Fusion

A student-led research publication of the George Washington University School of Medicine and Health Sciences | Spring 2020, Volume XIII

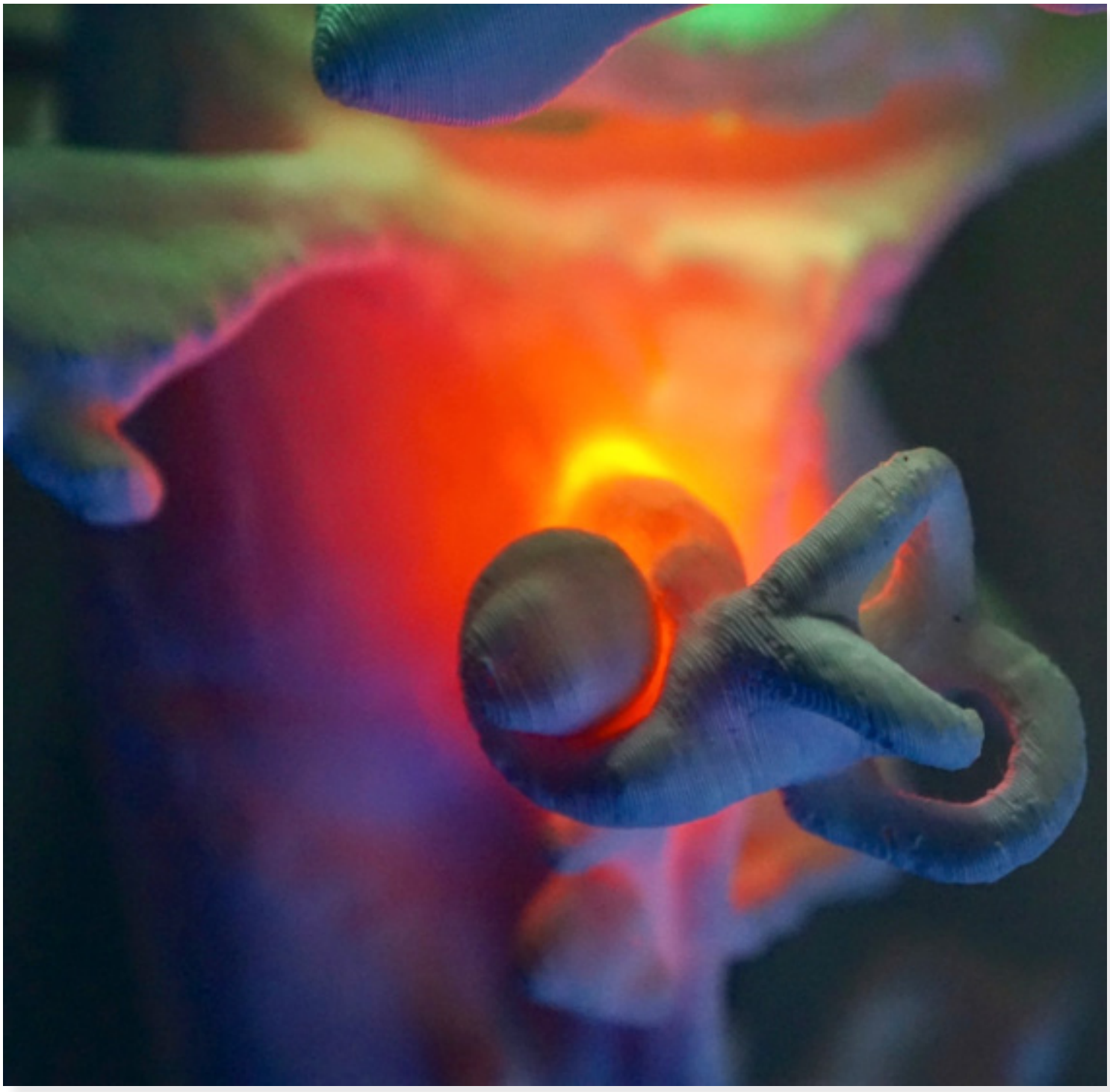


Table of Contents:

ON THE COVER: An image from a negative-space 3D printed model of the ventricular and cisternal system in the brain obtained from an MRI analysis and labeled with voice-activated LED lights. This image was produced by Cullen Fleming, MSIV, while doing research in neuroradiology under the guidance of research advisor Ramin Javan, MD, associate professor of radiology.

Photos like Flemings, capturing the beauty and intricacy of science, are featured annually in the George Washington University (GW) School of Medicine and Health Sciences (SMHS) Art of Science Contest. The competition began in 2018 as a means of highlighting the research that SMHS medical students, graduate students, and postdoctoral fellows are conducting.

Each year prizes are awarded for the top entries and the winning images are displayed in Ross Hall, alongside those from previous years.

WILLIAM H. BEAUMONT RESEARCH PRIZE WINNERS

BASIC SCIENCE RESEARCH: INFECTIOUS DISEASE

BASIC SCIENCE RESEARCH: MISCELLANEOUS

BASIC SCIENCE RESEARCH: ONCOLOGY

CLINICAL PRACTICE INNOVATION AND PUBLIC HEALTH/POLICY: CLINICAL PRACTICE INNOVATION AND POLICY

CLINICAL PRACTICE INNOVATION AND PUBLIC HEALTH/POLICY: PUBLIC HEALTH

Fusion

is a publication of the William H. Beaumont Medical Research Honor Society, in collaboration with SMHS Communications and Marketing.

Table of Contents:

GW MEDICAL STUDENT RESEARCH

FOURTH-YEAR MEDICAL STUDENT DARA BAKER, BS '16, was awarded a fellowship as part of the National Institutes of Health (NIH) Medical Research Scholars Program. The year-long research immersion program fosters career development among budding physician scientists. Baker is using induced pluripotent stem cell technology to develop retinal epithelial cells to treat degenerative eye diseases under the mentorship of Kapil Bharti, PhD, senior investiga tor at the National Eye Institute at the NIH.

In 2018, Baker received the William H. Beaumont Medi cal Society Student Research Awards for her abstract, The Role of DFMO in Helicobacter Pylori Infection: Modulation of ROS Response. In 2015, she received the Luther Rice Un dergraduate Research Fellowship through the GW Colum bian College of Arts and Sciences.

Robert Miller, PhD, GW vice president for research and senior associate dean for research at SMHS, presented Sarah McCormack, MSIV, with the 2019 Doris DeFord Speck and George Speck Endowed Prize.

Richard Simons, MD, senior associate dean for MD programs and professor of medicine at SMHS, presents the 2019 Walter Freeman Research Award for best research paper to (from left) Tina Boortalary, MD '19, (left) and Alastair Fritchen Murray, MD '19, (right).

METEOR Program

The Mentored Experience to Expand Opportunities in Research (METEOR) program is a competitive fellowship for underrepresented-in-medicine students. Students are supported for a six-week, pre-matriculation research summer and enroll in the research track. Participants also have the opportunity to work with a clinical and translational researcher who will serve as a mentor during their time in medical school, complete a second summer research internship after Year 1, and conduct a research elective during the third year of medical school. https://tinyurl.com/y86oxwmb

GW Research Showcase, formerly GW Research Days, is a one-day event highlighting the breadth of innovation and creativity across all disciplines at GW This event invites students and trainees to present their work and compete for top honors. Participants have the option of showcasing their research through interactive exhibits, in addition to poster presentations.

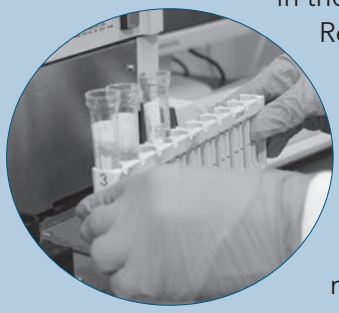
THE LAZARUS FAMILY SCHOLARSHIP PROGRAM

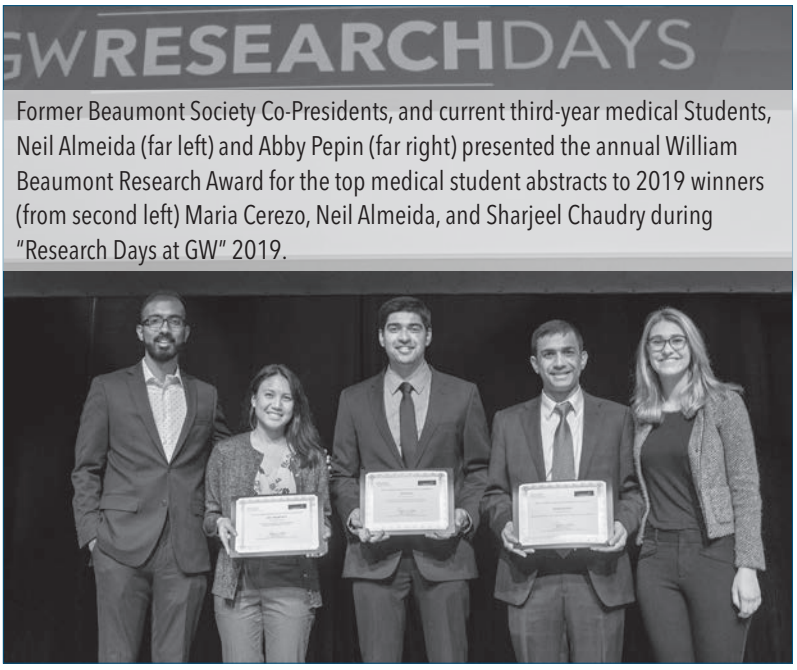
Christina Pugliese, MS IV, and Sowmya Mangipudi were the 2019 Lazarus Family Scholarship recipients. The program, established by Gerald Lazarus, MD, class of '63, and Audrey Jakubowski Lazarus, PhD, supports medical students as they pursue extraordinary educational opportunities in health care.

The program provides pivotal experiences for future leaders in health care, annually enabling one or more students to pursue a project or program. Students apply in the spring of their second year of medical school, and scholarship winners receive funding for their remaining years of medical school.

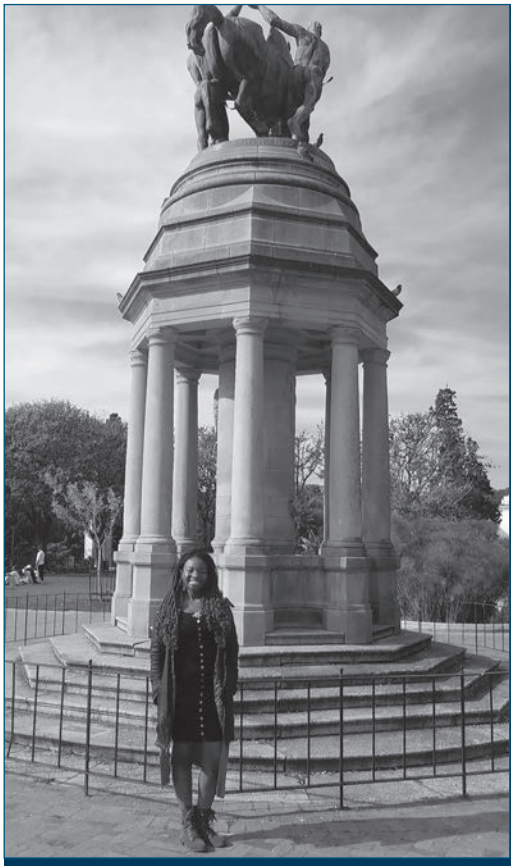
RESEARCH SCHOLARLY CONCENTRATION

Each year, roughly 50 students elect to participate in the Clinical and Translational Research Scholarly Concentration. The program promotes mentored research for students during the summer between MSI and MSII, and enables them to attend research lectures and follow-up with research scholarship. For details, see smhs.gwu.edu/oso/track-program/ clinical-and-translational-research





Former Beaumont Society Co-Presidents, and current third-year medical Students, Neil Almeida (far left) and Abby Pepin (far right) presented the annual William Beaumont Research Award for the top medical student abstracts to 2019 winners (from second left) Maria Cerezo, Neil Almeida, and Sharjeel Chaudry during "Research Days at GW" 2019.



REHEMA THOMAS is only in her second-year MD student, but she already has a head start on a specialzation in radiation oncology. During the summer of 2019, Thomas participated in the prestigious American Society for Radiation Oncology's (ASTRO) Minority Summer Fellowship.

"Radiation oncology is a field that's lacking in diversity, and that is something I want to make a change in," she said. "I want to make a difference in these outcomes because everyone deserves an equal chance at survival and beating cancer."

During her summer, Thomas worked with ASTRO member Curtiland Deville, MD, clinical director of radiation oncology at Johns Hopkins Kimmel Cancer Center at Sibley Memorial Hospital, on the use of photon and proton therapies in soft tissue sarcomas.

Letter from the Presidents

Andrea Klein, MSII

Hira Mohyuddin, MSII

As the co-presidents of the William H. Beaumont Medical Research Honors Society, we proudly present the 2020 edition of Fusion, the official medical research publication of The George Washington University (GW) School of Medicine and Health Sciences (SMHS). Fusion is an entirely student run publication that serves as a platform for medical students to share their work with the GW community. The fourteenth edition of Fusion received a record number of submissions spanning a broad range of research areas, including basic science, clinical research, translational research, biomedical engineering, quality improvement, public health and policy, education, and clinical practice innovation.

This past year has been an exciting time for the GW research community. The GW Strategic Initiative for improving the Research Ecosystem has set significant change in motion with four main goals: increasing support for faculty investigators, enhancing GW's research reputation by promoting university-led discoveries, aligning the missions of the research and academic enterprises, and enriching the student research experience by increasing access to faculty investigators. Additionally, the current leadership of Beaumont has spearheaded novel programs designed to provide new medical students with a structured path towards research success during medical school. Our most significant new program consists of a lecture and workshop series on navigating the research community, obtaining funding, and organizing a research project.

We would like to thank our mentors David Leitenberg MD, PhD, director of immunology in the Department of Laboratory Medicine at Children's National Hospital and associate professor of microbiology, immunology, and tropical medicine at SMHS; and Alison Hall, PhD, associate dean for research workforce development at SMHS, for their guidance as senior researchers and advisors for the Fusion journal. We are grateful for the efforts of the executive and editorial board members (listed on the table of contents) and their contributions to the journal.

We hope you enjoy this edition of Fusion and that you consider contributing next year!

Andrea Klein MSII
Hira Mohyuddin, MSII
Co-Presidents of the William H. Beaumont Medical Research Honor Society

Letter from the Editors

Scientific discovery and experimentation advance patient care and shape the way physicians practice. With an array of scholarly concentrations available to students at the George Washington University (GW) School of Medicine and Health Sciences (SMHS), our classmates advance the field of medicine in every aspect, from improving health care in low-resource regions to medical innovation and policy writing, and everything in between. As participants in these concentrations, medical students are tasked with going beyond the preclinical curriculum and addressing the problems of today's health care system. This formative appreciation for scientific discovery is key to deepening our knowledge and changing the way we — as the next generation of physicians — treat, cure, advocate for, and support our patients.

According to the Association of American Medical Colleges, the average pre-medical student matriculates with 1,251 hours of research. GW SMHS students are able to continue developing these research skills at the professional level in a variety of DC health care settings including: GW SMHS, Children's National Hospital, Washington DC Veterans Affairs Medical Center, and the National Institutes of Health. Early research experiences allow our students to be better prepared for careers in academia and show substantial interest in their chosen field to support a strong residency application. Given the time constraints of medical school, seeing a project through from conception to publication is no easy feat, and one that should be celebrated. Additionally, early involvement enables the student to be involved in clinical domains not previously explored and discover their true interests. Finding one's niche can be a winding and roundabout process, where faculty support can help a student not only develop research skills, but clarity of career interest.

As junior Fusion journal editors, we are delighted to highlight the diverse research initiatives unique to GW SMHS and driven by the strong intellectual curiosity present on our campus. Along with the research opportunities at GW SMHS, Fusion provides yet another opportunity for student involvement in all aspects of the research process including the art of presentation, manuscript writing, and presentation. Participation in research is beneficial for both the personal and professional development of our medical students, but even more so, for the better health for our society. Health care is an ever-changing field of practice with advances in medicine, expanded evidence sources, new treatment options, and changing governmental regulations and models of care. Early experiences in research equip our students with the ability to navigate this complex terrain and serve as leaders in the future.

Zach Falk, MSI
Aneka Khilnani, MSI
Zoe Shancer , MSI
Muhammed el Shatanofy, MSI
Co-Directors of Fusion


Zachary Falk, MSI


Aneka Khilnani, MSI


Zoe Shancer, MSI


Muhammed el Shatanofy, MSI

Faculty Advisor's Perspective

As the faculty advisor for this year's issue of Fusion, it is an honor to contribute my thoughts about medical education and research. As I've become more involved with medical student teaching over the last several years, I am continually struck by the diversity of student interests and backgrounds that each class brings to The George Washington University School of Medicine. The students that are admitted to the MD program at the George Washington University School of Medicine and Health Sciences (SMHS) have already achieved a significant level of academic success, but have also developed unique interests that set them apart as individuals. It is critical that, as students progress through medical school and postgraduate training, there be opportunities to preserve and foster the development of these existing and new unique interests. "Fusion" is a superb forum to celebrate some of the more individualized talents and interests of our students outside of the classroom.

Most students that enter medical school have a curiosity and enthusiasm about how the complexities of biological systems work and how this relates to clinical care. And just as importantly, many of our students have a strong interest in the critical role that public health systems play locally, nationally, and globally in impacting health. It is critical that this enthusiasm be supported and allowed to grow, as it will inform and influence student career paths and impact future attitudes toward patient care in multiple and often unforeseen ways.

The students involved in research and who have contributed to this issue of Fusion have a special role. You serve as role models to your peers by demonstrating a commitment to intellectual curiosity as you progress through medical school training.

Medical students at GW have multiple opportunities to pursue research experiences and complete a scholarly project outside of the required curriculum. Most commonly this involves participating in one of the nine scholarly concentrations that provide an academic structure and mentoring help for students throughout the four years of medical school. In order to support these endeavors, students are also encouraged to compete for external, nationally competitive research fellowships, as well as our own internal fellowship awards that provide valuable financial support for the students while they pursue summer projects. Our students' accomplishments are demonstrated by the many poster presentations at GW Medical Student Research day, presentations at more specialized national and international meetings, and publications in peer-reviewed journals.

As is evident in the following pages, there are many ways to achieve a meaningful research experience that span a broad range of interests and disciplines, including basic and translational science, clinical research, health policy and public health research, and education-related research. An additional essential component of a successful student research project is the dedication and enthusiastic guidance provided by our faculty mentors, both here at GW and at our DC area partner institutions, as well as outside academic centers nationally and internationally. We applaud and thank you for your efforts.

David Leitenberg MD, PhD, associate professor of microbiology, immunology, and tropical medicine at SMHS, and director of immunology in the Department of Laboratory Medicine at Children's National Hospital

Select gp120 V2 Domain Specific Antibodies Derived from HIV and SIV Infection and Vaccination Inhibit gp120 Binding to $\alpha_4\beta_7$

Matthew Liu, MSII
ADVISORS:
James Arthos, PhD,[1]
Anthony S. Fauci, MD[1]

[1] National Institute of Allergy and Infectious Diseases, National Institutes of Health

The GI tract is preferentially targeted during acute/early HIV-1 infection. The basis for preferential targeting of gut tissues is not well defined. Recombinant proteins and synthetic peptides derived from HIV and SIV gp120 bind directly to integrin $\alpha_4\beta_7$, a gut-homing receptor.[1]

To characterize the kinetic gp120-$\alpha_4\beta_7$ binding interaction, we developed a novel surface-plasmon resonance (SPR) based assay. In the presence of a physiologic 1mM $MnCl_2$ buffer, soluble $\alpha_4\beta_7$ demonstrated comparable affinities for surfaces coated with either MAdCAM-Ig fusion protein or recombinant A244 gp120. When $MnCl_2$ was removed, affinity for both MAdCAM and gp120 fell below the detection limit of this assay (Figure 1). This observation suggests that gp120 is likely to engage α4β7 only on cells with an enhanced potential to traffic to the gut. We replaced A244 gp120 with a synthetic cyclic 42 amino acid peptide fragment (cV2) derived from the V2 domain of 92TH023 gp120 (subtype A/E), whose sequence is nearly identical to that of A244 gp120 V2. The affinity of this peptide (cV2 92TH023) for α4β7 was close to that of A244 gp120, demonstrating that cV2 is sufficient to mediate the high-affinity interaction shown in Figure 1. When

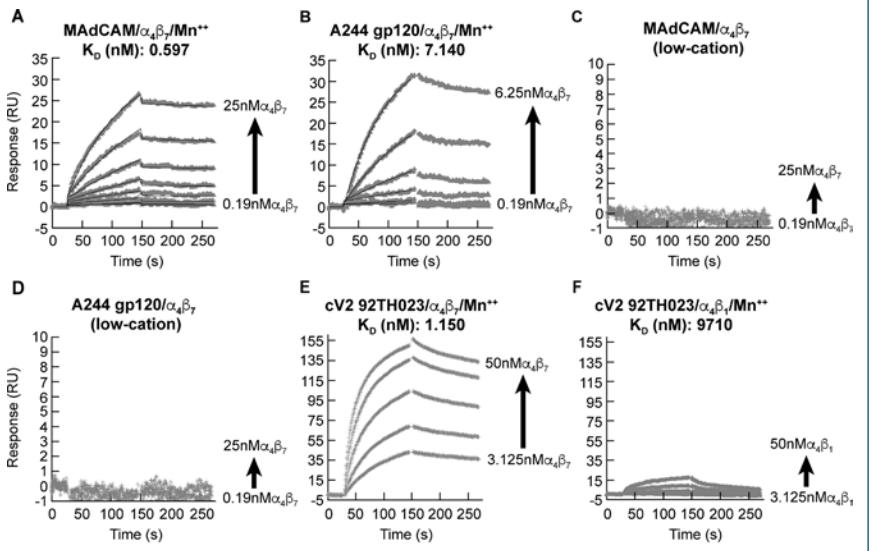


FIGURE 1: Specific affinity of α4β7 for HIV gp120, MAdCAM and SIV gp120

A) Sensorgram of increasing concentrations (2-fold) of soluble α4β7 passed over surface-immobilized MAdCAM in the presence of 1 mM MnCl2 for 120 sec, followed by a 120 sec washout/dissociation phase. Mass of bound α4β7 (y-axis) expressed as response units (RU). Affinity expressed as KD (nM) is shown. B) Same as in panel A, with immobilized A244 gp120. C) Same as in panel A with immobilized MAdCAM in the absence of divalent cations. D) Same as in panel A with immobilized A244 gp120 in the absence of divalent cations. E) Same as in panel A with immobilized cV2 92TH023 peptide. F) Same as in panel A with immobilized 92TH023 cV2 peptide and soluble α4β1 as the analyte. Each sensorgram is representative of three independent measurements of each analyte-ligand interaction.

we replaced $\alpha_4\beta_7$ with $\alpha_4\beta_1$, affinity for cV2 92TH023 was reduced by >8000 -fold, demonstrating binding specificity and the fact that V2, like MAdCAM, preferentially binds to $\alpha_4\beta_7$.

However, V2 peptides can adopt either α helical or β strand structures.[2] This is the case for a crystal structure of a linear V2 peptide derived from HIV isolate 92TH023 gp120 that complexes with mAb CH58 in a helical structure (Figure 2).[3] CH58 is a weakly-neutralizing mAb that was generated from an uninfected immunized individual who participated in the Rv144 vaccine trial.[4] It recognizes an epitope that maps within a short region of V2 (AA 168–181) identified by sieve analysis as sites of vaccine elicited immune pressure in the RV144 trial (Figure 2). Other V2-specific mAbs that recognize structures in this same region include mAb MK16C2 and mAb CAP228-16H, which were generated from a HIV-infected subject and gp120 immunized rabbit, respectively. We evaluated the ability of each of these mAbs to inhibit $\alpha_4\beta_7$ interactions with V2

Continued on p. 8

Continued from p. 7

using a cell-based adhesion assay where RPMI8866 cells expressing $\alpha_4\beta_7$ on the cell surface were allowed to adhere to synthetic V2 cyclic peptides. mAbs 2B4 and VRC01 were employed as specificity controls. mAbs CH58 and CAP228-16H, which recognize a helical structure, inhibited α4β7 adhesion to V2 by >90% while mAb 830A, which shows preference for the β strand, failed to show detectable interference (Figure 2).

In this study, we characterized the physical interaction between the HIV envelope and $\alpha_4\beta_7$, reasoning that such information could provide valuable insight regarding the role of $\alpha_4\beta_7$-expressing cells in HIV pathogenesis. We find that a subset of HIV and SIV V2 antibodies derived from both infected subjects and vaccine recipients can effectively block V2 $\alpha_4\beta_7$ interactions. Several of the vaccine-elicited weakly neutralizing mAbs have been linked with protection from infection. Rather than binding to the closed trimeric spike that is the primary target of broadly neutralizing antibodies, these mAbs recognize an alternative conformation of the V2 region. This suggests that $\alpha_4\beta_7$ also recognizes an alternative form of V2 that is conserved in both HIV and SIV.

