough, dyspnea, anosmia, ageusia and fatigue being amongst the most frequently experienced symptoms [3–5]. Pre-symptomatic transmission has been suggested as one of the

features that promote the widespread transmission of the virus [1, 5]. The spectrum of disease is remarkably broad, ranging from true asymptomatic or paucisymptomatic infection to fatal acute respiratory distress syndrome [4–5].

COVID-19 is often described as a biphasic illness with distinct stages [1]. The initial stage of infection with fever, cough and other symptoms is associated with the highest viral loads, which peak in the first 7 days of illness [1-2] Live virus remains detectable in the respiratory tract for up to 9 days and, in the majority of individuals, symptoms start to improve after the first week of symptoms. In a proportion of patients, however, a second phase, characterized by a dysfunctional host inflammatory response and the development of lung inflammation and lung injury, follows. The inflammatory response in moderate and severe COVID-19 has been variously described as a pro-inflammatory cytokine storm or a manifestation of profound immunosuppression [2]. There is, nevertheless, clear evidence of increased systemic inflammatory markers, including interleukin (IL)-6, IL-8, IL-1β, activation of coagulation pathways with increased markers such as D-dimer, neutrophil recruitment, activation and extracellular trap formation, deficient production in some patients of antiviral defense mediators such as interferon-α and -β, autoimmunity and T-cell activation, among multiple other interferon-α and -β, autoimmunity and T-cell activation, among multiple other mechanisms [1,4-5].

Recommendations for the treatment

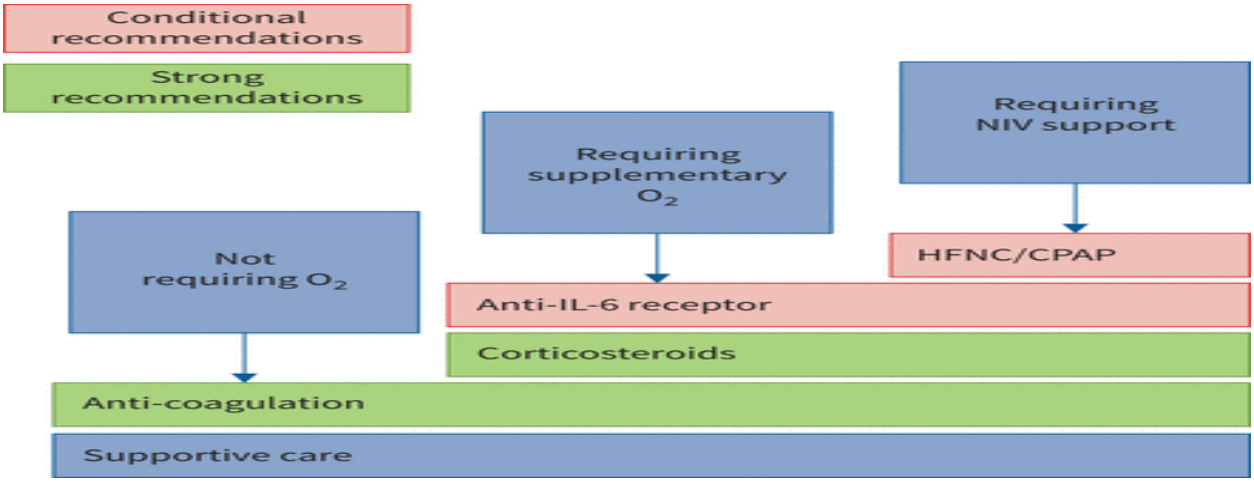
In view of the involvement of both the viral load and host inflammatory response in the disease, repurposing and development of new therapies in COVID-19 has focused primarily on antiviral, immunosuppressive and immunomodulatory treatments [1-5]. Randomized clinical trials have been conducted at an unprecedented rate to generate evidence for specific interventions [3]. During the early stages of the pandemic in particular, empirical use of antiviral and anti-inflammatory drugs, such as hydroxychloroquine, lopinavir–ritonavir, remdesivir and monoclonal antibodies, was widespread globally in the absence of formal guidelines or randomized trial evidence. It is therefore important to have both recommendations in favor of successful interventions but also evidence to avoid certain therapies if their benefit–risk balance is unfavorable. Treatment with corticosteroids to patients with COVID-19 requiring oxygen, noninvasive ventilation or invasive mechanical ventilation is strongly recommended.

SARS-CoV-2 infection has been associated with an increased risk of venous thromboembolism (VTE) attributed to features of coagulopathy [4]. The incidence of VTE is highly variable, ranging from 0% to 85% in reported studies. This variability likely relates to differences in population characteristics (especially regarding severity, age, comorbidities and setting) and diagnostic procedures. Pooled estimates of incidence recently reported in a systematic review of 48 studies were 17.0% for VTE, 7.1% for pulmonary embolism and 12.1% for deep vein thrombosis

[1,5]. This high incidence is associated with a pro-thrombotic state characterized by increased D-dimer levels, associated with the hyperinflammatory state triggered by the host's immune response against SARS-CoV-2 [1]. Anticoagulants used were low molecular weight heparin, unfractionated heparin and direct oral anticoagulants. Risk reduction was significant with both prophylactic and therapeutic anticoagulation therapy.

Discouraging use of antibiotics

ISARIC scientists also reported that the use of antibiotics to treat COVID-19 during the first wave was “very high”, despite bacterial infection being uncommon. The study was published in The Lancet Microbe and was conducted in collaboration with the Universities of Edinburgh and Liverpool and Imperial College London. It found that 85% of COVID-19 patients received one or more antibiotics during their hospital admission, with the highest use in critical care. 37% of patients were prescribed antibiotics prior to admission. The over-prescription of antibiotics raises concern about the potential impact on antimicrobial resistance globally. Overuse of antibiotics needs to be avoided to **prevent emergence of resistance**. When the current threat from COVID-19 subsides, the problem of antimicrobial resistance will remain a threat.



Conclusion

Treatment of COVID-19 is heterogeneous across Europe and the world, and evidence for COVID-19 treatment is accumulating rapidly. There is therefore a need for rapid, evidence-based treatment recommendations and information on how best to improve outcomes for hospitalised patients with COVID-19. Under the auspices of the WHO Sarajevo Office from March 2020 to March 2021, the Mayo Clinic METRIC Group conducted an intensive medicine exchange program to protect critically ill patients, nurses, technicians and physicians in the severe circumstances of the COVID-19 pandemic. The program is based on the CERTAIN

Workshop adapted to the pandemic on the principle of "less is more" in intensive care to prevent iatrogenic complications and protect nurses, technicians and doctors. In addition to accessing rational and practical guidelines for treatment recommended by international organizations (SCCM / ESICM), the program also consists of the exchange of experience and knowledge between colleagues in the region and the USA.

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SEDATION OF PATIENTS IN COVID INTENSIVE CARE UNIT

Nermina Rizvanovic

Management of analgesia/sedation in mechanically ventilated adults with acute respiratory distress syndrome (ARDS) due to COVID-19 is very challenging for medical professionals as well as health care systems.

Current guidelines recommend patient oriented sedation. Before any medication is administered, ventilator settings should be adapted to the patient. Protective ventilation is recommended. Mechanically ventilated COVID-19 patients should not be deeply sedated without a specific indication and without daily attempts to lighten sedation. First step in this process is to achieve analgesia. Behavioral Pain Scale (BPS) is promoted to measure a pain and the range BPS 3 represents a patients with no pain. Pain should be treated with intravenous opioids and non-opioid drugs. The next step is a minimal sedation. Richmond Agitation and Sedation Scale (RASS) should be used for sedation assessment. Given the overall safety profile, non-benzodiazepine sedatives (propofol and dexmedetomidine) are preferred. The goal is mild (RASS -1 to +1) or moderate (RASS -1 to +1) sedation, to obtain protective ventilation. Deep sedation (RASS <-3) remains at the end of lists, if the patient is not fully synchronized to the ventilator. Level of sedation should be reviewed twice daily to avoid oversedation or self extubation. Muscle relaxants should be avoided unless there is severe desynchrony despite deep sedation or high level of inspiratory efforts and in severe COVID-19 ARDS with PaO2/FiO2 <150.

The analgosedation guidelines for COVID-19 ARDS are based on the best scientific evidence in high-income countries. Clinicians are aware that widely adopted and optimal sedation strategies are still lacking. The tendency of local policies is to adapt the principles of "good practice" to the clinical conditions of patients and the availability of health resources.

Key words: analgesia, sedation, intensive care unit, COVID-19, ARDS

DILEMMAS IN THE TREATMENT OF PAIN DURING THE COVID 19 PANDEMIC

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Abstract

The problems associated with pain management during the current pandemic are multiple and they are caused by problems related to restricted access to pain services, as well as to the symptoms due to the Coronavirus disease 2019 (COVID-19).

The main risk for patients with chronic pain is limited access to the healthcare facilities and the inability to get help at the right time. It results from the fact that many patients cannot receive appropriate care, because of the risk of epidemic spread. Untreated pain can lead to increased pain, decreased quality of life and increased anxiety and depression in these patients. Pain is one of the commonest initial symptoms of COVID-19 infection pandemic worldwide since 2019, having a broad clinical spectrum from asymptomatic or mild forms to serious clinical conditions. Myalgia, arthralgia and headache are the most common pain symptoms in COVID-19. Mild pain symptoms associated with COVID-19 can be relieved by simple analgesics such as acetaminophen and non-steroidal anti-inflammatory drugs (NSAIDs). For moderate-to-severe pain, opioids with minimal effects on the immunosuppression (like buprenorphine) are recommended.

Telemedicine is a good opportunity to help patients suffering from various painful conditions during a pandemic. In our circumstances, as this is mainly an elderly patient population, a telephone consultation call was something we used to help patients treat chronic pain during the Covid-19 pandemic. Key words: chronic pain, pain therapy, Covid-19, telemedicine

Introduction

Pain is an unpleasant symptom because patients usually visit a doctor; it can precede the disease, go with it or be its chronic complication. Chronic pain is a major health, economic and social problem, as it impairs the quality of life (QoL) of patients with frequent development of chronic pain syndrome (40%) [1]. Although treatment of pain is a basic human right, the Covid-19 pandemic has forced the health care system around the world to reallocate health resources to intensive care units and facilities designed to treat Covid-19 positive patients [2].

The International Association for the Study of Pain (IASP) recently revised its definition of pain to “an unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage” [1]. The new definition includes six key notes that provide further context for understanding pain as a multidimensional, complex

experience: 1. Pain is always a personal experience that is influenced to varying degrees by biological,
psychological, and social factors. 2. Pain and nociception are different phenomena. Pain cannot be inferred solely from activity in sensory neurons. 3. Through their life experiences, individuals learn the concept of pain. 4. A person's report of an experience as pain should be respected. 5. Although pain usually serves an adaptive role, it may have adverse effects on function and social and psychological well-being. 6. Verbal description is only one of several behaviors to express pain; inability to communicate does not negate the possibility that a human or a nonhuman animal experiences pain [1].

Chronic pain

Chronic pain is a complex multidimensional experience severely compromising the QoL, it often limits the ability to work, sleep, and affects social interactions with friends and family. The overall prevalence of chronic pain in the general population is around 20%. Chronic pain is a real "disease per se" associated with multiple adaptations and changes in the nervous, endocrine and immune systems.With the aging of our population, the prevalence of chronic pain in older patients is increasing [1]. In fact, 60% of individuals older than 60 years have been found to have at least one chronic pain condition, commonly at multiple sites. Multi-morbidity is independently associated with chronic pain; up to 88% of patients with chronic pain have other comorbidities such as depression, cardiovascular and pulmonary diseases, diabetes mellitus, and cancer [2].

Pain during COVID-19 pandemic and COVID-pain

The COVID-19 pandemic has changed people's lifestyles, affected the lives of people worldwide and reduced person-to-person contact. During the COVID-19 pandemic, patients tend to stay away from hospitals due to fear of infection, which is why acute pain is largely untreated and can more easily progress to chronic pain, increasing the risk of disability and depressive status. Social isolation imposed during the pandemic can promote passive coping strategies, with further worsening of depressive mood and increasing suicidal ideation [2]. The COVID-19 pandemic has had negative physical and mental effects on patients with chronic pain, reducing exercise opportunities and increasing loneliness. In this global health pandemic, risk factors for pain morbidity and mortality have been amplified. When it comes to chronic pain, there are three important problems: the first - patients who already have chronic pain, the second - patients whose chronic pain worsened during an epidemic, and the third - patients who acquired pain after a Covid infection [2].

As many of these patients are elderly with multiple comorbidities, susceptibility to COVID could be higher. There may be potential immune suppression because of complex effect of chronic pain. During the lockdown state of COVID-19 pandemic, all the elective pain consultations and interventional pain procedures were either cancelled or postponed [2]. Untreated chronic pain

can lead to increased pain, decreased QoL and increased anxiety and depression in these patients [2]. Problems due to Covid infection further lead to social distancing, isolation, closure of many services for pain therapy, which eventually leads to an increased suffering in patients with chronic pain [1,2].

There is growing evidence that COVID-19 infection is associated with myalgias, referred pain, and widespread hyperalgesia. The importance of these associated conditions cannot be understated, as the pandemic continues to affect every facet of our lives, and the treatment strategies for chronic pain during this time are of vital importance [3]. It was found that 4 weeks after discharge from the hospital, 10–20% of patients treated in the ward suffered from myalgia. Chest pain and headache are other pain conditions observed in outpatients and inpatients until 35 days after the disease [3].

According to the recent research, potential mechanisms of COVID-pain (SARS-CoV-2/COVID-19-induced pain) occurs due to activation of ACE2/RAS (angiotensin-converting enzyme 2/ renin–angiotensin system) pathway and the direct virus-induced damage. Within the RAS, the virus/receptor (ACE2) interaction involves unbalance of the ACE/Ang II (angiotensin II)/AT1R (angiotensin 1 receptor) and the ACE2/Ang-(1–7)/MasR (Mas receptor) axes with down-regulation of ACE2 levels on cell surfaces, Ang-II accumulation, and impairment of the anti-nociceptive Ang-(1-7) pathway [3]. Therefore, direct damage to sensory neurons and/or glial cells is produced. Macrophages and other immune cells can stimulate the production of inflammatory mediators. These processes can facilitate the sensory cells injury and can lead to chronic pain through sensitization/activation processes [3]. Putative mechanisms of different pain symptoms during viral infection involve the overexpression of proinflammatory cytokines, such as TNF-α (tumor necrosis factor α) and PGE2 (prostaglandin E2), in the cerebrospinal fluid, which sensitize and stimulate neurons to produce calcitonin generelated peptide (CGRP). CGRP has a crucial role in the pathogenesis of neuropathic pain and possibly to direct a nociceptive transmission. TNF-α is responsible for the intensified breakdown of muscle proteins and PGE2 could increase the nociceptive signaling [3,4].

The exuberant immune-mediated inflammation is mostly responsible for systemic damage and the triggering of long-COVID problems (including widespread myalgia and joint pain) via peripheral and central mechanisms. Disease-related and predisposing factors contribute to the determinism of the damage. Recognizing the symptoms of COVID-19 infection is crucial for early detection of the disease, but symptoms of the disease are often not specific. Pain can be an early symptom of COVID-19 infection including myalgia/arthralgia, back pain, and headache.

Pain is also one of the commonest initial symptoms of COVID-19 infection pandemic worldwide since 2019 and having a broad clinical spectrum from asymptomatic or mild forms to clinical conditions that may lead to multi-organ failures. Myalgia and headache are the most common pain symptoms in COVID-19. In study of Murat et al. it was found that pain had occured in of 46.61% of the patients. Pain complaints had started on average 2.2 days before admission.

Among 133 patients reporting pain, the distribution of site was 69.2% myalgia/arthralgia; 50.4% headache; 43.6% back pain; 33.1% low back pain; 25.0% chest pain; 21.1% sore throat; and 13.6% abdominal pain. Among patients with pain complaints, the mean value of VAS (visual analogue scale) score was 4.8. [4].

There is a significant relationship between time of pain onset and pain intensity. Pain may be widespread and in some severe cases it could be the chief complaint. If the pain begins earlier, it can be more severe and widespread and become chronic. Intensity of the pain and widespread pain are related to the presence of pain at clinical presentation. The presence of pain at presentation and how early the pain begins can provide guidance on the character and prognosis of the pain. Whether the pain after COVID-19 infection becomes chronic or not is still unknown. More research is needed to evaluate how pain patterns change over time, particularly in various COVID-19 treatments, and the impact of disease severity and disease characteristics on pain patterns [4].

Many patients with respiratory failure get admitted to the intensive care unit (ICU) for ventilatory support. Pain in ICU patients can be associated with viral disease itself (myalgia, arthralgia, peripheral neuropathies), it may be caused by continuous pain and discomfort associated with ICU treatment, intermittent procedural pain and chronic pain present before admission to the ICU. Undertreatment of pain, especially when sedation and neuromuscular blocking agents are used, prone positioning during mechanical ventilation may trigger delirium and cause peripheral neuropathies [3,4].

Pain therapy

During the COVID 19, multimodal analgesia, or the concurrent use of multiple medications employing different mechanisms of action, has been associated with improved analgesia with fewer side effects [5]. Optimal analgo-sedation strategy in the critically ill should achieve effective analgesia, targeted sedation and reduced risk of delirium and agitation [2]. There is no reason to fear NSAIDs might increase risk of contracting COVID-19 or exacerbate symptoms in patients who were previously on NSAIDs treatment [6]. Discontinuation of prescribed NSAIDs for chronic pain conditions is not recommended at this time. Acetaminophen has been proposed as an alternative to NSAID use, but there are also issues with acetaminophen toxicity in high doses [5,6]. The effects of opioids on the immune system are complex and depend on the type of opioid, dose, nature of immunity, and the patient's situation. Opioids with minimal immunosuppressive characteristics should be used. Buprenorphine is highly recommended, tramadol and oxycodone can be used as a second option, while morphine and fentanyl are not recommended due to side effects and addiction potential [5]. Chronic opioid therapy may lead to opioid induced immune-suppression in some patients [5]. Steroid therapy (oral/injectable/interventional) may induce hypothalamic pituitary axis suppression [4,5]. Peripheral neuropathies are prevalent in COVID-19 patients and may require an addition of gabapentinoids to the pain treatment regime. Gabapentin and pregabalin, calcium channel

ligands, reduce respiratory drive and combined therapy with opioids might be potentially hazardous [5]. Interventional pain procedures are typically minimally invasive procedures that, when appropriately indicated, relieve acute and chronic pain as well as minimize the use of analgesics and are often performed on an outpatient basis [8].