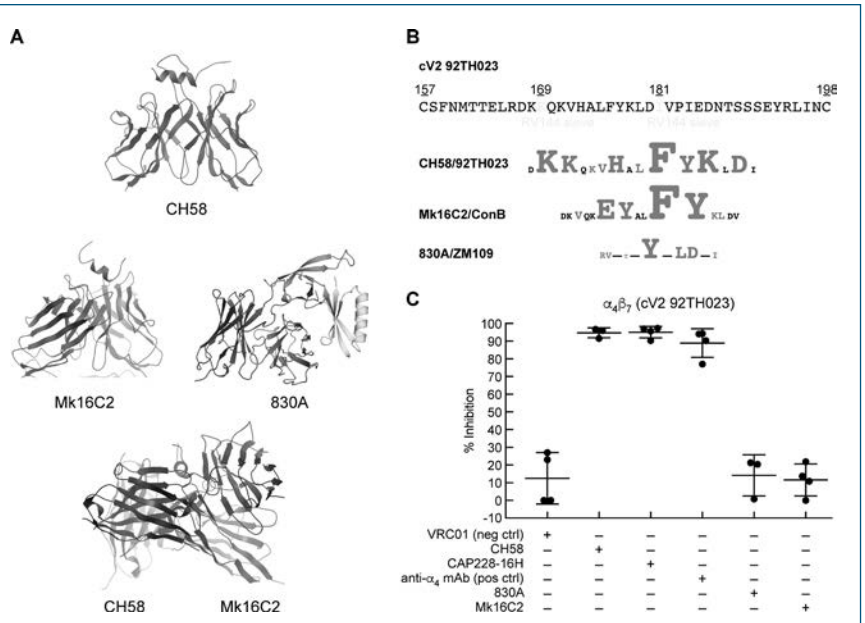


FIGURE 2: The structures of V2 mAbs in complex with peptides, and V2 mAb inhibition of α4β7 adhesion

A) Crystal structure of three V2 domain mAbs, CH58 (PDB ID: 4HPO), Mk16C2 (PDB ID: 6CEZ), and 830A (PDB ID: 4YWG) in complex with V2 peptides, and a superimposition of CH58 and Mk16C2 binding to opposite sides of the same helical region of a V2 peptide. Only the Fv regions are shown with the heavy chain, light chain, and the V2 epitope colored cyan, green, and magenta, respectively B) Amino acid sequence of the V2 domain of 92TH023. Residues in contact with each mAb are highlighted in magenta and the size of each amino acid is proportional to the contact surface area. C) Adhesion of RPMI8866 cells to cV2 92TH023 in the absence or presence of V2 mAbs: CH58, CAP228-16H, 830A, and Mk16C2. Adhesion was determined at OD590nm and listed as % inhibition in three or more independent experiments relative to cV2 92TH023 in the absence of any inhibitor (y-axis). Error bars indicate SD

REFERENCES:

1. Arthos J, Cicala C, Martinelli E, et al. HIV-1 envelope protein binds to and signals through integrin alpha4beta7, the gut mucosal homing receptor for peripheral T cells. Nat Immunol. 2008;9(3):301–9.
2. Aiyegbo MS, Shmelkov E, Dominguez L, et al. Peptide Targeted by Human Antibodies Associated with HIV Vaccine-Associated Protection Assumes a Dynamic alpha-Helical Structure. PLoS One. 2017;12(1):e0170530.
3. Liao HX, Bonsignori M, Alam SM, et al. Vaccine induction of antibodies against a structurally heterogeneous site of immune pressure within HIV-1 envelope protein variable regions 1 and 2. Immunity. 2013;38(1):176–86.
4. Rerks-Ngarm S, Pitisuttithum P, Nitayaphan S, et al. Vaccination with ALVAC and AIDSVAX to prevent HIV-1 infection in Thailand. N Engl J Med. 2009;361(23):2209–20.

Increased CD8+ T-cell Infiltration of the Brain Following Toxoplasma Gondii Exposure

Hira Mohyuddin, MSII

ADVISORS: Paul Marvar, PhD,[1] and Imtiaz Khan, PhD[1]

[1]The George Washington University School of Medicine and Health Sciences

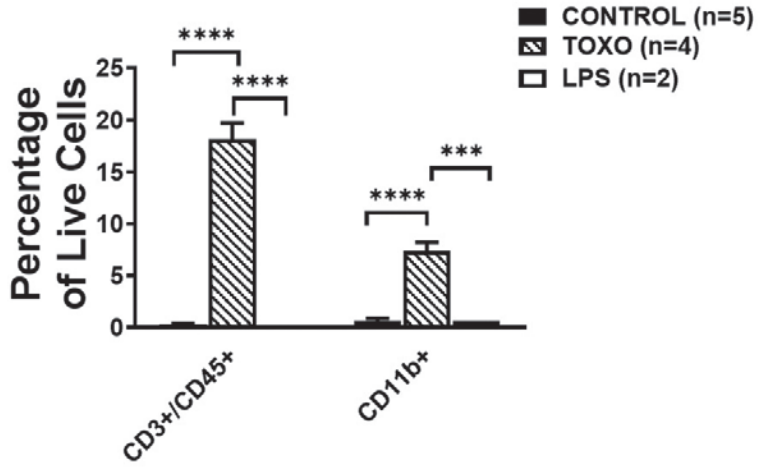


FIGURE 1:

Schizophrenia is an idiopathic neuropsychiatric condition with heterogeneous clinical presentations.1 For this reason, it is imperative to determine novel therapeutic targets and biological pathways mediating the pathogenesis of this disorder. Schizophrenia has been associated with chronic Toxoplasma gondii infection in numerous studies.1 Reactivation of latent Toxoplasma gondii infection in animals results from antigen specific CD8+ T-cell exhaustion and is reported as a complication of Toxoplasma gondii infection.2 The objective of this study was to determine whether Toxoplasma gondii (T. gondii) infection increases brain T-cell infiltrates as a potential trigger for the pathogenesis and behavioral alterations in schizophrenia. Namely, whether there would be an increase in the amount of T cells in brain tissue following infection with T. gondii and whether this differed from simple disruption of the blood brain barrier with lipopolysaccharide (LPS).

This study was conducted in a translational research lab. A total of 11 C57BL/6 mice were divided into three groups. One group (n=2, 12 weeks old) was injected with LPS 22 hours prior to sacrifice and brain collection. Successful blood brain barrier disruption has been reported between 18-24 hours following injection with LPS.3 The second group (n=4, 7 weeks old) was orally infected with ova transgenic parasites 5 weeks prior to sacrifice and brain collection. The control group (n=5, 8-12 weeks old) was not infected with T. gondii or injected with LPS prior to sacrifice and brain collection. Brain tissue was digested, stained with antibodies to determine the amount of CD4+, CD8+, CD3+/CD45+, and CD11b+ cells, and prepared for Flow Cytometry. Flow Cytometry results were analyzed with FlowJo and GraphPad Prism software.

The data from this study was analyzed with GraphPad Prism software. One-way ANOVAs were performed to compare the percentage of CD4+, CD8+, CD3+/CD45+, and CD11b+ cells from brain tissue between the different groups. The T. gondii infected group exhibited the highest average percentage of CD3+/CD45+ cells when compared to the LPS ($p<0.0001$) and control ($p<0.0001$) groups. The T. gondii group also exhibited the highest percentage of CD11b+ cells when compared to the control ($p<0.0001$) and LPS ($p=0.0003$) groups (Figure 1). Of the CD3+/CD45+ cells, the percentage of CD8+ and CD4+ was determined. The T. gondii group exhibited the highest percentage of CD8+ cells when compared to controls ($p=0.0377$) however there was no significant difference between the T. gondii and LPS groups or the control group and the LPS group. The control group exhibited the highest percentage of CD4+ cells when compared to the T. gondii group ($p=0.0080$) and the LPS group ($p=0.0035$) (Figure 2).

Compared to LPS and control groups, T. gondii infected mice exhibited the highest percentage of CD3+/CD45+ and CD11b+ cells. Additionally, when compared to the control group, the T. gondii group exhibited a higher percentage of CD8+ cells, which

Continued on p. 10

Continued from p. 9

suggests that T. gondii infection enhances CD8+ T-cell infiltration and may lead to enhanced T-cell exhaustion and the associated neurobiological and behavioral abnormalities in schizophrenia. In the future, we hope to further investigate whether schizophrenia-like brain and behavioral changes occur in mice infected with Toxoplasma gondii as a result of PD-1 mediated CD8+ T-cell exhaustion. In addition, we hope to determine whether antibodies targeting the PD-1 molecule will prevent these changes.

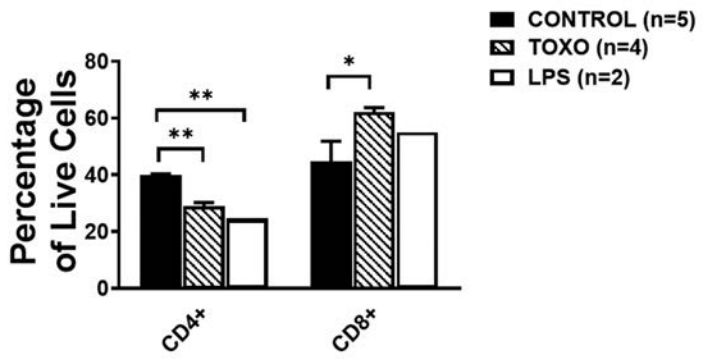


FIGURE 2:

REFERENCES

1. Xiao J, Prandovszky E, Kannan G, et al. Toxoplasma gondii: biological parameters of the connection to schizophrenia. Schizophrenia Bulletin. 2018;44(5);983–992.

2. Bhadra R, Gigley JP, Khan IA. PD-1–Mediated Attrition of Polyfunctional Memory CD8+ T Cells in Chronic Toxoplasma Infection. The Journal of Infectious Diseases. 2012;206(1);125-134.

3. Salkeni MA, Lynch JL, Otamis-Price T, et al. Lipopolysaccharide impairs blood–brain barrier P-glycoprotein function in mice through prostaglandin-and nitric oxide-independent pathways. Journal of Neuroimmune Pharmacology. 2009;4(2);276–282.

In vitro Analysis of Exocrine Pancreas Secretome on Islet Cell Phenotype – A Potential Therapy for Type 1 Diabetes

Melinda Z. Fu, MSII
CO-AUTHORS:
Matthew Klein,[1]
Emily Larkin MD,[1]
Norann Zaghloul, PhD '06, MS '01,[1]
ADVISOR: Magali J. Fontaine, MD, PhD[1]

[1]University of Maryland School of Medicine

Type 1 diabetes (T1D) is an autoimmune disease characterized by pancreatic β-cell destruction, resulting in insulin deficiency. The pancreas is anatomically unique because while it is predominantly an exocrine gland, 1-2% of it is composed of endocrine islets of Langerhans. Previous studies have focused on the role of the endocrine pancreas on regulation of exocrine function. However, there is evidence that the exocrine pancreas also plays a role in regulating the endocrine pancreas, yet the mechanism remains unclear.1 We previously showed that co-incubation of murine islets in vitro with trypsinogen induced β-cell proliferation. In this study, we report the potential role of another component of the exocrine pancreatic secretome, trypsin inhibitor, on inducing pancreatic β-cells into a proliferative phenotype in vitro. Islets were isolated from C57BL/6 mice by a midline incision, cannulation of the common bile duct with collagenase, and purification using a Ficoll gradient centrifugation. Islets were then plated in RPMI 1640/10% FBS/ 1% penicillin streptomycin and incubated at 37.50 C/ 5.0% CO2. After overnight recovery, islets were placed in media supplemented with 1/3 uL 1 ug/uL trypsin inhibitor (Sigma T0256). Following a five-day incubation, islets were harvested, dispersed and stained for insulin, glucagon, and Ki67 expression in order to identify β-cells, α-cells and proliferative cell populations, respectively. Cells were analyzed by flow cytometry with the gating scheme illustrated in Figure 1. The data from three separate experiments were analyzed using unpaired, two-tailed t-test using Prism software (Figure 2). Compared to islets incubated in media alone, the percent of islet cells incubated in trypsin inhibitor, showed a 7% increase in insulin expression (p>0.05), those expressing glucagon showed a 1.2% decrease (p>0.05), and those expressing Ki67 showed a 1.6% increase (p>0.05). However, the percent of islet cells expressing both insulin and Ki67 following trypsin inhibitor incubation was significantly

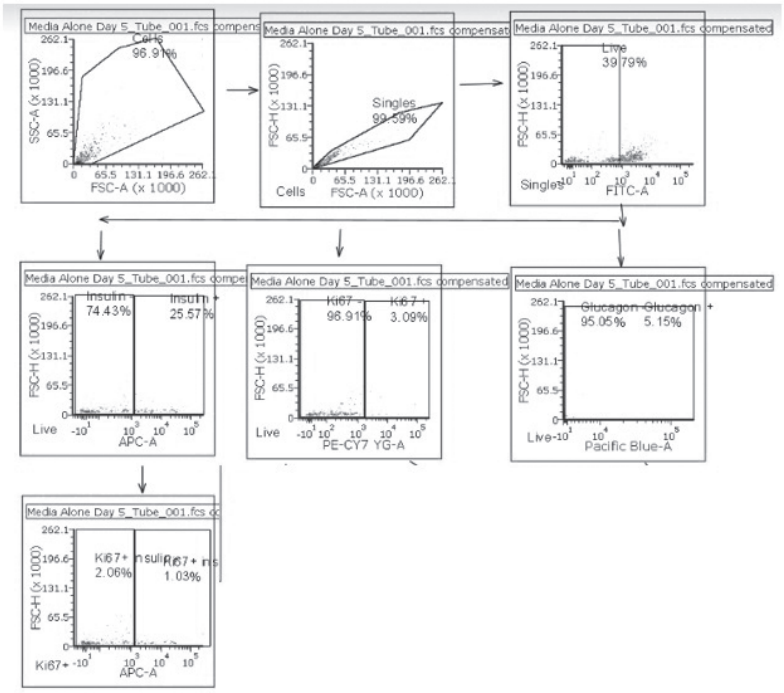


FIGURE 1: Flow cytometry gating scheme. Data was gated in the following order: cells, single cells, live cells. Then, live cells were gated for insulin, glucagon, and Ki67 expression, respectively Finally, a double gate was created by gating for Ki67 expression on top of the insulin gate.

These data suggest that the pancreatic exocrine secretome may play a role in regulating islet cell phenotype, which may pave a new avenue in T1D therapy via modulating β-cell mass.

Continued on p. 12

Continued from p. 11

increased by 4.4% compared to islet cells in media alone ($p<0.01$) (Figure 2). These data suggest that the pancreatic exocrine secretome may play a role in regulating islet cell phenotype, which may pave a new avenue in T1D therapy via modulating β-cell mass. Future studies will explore the functionality of islets treated in vitro with exocrine pancreatic secretome.

REFERENCES:

1. Demcollari TI, Cujba AM, Sancho R. (2017). Phenotypic plasticity in the pancreas: new triggers, new players. Current Opinion in Cell Biology. 49, 38–46. doi:10.1016/j.ceb.2017.11.014

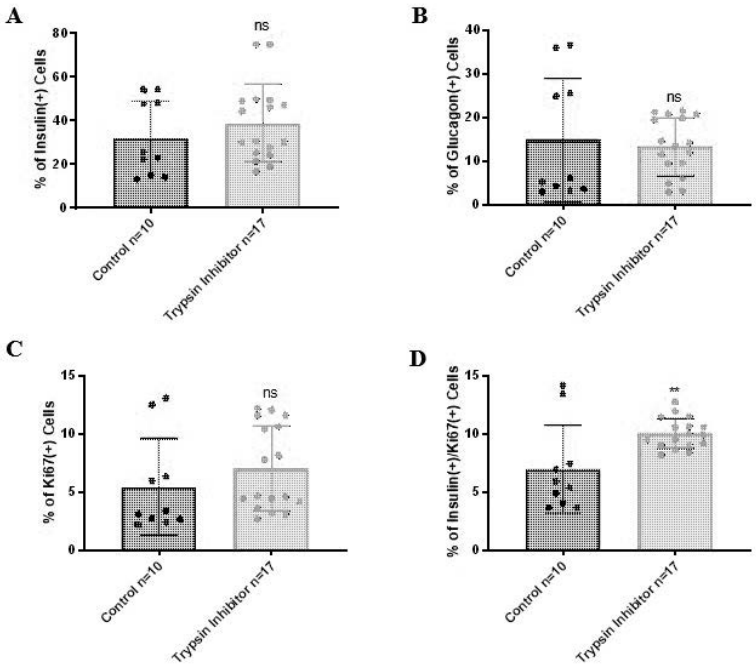


FIGURE 2: Cumulative data analysis from all three experiments showing no statistical significance iin the changes of percentage of cells that express insulin (A), glucagon (B), and Ki67 (C) between trypsin inhibitor treated islets and RPMI 1640 culture medium controls, except concurrent insulin and Ki67 expression with $p<0.01$.

Continued on p. 12

Cellular and Micro-Structural Brain Alterations in a Piglet Model of Cyanotic Congenital Heart Disease

Naeha Haridasa, MSII

ADVISORS:

Jingang Li, MD, PhD,[1] Van Lam MS1, Nobuyuki Ishibashi, MD[1]

[1]Center for Neuroscience Research, Children's National Hospital, Washington, D.C.

Significant neurodevelopmental delay is emerging as one of the most important current challenges for patients with congenital heart disease (CHD). Previous clinical studies demonstrate that reduced oxygen delivery due to CHD results in subnormal brain development.1,2 The piglet brain is a powerful new tool to study human brain development. We hypothesize that studies using the piglet model of chronic cerebral hypoxia will allow us to understand the underlying cellular events of chronic hypoxia in perpetuating neurodevelopmental damage in children with CHD.3 This study aims to evaluate the effect of chronic hypoxia on piglet brains through histological, DTI (diffusion tensor imaging) and NODDI (neurite orientation dispersion and diffusion imaging) analyses to determine the regional difference in the brain damage in CHD.

Piglets were exposed to either chronic hypoxia (10.5% O2: H(x) group, n=12) or sham-hypoxia (21% O2: N(x) group: n=12) from P3 to P14. Six piglets from each group were euthanized at day 14 (2-week N(x) and 2-week H(x)), and another 6 piglets from each group were subjected to grow under normal oxygen conditions from day 14 to six weeks of age (6-week N(x) and 6-week H(x)). Brains were extracted from piglets and examined using 1) immunohistochemical assays (Olig2+, CC1, PDGFR-α) to assess the cellularity alterations in white matter following chronic hypoxia, and 2) DTI (including fractional anisotropy (FA), axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD) images) and NODDI (including NDI, ODI, and KAPPA images) neuroimaging techniques.1,2 MRI-based piglet brain atlases were applied on DTI and NODDI images to evaluate structural differences between Hx and Nx brains.

Two-week Nx brains revealed a significant increase in the density of CC1-positive cells compared to 2-week Hx brains in white matter. A significant increase of fractional anisotropy (FA) intensity was also observed in the peripheral white matter of Nx brains compared to Hx brains at 2 weeks (Figure 1). Although the differences of FA intensity in the peripheral white matter disappeared between Nx and Hx at six weeks, central deep white matter revealed a significant decrease in FA intensity in Hx brains vs Nx brains at six weeks. Radial diffusivity (RD) mapping demonstrated a significant increase in the right anterior cortex in 2-week Nx brains compared to 2-week Hx brains. Orientation Dispersion Index (ODI) mapping also revealed a significant increase in central white matter regions between two weeks Nx and Hx (Figure 2). KAPPA mapping a significant increase in central gray matter regions between two weeks Nx and Hx.

The results reveal different cellular and microstructural alterations after chronic hypoxia between deep and peripheral regions in the piglet white matter. Studies using this model can provide important data needed to better interpret human imaging studies.

REFERENCES

1. Morton P, Ishibashi N, and Jonas R. ""Neurodevelopmental abnormalities and congenital heart disease: insights into altered brain maturation." Circulation research. 120.6 (2017): 960-977.

2. Morton P, Ishibashi N, and Jonas R, Gallo V. "Congenital cardiac anomalies and white matter injury." Trends in neurosciences. 38.6 (2015): 353-363.

3. Leonetti C, Back SA, Gallo V, Ishibashi N. "Cortical dysmaturation in congenital heart disease." Trends in neurosciences. (2019).

Utilizing a Novel Mass Cytometry Immunomonitoring Platform for the Characterization of Vaccine-Reactive, Epitope-Specific CD8+ T-cells in HLA-A*0201+ Patients with K27M+ Diffuse Midline Gliomas

Neil D. Almeida, MSIII
CO-AUTHORS: Jared Taitt, BS,[2] Takahide Nejo, MD, PhD,[2] Kaori Okada, PhD,[2] Maryam Shahin, MD,[2] Ryan Gilbert, BS,[2] Sabine Mueller, MD, PhD[2]
ADVISORS: Hideho Okada, MD, PhD,[2,3] Payal Watchmaker, PhD[2]

[1] George Washington University School of Medicine and Health Sciences
[2] University of California, San Francisco
[3] Parker Institute for Cancer Immunotherapy

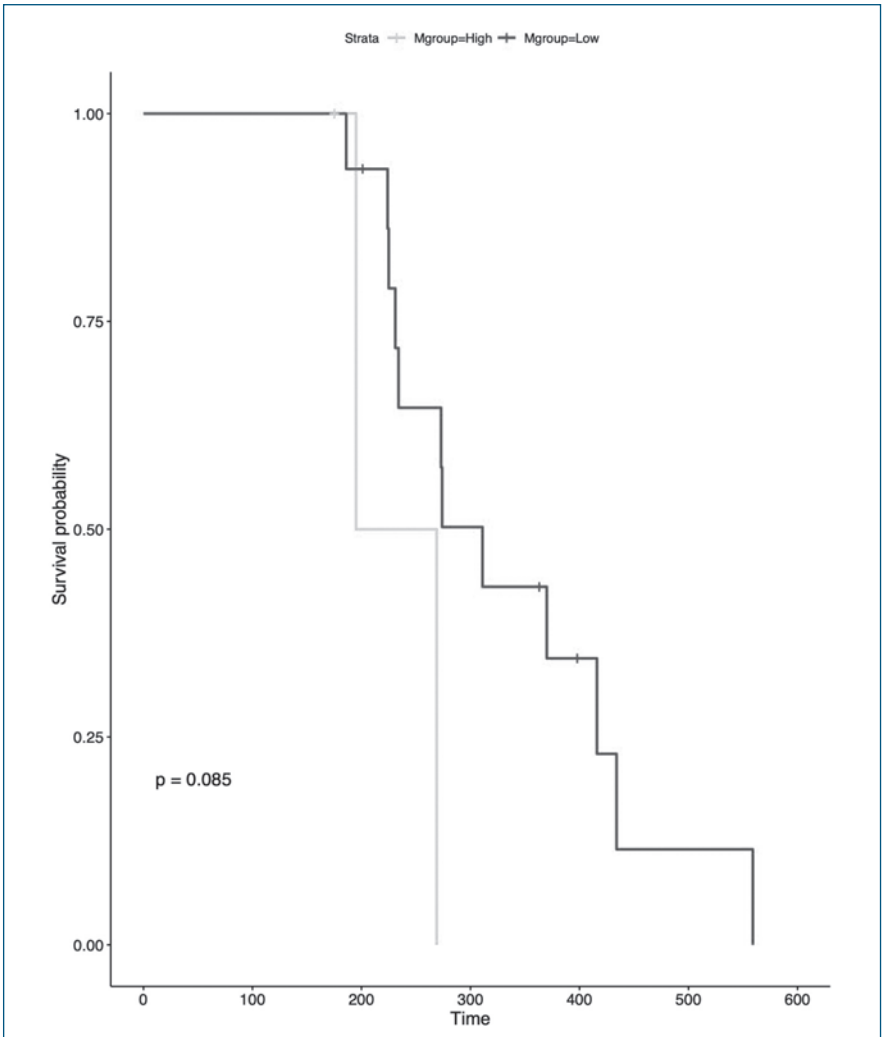


FIGURE 1: A multifaceted analysis incorporating patient-specific myeloid subpopulation proportions as well as H3.3K27M-specific CD8+ T-cells was conducted to elucidate potential trends that may exist between immune composition and clinical outcomes. While not statistically significant, patients with less than 25% of myeloid cells phenotyped as monocytic myeloid-derived suppressor cells (Mgroup) at baseline were found to have a hazard ratio (HR) of 0.10 (CI = 0.01-1.00, p-value = 0.051). Furthermore, non-statistically significant inverse trends between the baseline proportions of myeloid cells phenotyped as early myeloid-derived suppressor cells (Egroup) and H3.3K27M-reactive CD8+ T-cells (DexGroup) were observed.

Diffuse midline glioma (DMG), including diffuse intrinsic pontine glioma (DIPG), constitutes up to 20% of pediatric brain cancer and has a median survival of less than one year.1 We have identified a novel HLA-A*02:01-restricted neoantigen epitope encompassing the H3.3K27M mutation and implemented a pilot clinical trial through the Pacific Pediatric Neuro-Oncology Consortium (PNOC007). Newly diagnosed DIPG patients who are HLA-A2+ and H3.3K27M+ underwent radiation therapy, and then received the H3.3K27M peptide vaccine and tetanus toxoid (TT) peptide emulsified in Montanide in combination with poly-ICLC every three weeks for a total of 24 weeks.

Our objective is to characterize vaccine-induced H3.3K27M-specific T-cell subpopulations in peripheral blood mononuclear cells through the evaluation of surface markers correlated with activation, memory, and exhaustion phenotypes utilizing a novel H3.3K27M-specific dextramer-based mass cytometry method.[2]

Through this approach, the temporal expansion of vaccine-reactive CD8+ T-cells was observed in all patients (n = 4) who completed a minimum of 18 weeks of the study. These T-cells were subsequently stratified into discrete clusters on a tSNE plot using canonical CD8+ T-cell markers. Resultant clusters were further classified by their expression profiles, revealing distinct effector memory and exhausted subpopulations. Chronological monitoring of these groups indicates the time course-dependent development and persistence of vaccine-reactive exhausted and effector memory CD8+ T-cells in 75% of patients analyzed.

Furthermore, a comparative analysis of myeloid subpopulations revealed an inverse correlation between the expansion of monocytic myeloid-derived suppressor cells (M-MDSCs) and length of stay on the vaccine.3 Future plans include the analysis of regulatory T-cells (Tregs) and MDSCs of all enrolled patients to further investigate the relationship between the length of stay on the study and prevalence of immunosuppressive populations. This methodology offers insight into the progression of vaccine-induced patient immune responses and exhibits promise as a platform that may be extrapolated to other immunotherapies.

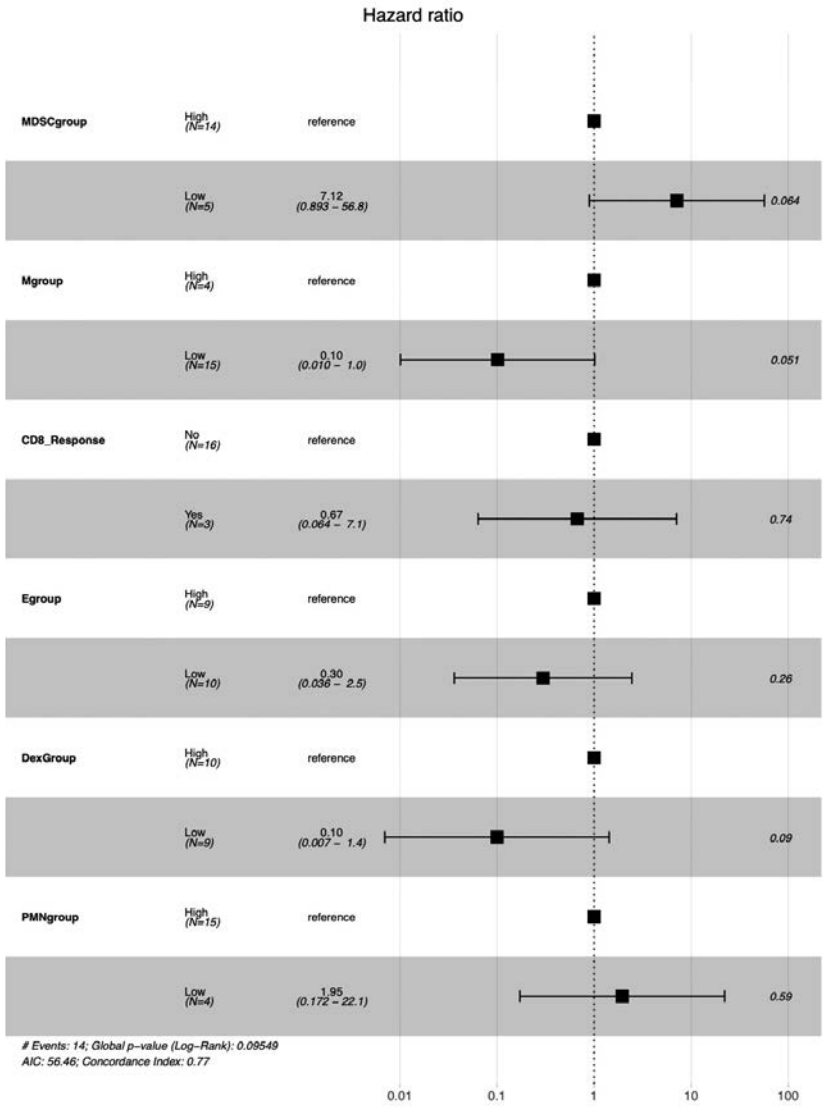


FIGURE 2: A Kaplan-Meier survival curve was conducted to elucidate the potential clinical implications of monocytic myeloid-derived suppressor cells (M-MDSCs). Patients were divided into cohorts containing greater (Mgroup=High) and less (Mgroup=Low) than 25% of myeloid cells phenotyped as M-MDSCs, revealing a trend of Mgroup=Low experiencing longer overall survival post-diagnosis, though not statistically significant (p-value = 0.085).

REFERENCES:

1. Warren KE. (2012). Diffuse intrinsic pontine glioma: poised for progress. Frontiers in oncology. 2, 205. doi:10.3389/fonc.2012.00205

2. Yang Z., Kim HJ, Villasboas JC, et al. (2019). Mass Cytometry Analysis Reveals that Specific Intratumoral CD4+ T-Cell Subsets Correlate with Patient Survival in Follicular Lymphoma. Cell Reports. 26(8), 2178–2193.e3. doi:10.1016/j.celrep.2019.01.085

3. Elliott LA, Doherty GA, Sheahan K, Ryan EJ. (2017). Human Tumor-Infiltrating Myeloid Cells: Phenotypic and Functional Diversity. Frontiers in immunology. 8, 86. doi:10.3389/fimmu.2017.00086

Clinically Relevant Genomic Alterations Identified by Targeted Exome Sequencing in U.S. Veterans with Prostate Cancer

Eman Dadashian, MSII

CO-AUTHORS:
Michael Nakazawa,[1,2] Neil Parikh, MD,[1,2] Nathisha Kalpage[1,2]

ADVISORS:
Nicholas Nickols, MD, PhD,[1,2] and Matthew Rettig, MD[1,2]

[1]David Geffen School of Medicine at University of California, Los Angeles
[2]U.S. Department of Veterans Affairs Greater Los Angeles

TABLE: PATIENT AND DISEASE CHARACTERISTICS

Characteristics	N = 81
Median age, years (range)	68
Gleason Score	
Gleason 6	1
Gleason 7	27
Gleason 8	19
Gleason 9	25
Gleason 10	7
Gleason unknown	2
Site of metastasis at sequencing	
bone	28
LN	15
viscera	6
Race	
White	30
African American	37
Hispanic/Latin American	8
Asian/Pacific Islander American	3
Native American	1
Declined to answer	2

Prostate cancer continues to be the most common non-cutaneous solid tumor diagnosed in men in the United States, with 13,000 new diagnoses among American male veterans annually, and is the second leading cause of death among American male veterans.[1,2] In an attempt to tailor treatments to each patient, specific mutations have been evaluated in tumors via targeted next generation sequencing (NGS).[3] Although studies using NGS in clinically aggressive prostate cancers have been done in the civilian population,[4,5] similar studies in veterans have not been performed to date. The purpose of this study was to characterize the genetic profiles of prostate cancer among a veteran population treated at the U.S. Department of Veterans Affairs Greater Los Angeles Healthcare System.

In this retrospective cohort study, we analyzed NGS data collected between August 2006 and September 2018. Archival or fresh prostate cancer tissue from 81 veterans (76 primary tumors, 5 metastases) underwent targeted sequencing via the Personalis ACE CancerPlus® next generation sequencing platform. The sequencing panel covers 181 genes frequently mutated in cancers. Clinically relevant genomic alterations were defined as changes in copy number or mutations (fusions, deletions, rearrangements, truncations) within established oncogene/tumor suppressor pathways such as DNA damage repair (DDR), PI3K/AKT, p53, MAPK, WNT and AR regulation. Patient demographic statistics and frequencies of mutations from the patient samples were tabulated.

The table presents the baseline characteristics of 81 prostate cancer patients in our study. A majority of patients had Gleason scores between seven and 10. At time of biopsy, the median age was 68, with metastases noted in the bone, lymph nodes, and viscera. Forty three percent of tissue samples from primary tumors had clinically relevant genomic alterations, including 6.2% with activating mutations in MAPK pathway members (KRAS, ERBB2, or BRAF), 3.7% with somatic mutations in DDR genes (BRCA2 or ATR), 7.3% with mutations in TP53 or RB1, 4.9% in APC, 1.2% in the WNT pathway (CTNNB1), 3.7% with mutations in the PI3K/AKT pathway (PIK3R1 or

AKT1), 3.7% with PTEN deletions, and 22.2% with alterations involving an AR regulated gene (SLC45A3 or TMPRSS) (Figure). Of the five metastatic tumor samples sequenced, one had a mutation in TP53 and one had an ETS gene fusion (Figure).

In this study, we demonstrate that NGS of prostate cancers in the veteran population is feasible and may help facilitate their enrollment in future precision oncology trials. Interestingly, only 43% of this cohort's tumors had detectable mutations, which is markedly different from other published data on prostate cancer where virtually 100% of patients have a detectable genetic lesion.[4] This difference in detected mutations may be due to genetic lesions that are present, but not recognized by the Personalis platform. Additionally, these tumors may be driven by epigenetic alterations that would require another approach to elucidate such events. Lastly, the genetic alterations of veterans' prostate cancer may be distinct from those in the civilian population, and are not readily detected by platforms such as Personalis. Thus, larger data sets, along with more robust sequencing platforms, are required for clarification.

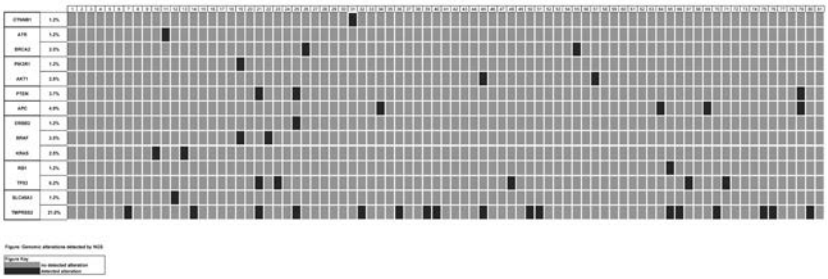


FIGURE: Each vertical row represents one of 81 patients, and each horizontal row represents the corresponding detected mutated gene. Vertical rows 37, 54, 61, 74, and 80 represent sequenced genes from the five biopsied metastatic sites while the rest represent genes from primary tumors.

REFERENCES:

1. Zullig LL, Sims KJ, McNeil R, et al. Cancer incidence among patients of the U.S. Veterans Affairs Health Care System: 2010 update. Military medicine. 2017; 182(7), e1883–e1891.
2. The Cancer Genome Atlas Research Network: Abeshouse A, Ahn J, Akbani R, et al. The molecular taxonomy of primary prostate cancer. Cell. 2015; 163(4), 1011–1025.
3. Morash M, Mitchell H, Beltran H, Elemento, O., & Pathak, J. The role of next-generation sequencing in precision medicine: a review of outcomes in oncology. Journal of personalized medicine. 2018; 8(3), 30.
4. Barata PC, Mendiratta P, Heald B, et al. Targeted next-generation sequencing in men with metastatic prostate cancer: a pilot study. Targeted oncology. 2018; 13(4), 495–500.
5. Mandelker D, Zhang L, Kemel Y, et al. Mutation detection in patients with advanced cancer by universal sequencing of cancer-related genes in tumor and normal DNA vs guideline-based germline testing. JAMA. 2017; 318(9), 825–835.

Ribavirin and DZNeP as Potential Therapeutics for Chordoma

Jayanidhi Kedda, MSII
CORRESPONDING AUTHORS: Sakibul Huq,[1] Betty Tyler[1]
ADVISOR: Henry Brem, MD[1]

[1]Hunterian Neurosurgical Laboratory, Department of Neurosurgery, Johns Hopkins University

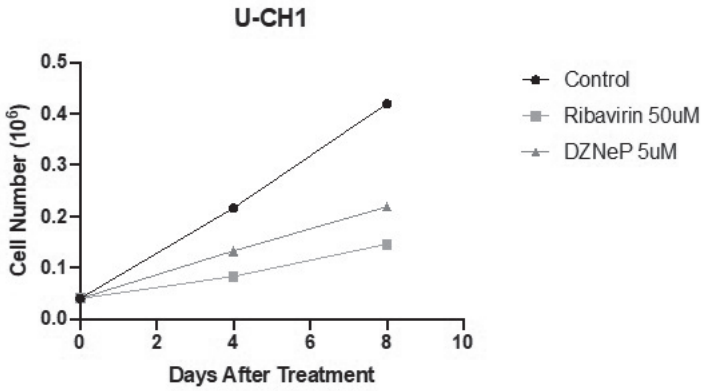


FIGURE 1: Proliferation assay of treated UCH-1 cells.

Chordoma is a rare and aggressive bone sarcoma of the skull base and sacrum. Due to its indolent nature, it often presents late into the disease progression. More than 30% of chordoma patients develop metastases, and ten-year survival rates remain approximately 50-60%. Though Although research has been increasingly active in this area to understand the tumor biology of chordoma, there are no currently FDA-approved treatments, leaving surgical resection and radiation as the mainstays of treatment. Introducing The development of new therapies for chordoma ultimately represents a substantial unmet medical need.[1]

We explored ribavirin, an antiviral drug approved to treat hepatitis C, as a potential therapeutic for chordoma. This drug was considered given its prior evidence of anti-tumor effects against other cancer types and also due to preliminary data from an assay indicating ribavirin directly decreases growth of chordoma cell lines. Ribavirin is known to target and inhibit eukaryotic initiation factor 4E (eIF4E), a regulatory subunit of the eIF4F complex that is known to be overexpressed in 30% of all cancers.[2] In studies examining the MAPK pathway, which can remove inhibitory control of eIF4E-Binding Protein 1 (4EBP1) on eIF4E via phosphorylation, almost all human chordomas showed immunoreactivity to not only eIF4E, but also to its phosphorylated form (p-eIF4E) and the phosphorylated form of 4EBP1, indicating its potential value as a new target for chordoma treatment.[3] However, as ribavirin has multiple cell targets, we also investigated DZNeP, a small-molecule inhibitor of S-adenosylmethionine-dependent methyltransferase activity. This includes inhibition of the histone methyltransferase EZH2, which has been implicated as a driver in a myriad of cancer types. Ribavirin also has been demonstrated to inhibit EZH2; we investigated the therapeutic potential of ribavirin and DZNeP in parallel in order to explore the comparative effectiveness of multiple potential targets in chordoma.[4]

Sacral and clival chordoma cell lines (U-CH1 and UM-Chor1, respectively) were utilized for in vitro experiments and treated with DZNeP and ribavirin in various micromolar concentrations. U-CH1 was assessed for cell growth via Cell Counting Kit 8 and proliferation assays, where cells were manually counted over three timepoints. UM-Chor1 was assessed for cell death (apoptosis) via flow cytometry with AnnexinV (AnnV) and Propidium Iodide (PI) staining. AnnV+/PI- staining indicates early apoptosis; AnnV+/PI+ indicates late apoptosis. Additionally, clonogenic assays were performed in both cell lines.

In proliferation assays of the U-CH1 cell line treated with ribavirin or DZNeP, a visible trend of steadily lower cell count over eight days for both ribavirin and DZNeP-treated cells was shown seen (Figure 1). Flow cytometry in the UM-Chor 1 cell line demonstrated a significant increase in the number of AnnexinV+ cells for those treated with DZNeP, and a trend toward apoptosis in cells treated with ribavirin (Figure 2). Clonogenic assays showed a trend toward decrease in clonogenic potential of U-CH1 but not UM-Chor1 cells when treated with ribavirin, while a decreased clonogenic potential was demonstrated in both cell lines when treated with DZNeP.

The use of ribavirin may present some currently mixed results in effectiveness against chordoma, but

this warrants further investigation as monotherapy and in combination therapy regimens with other treatment modalities, including radiation. The promising preliminary results using DZNeP imply that its targets may be a viable means for chordoma treatment. Further investigation into DZNeP through in vivo experiments may provide evidence pivotal for the treatment of this devastating cancer.

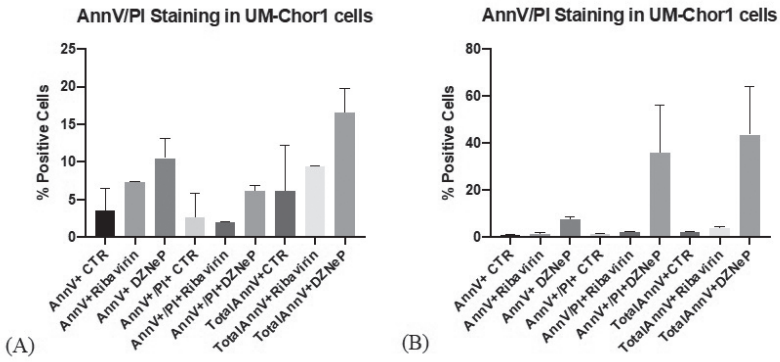


FIGURE 2: Flow cytometry data for UmChor1 cells at 6 days (A) and 9 days (B).

REFERENCES

1. Frezza AM, Botta L, Tramab A, et al. Chordoma: update on disease, epidemiology, biology and medical therapies. Curr Opin Oncol. 2019;31(2):114–120.
2. Casaos J, Gorelick NL, Huq S, et al. The Use of Ribavirin as an Anticancer Therapeutic: Will It Go Viral? Mol Cancer Ther. 2019;18(7):1185–1194.
3. Tamborini E, Virdis E, Negri T, et al. Analysis of receptor tyrosine kinases (RTKs) and downstream pathways in chordomas. Neuro Oncol. 2010;12(8):776–89.
4. Kim KH, Roberts CW. Targeting EZH2 in cancer. Nat Med. 2016;22(2):128–34.

BEAUMONT SOCIETY RESEARCH PRIZE WINNER

Functional Characterization of Next Generation Histone Deacetylase 6 Inhibitors

Guido D. Pelaez, MSII
CORRESPONDING AUTHORS: Satish Noonepalle, PhD,[1] Melissa Hadley, MS[1]
ADVISORS: Alejandro Villagra, PhD[1]

[1]The George Washington University School of Medicine and Health Sciences

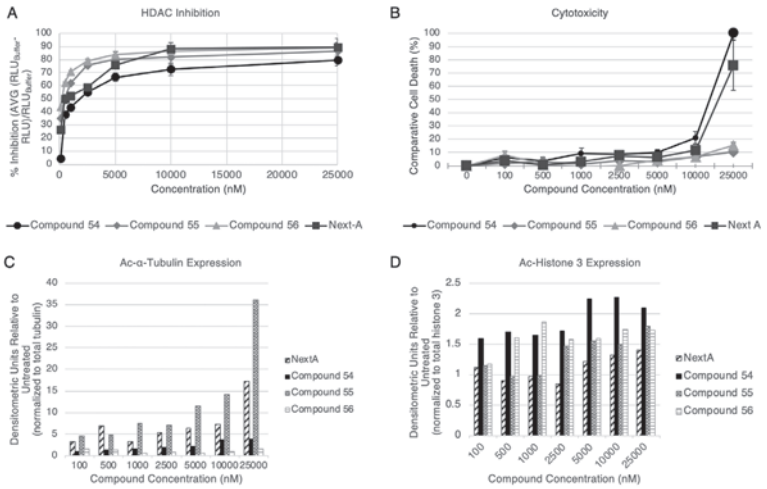


FIGURE 1: Functional characterization of next-generation HDAC6 inhibitors in comparison to Nexturastat A. SM1 Cells were cultured and treated with inhibitor ranging in concentration from 0.1 μM-25.0 μM for 24 hours. (a) HDAC6i potency was quantified using the HDAC-Glo™ I/II Assay (b) Compound cytotoxicity was evaluated using the CellTox™ Green Cytotoxicity Assay (c–d) Cells were lysed in RIPA buffer with 1X protease and phosphatase inhibitor for the evaluation of inhibitor specificity by immunoblot. Acetylated turbilin and histone 3 expression were analyzed by densitometry

Immune checkpoint blockade (ICB) has shown outstanding clinical success in the treatment of melanoma; however, a significant proportion of patients develop resistance or do not respond to ICB.[1] New focus has been placed on improving the efficacy of ICB through the inclusion of molecularly targeted agents such as histone deacetylase 6 inhibitors (HDAC6is). Histone deacetylases (HDACs) are important epigenetic modulators of gene expression that have been identified as prime cancer therapy targets. HDAC inhibitors have already shown significant anti-cancer effects through a primarily cytotoxic function;[2] however, recent studies also suggest that some inhibitors take on

Continued on p. 20

Continued from p. 19

a non-canonical role as modulators of immune-regulated signaling pathways.[3] For example, highly selective HDAC6is, including Nexturastat A (Next A), are able to heighten tumor immunogenicity and immune surveillance by modulating the expression of a variety of immunoregulatory proteins and shaping the inflammatory status within tumor microenvironments.[3] These non-canonical functions make HDAC6is ideal compounds for the potentiation of immunotherapeutic agents. This study characterizes the functional properties of three next-generation HDAC6is in comparison to NextA, as well as their non-canonical actions related to immune-regulated pathways and other non-cytotoxic cellular functions. Additionally, we aim to complement functional characterization with in vivo and ex vivo studies to determine anti-tumor activity in syngeneic melanoma models.

Three next-generation HDAC6is (SS-5-54, SS-5-55, SS-5-56), were compared to NextA at concentrations from 0.1 µM to 25 µM over 24 hours in vitro using murine melanoma SM1 cells. The potency and cytotoxicity of these inhibitors were quantified through HDAC-Glo™ I/II and CellTox™ Green Cytotoxicity assays, respectively. Immunoblotting was used to assess specificity with acetylated tubulin as a positive readout and acetylated histone 3 as a negative-unspecific readout. Highly specific HDAC6is were further evaluated for anti-tumoral activity and immunomodulatory effects in vivo using SM1 tumor-bearing C57BL/6 mice challenged with HDAC6i, αPD1, and combination therapy. Tumors were observed over 2 weeks, and subsequently resected, processed, and analyzed using flow cytometry against a comprehensive immune cell surface marker panel.

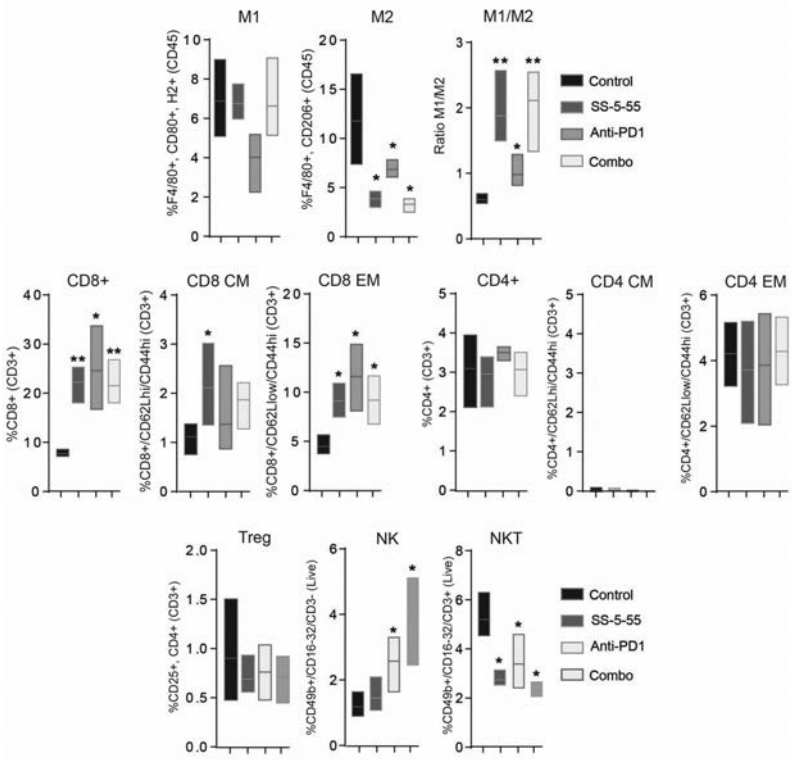


FIGURE 2: Compound SS-5-55 functions as an immunological agent.

We found that SS-5-55 best demonstrated characteristics of an ideal HDAC6 inhibitor with selectivity comparable to NextA. SS-5-55 exhibited significant potency beginning at low concentrations (2.5–5 µM) (Figure 1a), while maintaining low cytotoxicity above 10 µM where NextA becomes exceedingly cytotoxic (Figure 1b). Densitometric analysis of Western blots revealed that SS-5-55 increased acetylation of α-tubulin in a dose-dependent fashion, but not acetylation of Histone 3 (Figure 1c & d). This specificity reflects an essential characteristic of selective HDAC6 inhibition consistent with a non-canonical, immunomodulatory function. SS-5-55 demonstrated a 14.1-fold increase in acetyl-α-tubulin at 10 µM, whereas NextA led to a 7.2-fold increase.

Our results support the characterization of SS-5-55 as a minimally cytotoxic, selective HDAC6i that functions as an immunological priming agent capable of potentiating αPD1 immunotherapies.

Tumor-bearing mice treated with a combination of αPD1 and SS-5-55 showed significant reduction in tumor volume compared to individual therapies alone (data not shown). Combination therapy also demonstrated significant changes in the tumor microenvironment, exhibiting an increase in infiltrating

cytotoxic T-cell and natural killer T-cell composition, as well as cytotoxic T cell effector memory (Figure 2). Furthermore, combination therapy and SS-5-55 therapy alone demonstrated a significant increase in M1/M2 macrophage phenotype ratio; pro-tumorigenic M2 macrophages were significantly reduced, while pro-inflammatory M1 macrophages persisted.

Our results support the characterization of SS-5-55 as a minimally cytotoxic, selective HDAC6i that functions as an immunological priming agent capable of potentiating αPD1 immunotherapies. Further studies are needed to elucidate the compound's specific mechanism of action.

REFERENCES

1. Restifo NP, Smyth MJ, Snyder A. Acquired resistance to immunotherapy and future challenges. Nat Rev Cancer. 2016;16(2):121-6. doi: 10.1038/nrc.2016.2. PubMed PMID: 26822578; PMCID: PMC6330026.
2. Bose P, Dai Y, Grant S. Histone deacetylase inhibitor (HDACI) mechanisms of action: emerging insights. Pharmacol Ther. 2014;143(3):323-336. doi:10.1016/j.pharmthera.2014.04.004
3. Knox T, Sahakian E, Banik D, et al. Selective HDAC6 inhibitors improve anti-PD-1 immune checkpoint blockade therapy by decreasing the anti-inflammatory phenotype of macrophages and down-regulation of immunosuppressive proteins in tumor cells. Scientific Reports. 2019;9(1):6136. doi: 10.1038/s41598-019-42237-3.