Telemedicine

Telemedicine is a good opportunity to help patients suffering from various painful conditions during a pandemic [9]. Different communication methods can be used: audio, video, phone, email, fax, etc. The patient should be present at the first examination, while the telemedicine method could be used for subsequent consultations or control examinations. Telemedicine was recommended to patients with relatively stable conditions to prevent the spread of the Covid infection [9]. Tele-consultation in patients with rural background may not be practical due to issues pertaining to education, network, etc [10].

Conclusion

Mild pain symptoms associated with COVID-19 can be relieved with simple analgesics such as acetaminophen and NSAIDs. For moderate-to-severe pain, opioids with minimal effects on the immunosuppression are recommended.

In our circumstances, as this is mainly an elderly patient population, telemedicine was not entirely acceptable, so a telephone consultation call was something we used to help patients treat chronic pain during the Covid-19 pandemic.

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INTERVENTIONAL PAIN MANAGEMENT DURING COVID 19 PANDEMIC

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Chronic pain is an important condition worldwide which causes fatigue, limitations of daily life and reduced quality of life. Interventional pain procedures improve quality of life and function. There is a lot of invasive pain therapy interventions for different types of pain syndromes.

Most common interventions are intra articular and spinal injections such as epidural, intradiscal, facet joints and sacroiliac injections. Radiofrequency lesioning is one of the favorite therapies for pain relief. We can use this technique for long term pain management. We not only take care of patients with back pain but we also care for cancer, metabolic diseases and other illnesses with chronic pain.

Pain medicine physicians who perform interventions are also subjected to higher risk of infection. The pandemic has drastically affected the physical and mental health of interventional pain professionals. Most physicians are negative about the future and more than half want to quit practicing medicine. We learned how to use personal protective equipment and how to take care of ourselves.

At the beginning of the Covid 19 pandemic, all elective procedures were cancelled except urgent needs. Epidural or intra articular steroid injections were postponed especially. Interventional therapies were applied mostly for cancer pain.

Oral medications were preferred. We met and took care of patients with telemedicine. It is a new world for both physicians and patients.

Interventional pain procedures are resuming after vaccine discovery. We are starting to do postponed therapies.

The argument is how to use steroids with the vaccination. Glucocorticoid steroids have been considered immunosuppressive since the 1990s when it was discovered that they interfered with the signaling of inflammatory transcriptional regulators. While epidural steroids may be absorbed systemically, based on current dosing strategies and the pharmacodynamics of these injections, they are unlikely to demonstrate the immunosuppressive effects associated with chronic high-dose systemic steroid use. Neuraxial procedures containing corticosteroids may continue to be performed during the COVID-19 pandemic, provided that the risk/benefit ratio is assessed in each case, the lowest possible dose is administered and patients are informed of the possibility of immunosuppression and the potential risk. There

is no evidence that patients receiving epidural steroid therapy for the management of pain are at increased risk of adverse outcomes of COVID-19 vaccination.

Physicians should consider timing an elective corticosteroid injection such that it is administered no less than two weeks prior to a COVID-19 mRNA vaccine dose and no less than one week following a COVID-19 mRNA vaccine dose, whenever possible.

Physicians may consider the use of dexamethasone or betamethasone rather than triamcinolone or methylprednisolone.

Currently and in the near future we are looking forward to new therapies both for Covid 19 and pain management.

SEVERE FORMS OF COVID-19 AND SYSTEMIC COMPLICATIONS

Meldijana Omerbegovic

Introduction

COVID-19 pandemic, caused by novel severe acute respiratory syndrome (SARS) coronavirus-2 has been in focus of numerous, different scientific circles, health care professional communities as well as all other social and professional circles and the whole public communities all over the world for the last twenty-three months. Despite enormous efforts and struggle of all health-care systems with different resources and different organizational possibilities all over the world, despite the prompt discovery of vaccines in different countries and world-wide application of the vaccines, to varying degrees, twenty-three months after announcement of the first cases in Wuhan in China, COVID-19 has been still spreading at alarming pace in many countries, as no other disease in the history of mankind, with so high rates morbidity and mortality among all populations. The spectrum of the clinical manifestations of the disease is in the range from different forms of mild and moderate illness to severe condition. While the most of the patients have been asymptomatic or with signs of a mild infective illness with affection of the upper respiratory tract, the patients who develop moderate and severe conditions require intensive monitoring and intensive therapy with different supportive medications and different levels of respiratory support. Patients with most severe conditions require immunomodulatory drugs and other supportive measures.

Pathophysiology and clinical course

In numerous published papers on pathophysiology of COVID-19 three stages of the disease are depicted : asymptomatic phase, invasion and infection of the upper respiratory tract and involvement of the lower respiratory tract with progression to acute respiratory distress syndrome. It is postulated that the probable way of infection with SARS-CoV-2 begins with of binding to epithelial cells in the nasal cavity through angiotensin-converting enzyme-2 (ACE2) ,with local propagation and very limited innate immune response. In the next stage when the disease is clinically manifested with fever, malaise and dry cough, there happens the spreading of the virus down the respiratory tract with more intense innate immune response. Most people experience this mild clinical picture, when the disease is limited.

But in the less number of patients there might be a progression of the disease to the third stage with characteristic pulmonary infiltrates, while the small number of patients might develop very severe condition with multiple organ dysfunction. In the stage of involvement of lower respiratory tract the viruses invade the cells of alveolar epithelial cells with consequent replication and production of more viral particles. The invaded pneumocytes may release many different cytokines and pro-inflammatory factors like tumour necrosis factor-α (TNF-α),

interleukins (IL-1,IL-6,IL-8, IL-10 ,IL-12), interferons (IFN-λ and IFN-β), monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α). Subsequent accumulation of neutrophils, CD4 helper T cells and CD8 cytotoxic T cells and releasing of different enzymes and factors, lead to even severe inflammation and lung injury. The apoptosis of alveolar cells and damages caused by accumulated inflammatory cells induce widespread alterations of respiratory membrane with resultant acute respiratory distress syndrome (ARDS) and hypoxic respiratory failure. The characteristic of the ARDS in COVID-19 is related to the obstructive thromboinfammatory syndrome in the microcirculation of the lungs. The microthrombi within the pulmonary circulatory bed may lead to pulmonary hypertension, pulmonary haemorrhage and infarction, and secondary effects on heart. Mechanisms that may lead to acute respiratory failure might include direct infection of the cells by virus, cytokine release syndrome, and formation of microthrombi in the pulmonary vascular bed, while the clinical picture may vary from ARDS to severe cardiocirculatory insufficiency and multiple organ dysfunction syndrome(2,3). Despite enormous number of publications on the topic of COVID-19 there are numerous significant knowledge gaps about the pathogenesis, especially regarding the severe forms of the disease. Along with accumulation of the knowledge on different clinical signs and clinical course of COVID-19 it has become obvious even analysing the first cases of the disease that classification into different categories based on respiratory symptoms should be reconsidered and revised to include the symptoms of involvement of many other organs.

Effects of SARS-CoV-2 virus on different organs and tissues

The widely distributed the angiotensin-converting enzyme-2 receptors may have very important role in extensive disease distribution in many organs besides lungs with consecutive metabolism alterations and dysfunctions.

These extrapulmonary manifestations include heart and circulatory dysfunction, neurologic signs, hepatic dysfunction, renal dysfunction and renal failure, gastrointestinal symptoms, endocrine dysfunction, endothelial dysfunction and alterations of coagulation along with other manifestations. Patients with comorbid conditions, especially diabetes mellitus and coronary artery disease may develop more severe clinical picture of COVID-19 disease. Direct and indirect effects of the SARS-CoV-2 virus on mocardial injury may manifest like myocarditis, arrhythmias, disorders of systolic and diastolic function, myocardial ischemia and sudden cardiac death. Assessment of the biomarkers of myocardial injury and echocardiography besides standard monitoring may be very important in monitoring the condition of these patients(5). The events of infiltration of inflammatory cells and releasing of inflammatory mediators in myocardial tissue may lead to apoptosis or necrosis of cardiomyocytes and resultant dysfunction. Direct effects of the viral infection may result in the swelling of myocardial fibers and accumulation of adaptive immunity cells. Besides that there were also findings of endothelial cells alterations in the microvasculature of the heart (6,7).

Acute kidney injury is one of the major contributing factors for the mortality related to COVID-19, what is in accordance with findings of high expression of ACE 2 receptors in podocytes and proximal tubular epithelial cells(8). According to the findings of some authors invading the cells of renal tubules by SARS-CoV-2 virus may lead to complement-mediated activation and infiltration of CD68+ macrophages to the interstitial tissue with consecutive damage and fibrosis. These changes may lead to acute kidney injury along with other conditions like dehydration, nephrotoxic drugs, hypoxia, rhabdomyolysis, hypoperfusion due to hypotension and underlying diseases(9). Significant alterations of the haematopoietic system in the patients with COVID-19 include lymphocytopenia and leukopenia that may increase the susceptibility to bacterial infections. There is strong correlation between thrombocytopenia and the severity of the illness (10). Invading the hematopoietic cells by the virus may lead to altered hematopoiesis secondary to immune system response. According to some authors alveolar damage induced by virus may affect the resident megakaryocytes in the lungs, while endothelial damage may cause thrombus formation and thrombocytopenia (10,11).Severe alterations of coagulation in the patients with severe COVID-19 have been described as thrombus formation in different parts of venous and arterial circulation, hyperfibrinolysis, thrombocytopenia, sepsis-induced coagulopathy, and elevated activity of plasmin activity. On the other hand hypercoagulability, prolonged prothrombin time, and increased fibrin degradation products enhance the risk of disseminated intravascular coagulation(12). Many factors in severe COVID-19 lead to increased risk of thrombosis and these are prolonged inflammation, immobility, hypoxia and wide spread damage of endothelial cells by the virus(12).

Elevations of liver enzymes in all patients with COVID-19 have been documented since the first cases of the disease, but patients with severe forms have significant elevations of liver enzymes. Direct infection of hepatocytes by the virus may lead to acute liver failure. Many factors might be involved in liver injury such as severe hypoxia, hypoperfusion, direct invasion of the virus and medications that might interfere with metabolism of hepatocytes. In the situation of concurrent kidney and liver injury in patients with severe COVID-19 there appears increased risk of decreased metabolism of medications and developing of toxic effects of the drugs (13,14).

Dysregulation of glucose metabolism in COVID-19 has been described in the observational studies, what might be associated with dysregulation of ACE 2 receptors that have considerable expression in both exocrine endocrine pancreatic cells. In the patients with severe forms of COVID-19 accumulation of the immune cells and inflammatory cells, particularly neutrophils and macrophages may have impact on the cells and alterations of glucose metabolism(15).

The most common gastrointestinal symptoms in COVID-19 disease comprise diarrhea, abdominal pain and nausea, while diarrhea might be one of the initial signs of the disease.

Postulated mechanism of the involvement of gastrointestinal system is described as direct viral invasion and damage of the cells of gastrointestinal tract (15,16).

Among the different neurological manifestations in COVID-19,that have been described, the most common central nervous system symptoms were headache, dizziness, altered consciousness, ataxia and epilepsy, while the affection of peripheral nervous system was described by presence of numerous and different symptoms. In many cases of severe COVID-19 neurologic symptoms were displayed like acute cerebrovascular diseases and encephalopathy (17). Cutaneous manifestations in patients with COVID-19 have been described as erythematous rash, widespread urticaria and skin rash (18).

Multiple organ dysfunction in patients with COVID-19 disease

In the situation of appropriate innate and adaptive immune responses to with SARS-CoV-2 virus, patients usually develop relatively mild clinical picture with convalescence that might be expected in different periods after the initial symptoms.

In the situation of dysregulated responses of innate and adaptive immunity to infections with SARS-CoV-2 virus, the clinical course lead to more severe clinical picture with wide spread tissue damage and multiple organ dysfunction.

Elucidating the pathogenesis of multiple organ dysfunction in patients with severe forms of COVID-19 infection is a complex task as many questions regarding the pathophysiology of this disease have not been answered yet. Dysregulated immune responses may produce immune damage to various tissues. In the situation of disabled immune system the macrophages and neutrophils may accumulate in the injured tissues releasing the cytokines in the cytokine storm when the healthy cells are being destroyed by excessive inflammatory response (19,20).

Conclusions

Although the majority of patients with develop characteristic symptoms of respiratory infection in some patients with severe forms of COVID-19 the developed multi-organ dysfunction may include acute respiratory failure, acute liver dysfunction, acute kidney injury, cardiovascular dysfunction along with neurological disorders and numerous haematological alterations and derangements of coagulation. There are hypotheses that most important mechanisms are associated with the direct and indirect pathogenic features of SARS-CoV-2 virus. Postulated indirect mechanisms are related to disordered increased and prolonged inflammatory responses described as cytokine release syndrome characterized by elevated inflammatory mediators, dysfunction of endothelium, altered coagulation pathways and accumulation of inflammatory and immune cells into the tissues and organs.

Further research on the topic of pathophysiology, risk factors, clinical course, possible different preventive, therapeutic and modulatory measures in treating multiple organ dysfunction syndrome in COVID-19 disease are required. Increasing the knowledge on the pathogenesis of dysregulated immune response in severe COVID-19 and its effects on multiple organs may

improve clinical knowledge and enable introducing preventive measures besides the therapeutic and supportive measures that are administered in everyday healthcare process for the patients with most severe COVID-19 disease forms, with final aim of increasing the chances for survival of these patients

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PRONE POSITION IN COVID -19 PATIENTS

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Introduction

During March 2020. year, Clinical Center of Vojvodina became a covid hospital, receiving the first sick patient. Since then, the treatment of such patients has been continuously carried out in our Institution.

Prone position in patients undergoing mechanical lung ventilation (MLV) is not a new concept. In the seventies of the last century, the first papers on this topic were published by Brayan, but they went quite unnoticed by the professional public, because at that time mechanical lung ventilation, understanding and concepts related to it were not sufficiently developed

In his key work published in 1991. Gatinoni , which dealt with the pathophysiological effects of prone position on patients with ARDS (acute respiratory distress syndrome), laid the foundations of what we know today, and laid out the concept of the "wet sponge model".

Over the next twenty years or so, and especially in the period from 2000-2010, the expansion of scientific papers and further knowledge on this topic begins. The conclusion of all studies was unformed, that prone position leads to improved oxygenation. The key question was whether these positive effects on oxygenation could translate into improved treatment outcomes, and what was the impact of proning on the net treatment outcome.

The answer to that question was given by the PROSEVA study published in 2013, which unequivocally confirmed that it had a positive impact on the outcome, ie a reduction in mortality in proned patients who had ARDS.

Pathophysiological mechanisms of pronation

When a patient on the MLV is in a supine position, the following pathophysiological changes occur: gravitational forces act so that the mediastinum with the heart presses on the lungs in the value of additional 3-5 cm H2O. During respirations the abdominal organs exert additional pressure on the lungs, the expansion of the lungs under inspiration is less homogeneous and there are dependent (dorsal) and independent (ventral) parts of the lungs during ventilation, due to this, there is a more pronounced collapse of the alveoli in the dorsal regions and thus a more pronounced disorder of the ventilation / perfusion ratio. In the prone position, all these effects are less pronounced, lung aeration and ventilation are much more homogeneous.

Perfusion is unchanged, which leads to a consequent improvement in the V / Q ratio and better oxygenation.

Timing

Initially we used the knowledge gained from ARDS studies and applied it in a patients with covid -19 on MLV. PROSEVA study recommends that prone position should be used in severe forms of ARDS, where the PO2 / FiO2 ratio is less than 100, and as early as possible during the course of the disease. We applied the same rules to patients with covid -19.Current literature data on prone position in patients with covid -19 on MLV, primarily come from a study of Italian authors, with more than 1000 patients. This was multicenter retrospective study which gave us insight in their proning practices. Results were: improvement of oxygenation, patients with more severe forms were more often proned, and that they had more proning sessions.

Technique of prone positioning in patients on MLV

The performance of the procedure itself must be well planned and safely performed. We have made a local protocol (see appendix) of performing this procedure. It requires four to five people to participate.

Duration of one prone session

We applied attitudes derived from ARDS treatment. Attitudes have changed during time. Literature data indicate that periods of one prone session should be conducted as long as possible, because the desired effects of pronation occur as a function of time. Current recommendations are from 16-20 h continuously in patients on MLV.

Complications

Complications of the proning procedure in patients on MLV, are primarily complications related to the airway, such as displacement of endotracheal tube or nicking. Complications related to the positioning itself, such as pressure on certain parts of the body and pressure ulcers, as well as mechanical injuries to muscles or nerves. There is also a whole range of mechanical complications related to the loss of venous lines, urinary catheters .. etc.

General contraindications for prone pronation

General contraindications for placing patients in pronation are: acute hemorrhage, shock, hemoptysis, multiple fractures, spinal instability, increased intracranial pressure, tracheal surgery or sternotomy in the last two weeks.

Relative contraindications are state of shock, thoracic drains with large air losses, extensive abdominal surgery, immediately after pacemaker placement, extensive burns, lung transplantation ...

Prone position in nonintubated (awake) patients

Prone position in nonintubated (awake) patients is known for twenty years (Valer 2003). The first knowledge about proning in nonintubated patients in patients with covid-19 came to us

from the works of Chinese colleagues, where they showed their treatment protocols, which included self-proning of non-intubated patients. This practice was adopted very quickly in our hospitals, due to its obvious advantages. The benefits are similar to those in intubated patients, virtually this technique is without complications. The danger of applying this technique is that the growing respiratory insufficiency is not recognized in time, and that the process of once inevitable intubation is delayed.