Sensitivity of Malignant B-Cell Lines to PI3KD Inhibitors

Emily Sun MS II

ADVISOR:

Norman Lee, PhD[1,2]

[1]The George Washington University (GW) School of Medicine and Health Sciences, [2]GW Cancer Center

With an estimated 117,470 new cases of B-cell malignancies in the United States in 2016, B-cell malignancies are currently treated with phosphoinositide-3 kinase delta (PI3KD) inhibitors, such as idelalisib, a p110δ isoform-specific PI3K inhibitor.[1,2] Idelalisib, in combination with rituximab, is US FDA approved for the treatment of relapsed or refractory chronic lymphocytic leukemia (CLL).[3] However, despite idelalisib being an effective treatment for B-cell malignancies, 28% of patients are resistant to idelalisib therapy.[2] The mechanism of this resistance is unknown. Our laboratory's proposed mechanism of resistance is aberrant over-expression of the short isoform of PI3KD (PI3KCD-S), formed through alternative RNA splicing (AS) in idelalisib-resistant patients.

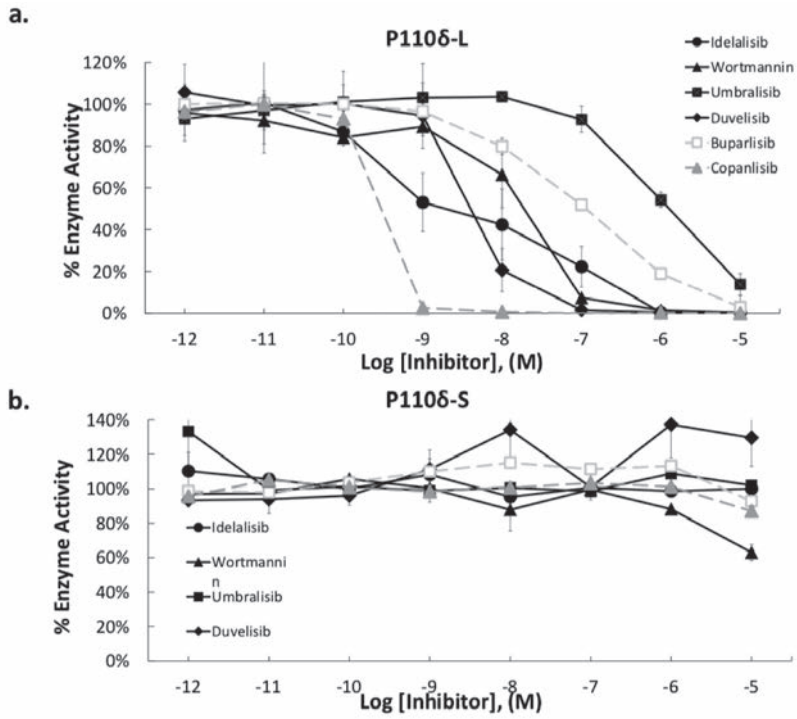


FIGURE C1: P110δ-S kinase activity is resistant to new PI3K inhibitors copanlisib and buparlisib a. The long isofor exhibits does-dependant sensitivity (inhibition) to currently available PI3K inhibitors used clinically to treat B-cell malignancies, including copanlisib and buparlisib b The short isoform is resistant to currently available PI3K inhibitors, including copanlisib and buparlisib

AS is a cellular post-transcriptional regulatory process that produces alternative mRNA transcripts, which encode distinct protein isoforms.[4] We hypothesize that a higher ratio of short to long (S/L) isoforms of PI3KD is associated with greater resistance to idelalisib.

Previous cell-free kinase assays in our laboratory have demonstrated

Continued on p. 22

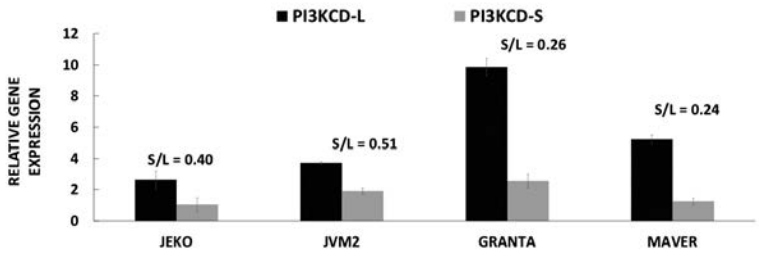


FIGURE 2: Gene expression of PI3KCD-S and PI3KCD-L RT-PCR was used to measure the expression of the long and short varients of PI3KCD The S/L ratio was calculated for each cell line. Malignant B-cell lines, JeKo-1 and JVM2, exhibiting the highest S/L ratio were resistant to the apoptotic and anti-prolierative effects of idelalisib

Continued from p. 21

that the recombinant short PI3KD isoform, but not the long isoform (PI3KCD-L), is resistant to the PI3KD inhibitors idelalisib, umbralisib, and duvelisib. We tested two additional PI3KD inhibitors, copanlisib and buparlisib, recently shown to be effective in treating B-cell malignancies. Both inhibitors were likewise ineffective in reducing activity of PI3KCD-S, while potently inhibiting activity of PI3KCD-L.

In the second phase of the experiment, we tested the sensitivity of malignant B-cell lines (JeKo-1, Maver-1, Granta, JVM-2), which express varying levels of the short and long mRNA variants of PI3KD, to idelalisib using Caspase-glo® 3/7 assay to measure apoptosis and BrdU assay to measure proliferation. The results demonstrate that the four cell lines possess varying sensitivities to idelalisib. More specifically, Granta and Maver cells showed greater sensitivity to idelalisib, while JeKo-1 and JVM-2 showed greater resistance to idelalisib. These results suggest that the expression level of PI3KCD-S may have an important role in conferring varying degrees of resistance to PI3KD inhibitors.

With these results, we correlated these varying degrees of resistance to idelalisib with S/L expression ratios measured by RT-PCR. Malignant B-cell lines JeKo-1 and JVM-2, the two cell lines that were resistant to the apoptotic and anti-proliferative effects of idelalisib, exhibited higher S/L ratios, while the two cell lines that were sensitive to the effects of idelalisib, Granta and Maver, showed lower S/L ratios. While these results are preliminary, a high S/L ratio is shown to be associated with resistance to the apoptotic and anti-proliferative effects of idelalisib, supporting our hypothesis that aberrant over-expression of PI3KCD-S contributes to primary and acquired resistance in patients with B-cell malignancies.

Malignant B-cell lines JeKo-1 and JVM-2, the two cell lines that were resistant to the apoptotic and anti-proliferative effects of idelalisib, exhibited higher S/L ratios, while the two cell lines that were sensitive to the effects of idelalisib, Granta and Maver, showed lower S/L ratios.

In the future, we aim to accomplish two additional tasks: 1) employ CRISPR to knock-out the PI3KD gene in malignant B-cell lines followed by ectopic over-expression of either the long or short variants of PI3KD, and 2) procure retrospective human patient specimens to measure the S/L expression ratio of PI3KD and correlate these findings to idelalisib resistance. We hypothesize that patients displaying resistance to idelalisib will present with malignant specimens exhibiting a high S/L expression ratio of PI3KD. Conversely, patients displaying sensitivity to idelalisib will present with malignant specimens exhibiting a low S/L expression ratio of PI3KD. These findings emphasize the role of PI3KCD-S in B-cell malignancies resistant to PI3KD inhibitors and the necessity for precision medicine in the clinical setting to improve therapy for patients with B-cell cancers.

REFERENCES

1. Teras LR, Desantis CE, Cerhan JR, Morton LM, Jemal A, Flowers CR. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA: A Cancer Journal for Clinicians. 2016; 66(6), 443-459. doi:10.3322/caac.21357

2. Woyach JA, Johnson AJ. Targeted therapies in CLL: Mechanisms of resistance and strategies for management. Blood. 2015;126(4);471-7. doi:10.1182/blood-2015-03-585075

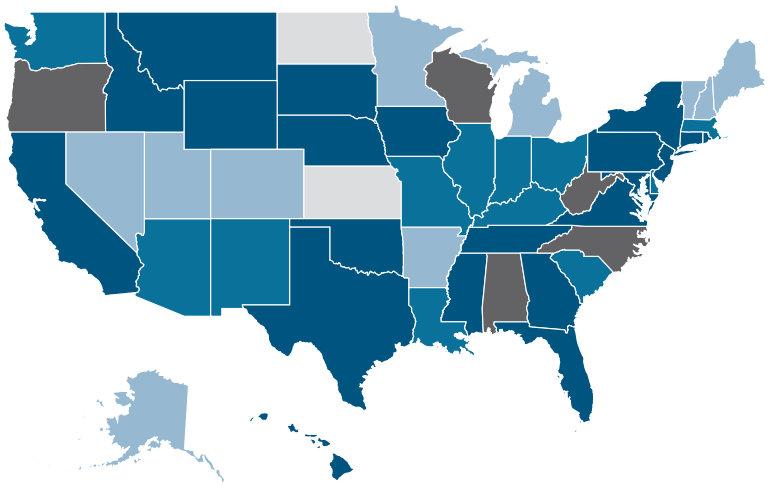
3. Cheah CY, Fowler NH. Idelalisib in the management of lymphoma. Blood. 2016;128(3);331-6. doi:10.1182/blood-2016-02-702761

4. Wang B, Ceniccola K, Hwang S, et al. Erratum: Corrigendum: Alternative splicing promotes tumour aggressiveness and drug resistance in African American prostate cancer. Nature Communications. 2017;8(1). doi:10.1038/ncomms16161

Postpartum LARC Coverage by State in Medicaid: Implications for Policy Improvement

Megan Fuerst, MSIV
ADVISORS:
Karen George, MD,[1,2] Jennifer Moore, PhD, RN2

[1]The George Washington University School of Medicine and Health Sciences
[2]Institute of Medicaid Innovation



	Device	Insertion
	Part of Global Payment	Separate Payment
	Part of Global Payment	Part of Global Payment
	Separate Payment	Separate Payment
	Separate Payment	Part of Global Payment
	No Data Collected	

FIGURE: Variation in Medicaid Postpartum LARC Insertion Coverage by State[2,4] Policies also reviewed from individual state medicaid agency websites

In the United States, approximately 45% of pregnancies are unintended, which is among the highest rates in the developed world. Long-Acting Reversible Contraceptives (LARC) are the most effective form of contraception and therefore are a crucial piece of achieving reproductive health equity for low-income populations.[1] Medicaid covers approximately 19.4 million low-income women of childbearing age (WCBA), and this benefit is required to cover family planning services without restrictive prior authorizations or cost-sharing.[2,4] In non-Medicaid expansion states, many WCBA only qualify for Medicaid after becoming pregnant and subsequently lose this coverage 60 days after delivery. As such, women who would like to start a LARC method would benefit from that method being available to them in the hospital after delivery and prior to discharge. This is called postpartum LARC insertion, which is a safe and highly effective method of contraception recommended by the American College of Obstetrics and Gynecology.[1] Despite the perceived benefits of this insertion method, it is under-utilized among the Medicaid population and presents an enormous opportunity for policy improvement.

Barriers to postpartum LARC insertion exist at the state, health plan, provider and patient levels. The devices are expensive to stock and often poorly reimbursed by insurance carriers. The Center for Medicaid Services (CMS) has provided guidance on postpartum LARC insertion recommending that it be unbundled from the global maternity payment, but each state has the autonomy to make its own policies. Coverage policies also depend on factors such as state distribution of Medicaid through Managed Care of a Fee for Service Model or state expansion of Medicaid through the Affordable Care Act.

This research project evaluated the language that State Medicaid Agencies used in describing their LARC policies and postpartum LARC access in particular in order to evaluate the variation that exists across states. The biggest variation in language regarded if the insertion procedure and the device itself were reimbursed separate from the global maternity payment as recommended by CMS. The results are highlighted in the map created in Figure 1.[2,4] The majority of states do reimburse for the LARC device or insertion outside of the global payment. However, little correlation could be found among state

Continued on p. 24

Continued from p. 23

political preference, demographics, or Medicaid distribution method.

A literature review revealed evidence from two states demonstrating that after an unbundling policy change was implemented, more patients did receive LARC devices in the immediate postpartum period.[3,5] The policy review also highlighted unique innovations to payment barriers. For example, the state of Texas contracts with specialty pharmacies that bill Medicaid directly and ship LARC devices to providers to avoid high upfront costs.[2]

When thinking about reproductive health policy, it is equally important to acknowledge the historical context where black and poor women are frequently victims of reproductive coercion, forced sterilization, and racism. Many of these issues still exist today creating distrust of LARC in these communities.[1] The goal of any policy would be to create an environment where women can choose their preferred method of family planning, while recognizing that unique barriers to LARC also need to be addressed. In conclusion, this research is only a small piece of the puzzle in terms of improving reproductive equity for all women. More research needs to be done to better understand what policy innovations will improve access to LARC among WCBA receiving Medicaid while preserving reproductive equity. In the short-term however, unbundling LARC device and insertion from the global maternity payment may be an easy first step.

When thinking about reproductive health policy, it is equally important to acknowledge the historical context where black and poor women are frequently victims of reproductive coercion, forced sterilization, and racism. Many of these issues still exist today creating distrust of LARC in these communities.[1]

REFERENCES:

1. Committee on Obstetric Practice. Immediate Postpartum Long-Acting Reversible Contraception. American College of Obstetrics and Gynecology. 2016. (Accessed Jan. 1, 2020 at www.acog.org/Clinical-Guidance-and-Publications/Committee-Opinions/Committee-on-Obstetric-Practice/Immediate-Postpartum-Long-Acting-Reversible-Contraception)

2. Wachino V. State Medicaid Payment Approaches to Improve Access to Long-Acting Reversible Contraception. Department of Health and Human Services Centers for Medicare and Medicaid Services, 2016. (Accessed Oct. 4, 2019 at www.medicaid.gov/federal-policy-guidance/downloads/cib040816.pdf)

3. Goldin Evans M, Broyles S, Frederiksen B, et al. Long-acting reversible contraceptive utilization after policy change increasing device reimbursement to wholesale acquisition cost in Louisiana. Am J Obstet Gynecol. 2019 Aug;221(2):128.

4. Kaiser Family Foundation. Medicaid Coverage of Intrauterine Devices (IUDs) and Implants and Reimbursement Policy. (Accessed Oct. 4, 2019, at www.kff.org/womens-health-policy/state-indicator/medicaid-coverage-of-intrauterine-devices-iuds-implants-and-reimbursement-policy/)

5. Steenland MW, Pace LE, Sinaiko AD, Cohen JL. Association Between South Carolina's Medicaid's Change in Payment for Immediate Postpartum Long-Acting Reversible Contraception and Birth Intervals. JAMA. 2019 July 2;322(1):76-78.

Intended or Unintended Consequences of Medicare's Merit Based Incentive Payment System (MIPS): Consolidation as a Requisite for Success

David M. Kauffman, MSII
ADVISORS: Brian Choi, MD, MBA,[1] William Borden, MD, MBA[1]

[1] The George Washington University School of Medicine and Health Sciences

The uncertainty surrounding Medicare Quality Payment Programs (QPP) such as the Merit Based Incentive Payment System (MIPS) has forced many organizations to strategize on how to achieve success under value-based payment systems. Originally promised larger payment incentives than received, many provider groups are questioning the effectiveness of MIPS in achieving stated policy goals. At present, the MIPS score measures a provider organization's performance in four key areas: quality, cost, promoting interoperability (PI), and improvement activities.1 The subsequent score received forms the basis for a negative, neutral, or positive Medicare Part B payment adjustment as shown in Figure. With the goal of investigating these trends and their implications for public policy moving forward, a financial model was created to predict the extent of PI participation for organizations of varying sizes. This model specifically analyzed the feasibility of PI measures because they are among the most capital-intensive measures and thus most useful in elucidating group decision-making. Ultimately, we sought to determine whether Centers for Medicare and Medicaid Services CMS incentives were likely to be effective in achieving their goals and the ramifications of the incentives on the United States health care system as it transitions to value-based care.

Group Size	Relative MIPS Percentile (Percentage Score)	PI Nonparticipation ($)	PI Incentive ($)	PDMP Query Incentive ($)
Individual (1)	25th to 50th (37%)	(580)	95	15
	75th (85%)	400	1,800	230
Small (2-15)	25th (0%)	(37,000)	N/A	N/A
	50th (37%)	(4,100)	670	80
	75th (85%)	2,800	13,000	1,600
Medium (16-99)	25th (37%)	(24,000)	4,000	500
	50th and up (85%)	17,000	75,000	9,700
Large (100+)	25th and up (85%)	40,000	180,000	23,000
Very Large (500+)	25th and up (85%)	200,000	890,000	120,000

TABLE: Financial Incentives by Group Size and Percentile Performance. This table summarizes the incentives and financial penalties for varying levels of compliance with MIPS measures as determined by the financial model. PI Nonparticipation is the Medicare payment adjustment received if the group decides to report a zero for PI measures to CMS. PI Incentive is the Medicare revenue gain if the group participates in PI to the percentage score of their respective percentile of overall MIPS performance. The PDMP Query incentive is the revenue gain if the group decides to pursue the 5 bonus points by searching a state PDMP database before prescribing an opioid.

Solo, small, medium, large, and very large practices were modeled using available data and final rules published by the US Department of Health and Human Services (HHS).1 MIPS payment adjustment projections were extrapolated for the range of possible MIPS scores as shown in Figure. The approximation of group MIPS performance under varying conditions was performed using quartile MIPS performance data generated from a sample distribution of approximate MIPS scores.2

The resulting financial incentives for MIPS participation are shown in Table. MIPS incentivizes performance proportionally, and as a result, the scale of operations is critical to the financial viability of compliance. Larger groups have a greater capacity to implement operational changes and make capital investments due to their financial leverage and advanced organizational structure. Also, larger groups likely have dedicated clinical leaders, more sophisticated electronic health record support, and contracts with experienced consultants to ensure maximal compliance with MIPS objectives. Small groups may not have the capital nor dedicated administrators to comply fully with

Continued on p. 26

Continued from p. 25

MIPS objectives, placing them at a disadvantage. Rather than invest in technological solutions to advance their health care practice, smaller organizations are more likely to maintain financial viability through non-compliance.

Our analysis demonstrates that current MIPS policy creates a "reverse Robin Hood" effect whereby larger groups gain additional Medicare revenue on the backs of lower performing, smaller groups. These larger groups inevitably absorb smaller groups that cannot survive under these conditions, making MIPS policy an effective force of consolidation in the health care marketplace. It is conceivable that a long run goal of MIPS was to encourage consolidation so entities would be more responsive to policy changes in the future. In this way, MIPS may lead to an increase in overall health care quality in the U.S. health care system through the adoption of CMS value-based measures. Another goal may have been to encourage the creation of large entities capable of assuming financial risk in order to lower total Medicare expenditures. While the QPP value-based payment system is still in its infancy in the United States, current policy may also be incentivizing a provider market with less competition.

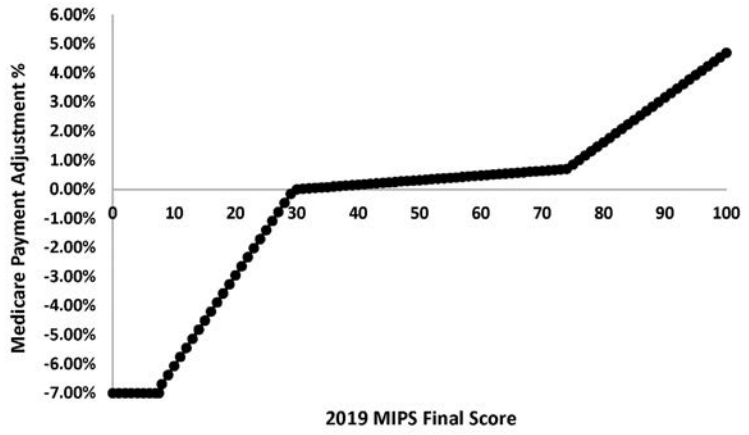


FIGURE: Projected Payment Adjustments by MIPS Score for PY2019 [1]. CMS projections for the base incentive (1.11%) and exceptional performance bonus (3.58%) were distributed among the range of MIPS scores possible in the model to predict Medicare Part B incentive payments as a function of MIPS score received.

REFERENCES

1. U.S. Department of Health & Human Services, Centers for Medicare and Medicaid Services. Medicare Program; Revisions to Payment Policies Under the Physician Fee Schedule and Other Revisions to Part B for CY 2019; Medicare Shared Savings Program Requirements; Quality Payment Program; Medicaid Promoting Interoperability Program; Quality Payment Program-Extreme and Uncontrollable Circumstance Policy for the 2019 MIPS Payment Year; Provisions From the Medicare Shared Savings Program-Accountable Care Organizations-Pathways to Success; and Expanding the Use of Telehealth Services for the Treatment of Opioid Use Disorder Under the Substance Use-Disorder Prevention That Promotes Opioid Recovery and Treatment (SUPPORT) for Patients and Communities Act. (2018). Available from: www.federalregister.gov/documents/2018/11/23/2018-24170/medicare-program-revisions-to-payment-policies-under-the-physician-fee-schedule-and-other-revisions

2. U.S. Department of Health & Human Services, Centers for Medicare and Medicaid Services, Quality Payment Program. 2017 Quality Payment Program Experience Report Appendix. (2019). Available from: qpp.cms.gov/about/resource-library

Web-Based Quality of Life Data Collection: A Review in Radiation Oncology

Ian Messing, MSII
ADVISORS: Yuan J. Rao, MD,[1] Sharad Goyal, MD,[1] Martin Ojong-Ntui, MD[1]

[1]The George Washington University School of Medicine and Health Sciences

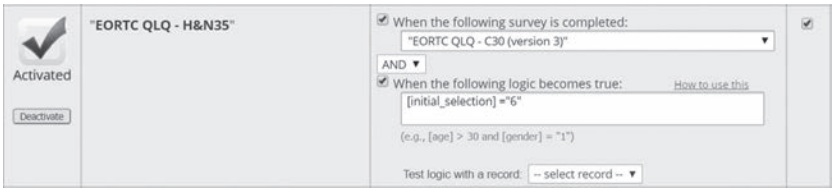


FIGURE 1: Surveys were queued based on the designed branching logic. In this instance, H&N35 would be queued upon completion of QLQ30 and upon selection of "Subsequent Follow-Up QoL Head and Neck Cancer" (initial selection 6) by the team member

Radiation oncology (RadOnc) providers regularly incorporate quality of life (QoL) assessments into their practice to assess treatment toxicities and late effects of therapy. However, routine QoL assessments may burden patients and providers and disrupt clinical workflow.[1] Electronic QoL assessment systems mitigate obstacles to collecting and analyzing patient data, such as poor handling of paper forms, transcription errors, and lack of validation checks.[2] Electronic collection systems provide an efficient and convenient means to the same end. To maximize effectiveness, these platforms must be implemented in a logical manner and emphasize protection of patient information. In this abstract, we outline our method for designing and implementing a web-based QoL questionnaire and repository in our RadOnc clinic.

Our institution provides Research Electronic Data Capture (REDCap) to easily build online surveys and databases.[3] REDCap is a noncommercial, secure, and HIPAA-compliant web-based platform. This fast, flexible program can be used to export data to common data analysis packages and create custom ad hoc reports.

Our institution utilizes the EORTC Quality of Life Group's core questionnaire, the EORTC QLQ-C30 (QLQ30), and site-specific modules to assess QoL of patients who received treatment for head and neck cancer (HNC), endometrial cancer, and cervical cancer. The EORTC QLQ-H&N35 (H&N35) is a widely used tool to measure QoL in HNC patients and has been validated in large-scale studies.[4,5] We recreated a version of both the QLQ30 and the H&N35 in REDCap.

The project was designed using longitudinal data collection. Due to variations in type and frequency of patient encounters, we define events by patients' unique medical record numbers (MRN) and type of encounter. Combined with the assessment date, we can analyze patient encounters over time.

A team member initiates patient encounters by accessing REDCap, providing the patient's MRN, and selecting the visit type. To access the H&N35, team members indicate that they are preparing a subsequent follow-up visit for an HNC patient.

The project is designed with branching logic to queue a validation survey. We included this step to authenticate the response collection and to familiarize patients with the platform. Upon completion, the patient will be presented with the QLQ30 and then the H&N35.

The project was designed to reduce patient decision-making and effort. Along with branching logic (Figure 1), survey sections are displayed as matrices of fields and separated over different web pages when answer choices or response prompts change (Figure 2). This design was implemented to limit patient confusion and promote data quality. Data validation techniques are also employed to ensure appropriate completion of each survey.

After checking in at our clinic, a team member escorts the patient to an examination room, accesses the project in REDCap, enters initial patient information, and selects the visit type. Next, the team member assesses the completion of the initial validation survey and the first questionnaire is selected and opened. The patient uses a laptop computer to complete the QoL surveys queued in the web-browser.

Development of a simple and effective web-based platform for survey administration presents many challenges. The REDCap program facilitated this objective by enabling

Continued on p. 28

Continued from p. 27

efficient administration of web-based surveys. The QLQ30 and H&N35 were foundational starting points upon which to expand our platform and assess other treatment sites. Given the simplicity of the REDCap platform, we have successfully administered surveys on tablet computers and aim to expand their utility.

FIGURE2 : Matrix fields were utilized to limit patient confusion and promote data quality and compliance. This was achieved by grouping items with similar prompts and responses.