Conclusions

Prone position of the patients on MLV

- We should prone severe cases of covid -19 patients on MLV(P/F ratio less than 100)
- Early on the course of the disease
- 16-20 h in duration
- be aware of complications and prevent them

Awake prone positioning

- Awake proning should be performed in all feasible cases
- 2-8 hrs in duration (or as feasible)
- be cautious on development of respiratory insufficiency and delayed endotracheal intubation

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Appendix

PREPARATION BEFORE PRONING
• EYE CARE, AB OINTMENT APPLICATION, ADDITIONAL EYE TUPFER
• CARE OF THE ORAL CAVITY, ASPIRATION OF THE ORAL CAVITY, PLACEMNT OF OROPHARINGEAL AIRWAY
• CHECKING THE POSITION AND SECURITY OF THE ET TUBE
• EMPTY THE URINE BAG
• CLOSE THE PROBE
•**PREPARATION OF A NECESSARY MATERIAL:**
• PREPARE TWO PILLOWS
• MAKE A SOFT PAD FOR FACE AN INNER DIAMETER ABOUT 15-20 CM
• PREPARE SEVERAL PADS FOR ARM AND LEGS

• NEW CLEAN SHEET ROLLED UP TO HALF IN LENGTH

PRONING TECHNIQUE

• THREE (OR TWO) TECHNICIANS ON EACH SIDE OF THE BED
• ANESTHESIOLOGIST HOLDS PATIENT HEAD AND COORDINATE PRONING
• REMOVE MONITORING AND PREPARE ELECTRODES TO BE PLACED ON THE BACK
• SEPARATE ARTERY OR CENTRAL VEIN IF NECESSARY
• PULL THE PATIENT CLOSE TO ONE SIDE OF THE BED,
• ROLL THE OLD SHEET AND PUT THE NEW ONE
• PUT THE PATIENT'S HAND UNDER THE HIP
• PULL THE PATIENT AGAIN
• PLACE TWO PILLOWS ON THE PRESSURE POINTS (CHEST AND HIPS)
• TURN THE PATIENT TO THE PADS AND PILLOWS
• WELL TIGHTEN NEW SHEET
• ANESTHESIOLOGIST TURNS PATIENT HEAD TO THE SIDE BY PUTTING IT IN PADS
• ALL PRESSURE POINTS ARE CHECKED (EYES, NOSE, MOUTH)
• CHECK THE PRESSURE IN CUFF
• PLACE HANDS NEXT TO HEAD (ALL JOINTS IN FLEXION)
• PLACE PADS AT THE PRESSURES POINTS (JOINTS, ELBOWS)
• CHECK THE POSITION OF THE FEET

WHAT DO WE KNOW ABOUT HEART INJURY IN COVID-19?

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The coronavirus disease COVID-19 pandemic caused by severe acute respiratory syndrome SARS-CoV-2 has demonstrated a broad spectrum of presentations ranging from asymptomatic disease to severe respiratory failure, myocardial injury and death. Up to 20%–30% of patients hospitalized with COVID-19 have evidence of myocardial involvement. Any associated cardiac complication is considered detrimental to the survival of COVID-19 patients.

COVID-19 has various cardiovascular consequences including alteration in cardiac biomarkers (due to ischaemic/non-ischaemic causes), myocarditis, arrhythmia, cardiogenic shock, cardiac arrest, and thromboembolism. Ischaemic myocardial injury can result in myocardial infarction (ST/non-ST-elevation), and myocardial injury with disseminated intravascular coagulation. Non-ischaemic myocardial injury gives rise to myocarditis, stress-induced cardiomyopathy and myocardial injury with cytokine release syndrome.

Cardiovascular epidemiology and COVID-19

Approximately 12% of COVID-19 patients have been found to have sustained acute heart injuries. Moreover, in a review study was indicated that in approximately 5–25% of hospitalized COVID-19 cases, elevations in cardiac Troponin, as a biomarker of myocardial injury, have been reported. It is also shown that patients with acute myocardial injury were older, with a higher prevalence of preexisting cardiovascular disease (CVD) and more likely to require ICU admission. According to reports from China, up to 40% of patients admitted to hospitals with COVID-19 had preexisting CVD. Among patients with serious symptoms of COVID-19, it has been found that 58% suffered from high blood pressure, 25% had heart disease, and 44% of them suffered from arrhythmia.

The pathophysiology of patients with COVID-19

COVID-19 might have a direct and indirect effect on the cardiovascular system. The inflammatory process, cytokine storm, and lung injury that are linked to COVID-19. Patients with more severe disease and with another risk factor, such as increasing age, male sex, obesity, comorbidities, cancer, and ICU admission, are at higher risk of these events.

It has been proposed that there is a relationship between acute myocardial injuries induced by COVID-19 infection and angiotensin-converting enzyme-2 (ACE2). COVID-19 can damage

cardiomyocytes by identifying ACE2, receptor infections and triggering various inflammatory responses, and direct damage to infected myocardial cells *via* ACE2 receptors, found on these cells, may lead to an inflammatory storm and/or an imbalance of oxygen supply caused by ARDS. On the other hand, cardiovascular symptoms occur frequently in COVID-19 patients as a result of systemic inflammatory responses and immune system dysfunction during the course of disease development. It has been reported that myocardial injury can occur with COVID-19 infection due to a 'cytokine storm' that is stimulated *via* an imbalanced response involving Th1 and Th2 cells and can cause respiratory dysfunction, hypoxemia, shock, or hypotension, ARDS, heart failure, liver damage, renal failure, shock, as well as multi organ failure. In this line, hypoxemia, respiratory failure, shock, or hypotension caused by pulmonary infections typically results in an insufficient oxygen supply to myocardium. Because the burden on the heart is increased and there is an imbalance in the oxygen 'supply and demand', myocardial damage occurs during an infection, particularly for patients with chronic CVD. Moreover, one of the significant concerns is drug associated heart damage in the course of the COVID-19 treatment, especially with the use of antiviral medications.

Factors associated with **myocardial injury** include age, presence of comorbidities, ferritin and fibrinogen levels and kidney, liver or other organ dysfunction, especially kidney injury. Thus, optimisation of organ dysfunction is a key point in the treatment of COVID-19 with myocardial injury. Several theories have been put forward to explain the mechanism of myocardial injury including the complex interaction between hypoxaemia, ischaemia and the procoagulant state in the setting of pneumonia. The cytokine storm that results from uncontrolled viral infection can lead to acute coronary syndrome. Prior coronary disease leads to higher endothelial inflammation and can even cause plaque rupture. Viral infection can even activate the coagulation process and endanger the anticoagulant property of endothelium to form thrombus. Thus, by blocking the compromised cardiac blood flow it further exacerbates the injury.

Heart valves can also be affected by the virus, this effect has also yet to be fully understood and it is still questionable if COVID-19 can impair the function of the cardiac valves. Angiotensin-converting enzyme 2 (ACE2) acts as the gateway for the COVID-19 virus to the host cells. It is also widely seen in cardiac valves, especially the human aortic valve. Stenotic valves have an extensive abnormal expression of such receptors in macrophages. ACE2 cells in heart valves can be targeted easily by COVID-19 and can cause hindrance of normal blood flow in such valves. A cytokine storm can also indirectly damage the cardiac valves.

Cardiac arrhythmias are frequent and may remain even after recovery from COVID-19. Arrhythmias such as atrial fibrillation, ventricular and supraventricular tachycardia and

complete heart block can appear in any phase of the disease (infective, recovery or post-recovery phase). Another mechanism of arrhythmias in COVID-19 is multi-drug usage and their interactions. The pro-arrhythmic state - dysfunction and altered drug clearance also increases arrhythmogenicity. Additionally, some drugs used for treatment for viral replication prolong the QT interval. Thus, torsades de pointes may occur in susceptible patients treated with chloroquine/hydroxychloroquine, lopinavir/ritonavir, macrolides (especially azithromycin) and fluoroquinolones. Arrhythmia in these patients may also occur in the presence of prior heart diseases, electrolyte abnormalities and usage of other QT-prolonging drugs such as anti-emetics, proton pump inhibitors, sedatives.

In COVID-19, viral **myocarditis** is a common and important cause of myocardial injury and presents similarly to myocardial infarction with a rise of cardiac biomarkers, cardiomyopathy features on echocardiography and normal coronary arteries. It is often fulminat, and mostly self-resolving, though ccasionally it results in arrhythmias, heart failure, cardiac arrest and sudden death. The diagnosis of myocardiatis is relatively inaccurate because both tests and diagnostic protocols are lacking.

In different countries, data have also been given on myocarditis after the covid-19 vaccine, which occurred mainly after the second dose of the vaccine.

Approximately a quarter of hospitalised COVID-19 individuals were diagnosed with new-onset **heart failure**, especially in intensive care admissions (1/3 of admissions).

Condition also known as stress-induced cardiomyopathy, **Takotsubo cardiomyopathy**, can also occur in people with COVID-19.

The reduced ACE2 expression that occurs with COVID-19 enhance the influx of fluid into the heart muscle causing mild **myocardial edema**. This could be aggravated by systemic inflammation, also a feature of COVID-19.

Cardiogenic shock due to cardiac tamponade, acute decompensated heart failure, acute myocardial infarction and fulminant myocarditis can be observed.

Pericardial effusion and tamponade can occur as a consequence of COVID-19 infection. Early controlled invasive treatment of large pericardial effusions is necessary to prevent haemodynamic derangement. Pericardial tamponade as a reason for unexplained worsening in COVID-19 patients always has to be ruled out.

Long term consequences of COVID-19 on the heart

Follow-up clinical studies are starting to report the longterm COVID-19 consequences with many people still suffering from fatigue, dyspnea, and palpitations 3–6 months after the

recovery from acute infection. A German study suggested that 2 months after COVID-19 positivity, 78% of survivors had persistent heart involvement, of which 60% presented ongoing signs of myocarditis, revealed with cardiac magnetic resonance (CMR). Echocardiographic assessment of patients with recent COVID-19 may, as well, show abnormalities in terms of higher degrees of diastolic dysfunction, lower men values of LV, and presence of pericardial effusion, consistent with CMR findings, up to 2 months after COVID-19 recovery. The meaning of those imaging findings are currently unknown; however, persistent myocardial damage and fibrosis in the subacute and chronic phases after recovery suggest that COVID-19 may be an independent risk factor for the development of heart failure.

Assessment of cardiomyopathy in COVID-19

There is currnetly very little data to guide the optimal management of patients with COVID-19 disease who develop cardiomyopathy or mixed/cardiogenic shock.

1. Blood tests - Elevated serum troponin and NT pro-BNP identify patients at increased risk of death. Shows which patients are at greatest risk of developing cardiomyopathy or cardiogenic shock – unlikely to occur in the absence of elevated cardiac markers. C-reactive protein (CRP), ferritin, D-dimer, IL6 and LDH are markedly elevated in patients with profound systemic infalmmation in response to COVID19. These inflammatory biomarkers are also associated with poor prognosis.
2. ECG - With COVID-19 can include diffuse ST-elevations as seen in myopericarditis, nonspeciafic ST changes, low voltage in the limb leads and PVCs. Patient with COVID-19 can also present with STEMI often without evidence of coronary obstruction – perhaps secondary to myocarditis or direct cardiac injury from the virus.
3. Echocardiography - Can be useful to assess LV/RV structures and function, wall motion abnormalutues and to estimate cardiav hemodynamics. It is imortant to minimize sonographer time with COVID-19 positive patients to reduce the risk of spread, use POCUS (point-of-care-us). There is minimal role for TEE/MRI, both of which pose significant risk of aerosolization to the imaging team.
4. Pulmonary Artery Catheter Assessment (PAC) - PAC provide information about hemodynamic status and cardiac filling pressure. Although these data may be useful to direct inotropic and mechanical support in cardiogenic shock, the potential risk of exposure to privider limits the routine use. Rather than a PAC, hemodynamic monitoring in the most patients can consist of mBP (via an arterail line), central venous pressure assessment from a central venous catheter and monitoring of central mixed venous oxygen saturation.

5. Endomyocardial Biopsy - Though endomyocardial biopsy can be helpful in the diagnois of myocarditis, there is currently no evidence to support the use of this procedure in COVID-19, especially if the information would not change management.

Management of Cardiomyopathy in COVID-19

The mainstay of management patients with severe COVID-19 disease who have cardiac involvement is supportive care.

1. Avoid overaggresive fluid resuscitation given challenges with oxygenation (target CVP 6-8mm Hg). Higher preload (CVP 12-15) may also be desirable when significant RV dysfunction and/or high positive end-expiratory pressure (PEEP) states are present
2. Target MAP 60 – 65 mmHg – norepinephrine infusion for hypotension
3. Consider dobutamine in the setting of worsening hypotension with cardiac dysfunction
4. Epinephrine and vasopressin for refractory hypotension
5. Angiotensin II for refractory vasoplegia
6. Mechanica support – ECMO VV or VA
7. Anti-viral and anti-inflammatora therapies – hydroxychlorquine and azithromycin, anti-inflammatory therapy such as intravenous immune globulin (IVIG), tocilizumab, anakinra, iv steroids and antiviral treatment such as remdesivir, lopinavir and ritonavir. Further research into the cardiovascular and clinical outcomes with these treatments will be necessary to guide recommendations.

Influenza virus vaccines and cardiovascular disease prevention. The beneficial effects of the influenza vaccine in patients with CVD have been conclusively demonstrated in several epidemiological and clinical studies. Although this an area requiring further studies, the use of influenza vaccination might help to reduce symptoms of CVD in COVID-19 patients with concomitant CVD.

Conclusion

Unfortunately, there is still a lot to be learned about the effects of the COVID-19 virus. With acute cardiac injury due to COVID-19 there is likely to be a diverse response depending on mechanism of myocardial injury, severity of acute illness, therapy, hemodynamic response, host factors, immune-mediated factors and postrecovery care and follow-up. The future studies should provide data if the treatment for acute phase of illness such as antifibrotic therapy, anti-inflammatory therapy, cell-based therapy or antiviral therapy affects long-term as well as short-term cardiovascular outcome. The type of testing and cost-effectiveness of sreening tests for

post-COVID-19 myocardail dysfunction should be identified. Future studies will clarified whether there will be „post COVID-19 cardac syndrome“ and how best to manage patients recovering from COVID-19 cardiac involvement.

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SECONDARY INFECTIONS IN THE CRITICALLY ILL COVID-19 PATIENTS

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The SARS-CoV-2 (COVID-19) outbreak has emerged as a serious global health problem. Coexistence of bacterial or fungal infections as co-infection or super-infection are important factors that determine the prognosis of patients infected with viruses.

Why is there a predisposition to secondary infections?

Viral pathogens including but not limited to COVID-19 are known to weaken the host immunity and lay the groundwork for the development of secondary infections. Tissue destruction, enterocyte infection, high cytokine release and dysregulation, comorbidities predisposing to infections themselves such as diabetes mellitus, transplantation, etc. invasive medical devices during the ICU stay, epidemic-induced emergency states causing less than ideal infection control measures, severe lymphocytopenia, acquired immunosuppression and bacterial translocation all contribute to the increased rates of secondary infections. Respiratory viral infections may alter innate immune function in affected pulmonary tissue, promoting bacterial growth. Pus-filled pulmonary alveoli create a nutritive environment for bacteria such as *Pseudomonas aeruginosa* and *Staphylococcus aureus*. Macrophages are overwhelmed by already increased burden of apoptotic cells and thus become limited in their capacity to phagocytose bacteria. Both dendritic cells and macrophages have diminished antigen-presenting ability. Viral lung infection modifies the respiratory tract microbiome and altered epithelial cells disrupt the mucocilliary clearance. B cell are depletion has been reported in bone marrow and spleen of COVID-19 deceased.

Superinfection rates and causative organisms:

The reported respiratory co-infection/super-infection rates are highly variable (5-29%). In different retrospective series, 3-8% community acquired coinfections and 11% hospital acquired superinfections rates were reported. Superinfections were identified in 13.5–44% of ICU patients. Empiric broad spectrum antibiotic use, immunomodulant drugs such as steroids anti cytokine therapies, use of mechanical ventilation are predictors of superinfections.

Many different types of bacteria (*S. aureus, P. aeruginosa, S. pneumonia, Klebsiella spp., E. coli, S. maltophilia, Enterobacter, H. influenza, M. catarrhalis)*, viruses (Influenza virüs, CMV, HSV, EBV and fungi were detected as the cause of secondary infections in COVID-19 patients.

In our early series (182 COVID PCR positive patients) from Hacettepe Anesthesiology COVID ICU, we detected 36% coinfections and 32% superinfection. *Enterococcus spp* (15%) was the most common agent in the bloodstream, *Candida* spp. (32%) in the urinary tract, *Acinetobacter (*32%) in the respiratory tract, and *E.coli* (11%) in the catheter related bloodstream infections

were the other common microbial agents. *Aspergillosis* (35%) was the most common opportunistic infection, followed by *Pneumocystis jiroveci* (11%) and CMV (9%). Both median length of ICU stay and mortality rates were higher in the secondary infection groups than in the group without any additional infection.

There are many problems with the diagnosis of bacterial coinfections. Most important of all; the isolated bacteria are from nasopharyngeal samples, not from bronchoalveolar lavage therefore it is difficult to differentiate colonization from infection. *M. tuberculosis*-COVID-19 coinfections are also reported and the mortality was likely to occur in elderly patients with comorbidities. Superinfections by antibiotic-resistant bacteria occur in 1.3% in ICU but are associated with a very high mortality rate. In a study from Switzerland in 220 SARS-CoV-2 patients, the median time to respiratory tract infection was around 12.5 days, and the time to blood stream infection was about 14 days. Antibiotic or antifungal treatment was given in 44% of those patients.

Blood stream infections in critically ill patients with COVID-19 increased the mortality risk. The rate of ventilator associated mortality has been reported to be 54%, with a 44% mortality rate. The causative organisms were multi-drug resistant (MDR) in 67% of cases. Carbapenem-resistant *K. pneumoniae*, A. baumannii, MRSA have all been reported as MDRs of concern.

Invasive pulmonary aspergillosis (IPA):3.3-36%. Fungi of the genus Aspergillus are frequently isolated. However, it is difficult to determine whether this is just a colonization or a true infection.

Biomarkers (C-reactive protein, procalcitonin) levels are commonly followed up during COVID-19 disease but they are of limited value. Immunomodulatory treatments increase the rate of superinfections as well as they considerably reduce the value of C-reactive protein and procalcitonin to detect secondary bacterial infections in COVID-19 patients. Clinicians should suspect and search aggressively for secondary infections in any clinical deterioration in during COVID-19 infection. Thorax CT can be used for determination of the typical infiltrate associated with bacterial or fungal superinfections. Other infections such as urinary tract infections, skin and soft tissue infections, intraabdominal infections etc., should also be considered. Appropriate microbiological tests should be obtained.