REFERENCES

1. de Bree R, de Leeuw IM, Keizer AL, et al. Touch screen computer-assisted health-related quality of life and distress data collection in head and neck cancer patients. Clinical Otolaryngology. 2008;33(2):138-142. doi:10.1111/j.1749-4486.2008.01676.x

2. Wilcox AB, Gallagher KD, Boden-Albala B, Bakken SR, Research Data Collection Methods: From Paper to Tablet Computers. Medical Care. 2012;50 Suppl(1):S68-S73. doi:10.1097/MLR.0b013e318259c1e7

3. Harris PA, Taylor R, Thielke R, Payne J, Gonzalez N, Conde JG. Research electronic data capture (REDCap)—A metadata-driven methodology and workflow process for providing translational research informatics support. Journal of Biomedical Informatics. 2009;42(2):377-381. doi:10.1016/j.jbi.2008.08.010

4. Singer S, Arraras J, Chie Wc, et al. Performance of the EORTC questionnaire for the assessment of quality of life in head and neck cancer patients EORTC QLQ-H&N35: a methodological review. Quality Of Life Research. 2013;22(8):1927-1941. doi:10.1007/s11136-012-0325-1

5. Bjordal K, Hammerlid E, Ahlner-Elmqvist M, et al. Quality of life in head and neck cancer patients: validation of the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-H&N35. Journal of Clinical Oncology. 1999;17(3):1008-1019. doi:10.1200/JCO.1999.17.3.1008

Can Emoji's Assess Patients' Moods and Emotions in the Emergency Department? An Emoji Based Study

Theodore Quan, MSII

ADVISOR:
Ali Pourmand, MD, MPH '06[1]

[1]The George Washington University School of Medicine and Health Sciences

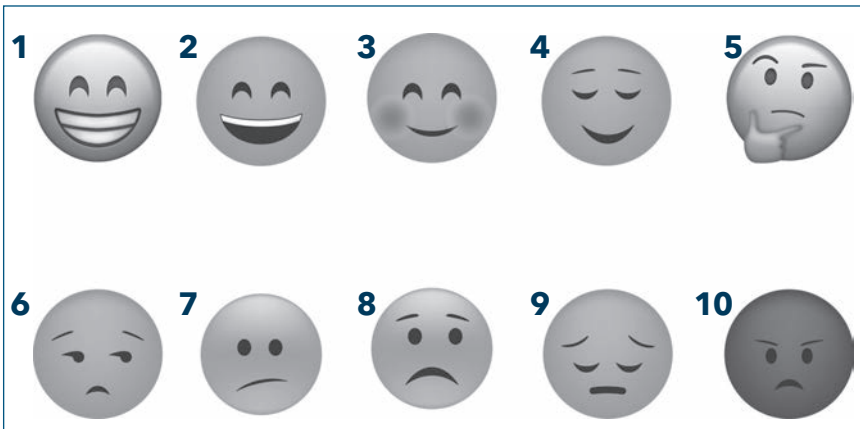


FIGURE: Ten different emoji faces.

Interpersonal communication has been drastically altered due to innovations in technology.[1] Emojis are currently an undeniable part of the world's communication language and are utilized by 92% of the online population.[2] They represent emotional and personality nuances which would be present in face-to-face communication.[3] We sought to determine whether emojis may be a tool that can effectively and efficiently evaluate a patient's mood in a busy emergency department (ED) setting.

This was a prospective study performed at the ED of an urban academic center. Patients 18 years of age or above with lower acuity level at arrival (an Emergency Severity Index (ESI) between 3 and 5) were prospectively enrolled. Upon arrival to the ED, a screen with 10 different emoji faces ranging from one (extremely satisfied, smiling face)

to 10 (extremely dissatisfied, angry, red face) was given to each patient (Figure). Every 30 minutes after their arrival, patients were asked to identify their emotional state by selecting one mood-determining emoji. The change in emojis throughout the patient's visit was recorded. The patient's age and length of stay (LOS) were examined to assess the effect that these variables may have had on the patient's first and last selected emoji, and the change between the two. The analysis included time series, Spearman correlation, multiple linear regression, categorical, nonparametric statistics and McNemar-Bowker Test of symmetry for paired emoji data.

The study included 348 patients with valid emoji data. On the emoji scale, the mean emoji upon arrival to the ED and upon discharge were 5.8 and 5.3 respectively (P=0.0004; Wilcoxon signed rank test), showing significant improvement in patient mood. When the patients first arrived at the ED, 7% and 9% of the patients selected emoji #1 and emoji #10, respectively. Upon discharge, 10% and 9% of the patients selected emoji #1 and emoji #10, respectively. About 32% of the patients did not change their emoji during their ED visit. About 30% exhibited improvements in their mood and a few displayed worsening mood (25%). The length of stay in the ED was not correlated to the change in emoji (P=0.11). The patient's age also did not have an effect on the change in emoji (P=0.64). The mean emoji at admission for male patients was significantly lower than those for female patients (5.4+2.6 vs. 6.2+2.6; P=0.006) and males displayed a slightly higher mood change (slope=0.52; P=0.065; Table).

Characteristics	No. (%), Average
Admission to ED	
First mood-determining emoji	5.8+2.7
Emoji #1 selected	26 (7.4)
Emoji #10 selected	30 (8.6)
Mood-determining emoji for males	5.4+2.6
Mood-determining emoji for females	6.2+2.6
Discharge from ED	
Last mood-determining emoji	5.3+2.8
Emoji #1 selected	36 (10.3)
Emoji #10 selected	32 (9.2)
Changes in Mood	
No change in mood	112 (32.2)
Improved mood	104 (29.9)
Worsened mood	88 (25.3)

TABLE: Patient mood in the ED from admission to discharge.

It is difficult for healthcare providers to ascertain a patient's emotional state to better assess how they are feeling about their medical issue or ED experience. Identifying tools that can improve this more nuanced but important aspect of emergency care could be useful. Our study has illustrated that emojis can be a useful tool in tracking a patient's mood during the ED visit. Patients are very familiar and comfortable with emojis, so their use requires little explanation. Emoji assessments are very quick and simple to perform and have the potential to impact overall management in the ED.

REFERENCES

1. Rodrigues D, Prada M, Gaspar R, et al. Lisbon Emoji and Emoticon Database (LEED): Norms for emoji and emoticons in seven evaluative dimensions. Behav Res Methods. 2018;50:392-405.

2. Aluja A, Balada F, Blanco E, et al. Startle reflex modulation by affective face "Emoji" pictographs. Psychol Res. 2018

3. Derks D, Bos AE, von Grumbkow J. Emoticons in computer-mediated communication: social motives and social context. Cyberpsychol Behav. 2008;11:99-101.

Development of a Clinical Checklist as a Standardization Tool for Improving the Care of Medical Foster Care Children with Medical Complexity

Prayerna Uppal, MSII
ADVISERS: Karen Fratantoni, MD, MPH,[1,2] Kathryn Detwiler[1]

[1] Goldberg Center for Community Pediatric Health, Children's National Hospital
[2] The George Washington University School of Medicine and Health Sciences

Children with medical complexity (CMC) are children whose health care status encompasses four main areas: chronic, severe health conditions; substantial health service needs; functional limitations, which are often severe; and high health resource utilization. Examples of children with medical complexities include, but are not limited to, those with congenital heart disease, cerebral palsy, spina bifida, sickle cell disease, and HIV/AIDS.[1] These patients require individualized care, often involving round-the-clock caretakers who ensure adherence to multiple medications, address specific dietary and feeding needs, and understand how to use medical technology associated with each patient's condition. Such a high level of care may place a larger burden on parents of CMC than is feasible. Under these circumstances, medical foster care services provide additional support for families with medically complex children.[2]

Second Family is a non-profit organization with medical homes throughout Maryland that house many of these CMC in the medical foster care system. Once patients enter Second Family, they receive primary care services through Children's National Hospital (Children's National). However, in establishing this transfer of care, patients and their Second Family caretakers often arrive at appointments without adequate knowledge of patients' medical and social background and needs. These information gaps create significant challenges for clinical providers when making medical decisions. In order to reduce these gaps, improve each provider's care for Second Family patients, and foster collaboration between Second Family and Children's National, we created a checklist for Second Family caretakers to use to prepare for each patient's appointments.

We approached this project using the "Plan-Do-Study-Act" (PDSA) cycle, a quality improvement tool created as part of the Institute for Healthcare's Model for Improvement. This cycle involves creating a plan or initiative and collecting the necessary data (plan), testing the plan or initiative (do), studying the testing results (study), and then refining the initial plan accordingly (act). Our project was designed as follows:

- **1) Plan:** To develop a standardized clinical checklist for complex care visits with Second Family patients at Children's National.
- **2) Do:** We identified important elements for the checklist through a literature review on the needs of CMC, consultations with Complex Care pediatricians, and observation of patient-provider and caretaker-provider interactions during Complex Care visits at the Child Health Center and Adolescent Health Center.
- **3) Study:** We collected feedback on the checklist through focus groups of stakeholders (parents and caretakers of Second Family patients, the Pediatric Medical Specialist at Second Family, Complex Care Team social workers, case managers, nurses, and physicians).
- **4) Act:** We revised the checklist until we reached a final product.

We approached this project using the "Plan-Do-Study-Act" (PDSA) cycle, a quality improvement tool created as part of the Institute for Healthcare's Model for Improvement.

Through implementation of this checklist, we not only aim to improve the Complex Care Team's ability to care for Second Family patients, but also intend to educate Second Family caretakers regarding what information they need bring to healthcare visits. We hope that our checklist will serve as a tool or template for other measures of standardizing care among children with medical complexities and their caretakers, families, and

providers. This tool may also be expanded and externally validated via use in other populations, such as Second Family patients visiting Children's National's Emergency Department, foster families with CMC not in a group medical home, adults with medical complexities, and general primary care visits.

REFERENCES:

1. Simpser E, Budo P. (2016) Children and Young Adults with Medical Complexity: An Emerging Population [white paper]. Retrieved April 18, 2018 from Pediatric Complex Care Association: https://pediatriccomplexcare.org/wp-content/uploads/2016/03/PCCA-CMSWhite-Paper012716.pdf
2. Seltzer, R, Henderson, C, Boss, R. Medical foster care: what happens when children with medical complexity cannot be cared for by their families? Pediatric Res. 2016; 79:191–196

Exploring the Relationship Between Telehealth Utilization and Overall Hospital Utilization Patterns in the Medicare Population at UCSF

Prasantha Vemu, MSII

ADVISOR: Sara Murray, MD, MAS[1]

[1] Division of Hospital Medicine, University of California, San Francisco (UCSF)

The advent of telehealth services has been a critical turning point in healthcare delivery that has been expanding access, reducing costs, and improving health outcomes. Under the current fee-for-service Medicare payment model, telehealth coverage is limited to rural areas, which are defined as health professional shortage areas, to reduce overutilization and keep costs down.[1] A recent study showed that telemedicine utilization in rural Medicare populations, particularly for mental health, complemented healthcare management, but did not increase utilization.[2] Moreover, factors such as geographical restrictions on telehealth coverage may be impeding the growth of telehealth. Others argue that expanding telehealth service coverage may increase utilization and drive up healthcare costs.[1,3] While these are valid points, the impact of telehealth on overall healthcare utilization patterns is not well understood in the Medicare population. The University of California, San Francisco (UCSF) is a quaternary care center that is uniquely positioned in that it has consistently offered telehealth to all patients regardless of payer status. Thus, many Medicare patients who utilize UCSF's telehealth are not covered for telehealth services. In the current study, we determined if there was a relationship between telehealth utilization and overall hospital utilization in the Medicare population at UCSF. Subset analyses on Medicare patients was performed using data from two of the highest utilizing telehealth clinics: Symptom Management Clinic and Endocrinology Clinic. To determine if telehealth services among Medicare patients was associated with decreased hospital utilization, we used ED visits as the primary outcome and outpatient visits as well as patient portal interactions as covariates.

Results show that there was a significantly smaller percentage of telehealth patients that utilized the ED versus non-telehealth patients in both clinics (40% vs. 48%, respectively, for Symptom Management Clinic and 11% vs. 24%, respectively, for Endocrinology Clinic). We used a Poisson regression to model our data and it showed that the incidence rate of ED visits among telehealth users (IRR, 95% CI) is significantly less than that among non-telehealth

Our findings indicate that telehealth utilization is associated with an overall decrease of ED utilization in the Medicare population. However, the relationship between telehealth use and other utilization patterns (e.g. clinic visits, emails) is likely confounded by variables such as the underlying disease and technological literacy.

Continued on p. 32

Continued from p. 31

users in the Symptom Management Clinic and Endocrinology Clinic (0.78 and 0.52, respectively). There was heterogeneity in the relationship between telehealth visits and office visit patterns, with the Symptom Management Clinic demonstrating equivalent office visit utilization between telehealth and non-telehealth users while the Endocrinology Clinic showed a slightly greater percentage of telehealth users who had office visits compared to non-telehealth users (99.1% vs. 97.5%, respectively). Lastly, telehealth users had significantly more patient portal interactions on average when compared to non-telehealth users in both clinics. Our findings indicate that telehealth utilization is associated with an overall decrease of ED utilization in the Medicare population. However, the relationship between telehealth use and other utilization patterns (e.g. clinic visits, emails) is likely confounded by variables such as the underlying disease and technological literacy. Future studies are needed to better understand the impact of telehealth on overall care utilization.

REFERENCES

1. United States Congress, "Mandated Report: Telehealth Services and the Medicare Program." Mandated Report: Telehealth Services and the Medicare Program, March 2018: Chapter 16. www.medpac.gov/docs/default-source/reports/mar18_medpac_ch16_sec.pdf?sfvrsn=0.

2. Mehrotra A, Jena AB, Busch AB, et al. Utilization of Telemedicine Among Rural Medicare Beneficiaries. JAMA, 315(18), 2015–6.

3. Ashwood JS, Mehrotra A, Cowling D, Uscher-Pines L. 2017. Direct-to-consumer telehealth may increase access to care but does not decrease spending. Health Affairs. 2017.36(3): 485–491.

Experiences of Training Community Health Workers on Hypertension Prevention in Rural Uganda

Rowanne Ali, MSII (top)
AND Abdelrhman Elnasseh, MSII (bottom)
ADVISORS:
Rawlance Ndejjo, BEH, MSc,[1] Ken Kabali, MD, MPH,[2] Edward O'Neil, MD '87[2]

[1] Department of Disease Control and Environmental Health, School of Public Health, College of Health Sciences, Makerere University, Kampala, Uganda
[2] Division of Research, Omni Med, Mukono, Uganda

Low-income countries are facing the double burden of communicable diseases and rising prevalence of noncommunicable diseases (NCDs).[1] Traditionally, community health workers (CHWs) have played a significant role in the prevention and control of communicable diseases such as malaria, tuberculosis, and HIV.[2] However, the involvement of CHWs in NCD prevention and control has not been fully explored, especially in many Low- and Middle-Income Countries (LMICs) including Uganda.[3] This direct participant observational study examines how well CHWs receive, comprehend, and engage with Omni Med's hypertension quarterly training. Omni Med is a non-profit organization working to reduce global health inequity in developing countries through innovative programs focused on community education, building sustainable solutions, and health volunteerism. CHW demographics and contacts were obtained from Omni Med. Starting August 2019, CHWs were invited for a day-long training targeting hypertension risk factors such as the effects of high-stress levels, alcoholism, and excess carbohydrate consumption. After each training, CHWs were assessed on their understanding of the topics and given the opportunity to ask questions and brainstorm solutions. Their responses were collated and used to cater future sessions to their goals, concerns, and knowledge base.

Since the implementation of the training, 269 CHWs have been trained. Dialogues and brainstorming sessions with CHWs demonstrated that they grasped the effects of diet, alcohol, and stress on blood pressure and agreed that these three rampant risk factors existed in their villages given the state of widespread poverty.[4] From these dialogues and brainstorming sessions emerged three key themes which affirmed the CHWs comprehension and engagement with the training material. First, CHWs provided further points of discussion on the causes of hypertension and frequently brought up other chronic NCDs like diabetes and their relationship to hypertension. Second, they provided insight into some of the physical and mental health misconceptions that exist within their communities. For example, some CHWs seemed to think that certain home-brewed alcohol is "good for you," so we have tried to clarify this by dispelling the misconception and educating them on the health consequences of all kinds of alcohol. Third, they have demonstrated a willingness to spark change for improved health outcomes through education and health promotion measures. Relatedly, CHWs suggested that male CHWs should talk with male community members and females CHWs with female community members to promote a more trusting environment of mutual understanding with sensitive topics. After the training, CHWs exhibited greater confidence in their understanding of hypertension and desire to play key roles in its prevention and control within their communities. Future training for CHWs should consider providing a broader package of information beyond hypertension to cover more NCDs.

REFERENCES

1. Alwan AA, MacLean DR, Riley LM, et al. Monitoring and surveillance of chronic non-communicable diseases: progress and capacity in high-burden countries. Science Direct 2010; 376:1861–1868

2. Bollyky TJ, Templin T, Cohen M, et al. Lower-Income Countries that Face the Most Rapid Shift In Noncommunicable Disease Burden Are Also The Least Prepared. Health Aff 2017; 36; 1866–1875

3. Mishra SR, Neupane D, Preen D, et al. Mitigation of non-communicable diseases in developing countries with community health workers. Globalization and Health 2015. 43:11

4. McGee R. Meeting the International Poverty Targets in Uganda: Halving Poverty and Achieving Universal Primary Education. Development Policy Review 2002; 18: 85–106

Parents' Views of Preimplantation Genetic Testing for Sickle Cell Disease after Education in Clinic

Monica Attia, MSII
CO-AUTHOR: Shawn Kripalani, MSII
ADVISOR: Robert Nickel, MD[1]

[1] Department of Hematology, Children's National Hospital

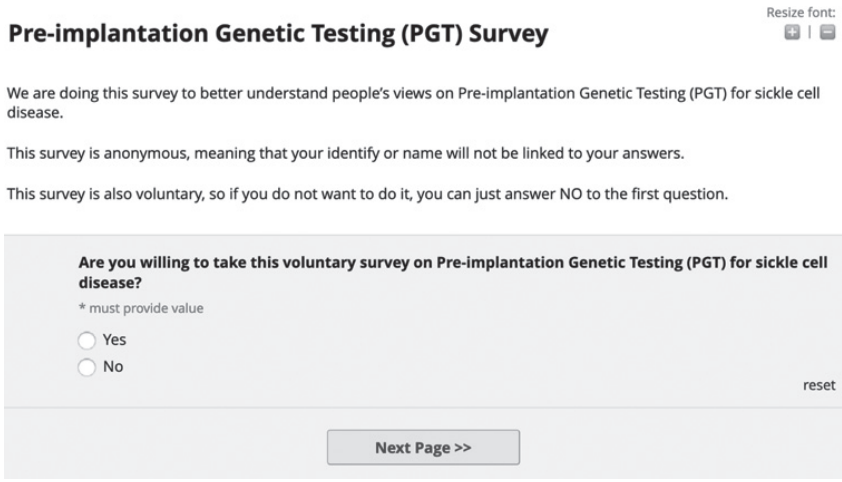


FIGURE: Page one of PGT survey completed by parent participants.

Preimplantation genetic testing (PGT) is a screening modality used in conjunction with in-vitro fertilization (IVF). For parents concerned about having a child with sickle cell disease (SCD), PGT is an option to have progeny negative for the SS phenotype. Parents who already have a child with sickle cell disease (SCD) may also consider PGT as an option to have a sibling who is an HLA subtype match. Parents' views of this pre-conceptive diagnostic screening are not well known1 and little work has been done in educating parents about this process2,3. This study sought to describe parents' opinions on PGT after a clinic-based educational intervention.

Methods

A five-page educational handbook was created on PGT for SCD. At the Children's National Hospital (Children's National) Hematology-Oncology Clinic, parents of children with SCD were encouraged to read this handbook in the waiting room and ask their provider questions about the material during their clinic visit. After this visit, parents were then asked to complete a 24-question anonymous survey via REDCap (see figure 1 below). An IRB waiver of consent was granted as no personal health information was collected. Non-biological parents and other guardians were excluded. Categorical data from the survey was analyzed with the chi-square or Fisher exact test ($p<0.05$=significant).

Results

Between May and July 2019, 83 biological parents of children with SCD were enrolled into the study. Sixty-seven (81%) of these parents, including 52 mothers and 15 fathers with a median age of 34 years, completed the questionnaire. While 53 (79%) indicated that they had previously heard of bone marrow transplant for SCD before the date of the questionnaire, only 16 (24%) indicated that they had also heard of PGT for SCD ($p<.0001$). When asked about their opinion of informing the parents of SCD children about PGT, 45 (67%) stated that "knowing about PGT was 'very important'," 20 (30%) responded PGT education was "important," one responded (2%) "a little important," and one (2%) "not important." The majority (69%) of parents indicated that education on this topic should occur "at the very first hematology clinic visit." Nine (13%) responded that they would pay retail price (~$20,0000) for PGT and 65 (97%) answered that they think PGT should be covered by health insurance. Among parents who indicated that they might want to have more children (n=32), 29 (91%) answered that they would be interested in using PGT if covered by insurance.

Conclusion

Most parents of children with SCD seen in the Children's National hematology-oncology clinic do not know about PGT, but when educated about this option, they view this knowledge as important. Routine follow-up appointments in early childhood may be an opportune time for educating patients on PGT. Though the current cost of PGT remains a major barrier, this preconceptive diagnostic screening method may prove to be a major influence in reducing the number

of pediatric patients with SCD, and providers should be sure educate parents on PGT to help ensure access to this option.

REFERENCES

1. Darbari I, O'Brien JE, Hardy SJ, et al. Views of parents of children with sickle cell disease on pre-implantation genetic diagnosis. Pediatr Blood Cancer. 2018;65(8):e27102.
2. Cooper AR, Jungheim ES. Preimplantation genetic testing: indications and controversies. Clin Lab Med. 2010;30(3):519–531. doi:10.1016/j.cll.2010.04.008
3. Baruch S, Kaufman DJ, Hudson KL. Preimplantation genetic screening: a survey of in vitro fertilization clinics. Genetics in Medicine, journal of the American College of Medical Genetics. 2008;10(9):685–90.

Assessment of Patterns in Surgical Backlog Within Ethiopian Public Hospitals as a Primary Step in Quality Improvement of Safe Surgeries

Tirsit Makonnen, MHS, MSIII[1,2]

ADVISORS: Munir Kassa, MD,[1] Tsion Firew, MD,1 Miklol Mengistu MD[3]

[1]Ethiopian Federal Ministry of Health, Health Service Quality Directorate

[2]The George Washington University School of Medicine and Health Sciences

[3]Gondar University Comprehensive Specialized Hospital

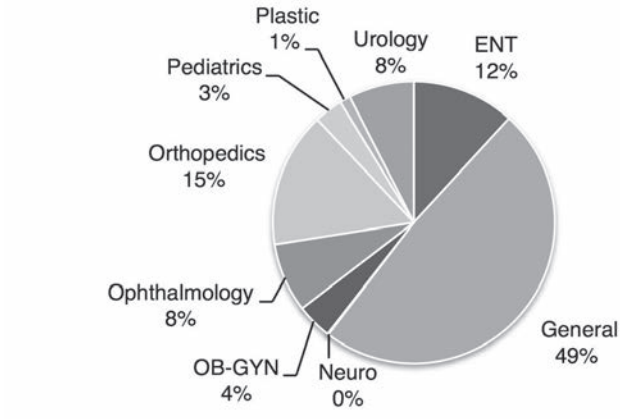


FIGURE 1: Summary of Surgical Backlog Assessed by Specialties Among Six Ethiopian Public Hospitals

The Lancet Commission on Global Surgery established the goal for nations to achieve universal access to safe, affordable surgical and anesthesia care when needed.1 In Eastern sub-Saharan Africa, over an additional 17 million surgical procedures are needed annually to prevent morbidity and mortality.1 The Commission set out universal targets to achieve the proposed goals; one of which is for 100% of countries to track surgical volume and preoperative mortality rate (POMR).1 The Ethiopian Federal Ministry of Health's Health Service Quality Directorate recognizes this importance by listing it under its National Health Care Quality Strategy.2 This investigation looks to study the details of surgical backlog among six Ethiopian public hospitals in the Amhara region.

Standardized surveys were sent out to the surgical department of six Ethiopian public hospitals in the Amhara region: Debre Markos Referral Hospital, Dessie Referral Hospital, Debre Birhan Referral Hospital, Debre Tabor General Hospital, Gondar University Comprehensive Specialized Hospital, and Feleghiwot Referral Hospital. Among the questions asked was the total number of patients on the waiting list for elective surgery under one of nine surgical departments; ENT, General, Neurosurgery, OB-GYN, Ophthalmology, Orthopedics, Pediatrics, Plastics, and Urology. In addition to the survey, first person interviews with the chair of various surgical departments were conducted at Gondar Hospital.

When looking broadly at all centers, there were a total of 4207 cases of backlog. According to Figure 1, the departments with the greatest backlog were General with 2044 cases accounting for 49% of the

Continued on p. 36

Continued from p. 35

total, Orthopedics with 652 cases at 15%, and ENT with 496 cases at 12%. Each hospital has its own profile of needs, reflecting the complexities faced by regional health bureaus. As a case sample, in depth analysis was conducted at Gondar Hospital which recorded 1,762 cases. The pattern of backlog varied compared to that of the overall findings, with 45% of cases within General Surgery, while 30% were within ENT. Figure 2 highlights how the diagnoses associated with the highest backlog are tonsillitis at 44%, and goiters at 30% of all hospital surgical cases. First person interviews conducted among the various surgical department heads highlighted that the main causes of backlog are due to either space or equipment limitations; the quality and quantity of human resources are adequate.

One limitation of the study is the varying methodologies used to monitor backlogs. For example, Ophthalmology at Gondar's Hospital maintains its own records in hard copy, while records from other departments are maintained on a centralized electronic system. Another limitation is recognizing that low backlog does not necessarily indicate low burden. At Gondar Hospital, there is lack of

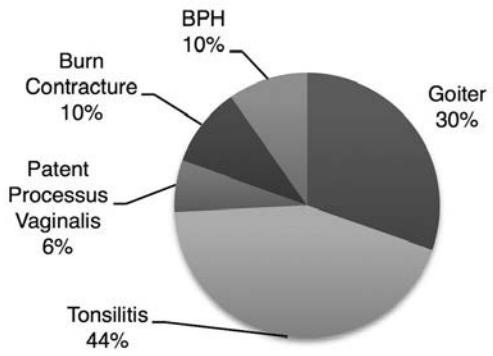


Figure 2: Summary of Surgical Backlog Assessed by Diagnoses at Gondar Hospital

FIGURE 2: Summary of Surgical Backlog Assessed by Diagnoses at Gondar Hospital

OB-GYN backlog burden because of public health campaigns to champion maternal and child health outcomes. Simultaneously, there is also minimal backlog within Neurosurgery because cases that the hospital is unable to support are referred elsewhere, highlighting that the burden may be shifted to another site. In conclusion, assessing the tremendous baseline of surgical backlog is the first step to tracking the hospitals' surgical volume and POMR. Individual hospitals must be investigated in depth to assess their specific needs. It is recommended that future steps be taken to minimize the backlog and determine evidence based methods to prevent future occurrences. The success and limitations of these future steps can be used to inform strategies at other Ethiopian public hospitals.