Standard measures should be taken to prevent ventilator associated pneumonia (VAP). If during COVID-19 treatment, a secondary respiratory worsening occurs, one should re-consider the use of antibiotics after taking adequate respiratory samples and performing radiological diagnostics. Hyperinflammatory phase (adaptive immune reaction), cardiogenic failure (myocarditis is common), pulmonary embolism, fluid overload should also be ruled out.

Treatment:

Hand hygiene, infection control surveillance, antimicrobial stewardship, environmental disinfection, and waste separation should be carried out at least as for patients without COVID-19. The prevalence of bacterial infection varies depending on the country and on the time after

the onset of symptoms. Despite low rates of confirmed bacterial infections, there has been widespread use of empiric antibiotics especially at the early stages of COVID-19 infections, which may result in infections with MDR organisms. Therefore; the prescription of antibiotics for patients with suspected or confirmed mild COVID-19 with a low suspicion of a bacterial infection is not recommended. Antibiotics should be administered to the patients with the most severe presentations. Antibiotic treatment should be rapidly re-evaluated, stopped or switched to an oral form, duration should not exceed 5 days. Once-a-day administration or continuous administration of Beta-lactams should be considered to decrease the use of personal protective equipment. Macrolides and quinolones should be avoided because of their cardiac side effects. If atypical coverage is necessary (e.g. COVID-19 not yet confirmed and suspicion of Legionella infection) then doxycycline is given.

The choice of empiric regimens should take into account possible side effects (*e.g.* QT prolongation, diarrhea), local epidemiology of drug resistance, and impact of drug resistance on the patient. Antimicrobial stewardship programs, infection prevention and control measures can reduce the microbial load, circulation of pathogens, with a reduction in dissemination of antimicrobial resistance.

Conclusion

Higher clinical suspicion for secondary infections is needed in COVID-19 patients because these secondary infections negatively affect COVID-19 infected patients' outcomes. Effective infection prevention and control measures together with antimicrobial stewardship programs are essential during COVID19 pandemic.

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COVID 19, ANTIBIOTIC STEWARDSHIP AND ANTIMICROBIAL RESISTANCE IN INTENSIVE CARE UNITS, CASE REPORT

Vesna Cengic, Nermin Ismic

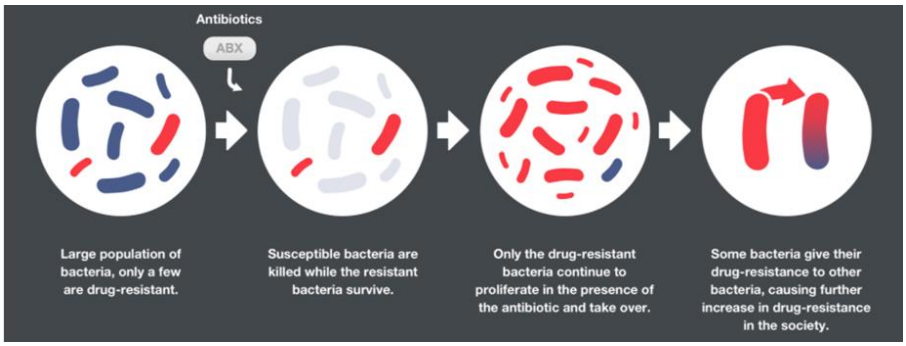
Background

Since the beginning of the coronavirus disease 2019 (COVID-19) pandemic, the official number of infected people in BiH is 269,000, and there have been >12,000 death cases. The average mortality rate in BiH is 4.4%, while in the world it is 1.9% (1,2). Intensive care unit (ICU) admission rate among hospitalised COVID 19 patients varied among different studies between 6-19% (3,4). Because high burden of antimicrobial resistance and high incidence rate of Multi drug resistant (MDR) organism in ICU antimicrobial stewardship is an integral part of ICU patient treatment.

Among patients with COVID-19, the most common clinical manifestations are fever, cough and dyspnea, regarding laboratory findings it is elevated C-reactive protein (CRP) and lactate dehydrogenase (LDH) serum levels. Those requiring hospitalisation usually have bilateral radiological infiltrates (5). These are all hallmarks of community acquired pneumonia and therefore, most doctors start treatment with antibiotics even though COVID-19 is a viral disease. The reason for frequent antibiotic therapy also seems to be earlier studies that have reported a high rate of co-infection or secondary bacterial pneumonia (11–35% of cases) in hospitalized influenza patients caused mostly by Streptococcus pneumoniae and Staphylococcus aureus (6). But for COVID-19 the incidence rate for bacterial co-infections is lower; a retrospective cohort study in a UK secondary-care setting showed that only 3.2% had early confirmed bacterial isolates identified (0-5 days after admission), rising to 6.1% throughout admission (7).

This excessive prescription of antibiotics and long duration of treatment leads to increased antibiotic resistance. Antibiotic resistance occurs as bacteria adapt to the continuous presence of antibiotics. Since many of the antimicrobial compounds are naturally produced molecules, bacterias living among them had to find a way to fight them in order to survive. Because of this bacterias are „intrinsically“ resistant to one or more antimicrobials. But in the clinical setting the problem is the “acquired resistance” in a bacterial population that was originally susceptible to the antimicrobial compound. This kind of resistance occurs due to changes, or mutations, in the DNA of the bacteria, or the acquisition of antibiotic resistance genes from other bacterial species through horizontal gene transfer (8).

In a large population of bacteria only a few (probably <1 in 1,000,000) have natural resistance to a given antibiotic (9). If this antibiotic is used for too long and too often, antimicrobial resistance will develop. As we see in picture 1 horizontal gene transfer of resistance mechanisms seems to be the mechanism of acquiring antibiotic resistance. There is also evidence that antibiotics can induce hypermutation in bacteria and exacerbate resistance. Antibiotics are not only selectors for resistance but are also promoters (10).



Picture 1. How does antimicrobial resistance develope (11)

Patients who are infected with resistant bacteria are more difficult to treat, sometimes impossible; they require longer hospitalization and have higher mortality risks. These multidrug resistance bacteria have to be treated with more expensive medications because they are resistant to the first line antibiotics. All this increases healthcare costs and is an economical burden for society. According to the antibiotic resistant thread report 2019 from the Center for Disease Control and Prevention (CDC) more than 2.8 million antibiotic-resistant infections occur in the U.S. each year, and more than 35,000 people die as a result (12). World Health Organisation (WHO) has declared that antimicrobial resistance (AMR) is one of the top 10 global public health threats facing humanity (13).

Another problem of antibiotic overuse is *Clostridium difficile* infection. Exposure to two or more antibiotics increases the chance of *clostridial* infection (14). CDC says that one in 11 people over age 65 diagnosed with a healthcare-associated *C. difficile* infection die within one month (15).

Antibiotic stewardship is an apt descriptor of related activities that help optimize antimicrobial therapy, ensuring the best clinical outcome for the patient while lowering the risk of subsequent development of antimicrobial resistance (16).

Intensive care unit (ICU) antibiotic stewardship is composed of rapid identification of patients with bacterial infections, better empirical treatment selection, using pharmacokinetic-pharmacodynamic (PK-PD) characteristics to optimize antibiotic dosing and administration modalities, de-escalation once culture results become available, shortening therapy duration, and educing the numbers of patients treated unnecessarily (17).

Studies showed that one of the most effective interventions to reduce mortality in patients with sepsis is early administration of appropriate antimicrobials (18-20). Therefore, for adults with possible septic shock or a high likelihood for sepsis, Surviving sepsis campaign recommends administering antimicrobials immediately, ideally within one hour of recognition. It is recommended that appropriate routine microbiological cultures (including blood) should be obtained before starting antimicrobial therapy in patients with suspected sepsis and septic shock if it results in no substantial delay in the start of antimicrobials (i.e., < 45 min) (21).

In the ICU setting it is not possible to contribute high blood Procalcitonin (PCT) concentrations only to bacterial infection because there are various non-septic conditions in ICU-patients which can be the cause of high PCT: major trauma, surgery, acute respiratory distress syndrome, multiorgan failure, cardiogenic shock, severe burns etc. (22-24), so it is not recommended using PCT to guide antimicrobial initiation in addition to clinical evaluation (21,25).

As mentioned earlier, one of the most important interventions in treating sepsis is choosing the right empirical antibiotic. First all hospitals should regularly generate and disseminate a local antibiogram specific to their intensive care population (25). In patients with suspected sepsis and VAP and high risk for multidrug resistant (MDR) organisms, it is recommend to include coverage for *Methicillin-resistant Staphylococcus aureus (MRSA)* and two antimicrobials with gram-negative coverage for empiric treatment over one gram-negative agent (21,25).

Empirical coverage for *MRSA* should be initiated in patients being treated in units where >10%–20% of *S. aureus* isolates are methicillin resistant, and in patients in units where the prevalence of *MRSA* is not known (23) or in patients with risk factors for *MRSA*: prior history of *MRSA* infection or colonization, recent IV antibiotics, history of recurrent skin infections or chronic wounds, presence of invasive devices, hemodialysis, recent hospital admissions and severity of illness (21,26,27).

Double gram-negative coverage is rarely necessary except for patients with highly resistant organisms (28).

ICU patients have altered pharmacokinetic (PK). Antibiotic doses recommended for other groups of patients are most likely insufficient for ICU patients due to to increased volume of distribution and decreased elimination. These PK changes can result in insufficient serum aminoglycosides or β-lactam concentrations (or both) when standard doses are administered, emphasizing the need to change to more personalized antibiotic dosing: prolonged infusion over intermittent boluses, carefully monitoring peak levels and antibiotic concentration during the course of therapy when treating resistant pathogens (17,29,30).

Antimicrobial therapy can be de-escalated once respiratory tract, blood, or other specimen culture results become available, if the isolated pathogen is not an resistant organism (for example, *P. aeruginosa, Acinetobacter spp.*, or *MRSA*) or if the organism is sensitive to a narrower-spectrum antibiotic than that prescribed empirically (21,25).

For adult septic patients it is suggested to use short-course over long-course antimicrobial therapy (21), and for patients with hospital acquired pneumonia (HAP) and ventilator associated pneumonia (VAP) it is recommended to use 7-day therapy over longer duration (25). Systemic reviews of randomized control trials (RCT) for HAP/ VAP (31) and RCTs for urinary tract infections (32), bacteremia (33,34), and intraabdominal infections (35) showed that the shorter course was just as effective as the longer course in terms of increased 28-day antibiotic-free days, reduced recurrent VAP due to MDR pathogens, microbiological failure, and mortality; but associated with fewer adverse consequences.

PCT levels plus clinical criteria should be used to guide the discontinuation of antibiotic therapy, rather than clinical criteria alone (21,25). A meta-analysis performed by the Surviving Sepsis Campaign suggested improved mortality and lower antibiotic exposure in patients who were managed using procalcitonin versus control while there was no effect on length of stay in ICU or hospital (21).

Despite existing guidelines, hospitals still face significant problems with inappropriate antimicrobial use. The enforcement of clinical practice guidelines and protocols, implementing antibiotic stewardship activities and raising awareness about harmful effects of antIbiotics are necessary in reducing antibiotics resistance. We present a case which illustrates the problem of irrational use of antibiotics in an intensive care unit.

Case presentation

We present a case of a 56-year-old patient with coronavirus disease who was admitted to the ICU because of severe acute hypoxemic respiratory failure.

In the earlier course of treatment, he was given therapeutic doses of low molecular weight heparin (LMWH), dexamethasone 6 mg, fluconazole, clarithromycin and ceftriaxone in a duration of 10 days. In addition to that, on the 11th day of his illness he was prescribed tocilizumab in a dose of 8 mg/kg.

Noninvasive ventilation (NIV) was applied immediately upon admission to the ICU. Because of worsening of acute hypoxemic respiratory failure, worsening of radiological findings on chest X-ray, and elevated total leukocyte count (13.5×109/L) and neutrophil count (94.9%), 48 hours after admission to the ICU, a multiplex PCR test was performed on a sputum sample, which identified Acinetobacter baumannii. Treatment with cefepime intravenously and colistin nebulization was started. After a few days antibiogram for the sputum sample showed that

Acinetobacter baumannii is intermediary sensitive to cefepime and ampicillin/sulbactam and resistant to carbapenems, so the dual antibiotic therapy was continued for 15 days. Dexamethasone was substituted with methylprednisolone, 250 mg on the first day followed by 80 mg twice a day; the dose was tapered in the following days and methylprednisolone was discontinued after 10 days.

At the end of the dual antibiotic therapy, the patient had diarrhea and Clostridium difficile was identified as the causative microorganism. The patient was first given metronidazole, and later on vancomycin per os. After the course of dual antibiotic therapy, Acinetobacter baumannii was identified in the obtained urine cultures, but because there were no systemic signs of infection, therapy was not initiated, only the indwelling urinary catheter was removed. After over 30 days of treatment in the ICU, 15 days on NIV and then on high flow nasal cannula, slowly lowering flow and FiO2, the patient was discharged to the medical ward.

Conclusion

Excessive prescribing and use of antibiotics during a Covid-19 pandemic increases antimicrobial resistance, a problem that has already reached crisis proportions worldwide.

In addition to preventing the spread of covid 19 among patients and health care givers in hospitals, about which we have learned a lot since the beginning of the pandemic, we should also focus on the prevention of superinfections and the antibiotic stewardship because of the evolving problem of antimicrobial resistance.

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THE DECISION TO INTUBATE COVID 19 PATIENT: TIMING AND DIFFICULTIES

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Introduction

More than 250 million people has been infected and more than 5 million died due to COVID 19 since the March 2nd 2020, when the World Health Organization declared it pandemic disease. Although majority of patients are known to recover uneventfully, a number of those who will seek for hospital care and eventually intensive care for respiratory failure, oxygen treatment and mechanical ventilation, is substantial. This very often overwhelms health care system and hospitals, leading to a tremendous burden for the health care providers.

The major morbidity and mortality from COVID-19 is due to acute viral pneumonia that evolves to acute hypoxic respiratory failure. Respiratory support is often required, and the optimal patient management is still unknown. Different strategies following different protocols have been used with variable success: from the use of different level of supplemental oxygen including high-flow systems, noninvasive ventilation, adjunctive and rescue therapies, such as prone positioning in both awake or intubated patients, to intubation and invasive mechanical ventilation.

Although experience in management of Covid 19 patients has led to more knowledge and adjustments of clinical practice, pathophysiology of illness is still not well understood. Also, it is not easy to compare results between institutions; there is a huge difference in equipment, supplies, organization, infrastructure and work force. Patient selection, appropriate monitoring and level of care are important in effective delivery of respiratory care, which may affect outcome. Because of that, it is very difficult to establish winning strategy in the management of COVID-19 hypoxic respiratory failure.

Noninvasive respiratory oxygen support

In the early phases of pandemic, concerns for aerosol generation and infection control led to the use of early intubation and invasive mechanical ventilation as the initial strategy for treatment of hypoxia in COVID-19 patients. In addition, early endotracheal intubation was recommended to limit the risk of prolonged intense respiratory efforts that might lead to patient self-induced lung injury (P-SILI). Soon, it became clear that pathophysiology of respiratory failure and pneumonia in COVID-19 has different phenotypes: L type (Low elastance, V/P ratio, lung weight and lung recruitability) or H type (High elastance, high right to left shunt, lung weight and lung recruitability). It was speculated that different phenotypes might need different respiratory management. Further, P-SILI as a clinical entity is not very

clearly defined and not all potential negative mechanisms are well documented. Deleterious effects are suspected only in the subset of the most severe ARDS, where pathophysiology of illness is not comparable to COVID-19, at least in stage when noninvasive support is applied. COVID-19 respiratory failure is dominantly hypoxic with sustained compliance and applying mostly high FiO2 and PEEP, with limited support of the spontaneous breaths, could limit tidal volume and respiratory effort which may actually be beneficial.

Invasive mechanical ventilation has a long history of known complications, which could also have negative impact on outcome. Altogether, there is no enough evidence to support early intubation in order to avoid P-SILI. However, the most challenging step is timing of the initiation of invasive mechanical ventilation.

Timing of intubation and initiation of mechanical ventilation

It is now suggested in literature that a trial of noninvasive support modalities (NIV) should be applied before patient is considered for intubation and invasive mechanical ventilation. With this strategy a number of unnecessary intubations may be avoided. Some step-up approach protocols, with gradual increase of respiratory support are common; depending on the institution, progressing from high flow nasal oxygen (HFNO) to different modalities of noninvasive ventilation (helmets, face or full-face masks) has been implemented.

Instead of early intubation, more individualized approach and timely intubation are now preferred. Both premature or delayed intubation should be avoided. However, decision to intubate is challenging and involves clinical judgment. Close monitoring of the respiratory function and overall clinical status is recommended. High risk patients are those that are unstable and deteriorate in spite of applied respiratory support:

1. Patients with rapid progression over hours
2. Patients with a persistent need for high flows/fraction of inspired oxygen (eg, >60 L/minute and an FiO2 >0.6)
3. Patients with hypercapnia, increasing work of breathing, decreasing tidal volume, worsening mental status, increasing duration and depth of desaturations
4. Patients with hemodynamic instability or multiorgan failure

Military Medical Academy protocol for respiratory support in patients with Covid 19

In April 2020, before specialized COVID-19 hospital of the Military Medical Academy started with patient admission, a protocol for the gradual increase of respiratory support has been developed. The following step-up approach has been defined:

1. If the patient has SpO2 <90% on the first assessment at the admittance in the intensive care unit, noninvasive respiratory support is recommended,
2. Initiation of NIV (FiO2 100%; PEEP 5; Asb 0) is the first step of the respiratory support
3. Full Face masks are the first choice

4. Guidance for the increase or decrease of the support are SpO2 and respiratory rate (RR) monitoring
5. If SpO2 > 93% and RR < 30 (and decreasing) no change in respiratory support is needed
6. If patients show no improvement, addition of Asb 3-10 and/or increase PEEP may be tried
7. If no improvement and further deterioration in respiratory distress is present (predominantly high RR) intubation is indicated
8. HFNO as the first choice is selected only if SpO2 > 93% or patients have episodes of short hypoxia on admission
9. Intention is to try to avoid intubation, however, with no challenge on patient safety or delaying invasive mechanical ventilation if indicated.