REFERENCES

1. The Lancet Commision on Global Surgery. Global Surgery 2030: evidence and solutions for achieving health, welfare, and economic development. The Lancet. 2015; 386; 569-624.

2. Ethiopian Heath Quality Services Directorate. (2015). Ethiopian Natonal Health Care Quality Strategy 2016-2020. Ethiopian Federal Ministry of Health.

Utilizing Role-Play in Teaching Medical Spanish

Khashayar Mozaffari, MSII
ADVISORS:
Benjamin Blatt, MD,[1,2] Victor A. Valdivia Ruiz, PhD[3]

[1]The George Washington University (GW) School of Medicine and Health Sciences
[2]The GW Medical Faculty Associates
[3]GW Department of Romance, German, and Slavic Languages and Literatures

Exam category	Pre-course mean ± SEM (%)	Pre-course range (%)	Post-course mean ± SEM (%)	Post-course range (%)	WSR *p*-value
Multiple choice	95.24 ± 2.32	86.11-100.00	99.21 ± 0.79	94.44-100.00	0.10
Oral translation: English to Spanish	80.00 ± 5.85	60.00-100.00	93.57 ± 3.22	80.00-100.00	0.08
Oral translation: Spanish to English	81.43 ± 3.88	70.00-95.00	95.71 ± 2.76	80.00-100.00	0.03*
SEM: Standard error of the mean WSR: Wilcoxon signed-rank test * indicates statistical significance					

TABLE: Comparison of pre-course and post-course examination scores in the intermediate group

There are 58.9 million Hispanics in the United States.[1] This number makes up 18.1% of the nation's population and is expected to increase to 24.5% by 2050.[1] Nearly 40% of Hispanic patients are categorized as having limited proficiency in English.[2] With the aim of training future health care providers with adequate Spanish proficiency, many health sciences institutions have implemented medical Spanish courses. Although interactive courses have shown efficacy in teaching field-related terminology, there are still significant barriers to implementing a medical Spanish curriculum.[2,3] According to a national survey of medical schools in the United States, lack of time is the most frequently reported obstacle.2 Role-play may offer a time-efficient manner for students to learn Spanish and reduce this barrier. In our study, we investigated the potential benefit of role-play in a medical Spanish course.

Methods:

Upon receiving approval by the Institutional Review Board, 19 incoming second-year medical students were recruited to participate. Based on their performances on a placement test composed of multiple a Spanish-speaking patient, an English-speaking provider, and an interpreter to practice scenarios that one may encounter when providing health care. The scenarios consisted of patients presenting to the emergency department, outpatient clinic, and inpatient hospital setting. At the end of the course, students took a post-course examination to determine if there had been an improvement in their Spanish language proficiency. Due to the non-normal distribution of scores, statistical analysis was performed using Wilcoxon signed-rank test. Statistical significance was determined using a p-value < 0.05.

Results:

Seven students, who were all members of the intermediate group, completed the course. Class attendance among this group was 77.40%. When comparing pre-course to post-course examination scores, there was improvement of scores in all categories (Table). In particular, we found statistically significant improvement in oral translation of phrases from Spanish to English (p-value= 0.03).

[W]e found statistically significant improvement in oral translation of phrases from Spanish to English (p-value= 0.03).

Conclusions:

We investigated utilizing role-play as the central teaching method in a medical Spanish course. The cohort demonstrated statistically significant improvement in oral translation of phrases from Spanish to English, indicating an improvement in Spanish proficiency. More importantly, this was accomplished through a minimal time requirement of one hour per week, as limited time poses a barrier to implementing a medical Spanish curriculum. Such findings highlight the benefit of this teaching methodology and call for further evaluation in a larger sample size.

Continued on p. 38

Continued from p. 37

REFERENCES:

1. Alonzo F. (2018, 09 12). Hispanic Heritage Month 2018. (Accessed July 27, 2019, www.census.gov/content/dam/Census/library/visualizations/2018/comm/hispanic-fff-2018.pdf.)
2. Morales R, Rodriguez L, Singh A, et al. (2015). National survey of medical Spanish curriculum in US medical schools. Journal of general internal medicine. 30(10), 1434–1439.
3. Mueller R. (2017). Development and evaluation of an intermediate-level elective course on medical Spanish for pharmacy students. Currents in Pharmacy Teaching and Learning. 9(2), 288–295.

Community Organization Factors Affecting Veteran Participation in Adaptive Sports

Zachariah G. Whiting, MSII

ADVISORS: David Falk, MD;[1] Kenneth K. Lee MD;[2] Jonathan Lee;[2] Beth Weinman, DO;[3] Jesse M. Pines, MD, MBA, MSCE[4]

[1]University of Pennsylvania
[2]Zablocki VA Medical Center – Milwaukee
[3]Medical College of Wisconsin
[4]US Acute Care Solutions

Variable	P-value
Season	
All Year	0.1464
Spring	0.3618
Summer	0.2499
Fall	0.1219
Winter	0.2804
Age Group	
0-10	<0.0001*
11-17	<0.0001*
18-25	0.0480
26-34	0.0784
35 and up	<0.0001*
VA Association	
VA Partner	0.0234
VA Partner Type	0.0174

FIGURE 1:

Adaptive sports are broadly defined as conventional sports that have been modified to meet the needs of people with physical and/or intellectual disability. Recently, an emerging body of literature dedicated to individuals with disability has demonstrated that participation in adaptive sports is associated with certain benefits, including chronic disease prevention, increased muscle strength, improved sense of self esteem and self image, as well as better social integration.[1,2] Additional studies have even suggested participation in adaptive sports makes a difference in attaining employment.[3] Among those with disability, U.S. Military veterans are a particular group of interest in part due to the influx of veterans living with disability in the post-9/11 era. Data from the 2014 Census demonstrates that there are at least 3.8 million veterans living with service-related disability.[4] Given the documented physical, psychosocial, and socioeconomic benefits associated with adaptive sports, it is critical that we continue investigating means to increase participation rates among veterans with disability. Known barriers to participation include difficult access to transportation, limited information about programs and their offerings, individual cost, and program funding.5 Many of these obstacles are cost-related. Despite the large number of adaptive sports programs in the United States, little is known about the organizations that provide adaptive services. To our knowledge, there are no studies that specifically focus on the organizational factors U.S. Military veterans find desirable when considering getting involved in adaptive sports.

Objective:

The aim of this study was to capture the factors within adaptive sports organizations and their surrounding communities that impact U.S. military veteran participation in adaptive sport activities.

Design, Setting, and Participants:

This study was approved by the Institutional Review Board at the George Washington University, as well as the Milwaukee, VA. A 9-question survey was created by the investigators of the study and distributed to 121 programs across the United States (Figure 1). Participating organizations were identified if they were advertised in the resources section under "Sports and Recreational Organizations" on www.sportsabilities.com/[STATENAME]. Additionally, surveys were sent to programs known to the authors, but not listed on the Sports Abilities website. Chi-Square Tests were used to explore possible factors, including program status, the total number of participants and veteran participants, participant age, sports offered, seasonality, and relationship with the VA, potentially affecting veteran participation in adaptive sports programs. Due to the high number of tests performed, to control the family-wise error, p-values were not

considered to be significant unless they were smaller than 0.005.

Intervention:

Prospective, cross-sectional nine-question survey about the program's demographics.

Main Outcomes and Measures:

Demographic data.

Results:

In total, 85 programs responded to our survey, yielding a response rate of 70%. Age of participants within an organization was significantly associated with percentage of veteran participation. Contact level, seasonality, and VA partnership were not associated with percentage of veteran participation (Figure 2). No individual sport was significantly associated with percentage of veteran participation, though fly-fishing approached statistical significance ($p = 0.007$)

Conclusions and Relevance:

Older age among participants within an adaptive sports organization was associated with a higher percent of veteran participation, suggesting that the camaraderie developed with similar aged individuals is important to veterans when choosing adaptive sports programs. No sport was significantly associated with percent of veteran participation, illustrating that factors beyond the specific activities offered by a program impact veteran participation rates.

REFERENCES:

1. Lape EC, Katz JN, Losina E, et al. Participant-reported benefits of involvement in an adaptive sports program: a qualitative study. PM&R. 2017;10(5):507-15.

2. Laferrier JZ, Teodorski E, Cooper RA. Investigation of the impact of sports, exercise, and recreation participation on psychosocial outcomes in a population of veterans with disabilities: a cross-sectional study. American Journal of Physical Medicine & Rehabilitation. 2015;94:1026-1034.

3. Kim W, Lee L, Lans D, et al. Perception of employment by veterans participating in the national veterans wheelchair games: a survey study. PM&R. 2018;10(3):263-8.

4. Veteran's Day 2015: Nov. 11, 2015. Washington, D.C.: 2014 American Community Survey, 2015. (Accessed Sept. 9, 2019 at www.census.gov/newsroom/facts-for-features/2015/cb15-ff23.html.)

5. Blauwet CA, Yang HY, Cruz SA, et al. Functional and environmental factors are associated with sustained participation in adaptive sports. PM&R. 2017;9(7):668-75.

1. Name of Organization: _____
2. Your position within your organization: _____
3. Is your program an independent organization or a rehabilitation center/association?
   a. Independent (Example: Kansas City Flyers Wheelchair Basketball Team)
   b. Rehabilitation Center/Association (Example: XYZ Adaptive Sports Organization)
   c. Other (fill in the blank)
4. How many individuals with disability participated in your adaptive programming in 2017?
   a. (fill in the blank)
5. How many of your participants were U.S. Military veterans in 2017?
   a. (fill in the blank)
6. Which of the following age groups participate in your adaptive sports activities? (Please select all that apply)
   a. 10 and under
   b. 11-17
   c. 18-25
   d. 26-34
   e. 35 and older
7. Which adaptive sports are offered at your organization? (Please check all that apply)
   a. Airgun
   b. Alpine Skiing
   c. Archery
   d. Badminton
   e. Biathlon
   f. Bobsled
   g. Bocia
   h. Bowling
   i. Camping
   j. Canoeing
   k. Curling
   l. Cycling
   m. Dragon Boating
   n. Fencing
   o. Fishing
   p. Flyfishing
   q. Goalball
   r. Golf
   s. Hand-cycling
   t. Hiking
   u. Horseback Riding
   v. Ice-skaing
   w. Judo
   x. Kayaking
   y. Mountain Biking
   z. Nordic Skiing
   aa. Paddleboarding
   bb. Pickleball
   cc. Power Soccer
   dd. Powerlifting
   ee. Racquetball
   ff. Rock Climbing
   gg. Ropes Course
   hh. Rowing
   ii. Sailing
   jj. Skydiving
   kk. Sled Hockey
   ll. Snowboarding
   mm. Snowshoeing
   nn. Swimming
   oo. Table Tennis
   pp. Target Shooting
   qq. Track & Field
   rr. Triathlon
   ss. Volleyball
   tt. Wheelchair Basketball
   uu. Wheelchair Football
   vv. Wheelchair Lacrosse
   ww. Wheelchair Racing
   xx. Wheelchair Rugby
   yy. Wheelchair Softball
   zz. Wheelchair Squash
   aaa. Wheelchair Tennis
   bbb. Whitewater Rafting
   ccc. Yoga
8. Does your organization provide services throughout the year or seasonally? (i.e. winter only)
   a. All year
   b. Seasonal only (select all that apply)
      i. Spring ____
      ii. Summer ____
      iii. Fall ____
      iv. Winter ____
9. Does your organization have a partnership with local Veterans Affairs Medical Center?
   a. Yes
      i. Formal (ex: have a Memo of Agreement)
      ii. Informal (ex: work together occasionally)
      iii. Peripheral (ex: advertise only)
   b. No
   c. I don't know

FIGURE 2:

A Systematic Review of Gender Differences in METs After Cardiac Rehabilitation

Neel A. Duggal, MS III
ADVISORS:
David Scalzitti, PhD, PT,[1] Joshua G. Woolstenhulme, PhD, DPT, PT[1]

[1]The George Washington University School of Medicine and Health Sciences

Cardiac rehabilitation (CR) programs employ a multipronged approach of exercise and lifestyle modifications to reduce cardiometabolic risk factors, improve physical function, and improve quality of life for patients with a wide range of cardiac pathologies. Prior research has demonstrated that cardiac rehabilitation can benefit both men and women's exercise capacity after sustaining a myocardial infarction (MI).1 However, women are consistently underrepresented in CR and are often referred to CR only when they present with greater cardiovascular risk than men.2

The purpose of this systematic review is to investigate the differences in functional capacity, measured by metabolic equivalents (METs), between men and women after an intensive cardiac rehabilitation program for MI recovery. While several systematic reviews have compared compliance and referral rates between men and women to cardiac rehabilitation, none have assessed potential differences in functional capacity or other health outcomes.

Search strategies were developed using MeSH heading and free-text terms for four databases: PubMed, SCOPUS, and CINAHL, and Cochrane. Article duplicates were eliminated and the remaining titles and abstracts were screened. Papers were considered relevant if they compared outcomes in cardiac rehabilitation between men and women, if they were published in English and if they were classified as a randomized or observational study. Data was collected using a standardized form, recording study type, the study population, what, if any, cardiac rehabilitation was implemented, the time points at which the outcomes were measured and the functional exercise outcome regarding MET improvements.

	Women				Men			
Author	N	Baseline	Post-intervention	Change	N	Baseline	Post-Intervention	Change
Anio 2014	85	7.6	8.7	1.2	301	9.1	10.6	1.5
Balady 1996 (separated by age)	Age <65: 37	6.2	7.3		Age <65: 125	7.8	9.1	
	Age 65-75: 24	6.5	6.7		Age 65-70: 47	6.4	7.8	
	Age >75: 0				Age >70: 10	6.1	6.5	
Cannistra 1992	26	3.7	4.8	1.1	107	5.1	5.9	0.8
Caulin-Glaser 2007	71	4.9	6.3	1.4 (20%)	224	6.7	8.6	1.9 (14%)
Gee 2014	227	7.0	8.7	1.7	554	8.9	11.1	2.2
Ghashghaei 2012	84	5.9	7.9		72	8.4	10.9	
Gupta 2007 (Met-hrs):	53	7.0	19.8		149	9.5	23.9	
Johnson 2014 (By race)	African-Americans: 77			1.1	African-Americans: 92			2.0
	White: 227			1.4	White: 700			2.7
Keteyian 2017	2539	2.4	3.3	0.9 (40%)	5780	2.9	4.1	1.3 (45%)
Kligfield 2003	23	3.3	5.9	2.6	58	4.4	8.1	3.8
Lavie 1995	83	6.1	8.1	(33% increase)	375	6.7	9.4	(40% increase)
O'Farrell 2010	70	4.9	5.2	(6.1% increase)	317	6.6	7.3	(10.6% increase)
Sadeghi 2012	121	7.0	8.7		464	9.4	11.9	
Sarafzadegan 2008	147	6.9	8.7	1.8	400	9.7	12.2	2.5
St Clair 2014	260 non-Diabetics			1.5	682 non-Diabetics			2.9
	118			1.2	252			1.9

FIGURE: Metabolic Equivalents (kcal/kg/hour) by Gender

A total of 9,986 records were identified from the preliminary search and 15 studies were ultimately included in the review. No eligible randomized controlled trial was identified. All 15 studies utilized in this review reported that both men and women benefit from cardiac rehabilitation, as demonstrated by a statistically significant increase in peak METs in both gender groups after CR. Improvements in absolute METs during CR, reported by 13 studies, ranged from 0.9 to 2.6 for women and 0.8 to 3.8 for men. Percent improvements in METs from baseline, reported by four studies, ranged from 6.1% to 35% in women and 10.6% to 45% in men. Six studies showed MET improvement with CR to be greater than that of women by a statistically significant margin. However, only one study showed the reverse, a greater MET improvement with CR for women than men, to be true in a statistically significant fashion. The remaining eight studies showed no statistically significant differences between men and women in regards to change in METs with CR.

Although all 15 studies demonstrated that both men and women benefit from CR in terms of MET improvements, the majority of studies had more males than females as study subjects and thus in their CR programs. Given the proportional underrepresentation of women in these studies, however, it is difficult to speculate the existence of a true

difference in MET improvements and also the reasons for a such a difference. Further research is needed to solidify these differences in peak MET improvement between the genders, if they are true representations of the study population, with increased numbers of female study subjects included.

REFERENCES

1. Smith SC, Benjamin EJ, Bonow RO, et al. (2011). AHA/ACCF secondary prevention and risk reduction therapy for patients with coronary and other atherosclerotic vascular disease: 2011 update: a guideline from the American Heart Association and American College of Cardiology Foundation endorsed by the World Heart Federation and the Preventive Cardiovascular Nurses Association. Journal of the American College of Cardiology. 58(23), 2432-2446.
2. Anjo D, Santos M, Rodrigues P, et al. (2014). The benefits of cardiac rehabilitation in coronary heart disease: A gender issue? Revista Portuguesa de Cardiologia (English Edition). 33(2), 79-87.

BEAUMONT SOCIETY RESEARCH PRIZE WINNER

Bacterial Functional Profiling of the Cystic Fibrosis Airway Across Clinical States

Erin Felton MSII
ADVISOR: Andrea Hahn MD, MS[2,3]
CORRESPONDING AUTHORS: Aszia Burrell, BS;[2] Hollis Chaney, MD;[1,3] Iman Sami, MD;[1,3] Anastassios Koumbourlis, MD, MPH;[1,3] Robert Freishtat MD, MPH;[2,3] Keith Crandall PhD[4]

[1]George Washington University School of Medicine and Health Sciences
[2]Center for Genetic Medicine Research, Children's National Research Institute
[3]Children's National Hospital
[4]Milken Institute School of Public Health at George Washington University

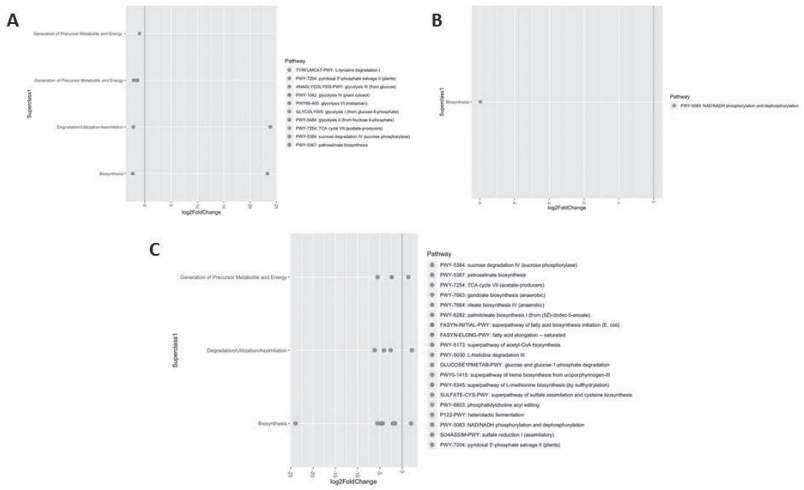


FIGURE: (A) Differential abundance of bacterial metabolic pathways between exacerbation onset samples (left) and end of antibiotic treatment samples (right). (B) Differential abundance of bacterial metabolic pathways between exacerbation onset (left) and follow-up samples (right). (C) Differential abundance of bacterial metabolic pathways between end of antibiotic treatment samples (right) and follow-up samples (left).

Introduction/Rationale

Cystic Fibrosis (CF) is an autosomal recessive disease affecting more than 30,000 people in the United States. Pulmonary exacerbations (PEx) are the most important cause of morbidity and ultimately mortality in patients with CF.[1] Despite many studies of bacterial taxonomy and microbial diversity in the CF airway, the microbiologic cause of PEx remains unknown. While early unbiased whole genome sequencing studies have yielded greater insights into species and strain specificity,[2] the role of bacterial functional pathways in CF PEx is understudied. We hypothesized that bacterial metabolic pathways would be associated with clinical state (PEx, end of antibiotic treatment, and follow-up).

Methods

Twenty seven persons less than 18 years of age with cystic fibrosis, who were admitted to the hospital for a PEx, were recruited to participate in this prospective observational study. Sputum or oropharyngeal swabs were collected at hospital admission, at the end of the antibiotic treatment course, and again at the next follow up clinic appointment within three months. Bacterial DNA was extracted using QIAamp DNA Microbiome kit (Qiagen) and shotgun DNA sequencing was performed using NextSeq (Illumina).

Continued on p. 42

Continued from p. 41

HUMAnN2 was used to evaluate bacterial pathway abundance and DESeq2 was then used to evaluate the differential abundance of generalized bacterial metabolic pathways based on clinical state.

Results

Several pathways related to virulence, pathogenicity and bacterial metabolites were upregulated in follow-up samples when compared to PEx onset or end of antibiotic treatment samples. Interestingly, we found several long chain fatty acid (LCFA) biosynthesis pathways that were upregulated in follow-up samples (Figure). These include gondoate (log2 fold change 1.59, p=0.012), oleate (log2 fold change 1.746, p=0.048), palmitoleate (log2 fold change 1.766, p=0.043), and pathways of fatty acid elongation (log2 fold change 2.06, p=0.012). While short chain fatty acids (SCFAs) have been shown to reduce inflammation, LCFA's have previously been associated with increased lung inflammation in asthma, another important airway disease.

Conclusions

While most current research on LCFAs and the lung pertain to fatty acids introduced through diet or in the lab, we hypothesize that LCFAs produced by lung pathogens in the CF airway can have a physiologic effect like gut derived bacterial SCFAs.

Gut derived SCFA's have been studied extensively as yielding a protective effect on inflammation leading to protection in inflammatory diseases across multiple organ systems and to be associated with inflammatory illnesses.3 In contrast, LCFAs introduced through diet and in the lab have been shown to induce bronchial cell proliferation, airway remodeling and airway smooth muscle contraction – all important factors in lung inflammation and exacerbation.4,5

As we found long chain fatty pathways to be upregulated in follow-up samples, LCFAs produced by bacteria in the CF lung should be studied further for potential impact on future PEx. This may help us further characterize the role of bacteria produced LCFA's on the transition between clinical states.

REFERENCES

1. MacKenzie T, Gifford AH, Sabadosa KA, et al. Longevity of patients with cystic fibrosis in 2000 to 2010 and beyond: survival analysis of the Cystic Fibrosis Foundation patient registry. Ann Intern Med. 2014;161(4):233–241. doi:10.7326/M13-0636

2. Feigelman R, Kahlert CR, Baty F, et al. Sputum DNA sequencing in cystic fibrosis: non-invasive access to the lung microbiome and to pathogen details. Microbiome. 2017;5(1):20. Published 2017 Feb 10. doi:10.1186/s40168-017-0234-1

3. Ding Y, Yanagi K, Cheng C, Alaniz RC, Lee K, Jayaraman A. Interactions between gut microbiota and non-alcoholic liver disease: The role of microbiota-derived metabolites. Pharmacol Res. 2019;141:521–529. doi:10.1016/j.phrs.2019.01.029

4. Wendell SG, Baffi C, Holguin F. Fatty acids, inflammation, and asthma. J Allergy Clin Immunol. 2014;133(5):1255–1264. doi:10.1016/j.jaci.2013.12.1087

5. Matoba A, Matsuyama N, Shibata S, Masaki E, Emala CW Sr, Mizuta K. The free fatty acid receptor 1 promotes airway smooth muscle cell proliferation through MEK/ERK and PI3K/Akt signaling pathways. Am J Physiol Lung Cell Mol Physiol. 2018;314(3):L333–L348. doi:10.1152/ajplung.00129.2017

Do Initial Tidal Volumes Matter in the Setting of the Emergency Department?

Arjun Panda, MSIII

CO-AUTHORS:
Theodore Quan, MSII
Natalie Sullivan, PGY-4,
Andrew Sparks, MS,[2]
Michael Ferebee, PGY-4
ADVISORS: Massoud Kazzi, MD;[1]
David Yamane, MD[1]

[1]The George Washington University (GW) School of Medicine and Health Sciences
[2]The GW Medical Faculty Associates

Outcome	EDVT unadjusted OR (95% CI) or unadjusted ln[β (SE)]	Unadjusted P	EDVT adjusted OR (95% CI) or adjusted ln[β (SE)]	Adjusted P
Death	1.19 (0.97 - 1.47)	0.1033	0.99 (0.75 – 1.32)	0.9863
Vent Days	0.0332 (0.0375)	0.3752	0.0760 (0.0408)	0.0627
ICU Days	-0.0072 (0.0393)	0.8539	0.0468 (0.0442)	0.2901
Hospital Days	-0.0224 (0.0420)	0.5942	0.0331 (0.0485)	0.4951

TABLE: The Effect of Tidal Volume Settings in the ED on Patient Outcomes.

Learning Objectives

Mechanical ventilation is a lifesaving therapy however, it may pose a threat to patients if set inappropriately. Prior studies suggest that tidal volumes (TVs) based on ideal body weight (IBW) are associated with improved outcomes for intubated patients. We sought to determine whether TV settings based on IBW correlated with clinically relevant patient outcomes for patients intubated in the emergency department (ED).

Methods

We performed a retrospective review of electronic medical records from January 2016 to December 2018 for intubated patients in the ED. We collected data including: patient demographics, height, weight, lab values, and ventilator settings in the ED. We calculated IBW for all patients to determine the tidal volume per kilogram given in the ED. We stratified the TVs based on low (<8cc/kg), intermediate (8-10cc/kg), and high (>10cc/kg). We assessed the impact of TV on the following outcomes: ventilator days, intensive care unit (ICU) days, hospital days, and death. Multivariable logistic and general linear models were assessed adjusting for baseline demographics, clinical variables, and illness severity to better elucidate the independent effect of tidal volume on outcomes of interest. Length of stay (LOS) outcomes were natural logarithm (ln) transformed to meet the assumptions of normality and linear regression.

Results

Two hundred seventeen patients had full data record for analysis. Average age was 59.7 ± 15.4 years old (mean ± standard deviation). 90 (41.5%) patients were female and 127 (58.5%) were male. Median SOFA score was 8 with interquartile range 6–11. Median LOS for days on ventilator, days in ICU, and days in hospital were 3, 5, and 8, respectively. 64 (29.5%) patients experienced mortality. Adjusted analysis detected no independently significant relationship between any of the IBW ED tidal volume per kg and mortality, ICU days, or hospital days (Table).

Conclusions

This data suggests that the TV size did not significantly affect patient outcomes. There was no association between low, intermediate or high TV and mortality, ventilator days or hospital days.

Factors Associated with Emergency Department Length of Stay in Patients with Acute Gout

Murwarid Rahimi, MSII

COAUTHORS:
Steven Reinert, MS,[1]
Ross Hilliard, MD,[2]
Anthony Reginato, MD, PhD,[3] Deepan Dalal, MD, MPH[3]

ADVISOR: Nadine Mbuyi, MD[1]

[1]Lifespan Information Services, Brown University
[2]The George Washington University School of Medicine and Health Sciences
[3]Alpert Medical School, Brown University

Emergency department (ED) visits for acute gout have increased by approximately 20% between 2006 and 2014.1 Reducing the ED length of stay (LOS) can help reduce cost of care for gout patients and ED crowding.2 We assessed the ED LOS and factors associated with it in patients with acute gout. A retrospective analysis was conducted and included the first ED visit of adult patients with acute gout who presented to the 3 EDs affiliated with Lifespan Health Systems, the largest healthcare provider in Rhode Island. The ED LOS was the time spent by patient in the ED until they were discharged. Patients presenting to the ED and subsequently admitted to the hospital were excluded given the differential effect of system factors in these patients. Both patient factors, such as clinical presentation of gout, as well as systems factors were assessed. Univariate and multivariable analysis were completed. The univariate analysis demonstrated that patient factors such as older age (>65 years), comorbidities (hypertension, congestive heart failure), and worse ED severity score were associated with being in the upper quartile of ED LOS in addition to being treated in an academic setting. A multivariable analysis showed that persons of age greater than 65 years and a worse acuity score continued to be associated with longer ED LOS. Overall, the study

	< 4.3 hours in ED (n = 265)	> 4.3 hours in ED (n = 90)
Patient factors		
Age < 65	185/265 (69.8%)	51/90 (56.7%)
Male gender	213/264 (80.7%)	75/90 (83.3%)
Comorbidities		
Diabetes	68/228 (29.8%)	29/76 (38.2%)
Hyperlipidemia	132/228 (57.9%)	53/76 (69.7%)
History of gout	160/228 (70.2%)	54/76 (71.1%)
Hypertension*	162/228 (71.1%)	65/76 (85.5%)
Coronary artery disease	49/228 (21.5%)	21/76 (27.6%)
Heart failure*	32/228 (14.0%)	26/76 (34.2%)
Chronic kidney disease	44/228 (19.3%)	21/76 (27.6%)
Cerebrovascular disease	19/228 (8.3%)	4/76 (5.3%)
Other inflammatory arthritis	10/228 (4.4%)	3/76 (4.0%)
Clinical presentation of gout		
Oligo/polyarticular gout	33/265 (12.4%)	13/90 (14.4%)
Arthrocentesis*	21/265 (7.9%)	51/90 (56.7%)
ED Severity Score*		
Score 2 and 3	117/265 (44.1%)	67/90 (74.4%)
Score 4 and 5	148/265 (55.8%)	23/90 (25.6%)
Systems factors		
Type of Hospital*		
Academic center	204/265 (77%)	82/90 (91.1%)
Community center	61/265 (23%)	8/90 (8.9%)
Time of Day		
Time of day (12 am – 8 am)	52/265 (19.6%)	20/90 (22.2%)
Time of day (8 am – noon)	124/265 (46.8%)	51/90 (56.7%)
Time of day (noon – midnight)	89/265 (33.6%)	19/90 (21.1%)
Time of Year		
January to March	43/265 (16.2%)	21/90 (23.3%)
April to June	94/265 (35.5%)	28/90 (31.1%)
July to September	78/265 (29.4%)	19/90 (21.1%)
October to December	50/265 (18.9%)	22/90 (24.2%)
Weekend presentation	94/265 (35.5%)	24/90 (26.7%)

*Represents statistically significant results ($p < 0.05$)

TABLE: Factors Associatedwith Increased ED Length of Stay in Gout Patients

demonstrated patients with acute gout spent a longer time in the ED than the national median of 120-150 minutes. Older age and a higher acuity score in addition to procedural delays led to longer length of stay in the ED.

REFERENCES:

1. Mithal A, Singh G. OP0185 Emergency department visits for gout: a dramatic increase in the past decade, Annals of the Rheumatic Diseases. 2018;77:141-142.
2. Jinno S, Hasegawa K, Neogi T, Goto T, Dubreuil M. Trends in Emergency Department Visits and Charges for Gout in the United States between 2006 and 2012. J Rheumatol. 2016;43(8):1589–1592. doi:10.3899/jrheum.151432

Mortality of Hepatic Air on Point of Care Ultrasound in Cardiac Arrest: Does Location Matter?

Pradip Ramamurti, MSIII

CO-AUTHOR: Sajani Desai, MSII

ADVISORS: David Yamane, MD,[1] Aaran Drake, MD[1]

[1]The George Washington University School of Medicine and Health Sciences

Learning Objectives

Given the high mortality rate in patients with cardiac arrest, previous research has sought to determine factors that distinguish patients who are likely to have return of spontaneous circulation (ROSC) from those in whom continued resuscitation is futile.[1] Prior research utilizing multiple imaging modalities such as Ultrasound and CT scan has suggested an association of the presence of hepatic venous air with mortality.[2] As point of care ultrasound (POCUS) is already becoming more frequently used in the context of resuscitation, we sought to evaluate if the presence of any hepatic air, parenchymal or venous, on POCUS had a similar mortality association.

Methods

We completed a retrospective review of patients at George Washington University Hospital, who experienced non-traumatic cardiac arrest and had POCUS with adequate views of the hepatic parenchyma. The majority of these images were sub-xiphoid evaluations of cardiac activity, with incidental capture of the liver. Archived ultrasound images were independently reviewed to determine the presence of hepatic parenchymal and/or hepatic venous air. Electronic medical records were then reviewed to collect other clinical data, including admission rate to ICU and overall hospital mortality.

Results

From Jan. 1, 2017 through June 16, 2019, 87 patients met inclusion criteria, including 6 In-hospital cardiac arrests (ICHA) and 81 out of hospital cardiac arrest (OCHA) Ultimately, 68 (78.2%) died and 19 (21.8%) survived. Of those who died, 40 (58.8%) had hepatic air, while 28 (41.2%) had none. Of those who died with hepatic air, 38 (95%) demonstrated parenchymal air, while 27 (67.5%) demonstrated venous air. Of the survivors, nine (47.4%) had hepatic air, while 10 (52.6%) had none. Only a single survivor demonstrated hepatic venous air (11%). While the difference in mortality with respect to presence of undifferentiated hepatic air was not significant (p=0.37), there was a significant difference with respect to the presence of venous air (p=0.0046).

Our study demonstrated that the incidence of post-arrest hepatic air on POCUS was common, although the presence of air in parenchyma alone did not significantly distinguish patients with respect to mortality.

CONCLUSION

Our study demonstrated that the incidence of post-arrest hepatic air on POCUS was common, although the presence of air in parenchyma alone did not significantly distinguish patients with respect to mortality. Hepatic venous air, however, may be of prognostic value as it could act as an indicator of mortality. Further studies are necessary to better describe this phenomenon.

REFERENCES:

1. Lien WC, Chang WT, Huang SP, et al. Hepatic portal venous gas associated with poor outcome in out-of-hospital cardiac arrest patients. Resuscitation. 2004 March;60(3):303-7.
2. Reuter H, Bangard C, Gerhardt F, Rosenkranz S, Erdmann E. Extensive hepatic portal venous gas and gastric emphysema after successful resuscitation. Resuscitation. 2011 Feb;82(2):238-9.

The Utility of Bandemia in Prognostication and Prediction of Mortality in Sepsis

Amir Rashed, MSIV
CO-AUTHORS: Nivi Prasanna, MD,[1] Benjamin DelPrete, DO,[1] Andres Garza MD[1]
ADVISORS: David Yamane, MD,[1] Katrina Hawkins, MD '05[1]

[1]The George Washington University School of Medicine and Health Sciences

Sepsis remains a leading cause of death in the United States despite advancements in early recognition and initiating prompt treatment.[1,2] Bandemia, defined as a band count >10%, is highly indicative of underlying infection and is increasingly being used in the emergency department (ED) and the intensive care unit (ICU) for identification of sepsis.[3] Bandemia has been linked to worse outcomes, but its trend in the intensive care unit (ICU) is not well studied.[4,5] In this retrospective study, we assessed the severity of bandemia at 0 and 72 hours among patients admitted to the ICU for sepsis or septic shock to evaluate if there was a direct correlation between increasing bandemia and clinical deterioration among these patients.

This data suggests that the clearance of bandemia can be used as a marker of clinical improvement in sepsis. It also shows that worsening bandemia is predictive of deteriorating clinical status and higher mortality.

Methods

We performed a retrospective chart review of patients admitted to our tertiary care ICU for sepsis or septic shock from the ED. Patients were excluded if their bandemia was due to etiologies other than sepsis. We recorded the band counts, Sequential Organ Failure Assessment (SOFA) scores, vasopressor use, and the clinical course of 134 patients included in our study at 0 and 72 hours after admission. Worsening clinical course was defined as increasing SOFA scores or the initiation and continuation of vasopressor support at 72 hours. Patients were analyzed based on SOFA trends (SG=SOFA group) and vasopressor trends (VG=vasopressor group). They were distributed among groups 1-4 SG based on resolving, steady-state or worsening SOFA scores, and groups 1–4 VG based on improving, steady-state or worsening vasopressor requirement.

Results

Among the 134 patients included for analysis, the average SOFA score on admission was 6. Based on SOFA scores and vasopressor trends between hour 0 and hour 72, there was a statistically significant improvement in bandemia for patients in Group 1 (Range -10.3 ± 15.3, Mean -6) with resolving sepsis (P<0.0001 SG, P<0.0001 VG) and a statistically significant worsening in bandemia (Range 10.1 ± 6.4, Mean 7) for patients in Group 3 with worsening sepsis (P=0.0001 SG, P=0.0007 VG).

Conclusions

This data suggests that the clearance of bandemia can be used as a marker of clinical improvement in sepsis. It also shows that worsening bandemia is predictive of deteriorating clinical status and higher mortality. The presence of bandemia and its trend in the ICU can, therefore, be used to guide the safe de-escalation of antibiotic therapy in the ICU, and potentially decrease the total duration of antibiotic use.

REFERENCES:

1. Lu Y, Zhang H, Teng F, Xia W-J, Sun G-X, Wen A-Q. Early Goal-Directed Therapy in Severe Sepsis and Septic Shock: A Meta-Analysis and Trial Sequential Analysis of Randomized Controlled Trials. J Intensive Care Med. 2018;33(5):296-309. doi:10.1177/0885066616671710

2. Kochanek K, Murphy S, Xu J, Arias E. Deaths: Final Data for 2017. Natl VItal Stat Reports. 2019;68(9). www.cdc.gov/nchs/data/nvsr/nvsr68/nvsr68_09-508.pdf. Accessed Oct. 8, 2019.

3. Bone RC, Balk RA, Cerra FB, et al. Definitions for Sepsis and Organ Failure and Guidelines for the Use of Innovative Therapies in Sepsis. Chest. 1992;101(6):1644–1655. doi:10.1378/CHEST.101.6.1644

4. Cavallazzi R, Bennin CL, Hirani A, Gilbert C, Marik PE. Review of A Large Clinical Series: Is the Band Count Useful in the Diagnosis of Infection? An Accuracy Study in Critically Ill Patients. J Intensive Care Med. 2010;25(6):353-357. doi:10.1177/0885066610377980

5. Capp R, Horton CL, Takhar SS, et al. Predictors of Patients Who Present to the Emergency Department With Sepsis and Progress to Septic Shock Between 4 and 48 Hours of Emergency Department Arrival*[GP5]. Crit Care Med. 2015;43(5):983-988. doi:10.1097/CCM.0000000000000861

Differential Phenotypic Expression of Septic Shock in the Pediatric Population

Muneeb Rehman, MSII
ADVISOR: Ioannis Koultroulis MD, PhD,[1,2]

[1]Children's National Hospital
[2]The George Washington University School of Medicine and Health Sciences

Septic shock is a common condition characterized by host immunodysregulation secondary to an infectious etiology leading to hypotension and lactic acidosis secondary to organ breakdown.[1] Recent investigations suggest that this dysregulation is biphasic, being initially a hyperimmune reaction resulting in systematic inflammation followed by long term immunosuppression and associated sequalae.[1] Given that the major player in sepsis and septic shock is not the offending pathogen but rather the response of the host immune system to that pathogen, it is crucial to develop a more robust understanding of the immune system's essential role in this pathology and the role of conditions that modulate the immune system in the pathogenesis of sepsis, especially in vulnerable populations.[1] Classically, and more commonly in adults, sepsis presents with decreased systemic vascular resistance (SVR) and warm extremities due to systematic endothelial disruption (warm shock), while pediatric cases tend to exhibit increased SVR and cold extremities (cold shock).[2,3] However, in pediatric populations with still maturing immune systems, the phenotype of septic shock is less understood. The purpose of this study was to evaluate different phenotypes of septic shock in a selected pediatric population.

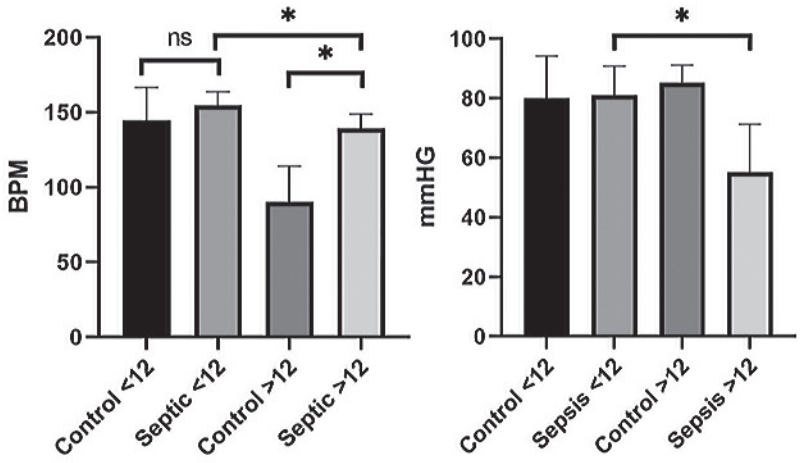


FIGURE: Beats per minute (BPM) and mean arterial pressure (MAP) in septic patients by age.

To do this, we created a case-control study in which we followed the hospital courses of sixteen pediatric patients hospitalized at the Children's National Hospital between 02/2018 and 07/2019, eight of whom were admitted for septic shock and eight of whom were admitted for another condition to serve as a control. Care was taken to ensure that the control group did not include patients with an inflammatory or infectious pathology or condition or had taken any immunomodulatory medication to avoid any confounding data. The study patients were then further subdivided by age and key metrics, including gender, history of chronic illness, etiologic agent as determined by blood cultures, recurrent antibiotics use, oxygen saturation, erythrocyte sedimentation rate, C-reactive protein levels, white blood cell count, temperature, heart rate, and blood pressure. Due to the emergent nature of septic shock, there is an inevitable variation in the exact time of clinical presentation and therefore a spread in when specifically our data was collected, however all data included within this study was collected within 24 hours of the presentation of initial symptoms of SIRS among children with septic shock.

We observed that patients aged less than 12 years exhibited a septic shock phenotype distinct from patients over the age of 12. Patients with septic shock above the age of 12 had higher heart rates compared to control, while patients younger than 12 did not significantly from control (Figure). Furthermore, we found that mean arterial pressure (MAP) was significantly lower in children with septic shock older than 12 compared to their younger counterparts (Figure). These findings could be due to fundamental differences in the physiology of children as compared to adults, such as the inability of children to modulate their cardiac contractility in the same manner as adults.[2] This, in turn, is complicated by the decreased cardiac function commonly seen in pediatric septic shock.[4] As such, in order to further unravel the fundamental basis of

Continued on p. 48

Continued from p. 47

these phenotypes, future work will be focused on the extraction and isolation of peripheral blood mononuclear cells from each of the patients present here with the end goal of examining and characterizing the immunometabolic status of each of these patients.[5] We hope that such an approach will help illuminate the fundamental principles underlying such observations, which in turn may prove crucial to developing novel methodologies for the treatment of sepsis.

REFERENCES

1. Frydrych LM, Bian G, O'Lone DE, Ward PA, Delano MJ. "Obesity and Type 2 diabetes mellitus drive immune dysfunction, infection development, and sepsis mortality." Journal of Leukocyte Biology. 2018;104:525-34.
2. Angus DC, Van Der Poll T. Severe sepsis and septic shock. New England Journal of Medicine. 2013;369:840-51.
3. Ceneviva, G Paschall JA, Maddei F, Carcillo JA. Hemodynamic support in fluid-refractory pediatric septic shock. Pediatrics. 1998;102., vol. 102, no. 2, 1998, doi:10.1542/peds.102.2.e19.
4. Arkin AA, Citak A. Pediatric shock. Signa Vitae - A Journal In Intensive Care And Emergency Medicine. 2008;3:13-23.
5. Murphy MP, O'Neill LAJ. Krebs cycle reimagined: the emerging roles of succinate and itaconate as signal transducers. Cell 2018;174:780-84.

The Kitchen Sink: Mortality Assessment of Salvage Therapies in Refractory Shock

Shannon Tillery, MSII

CORRESPONDING AUTHORS/ ADVISORS: Katie Januszewicz, MD,[1] Daniel King MD,[1] Andrew Sparks,[2] David Yamane MD,[1] Danielle Davidson MD[1]

[1]The George Washington University (GW) School of Medicine and Health Sciences
[2]The GW Medical Faculty Associates

Learning Objectives

Refractory shock remains a challenge with nearly ubiquitous mortality. Novel therapies are needed to maintain hemodynamics when conventional mechanisms, have failed. Several exploratory therapies display potential efficacy in the literature, however it remains unclear which therapy is superior.[1,2] We aim to clarify the efficacy of the current salvage therapies: Angiotensin II (ATII) vs Methylene Blue (MB) vs Vitamin C with thiamine and hydrocortisone (Vit C) for refractory shock. We hypothesize that these therapies will improve survivability and decrease the need for other vasopressors in patients with refractory shock.

Methods

This study is a retrospective review of patients with refractory shock started on ATII, MB, and/or Vit C in a single center mixed ICU. We collected baseline demographics, shock etiology, APACHE II, mortality, etc. The primary outcome was mortality and the secondary outcome was the change in standard vasopressor requirements after initiation of these therapies. The groups were analyzed based on whether they received one intervention alone, or a combination of therapies.

Results

Fifty six patients were included in the ATII group, 21 patients in the MB group, and 114 in the Vit C group (total n= 191). As monotherapy, for those that received ATII (34) mortality was seen in 85.3% (29), for MB (9) mortality was seen in 77.8% (7), and for Vit C (79) mortality was seen in 51.9% (41). After adjusting for APACHE II, those who received ATII (monotherapy/combination) had 2.85 times higher odds of mortality than those who did not receive the drug (CI 1.28 - 6.33, p=0.0103). Vit C, however, showed 65% lower odds of mortality when compared to those who did not receive it (aOR 0.35, CI 0.14 - 0.87, p=0.0231). No statistical significance was seen for MB (aOR 2.80, CI 0.53-14.78, p=0.2254). The vasopressor requirements decreased over the first 24 hours after starting therapy with these drugs, but ATII still required higher doses of norepinephrine and vasopressin compared to Vit C (p=0.0011, p=0.0026 respectively).

Conclusion

While these therapies have shown improvement in hemodynamics, this study questions the impact on overall mortality. These results could be due to the baseline low survivability in this patient population or due to not initiating these rescue therapies soon enough. More prospective studies are needed to further clarify their potential role in refractory shock.

REFERENCES:

1. Abril MK, Khanna AK, Kroll S, et al. Regional differences in the treatment of refractory vasodilatory shock using angiotensin II in high-output shock (ATHOS-3) data. J Crit Care. 2018;50:188-194.
2. Marik PE, Khangoora V, Rivera R, et al. Hydrocortisone, vitamin C, and thiamine for the treatment of severe sepsis and septic shock. Chest. 2017;151:1229-1238.

Durable Clearance Rates for In Situ and Invasive Melanomas Using Mohs Micrographic Surgery with MART-1 Immunostaining

Leora Aizman, MSIII
COAUTHORS:
Shannon Nugent;[1]
David Weiner, PhD;[1]
Tori O'Malley[1]
ADVISOR: Thuzar M. Shin, MD, PhD[1]

[1]University of Pennsylvania

Mohs micrographic surgery (MMS) is useful for treatment of melanomas located on specialty sites (head, neck, hands, feet, genitalia, pretibial leg), which have an increased risk of complications after conventional excision with post-operative margin assessment (CE-POMA).[1] We previously reported local recurrence rates of 0.34% (2/597 lesions) for melanoma in situ (MIS) after MMS with melanoma antigen recognized by T-cells 1 (MART-1) immunostaining in a cohort of 563 individuals over a mean follow up of 2.8 years (0.01-8.68 years).[2] The same treatment technique for invasive melanoma, assessed in a larger cohort, yielded a local recurrence rate of 1.3% (7/556 lesions).[3] We now present our 11-year experience, which includes five- and 10-year follow up data.

An IRB-approved retrospective cohort study was performed to evaluate the local recurrence rates of invasive and in situ melanomas treated using MMS with MART-1 immunostaining at the University of Pennsylvania between 2006 and 2017. Data for all patients were prospectively entered in an electronic database at the time of surgery and includes patient demographics, tumor characteristics, anatomic location, and previous treatment. Patients were excluded if there was evidence of locoregional or distant metastasis at the time of surgery or clear margin status was not achieved using frozen section interpretation alone (for example, cases for which MART-1 immunostaining was not reliable, such as desmoplastic melanoma, or required additional tumor resection in the operating room). Follow up information was obtained through patients' medical records or via telephone call as previously described.1 The primary outcome was biopsy-proven local recurrence, defined as the presence of a new lesion in the surgical scar where MMS was performed or within 2 cm of the original lesion.

Two thousand one hundred thirty-four primary or locally recurrent invasive and in situ melanomas without

Characteristics	Melanoma Type In Situ	Invasive	Combined
Number of Patients	1283.0	507.0	1790.0
Number of Tumors	1395.0	553.0	1948.0
Age at Surgery (years)			
Mean (range)	66.6 (18-100)	67.3 (25-94)	66.8 (18-100)
Gender (n, %)			
Female	509.0 (39.7%)	184.0 (36.3%)	693.0[2] (38.7%)
Male	774.0 (60.3%)	323.0 (63.7%)	1097.0 (61.3%)
Tumor Location (n, %)			
Head/Neck	1174.0 (84.2%)	468.0 (84.6%)	1642.0 (84.3%)
Trunk/Arms/Legs	154.0 (11.0%)	64.0 (11.6%)	218.0 (11.2%)
Hands/Feet/Genitalia	67.0 (4.8%)	21.0 (3.8%)	88.0 (4.5%)
Immunosuppression status (n, %)			
Immunosuppressed	17.0 (1.2%)	18.0 (3.3%)	35.0 (1.8%)
Most Recent Follow-up Time (days)			
Mean (range)	1296.7 (2-4304)	1078.5 (3-4110)	1234.8 (2-4304)
Median	1182.0	965.0	1113.0
Tumor Characteristics			
Recurrent Prior to Initial Surgery (n, %)	198.0 (14.2%)	68.0 (12.3%)	266.0 (13.7%)
Subclinical Spread (n, %)	472.0 (33.8%)	211.0 (38.2%)	683.0 (35.1%)
Breslow Depth mean (range) (mm)	-	0.7 (0.04-12.9)	-
Mitoses mean (range) (1/mm^2)	-	1.2 (0.0-38.0)	-
Ulceration present (n, %)	-	31.0 (5.6%)	-
Tumor Size			
Mean Length (mm)	2.1	2.3	2.1
Mean Width (mm)	1.6	1.9	1.7
Number of Stages (n, %)			
Mean (range)	1.41 (0-5)	1.53 (0-7)	1.44 (0-7)
0	1.0 (0.1%)	1.0 (0.2%)	2.0 (0.1%)
1	922.0 (66.1%)	341.0 (61.7%)	1263.0 (64.8%)
2	393.0 (28.2%)	160.0 (28.9%)	553.0 (28.4%)
3	63.0 (4.5%)	32.0 (5.8%)	95.0 (4.9%)
4	12.0 (0.9%)	11.0 (2.0%)	23.0 (1.2%)
5	4.0 (0.3%)	3.0 (0.5%)	7.0 (0.4%)
6	0.0 (0.0%)	4.0 (0.7%)	4.0 (0.2%)
7	0.0 (0.0%)	1.0 (0.2%)	1.0 (0.1%)

TABLE: Patient and Tumor Clinical Characteristics

Continued on p. 50

Continued from p. 49

clinical evidence of metastasis were identified in 1,973 patients. 186 cases of 183 patients were excluded because 98 patients declined to participate when consent was sought via telephone, 52 patients were without clinic follow up and unable to be reached, 29 patients were deceased and without clinic follow up, and four patients required additional resection following MMS. Follow up information was available for a total of 1,790 patients with 1,948 melanomas (Table).