After analyzing effect of applied strategy in the first 85 consecutive patients admitted to the ICU, it was revealed that predictors other than respiratory parameters may be of importance in predicting failed noninvasive respiratory support. Patients with more inflammation and cell damage (higher values of LDH, CRP and D-dimer) were more likely to predict fail of noninvasive respiratory support. Multivariant logistic regression identified LDH as the only independent predictor of failed NIV (Exp(B) 1.011; 95%CI 1.002-1019).
Also, there was no proven infection of medical staff in the red zone

Conclusion

Establishing a winning strategy in respiratory support for the acute hypoxic respiratory failure is still debatable. Moving away from early towards well-timed intubation, after a trial of noninvasive respiratory support has been suggested. Although more strong evidence is needed, it seems clear that decision to intubate should be individualized and based on clinical indicators.
Although respiratory support is in the focus of patient management, other determinants of severity of illness may be useful in predicting failed noninvasive respiratory support and worse outcome.

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CLINICAL CHARACTERISTICS, COMORBIDITES AND MORTALITY IN CRITICALLY ILL MECHANICALLY VENTILATED PATIENTS WITH COVID-19

Adisa Sabanovic

INTRODUCTION

From the first case in December 2019 in China to pandemic in March 2020 with more than 120 milion confirmed cases and more than 2.8 milion deaths, making this pandemia one of the deadliest in history. The spectrum of clinical features of COVID-19 infection in the intensive care unit (ICU) varies from mild pneumonia to a critical condition with acute respiratory distress syndrome (ARDS). Previous studies have described the epidemiological characteristics, clinical presentation, and outcomes of patients with COVID-19 pneumonia.

Approximately one in ten patients with SARS-CoV-2 becomes symptomatic. Symptoms of COVID-19 are highly variable, ranging from asymptomatic, mild, or severe pneumonia–like symptoms. A large number of COVID-19 pneumonia leading to ARDS and it is usually developed at day eighth or ninth after symptoms onset. Reportedly, in the most studies from Europe and North America 10-20% of the patients admitted to hospital were diagnosed with ARDS and they have been treated with different forms of mechanical ventilatory support according on level of respiratory failure, clinical condition and duration of illness. Mortality of patients with COVID19-pneumonia, especially the one with the most severe form of ARDS when invasive mechanical ventilation (IMV) has been required, is extremely large, and it is up to 40.5%.

A large number of patients hospitalized in ICU with COVID19 pneumonia have comorbidities that negatively affect the prognosis of the disease.

PATIENTS AND METHODS

This observational, retrospective, cross-sectional study was conducted between July 2020 and February 2021 in the Department of Anesthesiology and Intensive Care Unit at the Cantonal Hospital Zenica, Bosnia and Herzegovina.

Study included 92 adult patients with positive SARS-CoV 2 polimerase chain reaction (PCR) of nasopharingeal swabs,. All observed patients were invasively mechanically ventilated due to Covid-19 ARDS. Patients with milder form of ARDS treated only with noninvasive ventilatory (NIV) suport measures were excluded from the study.

After admission at the ICU, the treatment of the patients followed internal institutional protocol made by the council consists of an inernist, an infectologist and an aneshesiologist. The drug therapy included corticosteroides, anticoagulants, proton pump inhibitors, probiotics and vitamin supportive therapy. Efforts were made to avoid intubation where feasible using NIV suport measures and including prone positioning. The patients were selected for IMV by

attending anesthesiologist according to the criteria. Ethical Committee of the Cantonal Hospital Zenica was approved this investigation. All data were collected from the ICU electronic medical report and included: demographic ata, comorbidites, clinical symptoms and signs, and laboratory data.

Demographic data involved age and gender.

Observed comorbidities were: diabetes mellitus, hypertension arterialis, chronic obstructive pulmonary disease (COPD), chronic heart disease, cerbrovascular disease (CVD) and malignant disease. Additionally, a correlation of the prevalence of individual comorbidities with fatal outcome was analysed.

Clinical symptoms were recorded on the day of admission at hospital: cough, dyspnea, chest pain, exhaustion, abdominal pain, diarrhea, nausea, vomiting, anorexia, headache, anosmia and myalgia. Clinical singns included temperature, heart rate, systolic and diastolic arterial pressure.

Laboratory data included blood glucose level, capillary oxygen pressure and capillary carbon dioxide pressure. Blood samples were taken on the day of hospital admission, on the day of starting NIV suport measure and on the day of endotracheal intubation and starting IMV

. **RESULTS**

Average age of the patients was 60.05 years. Patients over 50 years, 71 (77.1%) (p=0.000), and males, 62 (67.4%; p=0.001) were predominated. The most common patient symptoms were exhaustion, myalgia, dyspnea and cough. Hyperthermia was recorded on the day of hospital admission. Tachycardia, hyperglycemia, hypoxemia were recorded at all observed study times. The most common comorbidity was hypertension arterialis with a very strong correlation with fatal outcome, followed by diabetes mellitus and chronic heart disease that were moderately correlated with fatal outcome.

DISCUSSION

In this observational, cross-sectional study, the demographic data, clinical symptoms and signs, laboratory data and comorbidities were retrospectively analyzed among 92 patients with COVID-19 pneumonia admitted to the ICU, mechanically ventilated and with fatal outcome. Average age of 60 years was strongly associated with poor prognosis. On the other hand, results found in the United States showing the median age of 47 years was associated with deterioration of respiratory status of the patients. The number of males in our study was significantly higher than females. In our study, the highest prevalence of exhaustion, myalgia, dyspnea, cough, anorexia and chest pain was recorded in elderly; up to 90% of patients have more than one symptom, as it was previously reported.

In our study, regarding clinical signs, hyperthermia was observed only on the day of hospital admission, indicating the following of protocol regarding of antipyretic and anti-inflammatory drugs during hospital treatment.

Hemodynamic instability in the form of tachycardia persisted at all observed time periods in our study as a compensatory response to the ongoing inflammatory process, hyperthermia,

hypoxemia and consequent hypoperfusion in patients with COVID-19 pneumonia. Hemodynamic instability is supported by the comorbidities of the observed patients and the damage of the heart muscle due to COVID-19 infection.

Despite therapeutic administration of insulin, hyperglycemia was also maintained throughout all three observed time periods in our mechanically ventilated patients with fatal outcome. This could be a sign of poorly regulated disease in patients with previously reported diabetes mellitus. In patients without diabetes mellitus, hyperglycemia can be classified as the result of a strong stress response to the inflammatory process, new-onset diabetes, unrecognized pre-diabetes or direct effect of the corona virus on the pancreas.

We found low level of capillary oxygen pressure at all three time periods, regardless of the different types of respiratory support administered. Severe hypoxemia, despite the application of mechanical ventilation, indicates a serious damage to the respiratory membrane due to COVID-19 infection, consequent ARDS, and poor outcome.

Studies have shown a higher mortality rate in COVID-19 patients with pre-existing conditions compared to patients without comorbidities. The most common comorbidities are hypertension, diabetes mellitus, cardiovascular diseases, arthritis, stroke and cancerous conditions. The presented study confirmed a very strong correlation of hypertension with a poor clinical outcom, and it was found in 56.5% patients, either as a single or in combination with other comorbidities. In our study, diabetes mellitus was recorded in 37.0% patients resulting in a moderate correlation with fatal outcome. History of COPD was revealed in 14.1% patients in our research resulting in moderate correlation with fatal outcome. Patients with COPD already have a disrupted anatomical-physiological component of the lung and increased vulnerability to severe forms of COVID-19 infection.

Chronic heart disease was noted in 16.3% patients in our study and a correlation with fatal outcome was moderate. History of CVD was recorded in 12% patients in our study with moderate correlation with fatal outcome.

CONCLUSION

Treatment of COVID-19 patients in ICU with mechanical ventilation has a high failure rate. Demographic data, clinical symptoms and signs as well as accompanying comorbidities can be a significant component in making decisions about diagnostic-therapeutic procedures.

PREDICTIVE FACTORS FOR NONINVASIVE MECHANICAL VENTILATION FAILURE AMONG COVID-19 CRITICALLY ILL PATIENTS - A RETROSPECTIVE COHORT STUDY

Mirza Kovacevic

INTRODUCTION

COVID-19 virus is a new, predominantly respiratory virus, first recognized in China, in December 2019. Severe clinical condition with acute respiratory failure (ARF) caused by COVID-19 virus poses a serious threat to citizens and healthcare systems or professionals. About 15-30% of patients with COVID-19 viral infection deteriorate to acute respiratory distress syndrome (ARDS) within the first two days of hospital admission and require some type of respiratory support. Conventional oxygen therapy by face mask, high-flow nasal oxygen, NIV or invasive mechanical ventilation (IMV) are used in the treatment of hypoxemic ARF observed in COVID-19 viral infection. The IMV requires endotracheal intubation, which is associated with major medical complications, and which leads to significant medical costs. The NIV is one of the first-line therapies in order to avoid endotracheal intubation in patients with ARDS. Limited data described a high rate of NIV failure in a previously reported ARF caused by other types of coronavirus infections, such as Middle East respiratory syndrome corona virus (MERS-CoV) or severe acute respiratory syndrome corona virus (SARS-CoV). Related factors that may impair ventilation and respiratory mechanics in NIV-treated patients and contribute to endotracheal intubation have not been precisely identified. Some studies have described risk factors for the requirement for NIV support in critically ill COVID-19 patients, but predictive factors for NIV failure are not sufficiently investigated. There is no consensus among anaesthesiologists on acceptable predictors for NIV failure. The aim of this study was to define predictive factors for NIV failure and the necessity of endotracheal intubation among COVID-19 critically ill patients, regardless of the severity of hypoxemia, clinical respiratory variables, or ventilation variables. We evaluated the predictive value of demographic parameters, clinical signs and symptoms, clinical index and scores, duration indicators, laboratory and radiological findings and created a corresponding model for prediction of NIV failure.

PATIENTS AND METHODS

This single centered retrospective cohort study was conducted over the period of seven months, between July 2020 and February 2021. During the observed period, 186 patients were admitted to the ICU with COVID-19 ARF, 73 adult patients fulfilled the study criteria and were included in the study. Inclusion criteria were patients with a positive reverse transcription polymerase chain reaction of nasopharyngeal swab samples for SARS-CoV-2, admitted to the ICU, presented with hypoxemic ARF and treated with NIV. Electronic data from the ICU medical reports were used. The patients were divided into two groups: Group 1 (54 patients, negative NIV outcome), patients whose ICU treatment started with NIV but required endotracheal intubation and invasive mechanical ventilation and Group 2 (19 patients, positive NIV outcome), patients whose ICU treatment started with NIV and finished successful weaning from NIV. One hundred and thirteen patients were excluded from the study due to non-fulfilment of

the study criteria. Exclusion criteria were: the patients treated with conventional oxygen therapy by face mask, the patients treated with NIV less than 24 hours, the patients with severe ARDS who required immediate endotracheal intubation, unconscious patients and other contraindications for NIV.

Ventilation strategy. Initial continuous positive airway pressure (CPAP) was delivered to the patient using an NIV mask with pressure values of 5-10 cmH2O. If hypoxemia (PaO2 <50 mmHg**)** or desaturation (SpO2<80%) persisted after NIV administration, the positive end-expiratory pressure (PEEP) was increased for 1-2 cmH2O, or inspiratory pressure was increased for 2-3 cmH2O to receive an inspiratory volume of 6-8 mL/kg. In the case of further exacerbation, when patients met the criteria for endotracheal intubation (severe acidosis pH <7.25; severe hypoxemia PaO2 <50 mmHg or impaired consciousness), IMV was used as the main ventilator support. In contrast, successful respiratory support with NIV was based on improving general clinical condition of the patient, respiratory and heart rate, mental state and improving the gas exchange index.

Pharmaceutical strategy. All patients were treated according to the diagnosis and treatment protocol of the new coronavirus infection. The therapy included corticosteroids, anticoagulants, proton pump inhibitors, and vitamin supportive therapy. Antiviral therapy antibiotics and immunomodulatory therapy in consultation with an infectologist, according to clinical status and laboratory findings.

Patients variables. The following variables were analysed: demographic parameters, clinical symptoms and signs, clinical index and scores, duration indicators and laboratory data. Demographic parameters involved age and gender. Clinical symptoms and signs included: fever, cough, dyspnoea, chest pain, weakness, abdominal pain, diarrhoea, nausea, vomiting, headache, anosmia, myalgia, anorexia, heart rate, mean arterial pressure (MAP) and temperature. Clinical index and scores: Charlson Comorbidity Index (CCI), Simplified Acute Physiology Score II (SAPS II) and Acute Physiology and Chronic Health Evaluation II (APACHE II). Radiographic Assessment of Lung Edema Score (RALES) was performed in two following time: T1- on the day of admission to the ICU and T2- on the day of starting NIV. Evaluated duration indicators were measured in days: length of symptoms to the day of hospitalization, length from admission day to starting of NIV, length of NIV and overall length of hospitalization. Laboratory data consisted of blood count, biochemistry and immunology data. Blood samples for blood count and biochemistry parameters were taken in three following time periods: T1- on the day of admission at ICU, T2- on the day of starting NIV and T3- on the day of endotracheal intubation for Group 1 or on the day of successful weaning from NIV for Group 2. Blood samples for analysis of immunological parameters C-reactive protein (CRP) and procalcitonin (PCT) were taken in two following time periods: T1- on the day of admission at ICU and T2- on the day of starting NIV.

RESULTS

There were statistically significantly more males versus females, 49 and 24, respectively ($p<0.01$). The mean age of the patients was 65.3 (±9.81) years. The NIV was applied with an overall success rate of 26%. The presence of dyspnoea, anorexia and increased MAP on the day of admission at hospital, higher RALES on the day of starting NIV and higher length of NIV

showed a statistically significant predictive value for NIV failure (p<0.05). The CCI score was statistically significantly higher in the Group 1 than in the Group 2 (3.37% versus 1.68%; p<0.045), but a predictive value for NIV failure was not recorded. Higher mean value of urea and creatinine were recorded in the Group 1 compared with the Group
2 (14.84 versus 9.77 and 110.87 versus 63.68, respectively) on the day of starting NIV as well as higher mean value of creatinine (140.40 versus 87.47) on the day of starting IMV. Increased mean value of urea and creatinine on the day of starting NIV as well as increased mean value of the creatinine on the day of starting IMV showed statistically significant predictive value for NIV failure (p<0.05). After multivariate stepwise logistic regression analysis of the parameters independently associated with NIV failure, the presence of dyspnoea on the day of admission to hospital (p<0.004), the RALES on the day of starting NIV (p<0.001), the length of NIV (p<0.025) and the mean value of urea on the day of starting NIV (p<0.004) were included in the predictive model of NIV failure (Table 1). The most important predictive factor in the proposed model of NIV failure was increased mean value of urea on the day of starting NIV (sensitivity 70.44%, specificity 73.72%; p<0.004) (Table 2).

Table 1. Multivariate analysis of the parameters independently associated with noninvasive ventilation failure

Parameters	Multivariate analysis			
	p	OR	95% CI	
			Lower	Upper
Dyspnea	0.004	0.08	0.00	0.91
Anorexia	0.356	2.52	0.34	18.76
MAP	0.067	1.48	0.98	2.28
RALES T2	0.001	1.18	1.06	1.30
LNIV	0.025	0.54	0.31	0.92
Urea T2	0.004	0.09	0.01	0.47
Creatinine T2	0.597	0.61	0.10	3.77
Creatinine T3	0.698	1.46	0.21	10.07

Table 2. The receiver operating characteristic curve (ROC curve) data of predictive model for noninvasive ventilation failure

Parameters	AUC	Sensitivity %	Specificity %	Cut off	p	95% CI	
						Lower	Upper
Dyspnea	0.64	44.40	84.20	0.50	0.05	0.50	0.79
RALES T2	0.70	70.40	73.75	31	0.009	0.56	0.84
LNIV	0.69	48.25	84.10	2.5	0.014	0.54	0.83
Urea T2	0.72	70.44	73.72	1.5	0.004	0.58	0.85

DISCUSSION

Our results confirmed previous NIV failure rate data of 56-76%. These results could be explained by a poorer response to NIV in patients with ARF due to COVID-19 infection

compared to patients with ARF due to community-acquired pneumonia, a heterogenity of the criteria for respiratory support measure. Dyspnoea has been reported in more than 50% of patients with COVID-19 and a significantly higher incidence has been found in patients in need of ICU care. Dyspnoea develops due to worsening of hypoxia, increased respiratory effort and the use of accessory muscles and tachypnea. Malnourished patients have decreased immunity and bone marrow function, pancytopenia and increased risk of severe morbidity. A severe form of COVID-19 infection in patients with anorexia could be explained by disruption of the angiotensin-converting enzyme 2 cell receptor function in the small intestine. In our research, the mean CCI was 3.37 in the group with a negative NIV outcome, but the CCI was not independently associated with NIV failure. Other authors found CCI median 2 (1–3) in the NIV + IMV group. The RALES system is often used to quantify the progression of lung involvement in patients with COVID-19. The RALES on the day of starting NIV is the second most significant factor in our predictive model of NIV failure. Burns et al. concluded that the only statistical significance for NIV success was lower level of the X-ray imaging score. The length of NIV of six days in our study showed a predictive value for negative NIV outcome; in the group with the positive NIV outcome, the length of NIV was four days. Similar results were reported by Mukhtara et al., the duration of successful NIV treatment was two to five days. Urea and creatinine values did not differ statistically significantly in patients with COVID-19 treated with a high-flow nasal cannula compared with NIV. The results of our study showed mean urea and creatinine values higher in the group with NIV failure; creatinine value did not show predictive significance for NIV outcome although higher urea value on the day of starting NIV proved to be the most significant factor in the predictive model of NIV failure. This result indicates accurate monitoring of the urea value in the patients treated with NIV.

There are some limitations of the study. The single centered, retrospective nature, without a control group and small number of patients could influence failure to achieve excellent prognostic accuracy of factors. A number of important laboratory data were not monitored due to collection

inconsistencies. For better insight into the predictors of NIV failure, future studies are needed, with more laboratory data (transaminases, immunological and coagulation data). In conclusion, the use of NIV remains a significant alternative to avoid IMV, during the COVID-19 pandemic. The predictive model developed in this study showed that the presence of dyspnoea on the day of admission at hospital, higher RALES score on the day of starting NIV, higher length of NIV and increased value of urea on the day of starting NIV are strongly related with NIV failure. In addition to respiratory parameters, this predictive model should be accurately monitored and considered in making timely therapeutic and diagnostic decisions.

FROM IMPLEMENTATION A MODERN MICU IN THE LOW-RESOURCES COUNTRY BOSNIA AND HERZEGOVINA TO FIRST CERTIFIED ECMO CENTRE

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Abstract

Background. Critical care medicine is a relatively young discipline, developed in the mid-1950s in response to the outbreak of poliomyelitis. The mass application of mechanical ventilation and its subsequent technical advancement helped manage large numbers of patients with respiratory failure. This branch of medicine evolved much faster in high-income (HIC) than low- and middle-income countries (LMIC). Seventy years later, mankind's encounter with coronavirus disease 2019 (COVID-19) represents another major challenge for critical care medicine especially in LMIC countries where over two thirds of the world population live.

Methods. Systematic analysis of written documents related to the establishment of the first multidisciplinary medical intensive care unit (MICU) in Bosnia and Herzegovina (Republika Srpska) and its development to certified ECMO centre at the present day.

Results. We describe the experience of setting up a modern critical care program under LMIC constraints as a promising way forward to meet the increased worldwide demand for critical care. Successful development is contingent on formal education and continued mentorship from HIC, establishment of a multidisciplinary team, the support from local health care authorities, development of a formal subspecialty training, academic faculty development, and research. Novel technologies including tele-education provide additional opportunities for rapid development and dissemination of critical care medicine programs in LMIC.

Conclusion. Critical care medicine is a critical public health need in HIC and LMIC alike. The challenges associated with the coronavirus pandemic should serve as a wakeup call for rapid development of critical care programs around the world.

Keywords:

Critical care medicine, Low-middle-income countries, development, COVID-19

DISASTER MEDICINE: RESPONSE TO NATURAL DISASTERS (PANDEMICS)

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- According to the World Health Organization definition of disaster: “A disaster is an occurrence disrupting the normal conditions of existence and causing a level of suffering that exeeds the capacity of adjustment of the affected community.”
- Another relevant organization, United Nation Office for Disaster Risk Reduction, defines disaster as: “A serious disruption of the functioning of a community or a society at any scale due to hazardous events interacting with conditions of exposure, vulnerability and capacity, leading to one or more of the following: human, material, economic and environmental losses and impacts.”
- Disasters can be caused by the nature (geological, meterological, biological), or caused by humans (war, terorism, industry, traffic).
- All disaster have their timeline: primary effect, secondary effect, occurring hours and days after the primary effect, and tertiary effect, occurring years or decades after the disaster.
- Disaster medicine is a field of medicine that unites emergency medicine, reanimation and disaster response.
- Disaster plan consists of three phases: prevention and preparedness, early response to disaster and early recovery, and recovery and development.
- These principles applies to response to pandemics as well, as the pandemics are natural disasters.
- First response to pandemic is mitigation. Medical response during pandemic is highly reliable on point of care tests and diagnostic tools. Allocating medical resources during pandemic is crucial, as well as establishing coordination and command of medical teams.
- The late effects of pandemics, after it is over, is exhaustion of health care system, need to rebuild functional healthcare system, as well as psychological effects on the population, such as posttraumatic stress disorders and burned out syndrome of medical personnel.

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WHAT HAVE WE LEARNED DURING COVID-19 PANDEMICS: VIRTUAL QUALITY IMPROVEMENT

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Poor quality of care including, diagnostic delay, therapeutic harm, and dying without dignity are prevalent in critical care medicine where information overload, resource constraints, and time pressure pose significant problems. COVID-19 pandemics brought additional challenge with a large influx of critically ill patients overwhelming intensive care unit (ICU) capacity largely due to a failure of public health measures. Challenges with hospital strain and misinformation pandemics further compromised patient care and outcomes. Clinical studies and large collaborative research registries have highlighted the fact that high quality supportive care is the most important *modifiable* outcome determinant of COVID-19 critical illness[1,2].

Prioritizing relevant information, respecting human factors, and standardization are necessary to facilitate timely, error-free, patient-centered supportive care in the ICU[3]. Mayo Clinic CERTAIN (Checklist for Early Recognition and Treatment of Acute Illness and iNjury) program focuses on standardized approach to the critically ill with the goal to maximize the quality of life and, when appropriate, quality of dying using a compassionate, humane approach to patient care (www.icertain.org). The design and content was informed by survey of clinicians from diverse international settings. The implementation of CERTAIN in 35 hospitals across five continents was associated with improved adherence to evidence-based processes of care, decreased length of stay, and reduced mortality[4]. During the COVID-19 pandemics, CERTAIN has been used to support clinicians in busy ICUs in the New York City (https://catalyst.nejm.org/doi/full/10.1056/CAT.20.0301), other parts of the United States (https://www.sccm.org/Clinical-Resources/Collaboratives/STOP-VIRUS-ICU-Learning-Collaborative), and with support of WHO office in Sarajevo, has also helped with rapid knowledge sharing with health care workers in the countries of former Yugoslavia[5].

Novel technologies including telemedicine, virtual simulation workshops, and virtual interdisciplinary learning community enable scalable quality improvement and knowledge translation to the bedside of critically ill patients worldwide, even under the challenging conditions of the pandemics.

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LACK OF ANESTHESIOLOGISTS IN COVID-19 PANDEMIC - WHETHER CLOSED-LOOP SYSTEMS IN ANESTHESIA CAN BE THE ANSWER?

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Technological advancement has made engineering tools helpful for anesthesiologists to maintain optimal safety and effectiveness, especially when the available resources are insufficient to some patients, for example during the COVID-19 pandemic. One of those tools are the closed loops systems in anesthesia that have become a field of research in recent times. In anesthesia, closed - loop systems provide an individual approach to each patient and thus fit into the practice of personalized medicine. They optimize anesthesiologist workload and increase their time to make decisions and ultimately improve the safety and quality of anesthesia care. Closed-loop systems in anesthesia are now increasing at each stage of general anesthesia (hypnosis, nociception and neuromuscular blockade) and recently some successful algorithms – single or multi-closed-loop controllers are developing. These devices aim to control a predefined target and to continuously titrate anesthetics whatever are the patients' comorbidities and surgical events to reach this target. According to the definition, closed-loop systems are pharmacological robots able to precisely titrate the dose of anesthetic drugs to a preset value, concerning hypnosis, analgesia and neuromuscular block. A closed-loop is a system wherein a controller monitors one or more system variables (BIS, TOF, arterial pressure, etc.) and adjusts in response administration of one or more agents to maintain the target in the expected range through a dedicated algorithm. In anesthesia, it is the current clinical practice to administer potent drugs that profoundly influence levels of consciousness, muscle relaxation, and analgesia by manual control based on the clinician's experience and intuition. Open-loop control (manual control) by clinical personnel can be tedious, imprecise, time-consuming, and sometimes of poor quality, depending on the skills and judgment of the clinician. The anesthetist forms part of the system, by analyzing the vital signs of the patient and acting as a human controller. The anesthetist closes the loop, by providing intermittent feedback to manually control anesthesia delivery to form a "temporary human closed-loop system".

Contrary to open-loop control, closed-loop control systems are based on appropriate dynamical systems models that merit investigation as a means of improving drug delivery. Automated systems can improve the stability of controlled variables and reduce the workload in clinical practice without increasing the risks to patients (1). New anesthetic techniques are based on computer tools that combine artificial intelligence methodologies such as fuzzy logic control systems are. The fuzzy logic are actually classified in the artificial intelligence field because they implement the reasoning of a human. The integration of artificial intelligence techniques such as fuzzy logic, neural network, and reinforcement learning with closed-loop drug delivery

systems has brought their applications closer to fully intelligent automatic systems (2). Closed-loop-feedback control means in predetermined time intervals a controller which acquires measurements of a variable (controlled), which are compared to the desired target value (set point): if there is a difference, the controller modifies the manipulated variable to restore the controlled variable to the setpoint (3).

First attempts with a closed-loop were performed with one variable and one agent: depth of sedation, depth of neuromuscular blockade, analgesia, arterial pressure control, and finally, fluid optimization. The new system developed by the researchers, Pharmacological Anesthesia Robot (Mcgill University), a real robot for anesthesia, administers drugs for general anesthesia and monitors their separate effects completely automatically, with no manual intervention. McSleepy meets DaVinci and conducts first-ever all-robotic surgery and anesthesia. Mc Sleepy can provide anesthesia for all three stages, and can calculate the appropriate drug dose for any given anesthesia in a time faster and more accurately than humans.

The future visions in closed-loop drug delivery systems are to provide treatment to patients suffering from chronic diseases. It includes closed-loop drug delivery/therapy for diabetes, gastrointestinal tract disease, cancer, cardiac ailments, and neurological disorders, from a perspective to show the research in the area of control theory. The development of physiological closed-loop control of ventilation has followed a similar path to that of manual clinical ventilation, starting with ensuring optimal gas exchange and prevention of ventilator-induced lung injury (4).

Although closed-loop anesthesia seems to be the solution to achieving perfectly controlled anesthesia, there are some limitations in these automated intelligent systems. There have been occasions when fuzzy logic systems did not match routine performance by an anesthesiologist, but this might be a matter of inadequate programming. Fuzzy logic still requires an expert anesthesiologist to set the rules. Fussy logic lacks clinical intuition; an advantage of anesthesiologists is that they sometimes rightly ignore the rules. However, lack of anesthesiologists and supervising multiple operating theaters encourage the role of automated fuzzy logic systems.

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CHILDREN AND CORONA VIRUS

Selma Sijercic

Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)

Children Data on individuals aged 18 years old and under suggest that there is a relatively low attack rate in this age group (2.4% of all reported cases). Within Wuhan, among testing of ILI samples, no children were positive in November and December of 2019 and in the first two weeks of January 2020. From available data, and in the absence of results from serologic studies, it is not possible to determine the extent of infection among children, what role children play in transmission, whether children are less susceptible or if they present differently clinically (i.e. generally milder presentations). The Joint Mission learned that infected children have largely been identified through contact tracing in households of adults. **Of note, people interviewed by the Joint Mission Team could not recall episodes in which transmission occurred from a child to an adult.**

https://www.who.int/docs/default-source/coronaviruse/who-china-joint-mission-on-covid-19-final-report.pdf

Sars-Cov-2 in children - insights and conclusions from the mandatory reporting data in Frankfurt am Main, Germany, March-July 2020

From the beginning of the corona pandemic until August 19, 2020, more than 21,989,366 cases have been reported worldwide - 228,495 in Germany alone, including 12,648 children aged 0-14. In many countries, the proportion of infected children in the total population is comparatively low; in addition, children often have no or milder symptoms and are less likely to transmit the pathogen to adults than the other way round. Based on the registration data in Frankfurt am Main, Germany, the symptoms of children in comparison with adults and the likely routes of transmission are presented below. The documentation of the mandatory reports includes personal data (name, date of birth, gender, place of residence), disease characteristics (date of report, date of onset of the disease, symptoms), possible contact persons (family, others) and i.a. possible activity or care in children's community facilities. All reports were viewed, especially with regard to likely transmission routes. From March 1 to July 31, 2020, 1,977 infected people were reported, including 138 children between the ages of 0 and 14 years. Children had fewer and milder symptoms than adults. None of the children experienced severe respiratory symptoms or the need for ventilation. 62% of the children had no symptoms at all (19% adults), 5% of the children were hospitalized (24% adults), and none of the children died (3.8% adults). After excluding a cluster of 34 children from refugee accommodations and 14 children from a parish, 78% of the remaining 90 children had been infected by an adult within the family, and only 4% were likely to have a reverse transmission route. In 5.5% of cases, transmission in a community facility was likely. The results of the

registration data from Frankfurt am Main, Germany confirm the results published in other countries: Children are less likely to become infected, and if infected, their symptoms are less severe than in adults, and they are apparently not the main drivers of virus transmission. **Therefore, scientific medical associations strongly recommend reopening schools.**

https://pubmed.ncbi.nlm.nih.gov/33214989/

Surveillance of Acute SARS-CoV-2 Infections in School Children and Point-Prevalence During a Time of High Community Transmission in Switzerland

Switzerland had one of the highest incidence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections in Europe during the second wave. Schools were open as in most of Europe with specific preventive measures in place. However, the frequency and transmission of acute unrecognized, asymptomatic or oligosymptomatic infections in schools during this time of high community transmission is unknown. There of, our aim was to pilot a surveillance system that detects acute SARS-CoV-2 infections in schools and possible transmission within classes. Fourteen out of the randomly selected sample of the *Ciao Corona* cohort study participated between December 1 and 11, a time when incidence rate for SARS-CoV-2 infections was high for the canton of Zurich. We determined point-prevalence of acute SARS-CoV-2 infections of school children attending primary and secondary school. A buccal swab for polymerase chain reaction (PCR) and a rapid diagnostic test (RDT) to detect SARS-CoV-2 were taken twice 1 week apart (T1 and T2) in a cohort of children from randomly selected classes. A questionnaire assessed demographics and symptoms compatible with a SARS-CoV-2 infection during the past 5 days. Results: Out of 1,299 invited children, 641 (49%) 6- to 16-year-old children and 66 teachers from 14 schools and 67 classes participated in at least one of two testings. None of the teachers but one child had a positive PCR at T1, corresponding to a point-prevalence in children of 0.2% (95% CI 0.0-1.1%), and no positive PCR was detected at T2. The child with positive PCR at T1 was negative on the RDT at T1 and both tests were negative at T2. There were 7 (0.6%) false positive RDTs in children and 2 (1.7%) false positive RDTs in teachers at T1 or T2 among 5 schools (overall prevalence 0.7%). All 9 initially positive RDTs were negative in a new buccal sample taken 2 h to 2 days later, also confirmed by PCR. Thirty-five percent of children and 8% of teachers reported mild symptoms during the 5 days prior to testing. In a setting of high incidence of SARS-CoV-2 infections, unrecognized virus spread within schools was very low. Schools appear to be safe with the protective measures in place (e.g., clearly symptomatic children have to stay at home, prompt contact tracing with individual and class-level quarantine, and structured infection prevention measures in school). Specificity of the RDT was within the lower boundary of performance and needs further evaluation for its use in schools. Given the low point prevalence even in a setting of very high incidence, a targeted test, track, isolate and quarantine (TTIQ) strategy for symptomatic children and school personnel adapted to school settings is likely more suitable approach than surveillance on entire classes and schools.

https://pubmed.ncbi.nlm.nih.gov/33796490/

Variation in SARS-CoV-2 seroprevalence across districts, schools and classes: baseline measurements from a cohort of primary and secondary school children in Switzerland

To determine the variation in SARS-CoV-2 seroprevalence in school children and the relationship with self-reported symptoms. Baseline measurements of a longitudinal cohort study (*Ciao Corona*) from June to July 2020.g., 55 schools stratified by district in the canton of Zurich, Switzerland, 2585 children (1339 girls; median age: 11 years, age range: 6-16 years), attending grades 1-2, 4-5 and 7-8. Variation in seroprevalence of SARS-CoV-2 in children across 12 cantonal districts, schools and grades, assessed using Luminex-based test of four epitopes for IgG, IgA and IgM (Antibody Coronavirus Assay, ABCORA 2.0). Clustering of cases within classes. Association of seropositivity and symptoms. Comparison with seroprevalence in adult population, assessed using Luminex-based test of IgG and IgA (Sensitive Anti-SARS-CoV-2 Spike Trimer Immunoglobulin Serological test). Overall seroprevalence was 2.8% (95% CI 1.5% to 4.1%), ranging from 1.0% to 4.5% across districts. Seroprevalence in grades 1-2 was 3.8% (95% CI 2.0% to 6.1%), in grades 4-5 was 2.4% (95% CI 1.1% to 4.2%) and in grades 7-8 was 1.5% (95% CI 0.5% to 3.0%). At least one seropositive child was present in 36 of 55 (65%) schools and in 44 (34%) of 131 classes where ≥5 children and ≥50% of children within the class were tested. 73% of children reported COVID-19-compatible symptoms since January 2020, with the same frequency in seropositive and seronegative children for all symptoms. Seroprevalence of children and adults was similar (3.2%, 95% credible interval (CrI) 1.7% to 5.0% vs 3.6%, 95% CrI 1.7% to 5.4%). The ratio of confirmed SARS-CoV-2 cumulative incidence-to-seropositive cases was 1:89 in children and 1:12 in adults. SARS-CoV-2 seroprevalence was low in children and similar to that in adults by the end of June 2020. Very low ratio of diagnosed-to-seropositive children was observed. **We did not detect clustering of SARS-CoV-2-seropositive children within classes, but the follow-up of this study will shed more light on transmission within schools.**
https://pubmed.ncbi.nlm.nih.gov/34312201/

The clinical and immunological features of pediatric COVID-19 patients in China

In December 2019, the corona virus disease 2019 (COVID-19) caused by novel coronavirus (SARS-CoV-2) emerged in Wuhan, China and rapidly spread worldwide. Few information on clinical features and immunological profile of COVID-19 in paediatrics. The clinical features and treatment outcomes of twelve paediatric patients confirmed as COVID-19 were analyzed. The immunological features of children patients was investigated and compared with twenty adult patients. The median age was 14.5-years (range from 0.64 to 17), and six of the patients were male. The average incubation period was 8 days. Clinically, cough (9/12, 75%) and fever (7/12, 58.3%) were the most common symptoms. Four patients (33.3%) had diarrhea during the

disease. As to the immune profile, children had higher amount of total T cell, CD8+ T cell and B cell but lower CRP levels than adults ($P < 0.05$). Ground-glass opacity (GGO) and local patchy shadowing were the typical radiological findings on chest CT scan. All patients received antiviral and symptomatic treatment and the symptom relieved in 3–4 days after admitted to hospital. The paediatric patients showed mild symptom but with longer incubation period. **Children infected with SARS-CoV-2 had different immune profile with higher T cell amount and low inflammatory factors level, which might ascribed to the mild clinical symptom. We advise that nucleic acid test or examination of serum IgM/IgG antibodies against SARS-CoV-2 should be taken for children with exposure history regardless of clinical symptom.**
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7194810/

Open schools! Weighing the effects of viruses and lockdowns on children

This review weighs the risk of infection with SARS-CoV-2 against the side effects of school closures on physical and mental health, education, and well-being of those affected by the school closures. Whereas short term effects – decreased learning and food security, and increased anxiety, violence against children, child labor and teen pregnancies – are frequently discussed, the long-term effects of school closures will be much more detrimental across the lifespan of the "Generation Corona": Existing pandemics of inactivity and myopia, already affecting billions of people, are worsening due to less physical exercise and less time spent outdoors, poor diet, weight gain, and increased screen time during lockdowns, causing future increases of stroke, heart attack, cancer, and blindness. Socio-emotional complications of isolation, learned helplessness, economic and existential insecurity will include increased depression and suicide, decreased empathy and increased loneliness. **Together with decreased educational attainment and economic productivity, the amount of ensuing increased future global morbidity and mortality justifies immediate action of school reopening.**
https://www.sciencedirect.com/science/article/pii/S221194932100003X

COVID-19 in children: analysis of the first pandemic peak in England

To assess disease trends, testing practices, community surveillance, case-fatality and excess deaths in children as compared with adults during the first pandemic peak in England. Children with COVID-19 between January and May 2020. Trends in confirmed COVID-19 cases, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) positivity rates in children compared with adults; community prevalence of SARS-CoV-2 in children with acute respiratory infection (ARI) compared with adults, case-fatality rate in children with confirmed COVID-19 and excess childhood deaths compared with the previous 5 years. Children represented 1.1% (1,408/129,704) of SARS-CoV-2 positive cases between 16 January 2020 and 3 May 2020. In total, 540 305 people were tested for SARS-COV-2 and 129,704 (24.0%) were positive. In children aged <16 years, 35,200 tests were performed and 1408 (4.0%) were positive for SARS-CoV-2, compared to 19.1%-34.9% adults. Childhood cases increased from mid-March and peaked on 11 April before declining. Among 2,961 individuals presenting with ARI in primary

care, 351 were children and 10 (2.8%) were positive compared with 9.3%-45.5% in adults. Eight children died and four (case-fatality rate, 0.3%; 95% CI 0.07% to 0.7%) were due to COVID-19. We found no evidence of excess mortality in children. Children accounted for a very small proportion of confirmed cases despite the large numbers of children tested. **SARS-CoV-2 positivity was low even in children with ARI. Our findings provide further evidence against the role of children in infection and transmission of SARS-CoV-2.**

https://pubmed.ncbi.nlm.nih.gov/32796006/

CONCLUSIONS

In many countries, the proportion of infected children in the total population is comparatively low; in addition, children often have no or milder symptoms and they are apparently not the main drivers of virus transmission.
Very low ratio of diagnosed-to-seropositive children was observed. We did not detect clustering of SARS-CoV-2-seropositive children within classes.
Schools appear to be safe with the protective measures in place.
SARS-CoV-2 positivity was low even in children with ARI (acute respiratory infection).

CLINICAL USE OF INHALATIONAL ANESTHETICS

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Desflurane, or I-653, a a volatile anesthetic that is more rapidly cleared and less metabolized than previous inhaled anesthetics such as sevoflurane, enflurane, or isoflurane.. It was developed in the late 1980s out of a need for a more rapidly acting and rapidly cleared inhaled anesthetic. Desflurane was granted FDA approval on 18 September 1992 Desflurane is indicated for the induction and maintenance of anesthesia in adults, as well as the maintenance of anesthesia in pediatric patients.

Pharmacodynamics Desflurane is a general inhalation anesthetic. It has a short duration of action as it is rapidly cleared Patients should be counselled regarding the risks of malignant hyperthermia, perioperative hyperkalemia, respiratory adverse reactions in pediatric patients, QTc prolongation, hepatobiliary disorders, pediatric neurotoxicity, and postoperative agitation in children.

Mechanism of action The mechanism of inhalational anesthetics is still not fully understood. They can block excitatory ion channels and increase the activity of inhibitory ion channels. The most notable agonism is at the $GABA_A$ channel. Desflurane is also an agonist of glycine receptors, antagonist of glutamate receptors, inducer of potassium voltage gated channels, and inhibits both NADH-ubiquinone oxioreductase chain 1 and calcium transporting ATPases.

An older school of thought is the unitary theory of general anesthetic action, suggesting that desflurane affects the lipid bilayer of cells. Studies of other halogenated inhalational anesthetics have shown that the lipid bilayer spreads out more thinly as the anesthetic incorporates into the bilayer. However, the anesthetic does not bind to lipid heads or acyl chains of hydrocarbons in the bilayer. The effect of incorporating into the lipid bilayer is not well described. By incorporating into the lipid bilayer, anesthetics may introduce disorder in the lipids, leading to some indirect effect on ion channels.

Toxicity Patients experiencing a desflurane overdose may experience deepening anesthesia, cardiac or respiratory depression. In the event of an overdose, patients may require symptomatic and supportive treatment to maintain airway, breathing, and circulation. Discontinue desflurane.

Drug	**Interaction**
Benzodiazepine	The risk or severity of adverse effects can be increased when Desflurane is combined with 1,2-Benzodiazepine.
Acebutolol	Desflurane may decrease the antihypertensive activities of Acebutolol.

Drug	Interaction
Aceclofenac	The risk or severity of hypertension can be increased when Desflurane is combined with Aceclofenac.
Acemetacin	The risk or severity of hypertension can be increased when Desflurane is combined with Acemetacin.
Adenosine	The risk or severity of QTc prolongation can be increased when Desflurane is combined with Adenosine.

1. Induction of Anaesthesia in Adults
2. In adults, a starting concentration of 3% is recommended, increased in 0.5-1.0% increments every 2 to 3 breaths. Inspired concentrations of 4-11% of desflurane usually produce surgical anaesthesia in 2-4 minutes. Higher concentrations up to 15% may be used. Such concentrations of desflurane will proportionately dilute the concentration of oxygen and commencing administration of oxygen should be 30% or above. After induction in adults with an intravenous drug such as thiopental or propofol, desflurane can be started at approximately 0.5-1 MAC, whether the carrier gas is O_2 or N_2O/O_2.
3. Desflurane should be administered at 0.8 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) until cerebral decompression in patients with known or suspected increases in CSFP. Appropriate attention must be paid to maintain cerebral perfusion pressure. (See section 4.4).
4. During induction in adults, the overall incidence of oxyhemoglobin desaturation (SpO_2 < 90%) was 6%. High concentrations of desflurane may induce upper airway adverse events. See section 4.8.
5. Induction of Anaesthesia in Children
6. Desflurane is not indicated for use as an inhalation induction agent in children and infants because of the frequent occurrence of cough, breath holding, apnoea, laryngospasm and increased secretions
7. Maintenance of Anaesthesia in Adults
8. Surgical levels of anaesthesia may be sustained with 2-6% concentration of desflurane when nitrous oxide is used concomitantly. Desflurane at 2.5-8.5 % may be required when administered using oxygen or oxygen enriched air. In adults, surgical levels of anaesthesia

may be sustained at a reduced concentration of desflurane when nitrous oxide is used concomitantly.

9. Maintenance of Anaesthesia in Children
10. Desflurane is indicated for maintenance of anaesthesia in infants and children. Surgical levels of anaesthesia may be maintained in children with end-tidal concentrations of 5.2 to 10% desflurane with or without the concomitant use of nitrous oxide. Although endtidal concentrations of up to 18% desflurane have been administered for short periods of time, if high concentrations are used with nitrous oxide it is important to ensure that the inspired mixture contains a minimum of 25% oxygen.
11. If added relaxation is required, supplemental doses of muscle relaxants may be used.
12. Blood Pressure and Heart Rate During Maintenance
13. Blood pressure and heart rate should be monitored carefully during maintenance as part of the evaluation of depth of anaesthesia. (See section 4.4)
14. Dosage in Renal and Hepatic Impairment
15. Concentrations of 1-4% desflurane in nitrous oxide/ oxygen have been used successfully in patients with chronic renal or hepatic impairment and during renal transplantation surgery. Because of minmal metabolism, a need for dose adjustment in patients with renal and hepatic impairment is not to be expected.
16. 4.3 Contraindications
17. Desflurane is contraindicated in patients:
18. • in whom general anesthesia is contraindicated
19. • with a known sensitivity to halogenated agents.
20. • with a known or suspected genetic susceptibility to malignant hyperthermia
21. • with a history of confirmed hepatitis due to a halogenated inhalational anesthetic or with a history of unexplained moderate to severe hepatic dysfunction (e.g., jaundice associated with fever and/or eosinophilia) after anesthesia with a halogenated inhalational anesthetic.
22. Desflurane is contraindicated for use as an inhalation induction agent in paediatric patients because of the frequent occurrence of cough, breath holding, apnea, laryngospasm and increased secretions.
23. 4.4 Special warnings and precautions for use
24. Desflurane should only be administered by persons trained in the administration of general anaesthesia using a vaporizer specifically designed and designated for use with desflurane. Facilities for maintenance of a patent airway, artificial ventilation, oxygen enrichment and circulatory resuscitation must be immediately available.
25. Warnings:
26. Malignant Hyperthermia (MH)

27. In susceptible individuals, potent inhalation anaesthetic agents may trigger a skeletal muscle hypermetabolic state leading to high oxygen demand and the clinical syndrome known as malignant hyperthermia. Desflurane was shown to be a potential trigger of malignant hyperthermia. The clinical syndrome is signaled by hypercapnia, and may include muscle rigidity, tachycardia, tachypnea, cyanosis, arrhythmias, and/or unstable blood pressure. Some of these non-specific signs may also appear during light anaesthesia: acute hypoxia, hypercapnia, and hypovolemia. Treatment of malignant hyperthermia includes discontinuation of triggering agents, administration of intravenous dantrolene sodium, and application of supportive therapy. Renal failure may appear later, and urine flow should be monitored and sustained if possible. Desflurane should not be used in subjects known to be susceptible to MH. Fatal outcome of malignant hyperthermia has been reported with desflurane.
28. Perioperative Hyperkalemia
29. Use of inhaled anaesthetic agents, has been associated with very rare increases in serum potassium levels that have resulted in cardiac arrhythmias, and death in children during the postoperative period. The condition has been described in patients with latent as well as overt neuromuscular disease, particularly Duchenne muscular dystrophy. Use of suxamethonium has been associated with most, but not all, of these cases. These patients showed evidence of muscle damage with increased serum creatinine kinase concentration and myoglobinuria. Despite the similarity in presentation to malignant hyperthermia, none of these patients exhibited signs or symptoms of muscle rigidity or hypermetabolic state.
30. Prompt and vigorous treatment for hyperkalaemia and arrhythmias is recommended. Subsequent evaluation for latent neuromuscular disease is indicated.
31. Paediatric Inhalation Induction
32. Desflurane is not indicated for use as an inhalation induction agent in children and infants because of the frequent occurrence of cough, breath holding, apnoea, laryngospasm and increased secretions.
33. Use in Children with Bronchial Hyperreactivity
34. Desflurane should be used with caution in children with asthma or a history of recent upper airway infection due to the potential for airway narrowing and increases in airway resistance.
35. Maintenance of Anaesthesia in Children
36. Desflurane is not approved for maintenance of anaesthesia in non-intubated children under the age of 6 years due to an increased incidence of respiratory adverse reactions. Caution should be exercised when desflurane is used for maintenance anaesthesia with laryngeal mask airway (LMA) or face mask in children 6 years old or younger because of the increased potential for adverse respiratory events, e.g. coughing and laryngospasm, especially with removal of the LMA under deep anaesthesia.

37. Obstetrics
38. Due to the limited number of patients studied, the safety of desflurane has not been established for use in obstetric procedures. Desflurane is a uterine-relaxant and reduces the uterine-placental blood-flow. (See section 4.6)
39. Isolated reports of QT prolongation, very rarely associated with torsade de pointes (in exceptional cases, fatal), have been received. Caution should be exercised when administering desflurane to susceptible patients e.g. patients with existing QTc prolongation.
40. Precautions:
41. With the use of halogenated anaesthetics, disruption of hepatic function, icterus and fatal liver necrosis have been reported: such reactions appear to indicate hypersensitivity. As with other halogenated anaesthetic agents, desflurane may cause sensitivity hepatitis in patients who have been sensitized by previous exposure to halogenated anaesthetics. Cirrhosis, viral hepatitis or other pre-existing hepatic disease may be a reason to select an anaesthetic other than a halogenated anaesthetic.
42. Desflurane, as other volatile anaesthetics, may produce a dose-dependent increase in cerebrospinal fluid pressure (CSFP) when administered to patients with space occupying lesions. In such patients, desflurane should be administered at 0.8 MAC or less, and in conjunction with a barbiturate induction and hyperventilation (hypocapnia) until cerebral decompression in patients with known or suspected increases in CSFP. Appropriate attention must be paid to maintain cerebral perfusion pressure.
43. In patients with coronary artery disease, maintenance of normal hemodynamics is important to avoid myocardial ischemia. Marked increases in pulse rate, mean arterial pressure and levels of epinephrine and norepinephrine are associated with a rapid increase in desflurane concentrations. Desflurane should not be used as the sole agent for anesthetic induction in patients at risk of coronary artery disease or in patients where increases in heart rate or blood pressure are undesirable. It should be used with other medications, preferably intravenous opioids and hypnotics.
44. During maintenance of anaesthesia, increases in heart rate and blood pressure occurring after rapid incremental increases in end-tidal concentration of desflurane may not represent inadequate anaesthesia. The changes due to sympathetic activation resolve in approximately 4 minutes. Increases in heart rate and blood pressure occurring before or in the absence of a rapid increase in desflurane concentration may be interpreted as light anaesthesia.
45. Hypotension and respiratory depression increase as anaesthesia is deepened.
46. Use of desflurane in hypovolaemic, hypotensive and debilitated patients has not been extensively investigated. As with other potent inhaled anaesthetics, a lower concentration is recommended for use in these patients.

47. Desflurane, like some other inhalation anaesthetics, can react with desiccated carbon dioxide (CO_2) absorbents to produce carbon monoxide that may result in elevated levels of carboxyhemoglobin in some patients. Case reports suggest that barium hydroxide lime and soda lime become desiccated when fresh gases are passed through the CO_2 canister at high flow rates over many hours or days. When a clinician suspects that CO_2 absorbent may be desiccated, it should be replaced before the administration of desflurane.
48. As with other rapid-acting anesthetic agents, rapid emergence with desflurane should be taken into account in cases where post-anaesthesia pain is anticipated. Care should be taken that appropriate analgesia has been administered to the patient at the end of the procedure or early in the post-anaesthesia care unit stay. Emergence from anesthesia in children may evoke a brief state of agitation that may hinder cooperation.
49. As with all halogenated anaesthetics, repeated anaesthesia within a short period of time should be approached with caution.
50. Facilities and equipment for maintenance of a patent airway, artificial ventilation, oxygen enrichment and circulatory resuscitation must be immediately available.
51. Glucose elevation
52. As with other halogenated anaesthetic agents, desflurane has been associated with some elevation of glucose intra-operatively.
53. 4.5 Interaction with other medicinal products and other forms of interaction
54. Concentration of other gases
55. The MAC for desflurane is reduced by concomitant N_2O administration. (see Table 1)
56. Non-depolarizing and depolarizing muscle relaxants
57. Commonly used muscle relaxants are potentiated by desflurane.
58. Anaesthetic concentrations of desflurane at equilibrium reduce the ED95 of suxamethonium by approximately 30% and that of atracurium and pancuronium by approximately 50% compared to N_2O/opioid anaesthesia. The doses of pancuronium, atracurium, suxamethonium and vecuronium needed to produce 95% (ED_{95}) depression in neuromuscular transmission at different concentrations of desflurane are given in Table 2. With the exception of vecuronium, these doses are similar to isoflurane. The ED_{95} of vecuronium is 14% lower with desflurane than isoflurane. Additionally, recovery from neuromuscular blockade is longer with desflurane than with isoflurane.
59. Pre-anaesthetic Drugs
60. No clinically significant adverse interactions with commonly used pre-anaesthetic drugs, or drugs used during anaesthesia (intravenous agents, and local anaesthetic agents) were reported in clinical trials. The effect of desflurane on the disposition of other drugs has not been determined.
61. Sedatives

62. Patients anaesthetised with different concentrations of desflurane who received increasing doses of fentanyl showed a marked reduction in the anaesthetic requirements or MAC. The administration of increasing doses of intravenous midazolam showed a small reduction in MAC. Results are reported in Table 3. These MAC reductions are similar to those observed with isoflurane. It is anticipated that there will be a similar influence on MAC with other opioid and sedative drugs.

63. **Table 3: Effect of Fentanyl or Midazolam on Desflurane MAC**

	*MAC (%)	%MAC Reduction
No Fentanyl	6.33 - 6.35	-
Fentanyl (3 mcg/kg)	3.12 - 3.46	46 - 51
Fentanyl (6 mcg/kg)	2.25 - 2.97	53 - 64
No Midazolam	5.85 - 6.86	-
Midazolam (25 mcg/kg)	4.93	15.7
Midazolam (50 mcg/kg)	4.88	16.6

64. * Includes values for ages 18 - 65 years
65. 4.6 Fertility, pregnancy and lactation
66. Due to the limited number of patients studied, the safety of desflurane has not been established for use in obstetric procedures. Desflurane is a uterine relaxant and reduces the uterine-placental blood-flow. Studies in animals have shown reproductive toxicity. (see section 5.3).
67. There are no adequate data from the use of desflurane in pregnant or lactating women, therefore desflurane is not indicated for use during pregnancy and lactation.

REGIONAL ANESTHESIA IN COVID 19 PANDEMIC

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The coronavirus disease (COVID-19) began in Wuhan, China, at the end of 2019 and spread rapidly across the country and worldwide, which was declared to be a pandemic (1). The virus mainly spread through respiratory droplets or direct contact. It may also be transmitted through aerosols with prolonged exposure to high concentrations of aerosol (2). Healthcare professionals working in anaesthesia and criticalcare departments and anaesthesia units are in an elevated risk of COVID-19 exposure as they perform aerosol-generating procedures (AGPs), involve intubation, extubation, (3).

The safety of both patients and healthcare workers should be taken into consideration when performing anesthesia management for patients who are confirmed or suspected to have COVID-19. Patients with acute and recent respiratory infections are at high risk of pulmonary complications during the perioperative period. A history of respiratory infection within a month is reported to be an independent predictor of risk for postoperative pulmonary complications. A previous systematic review reported that the incidence of postoperative pneumonia in patients under- going neuraxial anesthesia was lower than that in patients undergoing general anesthesia (3).

Uppal et al. recently published an joint statement by the American Society of Regional Anesthesia and Pain Medicine and the European Society of Regional Anaesthesia and Pain Therapy for the practice of regional anesthesia during the COVID-19 pandemic (4). They recommended safe regional anesthesia with a brief report (Fig 1)

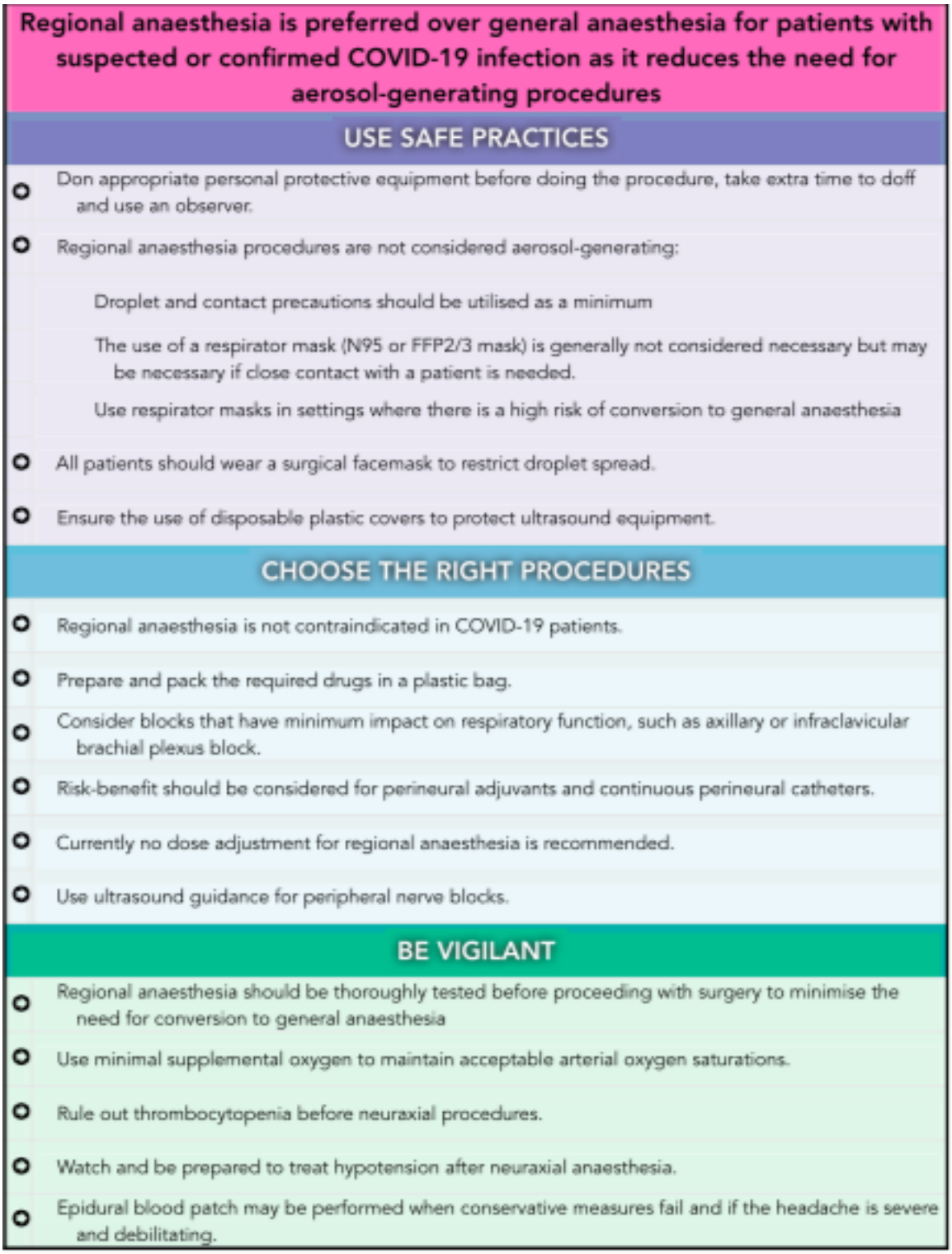

Fig 1: Recommendation for safe regional anesthesia (4).

Safe and reliable performance of regional anesthesia is more preferred than usual to avoid unplanned medical intervention such as conversion to general anesthesia, treatment of local anesthetic systemic toxicity, and epidural blood patch for postdural puncture headache (5). The use of ultrasound guidance and the performance by an experienced physician may reduce the incidence of failed block and complications. The use of long-acting local anesthetic prolongs the anesthetic effect of regional anesthesia, which contributes to avoiding conversion to general anesthesia and reducing postoperative opioids. Besides, a safe and sufficient dose of local anesthetic should be used.

Personal Protective Equipment

Although regional anesthesia is considered to have a lower risk of COVID-19 transmission than general anesthesia, safety protocols should be followed to prevent infection from droplets and contaminated sources. Personal protective equipment includes a surgical mask, eye protection, surgical gown, and double glove. The use of N95 masks should be considered depending on the risk of aerosol generation and droplet spread. Restrictions of staff and equipment in the operating room should be considered to minimize exposure to the virus(6).

Thrombotic complications seem to emerge as an important issue in patients with COVID-19. Approximately 20% of the patients present severe coagulation abnormalities, and almost all patients with severe and critical COVID-19 infection showed major coagulation disorders. Indications for the interruption/initiation of anticoagulant therapy with regards to neuraxial puncture and for deep peripheral nerve blocks should be well established when considering RA indication (7).

Based on the potential advantages related to the application of RA techniques in both COVD-free and COVID-positive patients, we believe that RA is a fundamental weapon for the anesthetists in the COVID-19 age. Although, the management of a confirmed or suspected COVID-19 patients requires caution and the careful evaluation of both actual therapy and the coagulation state to prevent undesirable side effects.

The SARS-CoV-2 virus is not the first and certainly will not be the last novel virus to achieve worldwide outbreaks. Having a well thought out RA plan to manage infected patients in this new normal will ensure the best possible outcome for both the patient and the perioperative management team.

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PREGNANCY AND COVID-19: ANESTHETIC TECHNIQUES

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Abstract

Pregnant women with Covid-19 are considered to be a high risk group for severe Covid-19 and adverse birth outcomes. Infection control preacutions should be taken on the labor and delivery ward to achieve protection for patients and health care workers. Neuraxial labor analgesia remains a gold standard for obstetric care even with present Covid-19 infection. Early epidural placement is desirable to avoid exacerbation of respiratory symptoms with labor pain as well as to reduce the need for general anesthesia if emergency cesarean delivery becomes necessary. Covid-19 is not an indication for cesarean section. A standard spinal anesthetic approach is the most frequently used technique, but when time is of the essence it can be transformed into a rapid sequence spinal (RSS) for urgent cesarean deliveries. All strategies should be used to avoid general anesthesia, but if it is considered necessary and unavoidable, provision of general anesthesia should follow general recommendation in the setting of Covid-19 infected patients.

Introduction

In Decembar 2019, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was reported in China, and just few months after that the disease (Covid-19) caused by this virus has been reported in every inhabited continent. On March 11th 2020, the WHO declared Covid-19 as a global pandemic[1]. There are more than 250 milions of people who were infected, more than 5 milions deaths by the virus. Currently, Europe is the world's hotspot with the highest number of test-positive cases of Covid-19.

Pregnant women with coronavirus (Covid-19) are considered to be a high risk group for severe Covid-19 and adverse birth outcomes. Pregnant and recently pregnant women with covid-19 are at increased risk of an admission to an intensive care unit and receiving invasive mechanical ventilation when compared with non-pregnant women with COVID-19 of similar age group. Preexisting maternal comorbidities, increasing maternal age, high body mass index, non-white ethnicity, pregnancy specific disorders like pre-eclampsia are significant risk factors[2].

Before the outbreak of the pandemic we were all committed to reach the highest standards in our field of anesthesia. We used to try to offer our patients as many choices as possible to choose what they want for better birth experience and focused mainly on decreasing maternal

morbidity related to maternal risk factors. Now we are all working with personal protective equipment (PPE), we learn to work fast, to avoid infection. And it is clear that our standards of care are at risk and we have to work in a low resource place in some aspects.

Infection control preacutions taken on the labor and delivery unit

Infection control interventions to reduce transmission of SARS-CoV-2 include the following:

1. Screening of the patients for clinical manifestations of Covid-19 (cough, headache, sore throat, myalgia, fever, shortness of breath, loss of taste/smell) and close contact with a confirmed case prior to and upon entry into the health care facility.
2. All patients and visitors should wear surgical masks upon entry into the health care setting for universal source control.
3. Universal testing with a rapid SARS-CoV-2 test upon presentation to the labor and delivery unit is reasonable, although it depends on symptoms, the prevalence of Covid-19 in the community, and the patient's vaccination status[3].
4. Appropriate infection control preparations when a screen-positive patient is identified (care for pregnant patients with Covid-19 in a well-ventilated, single-occupancy room with a closed door and dedicated bathroom. When caring for patients with Covid-19, health care workers should use contact and droplet precautions, and also in some cases airborne precautions, in addition to contact and droplet precautions.

Patient evaluation and monitoring

A pregnant woman who is Covid-19 positive should be evaluated including vital signs, physical examination and review of laboratory tests (complete blood count, coagulation status and arterial blood gas, if needed) to assess appropriate level of care and monitoring plan for potential deterioration. Routine monitoring should include frequent vital signs, continuous pulse oximetry and strict input and output measurements. Early multidisciplinary collaboration should be arranged to determine level of care, fetal monitoring, and delivery plan.

Labor analgesia

Neuraxial labor analgesia remains a gold standard for obstetric care even with present Covid-19 infection, unless otherwise contraindicated.

Neuraxial labor analgesia can be initiated with a single-shot spinal, standard epidural, combined spinal epidural (CSE), or DPE (dural puncture epidural) technique, depending on patient and provider specific factors[4].

Early epidural placement is desirable to avoid exacerbation of respiratory symptoms with labor pain as well as to reduce the need for general anesthesia if emergency cesarean delivery becomes necessary. Because patients with Covid-19 may require venous thromboembolism (VTE) prophylaxis, consideration of the timing and dose of the last anticoagulation medication

may be required[5]. It is also advisable to check a platelet count before the initiation of neuraxial procedures. Thrombocytopenia is associated with both pregnancy and Covid-19, although severe thrombocytopenia in laboring patients is rare. A meta-analysis[6] of 1779 patients with Covid-19 showed that platelet counts are lower in patients with more severe illness. The risk-benefit ratio of epidural analgesia should be weighed in the setting of thrombocytopenia. It is essential to monitor the rate of platelet count decrease, which should be considered in addition to the threshold of a specific number. If there is no other evidence of coagulopathy, epidurals can be safely used in a patient with a platelet count of 70,000/mm^3 or lower if the count is stable[5].

The risk of Covid-19 exposure for the anesthesiologist during neuraxial labor analgesia placement is low, because it is not an aerosolizing procedure. All health care workers in the room should wear contact and droplet precautions, while the patient should wear a surgical mask at all times. The number of personnel present during placement of neuraxial labor analgesia should be minimized, but with assistance readily available. The most experienced anesthesiologist present should perform the procedure to maximize the likelihood of successful placement and avoid dural puncture.

Although nitrous oxide can be used, the cleaning and prevention of aerosolization is more difficult to control and, thus, is not recommended. Intravenous remifentanil is an option, but it provides inferior analgesia to neuraxial techniques and the respiratory depression caused by remifentanil could potentially worsen the respiratory issues of Covid-19.

Anesthesia for cesarean section

Covid-19 is not an indication for cesarean section and obstetric and neonatal factors should play the predominant role in determining the need for surgical delivery. However, the rates of cesarean delivery are higher in patients with COVID-19 than in the general population.

Regional anesthesia is anesthesia of choice for cesarean section as it avoids aerosolizing procedures and potential difficult endotracheal intubation.

Conversion of labor epidural analgesia if any to cesarean delivery anesthesia is the easiest way, but baseline failure rate and conversion to general anesthesia is 5%[7]. Urgent nature of cesarean delivery represents an important risk factor for failed conversion and therefore, communication with the obstetricians is very important for having enough time to initiate surgical block and avoid general anesthesia.

A standard spinal anesthetic approach is the most frequently used technique, but when time is of the essence it can be transformed into a rapid sequence spinal (RSS) for urgent cesarean deliveries. This technique, first described in 2003, simplifies the process aiming to avoid the potential risks of general anesthesia[8].

A study from China[9] reported excessive hypotension with epidural anesthesia for cesarean section in 12 of 14 patients with Covid-19, though subsequent studies have disputed the

results. The use of a prophylactic intravenous infusion of a vasopressor is recommended to prevent hypotension associated with neuraxial anaesthesia during caesarean section.
Uterotonics can be associated with cardiovascular disturbance and should be administered by slow bolus or infusion.

General anesthesia

In some fetal and maternal emergency conditions as well as in the presence of contraindications to regional analgesia such as coagulopathy, general anesthesia can be seen as the technique of choice to facilitate an accelerated delivery.
In patients with Covid-19, general anesthesia should be avoid for two reasons. First, general anesthesia with Covid-19 infection may place pregnant women at increased risk of pulmonary complications[10] and second, the process of inducing general anesthesia in infected patients increases the potential risk of infection for providers present in the operative room[11]. Protocols and recommendations include minimizing the number of people in the room at the time of intubation, appropriate use of PPE, rapid sequence induction, and video laryngoscopy as the first line by experienced anesthetist.
One big study from 2021[12] that included over 17000 deliveries in north-west of England has shown a reduction in general anaesthesia rates for caesarean section (from 7.7% to 3.7%) during the peak of the COVID-19 pandemic.
General anesthesia for cesarean delivery remains the “back-up plan” to the preferred neuraxial approach. Still, there will be situations when it will be provided. In order to minimize the number of cesarean sections performed under general anesthesia anesthesiologists must be proactive rather than reactive when managing patients in the labor and delivery ward.

Conclusion

Most of the considerations for the management of the parturient with Covid-19 infection include best strategies to ensure safe care for the parturient and safe environment for the health care worker. Neuraxial labor analgesia continues to be the technique that provides optimal and diverse pain management during labor and the potential for conversion to an anesthetic for cesarean delivery if needed. All strategies should be used to avoid general anesthesia, but if it is considered necessary and unavoidable, provision of general anesthesia should follow general recommendation in the setting of Covid-19 infected patients.

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INFLUENZA A, PNEUMONIA AND PREGNANCY : CASE REPORT

Denis Odobasic, Senida Keser

Patient was admitted to the Infectious Diseases Clinic of the University Medical Center Tuzla on February 12, 2020 due to a mild headache, severe dry cough, chest pain, difficulty breathing, and muscle and joint pain. She did not measure temperature .Pregnancy 36 NG. Otherwise, she was healthy so far. There were no similar patients in the area. At the reception of tt 36.5, slightly dyspnoeic, moderately obese, less hydrated. finding: L 5.7 E 3.1, Hbg 84, Htc 0.24, Tr 59 CRP 194.5 ABS: Ph 7.40 Be -8.9, HCO3 17.5, SAT 93.1%, At 134 K 3.8, creatinine 174, other findings in reference values. X-ray pulmo: right hemidiaphragm partially relaxed. Bilateral paracillary and hilobasal paracardial denser peribronchovascular pulmonary pattern, which left basal paracardial-looking and mottled shadowing where the heart can partially erase. no pulmonary effusions seen.right right hilus differentiated, left covered with shadow of heart.cardiovascular shadow in supine position appears initially enlarged.

PCR test influenza A: positive

Dg. Influence A cum pneumonia, Grav hebd 36

Th. Ceftriaxon amp 1gx 2 i.v. Azithromycin amp a 500 mg i.v. Oseltamivir tbl 75 mg Pantoprazole and 40 mg i.v. Enoxaparin 40 mg sc, Oxygen therapy

Coagulogram: hyperfibrinogenemia, discrete deficiency of internal coagulation pathway factors, other tests in order.

On February 13, 2020, she was consularly examined (gynecologist, infectologist and anesthesiologist) and it was decided that due to the general condition of the patient, influenza with pneumonia, unfavorable pelvis score, prematurity, the birth would end with a caesarean section. Cesarean section performed under spinal anesthesia with oxygen support on the mask, passed without surgical and anesthetic complications. Intraoperatively, the patient received 2 doses of erythrocyte concentrate after the child was removed. .Patient gave birth to live female newborn tt 3220/53 apgar scora 8/8 .Postoperative patient placed in JIT due to intensive supervision.

14.2.2020 patient from JIT transferred to GAK.

On the first postoperative day, the patient is conscious, complains of suffocation and cough. Afebrile, easily dyspnoeic and on continuous oxygen therapy.

Th.same + syntocinon 10 ij each infusion

15.2.2020 control examination by an infectologist

The patient has no problems, the patient states that she feels much better, no cough, no fever. Control X-ray pulmo: no signs of infiltration

Lab finds L 8.4, E 3.63, Htc 0.28, Hbg 81,Tr 122 , CRP 42.8, creatinine 124, among other findings in reference values. Auscultatory finding on the lungs neat

The patient will be presented on February 16, 2020 at the expert council of the Infectious Diseases Clinic

Gynecologist's finding the wound is normal, the involution of the uterus is normal, the patient denies subjective problems

16.2.2020 finding of the council of the infectious disease clinic

Given the orderly findings of X-rays of the pulmo as well as biochemical findings, and the good general condition of the patient, it was concluded that the patient can be discharged home with a recommendation for a follow-up examination by a competent doctor. On the same day, a patient with GAK was discharged for home treatment

Discussion

This case for us was the first case of Covid -19 infection in pregnant women without distinction that there was no testing yet. The decision to perform this caesarean section under spinal anesthesia regardless of thrombocytopenia, deficiency of internal coagulation pathway factors and included NMH was the subject of discussion. What would happen if we went for general anesthesia and would this patient end up on a respirator?

Consular decisions about how to end this pregnancy and under what anesthesia were our guidelines and helped us a lot in later decisions in severe forms of Covid -19 infections that we have been encountering for the last 2 years in a pandemic.

SPONSORS