Six local recurrences (0.31%, 6/1948) were identified. The majority of lesions (5/6, 83%) that recurred were in situ and all lesions were 1 cm or larger at the time of surgery. One-third (2/6) of recurrences were recurrent at the time of initial MMS. The average time to recurrence was 1,347 days for MIS and 285 days for invasive melanoma. Five and ten-year minimum follow up information was available for 458 and 33 cases respectively. The five- and 10-year Kaplan–Meier local recurrence-free survival rates were 0.9946 (95% CI 0.9855-0.9980) and 0.9856 (95% CI 0.9490-0.9960) (Figure).

The overall local recurrence rate was low (0.31%) and remained durable at five- and 10-year follow up, despite the majority of tumors located on specialty sites, which have an average local recurrence of ~10% following CE-POMA.2 All recurrences after MMS were located on the scalp, cheek, eyelid/conjunctiva, or foot, highlighting the challenges of treating specialty site melanomas. Our data support the use of MMS with MART-1 immunostaining to achieve durable local clearance for specialty site melanomas.

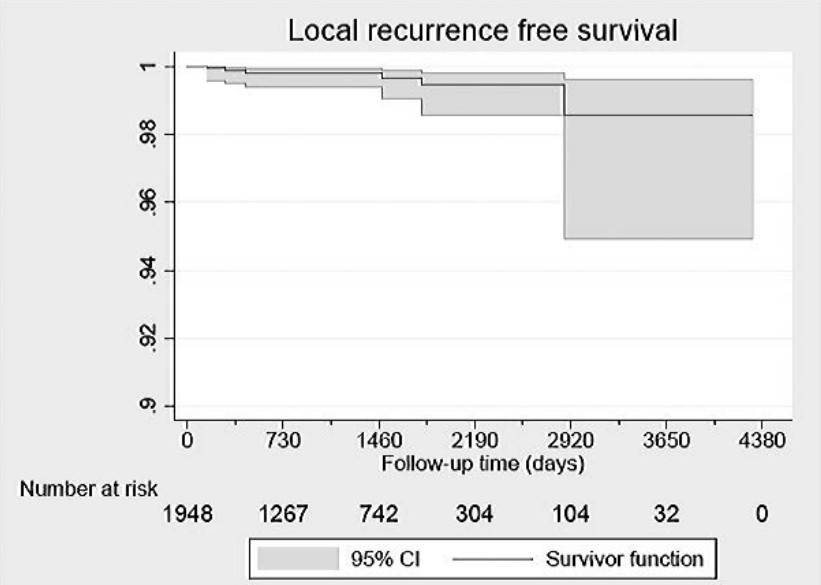


FIGURE: Local Recurrence-Free Survival Rate

REFERENCES

1. Rzepecki AK, Hwang CD, Etzkorn JR, et al. The "Rule of 10s" versus the "Rule of 2s": High complication rates after conventional excision with postoperative margin assessment of specialty site versus trunk and proximal extremity melanomas. J Am Acad Dermatol. 2018; doi: 10.1016/j.jaad.2018.11.008. [Epub ahead of print]
2. Etzkorn JR, Sobanko JF, Elenitsas R, et al. Low recurrence rates for in situ and invasive melanomas using Mohs micrographic surgery with melanoma antigen recognized by T-cells 1 (MART-1) immunostaining: tissue processing methodology to optimize pathologic stagin and margin assessment. J Am Acad Dermatol. 2015;72(5):840-850.
3. Valentin-Nogueras SM, Brodland DG, Zitelli JA, et al. Mohs Micrographic Surgery Using MART-1 Immunostain in the Treatment of Invasive Melanoma and Melanoma In Situ. Dermatol Surg. 2016;4(6):733-744.

Comparison of Oncologic Outcomes for Robotic vs. Open Radical Cystectomy Among Locally Advanced and Node-Positive Patients: An Analysis of the National Cancer Database

Akshay Reddy, MSII

ADVISORS:

Andrew D Sparks MS,[2] Michael J. Whalen, MD[1]

[1]The George Washington University (GW) School of Medicine and Health Sciences

[2]The GW Medical Faculty Associates

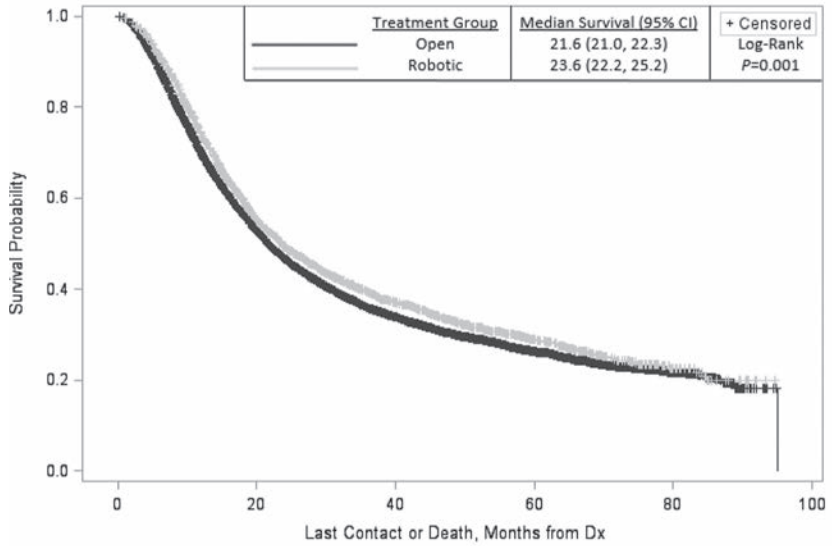


FIGURE: Kaplan Meier for overall survival with median survival statistics for ORC and RARC.

Since the early 2000s, there has been more than a 25-fold increase in the use of the robotic-assisted radical cystectomy (RARC) compared to more conventional, open radical cystectomy (ORC) for bladder cancer.[1] Proponents of this minimally invasive approach favor the decreased perioperative comorbidities associated with the modality, which includes decreased blood loss, recovery time, and complication rates.[2–4] Despite these advantages, the use of RARC has not gained the same popularity in the setting of higher grade malignancy, due to concerns of atypical recurrence from pneumoperitoneum-induced immunomodulation, tumor cell intravasation and port-site trauma.[5] Recent randomized control trials, notably the RAZOR study, have determined no differences in oncologic or mortality outcomes compared to the open approach in bladder cancer as a whole, but have not sub-stratified by tumor aggressiveness.[2,3] Given the putative mechanisms, likelihood of atypical recurrence would presumably be especially relevant in higher stage, locally advanced or node-positive disease, where the intrinsic metastatic potential of tumor cells may be greater. This study aims to compare the oncologic efficacy of RARC compared to ORC, among patients with stage pT3-4 or node-positive bladder cancer.

Methods

A retrospective cohort analysis of pT3-4N0-3 or pT(any)-4N1-3 patients who underwent RARC or ORC from 2010–16 was performed using the National Cancer Database (NCDB). Baseline demographic and clinicopathologic variables were compared between treatment cohorts. Primary outcome of overall survival was analyzed by way of Kaplan-Meier estimation with corresponding Log-Rank test, followed by multivariable Cox-Proportional Hazards regression. Secondary outcomes including 30-day mortality, 90-day mortality, 30-day readmission, positive margin status, receipt of adjuvant radiation or chemotherapy, and surgical inpatient length of stay were analyzed by way of Chi-square, Fisher's exact, or Mann-Whitney U test, followed by multivariable logistic or transformed linear regression.

Results

There were 9,062 ORC cases and 2,544 RARC cases that met inclusion criteria. RARC was significantly associated with superior unadjusted survival compared to ORC (Figure). Additionally, RARC was significantly associated with lower proportions of unadjusted 30- and 90-day mortality, positive margin status, and shorter surgical inpatient stay

Continued on p. 52

Continued from p. 51

(all respective P<0.05). However, after adjusting for confounding covariates (demographic variables, perioperative chemotherapy, clinical stage, pathological stage, clinical node status, and surgical margin status) multivariable analysis revealed no difference in mortality hazard or odds of secondary outcomes with the exception of inpatient stay (Table). RARC was also significantly associated with higher lymph node yield (increased incidence of >14 lymph nodes examined relative to ORC; 55% vs. 40%; P<0.01).

Conclusions

RARC is no less safe than ORC for patients with locally advanced or node-positive bladder cancer on the basis of overall, 30- and 90-day survival outcomes. Unadjusted mortality and surgical outcomes in this population demonstrate advantages to the robotic modality. Perioperative benefits including shortened inpatient stay favor RARC, but further randomized control studies are necessary to better elucidate differences between surgical approaches in this unique population.

Outcome	Open (n=9062)	Robotic (n=2544)	Adjusted Hazard Ratio (95% CI)	Adjusted *P*
Overall Mortality	5954 (65.7)	1564 (61.5)	0.97 (0.92 – 1.03)	0.3239
			Adjusted Odds Ratio (95% CI)	
30 Day Mortality	285 (3.2)	55 (2.2)	0.78 (0.58 – 1.06)	0.1113
90 Day Mortality	883 (9.9)	199 (7.9)	0.90 (0.76 – 1.06)	0.2137
30 Day Unplanned Readmission	803 (8.9)	222 (8.8)	0.99 (0.84 – 1.16)	0.8618
Positive Margin Status	1753 (19.8)	439 (17.7)	1.00 (0.88 – 1.14)	0.9652
Adjuvant Radiation	333 (3.8)	79 (3.2)	0.97 (0.75 – 1.26)	0.8169
Adjuvant Chemotherapy	2681 (30.7)	734 (30.1)	0.94 (0.85 – 1.04)	0.2306
			Adjusted ln [β (SE)]	
Surgical Inpatient Stay (days)	8 (6, 11)	7 (5, 9)	-0.1025 (0.0169)	<0.0001*

*=statistically significant, P <0.05; CI=confidence interval; ln=natural logarithm; β=parameter estimate; SE=standard error;
Note: For all comparisons, reference group = ORC

TABLE: Multivariate Analysis for Overall Mortality and Oncologic/Surgical Outcomes

REFERENCES

1. Tyritzis S, Collins J, Wiklund N. The current status of robot-assisted cystectomy. Indian J Urol. 2018. doi:10.4103/iju.iju_355_17
2. Parekh DJ, Reis IM, Castle EP, et al. Robot-assisted radical cystectomy versus open radical cystectomy in patients with bladder cancer (RAZOR): an open-label, randomised, phase 3, non-inferiority trial. Lancet. 2018. doi:10.1016/S0140-6736(18)30996-6
3. Bochner BH, Dalbagni G, Marzouk KH, et al. Randomized Trial Comparing Open Radical Cystectomy and Robot-assisted Laparoscopic Radical Cystectomy: Oncologic Outcomes. Eur Urol. 2018. doi:10.1016/j.eururo.2018.04.030
4. Novara G, Catto JWF, Wilson T, et al. Systematic review and cumulative analysis of perioperative outcomes and complications after robot-assisted radical cystectomy. In: European Urology. 2015. doi:10.1016/j.eururo.2014.12.007
5. Audenet F, Sfakianos JP. Evidence of Atypical Recurrences after Robot-Assisted Radical Cystectomy: A Comprehensive Review of the Literature. Bl Cancer. 2017. doi:10.3233/BLC-170127

"Being Healthy and Living Life as if I Never Had Cancer": The Meaning of "Living Well" From Adolescents with Cancer

Katherine Schreiner, MSII
ADVISORS:
Daniel H. Grossoehme, DMin,[1] Maureen E. Lyon, PhD[2,3]

[1]Rebecca D Considine Research Institute, Akron Children's Hospital
[2]The George Washington University School of Medicine and Health Sciences
[3]Center for Translational Research, Children's National Hospital

Background/Objective

Extensive resources are devoted to discovering novel cancer treatment modalities. Meanwhile, patient priorities and experiences throughout their diagnoses and in the palliative care setting must also be addressed. Specifically, among adolescents with cancer, patients' definitions of "living well" may elucidate treatment preferences, guide care teams and families, and influence future behavioral interventions. The objective is to develop an empirical definition of "living well" for adolescents with cancer to enhance shared decision-making.

Design/Methods

Video recordings were analyzed from the Next Steps: Respecting Choices interviews with N=30 adolescents ages 14-21 years with cancer and their families, a subsample of N=126 adolescent/family dyads participating in a randomized clinical trial, FAmily CEntered (FACE) Advance Care Planning. Videos were transcribed verbatim by the first author who did not conduct the interviews. Using Krippendorf's inductive semantic content analysis, two authors created a codebook from two transcripts by identifying consistent themes.1 Upon completion, the codebook was then used to independently code two additional transcripts to maximize the likelihood of code saturation. Coding proceeded of the remaining 28 transcripts. Reconciliation was resolved by consensus to maximize reliability. Triangulation increased validity.

Results

"Living well" had four domains: (1) exercising autonomy over one's total personhood; (2) participating in meaningful relationships with family and friends, in which shared experiences are more important than the experiences themselves; (3) wholeness—emotional, physical, and spiritual health; physical health includes nutritious eating and sleep hygiene; (4) living a productive life, engaging in meaningful activities, and living for more than your own interests.

Conclusions

By determining what "living well" means for adolescents with cancer, care teams and families can more easily understand patients' priorities. A firm grasp on patients' definitions of "living well" could relieve significant burden from families and increase families' willingness to honor adolescent treatment preferences. Findings may guide future psychosocial interventions.

REFERENCES

1. Krippendorff, K. (2004). Content Analysis: An Introduction to Its Methodology (2nd ed.). Thousand Oaks, CA: Sage.

Medium Term Outcomes in Surgically Treated Proximal Humerus Fractures: Is Age Just a Number?

Peter Berger, MSIV
CO-AUTHORS:
Christine Piper, MD,[3] Jessica Heyer, MD, PGY5[1]
ADVISORS:
Teresa Doerre, MD,[1]
Andrew Neviaser, MD[2]

[1]The George Washington University (GW) School of Medicine and Health Sciences
[2]The Ohio State University College of Medicine
[3]The GW Medical Faculty Associates

Characteristics	n=41
Age, years (mean [SD])	61.46 [17.08]
Gender, male (%)	41.46
Side, left (%)	36.59
BMI (mean [SD])	26.17 [5.47]
Length of follow up, years (mean [SD])	2.60 [1.36]

SD: Standard deviation; BMI: Body mass index

TABLE 1: TBaseline patient demographics

Proximal humerus fractures are common orthopaedic injuries, constituting approximately five percent of all fractures in some studies.[1] These fractures exhibit a bimodal distribution; younger males sustain these injuries in higher energy mechanisms, while older females sustain these fractures with low energy falls.[1]

Similar research has been done on clinical outcome measures following proximal humerus fractures by Slobogean et al.,[2] but their study had several notable differences. The cohort was smaller, limited to individuals over the age of 55, and included patients who underwent either operative or non-operative management.

Spross et al. conducted a retrospective review of 269 patients with surgically treated proximal humerus fractures and found older age to be a risk factor for worse clinical outcome scores in these patients.[3] Unlike this study, the present investigation assesses patient reported outcomes using the American Shoulder and Elbow Society Survey (ASES)4 and objective range of motion measurements in patients who underwent surgery for proximal humerus fractures

Methods

All proximal humerus fractures from September 2011 to February 2016 treated at one institution by a single surgeon were reviewed under IRB #121615. Patients were contacted by phone or at a clinic follow up appointment to complete a validated clinical outcomes survey (ASES), which assesses difficulty with a number of routine tasks involving the use of the affected shoulder. If patients had less than one year of clinical follow up they were asked to return to the office for range of motion evaluation.

Results

Of the 127 patients with qualifying injuries, 57 had greater than one year follow up and had completed the ASES survey. Sixteen patients were excluded because their index surgery was for a revision or non-union, or sufficient documentation was not available for analysis, leaving 41 patients for evaluation in this study. Patient characteristics are shown in Table 1. The impacts of age, body mass index (BMI), and range of motion (initial and final) on ASES were examined in a univariate comparison using Pearson correlations (r), all of which were found not to be significant in predicting outcome (ASES) score ($p>0.05$ for all) (Table 2).

Discussion

Our data suggest that older patients are no more likely to fare worse than younger patients at least one year after surgery. While early range of motion is conventionally thought of as crucial to help avoid stiffness, we did not find that difficulty with early passive range of motion was associated with unsatisfactory clinical outcomes. That is, even if patients lose range of motion in their injured shoulder, this does not significantly affect their quality of life.

There are several limitations to this study. This is a retrospective study, and as such cannot determine the temporal association or causality of our outcomes of interest. Other pitfalls specific to our outcomes of interest are inconsistency in range of motion measurements and differences

in patient response rates that also are associated with outcomes of interest.

Conclusion

Counseling patients on their functional prognosis following a traumatic injury is challenging. While existing evidence suggests that older patients are likely to have worse outcomes, our study suggests that it is not clear that older patients are at risk of worse self-reported outcomes than younger patients one year after surgical treatment for fractures of the proximal humerus.

n=41	Mean	SD	r	p-value
ASES score	85.59	16.63		
Age, years	61.46	17.08	-0.03	0.87
BMI	26.17	5.47	0.17	0.28
Initial PROM, degrees	94.81	30.08	0.09	0.72
Final Elevation, degrees	141.20	25.75	0.21	0.90
Final External Rotation, degrees	53.95	10.65	0.13	0.78
Final Internal Rotation, degrees	7.81	1.36	-0.09	0.68

ASES: American Society of Shoulder and Elbow Surgeons; SD: standard deviation; BMI: body mass index; PROM: passive range of motion.

TABLE 2: Univariate association between predictors and postoperative ASES score

REFERENCES

1. Passaretti D, Candela V, Sessa P, Gumina S. (2017). Epidemiology of proximal humeral fractures: a detailed survey of 711 patients in a metropolitan area. Journal of Shoulder and Elbow Surgery. 26(12), 2117–2124. https://doi.org/10.1016/j.jse.2017.05.029
2. Slobogean GP, Noonan VK, Famuyide A, O'Brien PJ. (2011). Does objective shoulder impairment explain patient-reported functional outcome? A study of proximal humerus fractures. Journal of Shoulder and Elbow Surgery. 20(2), 267–272. https://doi.org/10.1016/j.jse.2010.06.005
3. Spross C, Grueninger P, Gohil S, Dietrich M. (2015). Open Reduction and Internal Fixation of Fractures of the Proximal Part of the Humerus. JBJS Essential Surgical Techniques. 5(3), e15. https://doi.org/10.2106/jbjs.st.n.00106
4. Richards RR, An K-N, Bigliani LU, et al. (1994). A standardized method for the assessment of shoulder function. Journal of Shoulder and Elbow Surgery. 3(6), 347–352. https://doi.org/10.1016/s1058-2746(09)80019-0

CyberKnife Radiosurgery Treatment of Trigeminal Neuralgia: A Single Institution Examination With Long-Term Follow-Up

Eric Chalif, MSII
CO-AUTHOR:
Khashayar Mozaffari, MSII[1]
ADVISORS:
Donald McRae, PhD,[2] Nadim Nasr, MD,[2] Robert Hong, MD,[2] Jonathan H. Sherman, MD[1]

[1] The George Washington University School of Medicine and Health Sciences
[2] Virginia Hospital Center

During the past decades, frame-based stereotactic radiosurgery, and Gamma Knife® in particular, has demonstrated its efficacy and safety as therapy for Trigeminal Neuralgia (TN).1 However, few studies exist using non-frame-based radiosurgery devices such as CyberKnife (CK), especially those that report long-term follow-up. Our primary objective in this study is to evaluate the long-term effectiveness of CK stereotactic radiosurgery on TN pain response.

From 2010 to 2019, 38 patients were treated for symptomatic trigeminal neuralgia at Virginia Hospital Center: 68.4% patients were female, mean age was 72.3 years-old (range, 30 – 93). We performed a retrospective chart-review of these patients in order to collate predefined variables, followed by a prospectively collected follow-up phone survey to collect most recent health data. CK outcome was measured using the Barrow Neurological Institute (BNI) scores for pain and hypoesthesia, which was statistically evaluated by univariate and multivariate analyses. We considered a successful CK treatment as a decrease in BNI pain score from pre-treatment to follow-up.

CK treatment was initially successful in 87.5% of patients, with time to max pain relief ranging from three weeks to 36 weeks (mean, 10.5 weeks). Continued success at most recent follow-up was reported in 81.3% of patients (mean follow-up, 37.1 months). The median pre-treatment BNI pain score was V and the median BNI pain score at most recent follow-up was IIIa, indicating an improved quality of life. Trigeminal pain recurred in 18.8% of patients (range, 1.3 – 2.0 years). New-onset bothersome trigeminal hypoesthesia (defined as BNI hypoesthesia=II/III) was reported in 68.6% of patients. Increased CK success was found to correlate with increased BNI hypoesthesia scores (p=.001) as well as with increased side effects such as

Continued on p. 56

Continued from p. 55

dysphagia and paresthesia. (p=.003). Additionally, increased CK success was found to correlate with an idiopathic pathogenesis of TN pain in comparison to TN pain derived from stroke/tumor/surgery (p=.034). Interestingly, CK success did not correlate with typical nor atypical TN classification.

Our results demonstrate that CK stereotactic radiosurgery is an effective long-term therapy for treating TN. However, patients should be aware that such symptoms as hypoesthesia, paresthesia, and dysphagia can occur that correlate with an effective treatment. Furthermore, TN pathogeneses should be taken into account to be used as a possible predictor of success during CK treatment planning.

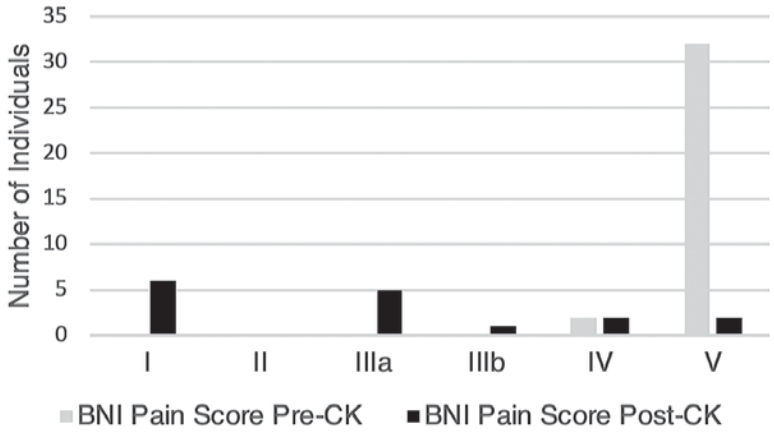


FIGURE: Bar graph of BNI scores

REFERENCES:

1. Tuleasca C, Régis J, Sahgal A, et al. Stereotactic radiosurgery for trigeminal neuralgia: A systematic review. Journal of Neurosurgery. 2019;130(3):733-757.

Unilateral Versus Bilateral Botulinum Toxin Injections in Adductor Spasmodic Dysphonia in a Large Cohort

Ishaan Dharia, MSIII
ADVISOR: Steven Bielamowicz, MD[1]

[1]The George Washington University School of Medicine and Health Sciences

	Unilateral	Bilateral	Chi-Squared
Optimal Effect	47%	55%	p= 0.000
Optimal Side Effect	77%	73%	p= 0.023
Optimal Effect/Side Effects	33%	36%	p= 0.0228

FIGURE: Chi-Square Analysis of Those Injections Resulting in an Optimal Effect of three Months or Greater and an Optimal Side Effect Duration Less Than or Equal to two Weeks.

The primary treatment of adductor spasmodic dysphonia is repeated injections of Botulinum toxin type A (Botox) into the thyroarytenoid muscles.1 Dosing can be performed into either one or both thyroarytenoid muscles.2 The objective of this study is to evaluate the treatment effect and side effect profile across a large number of injections. A study with the same objective was performed previously in 2002 on 45 patients.2 This current study is a retrospective study of all patients with adductor spasmodic dysphonia with or without tremor treated by the senior laryngologist at The George Washington University. In the current study, 272 patients (214 females and 58 males) were included in the analysis. Duration of effect and side effects (vocal weakness and liquid dysphagia) after each injection were recorded into a database. This data was analyzed using Chi-square analysis. A total of 4023 injections (2708 bilateral and 1315 unilateral) were evaluated in this study. Optimal effect duration (greater than or equal to three months) was more commonly seen in the bilateral injection patients (55%) compared to the unilateral injection patients (47%) with a p=0.0001. Optimal side effect duration (less than or equal to 2 weeks) was also better for the bilateral injection patients (73%) compared to the unilateral injection patients (77%) with a p=0.023. Having both optimal effect and side effect in the

same injection was more commonly seen in the bilaterally injected patients (36%) compared to the unilateral patients (33%) with a p=0.0228. This study shows that bilateral injections of Botox are more effective in producing optimal effect/side effect profiles.

REFERENCES:

1. Patel PN, Kabagambe EK, Starkweather JC, et al. Outcomes of onabotulinum toxin a treatment for adductor spasmodic dysphonia and laryngeal tremor. JAMA Otolaryngol HNS. 2018;144(4):293-9.
2. Bielamowicz S, Stager SV, Badillo A, Godlewski A. Unilateral versus bilateral injections of botulinum toxin in patients with adductor spasmodic dysphonia. J Voice. 2002;16(1):117-23.

Effect of Premedication with Midazolam on Recovery and Discharge Times After Tonsillectomy and Adenoidectomy

Andrew Garcia, MSII

ADVISORS:
Claude Abdallah MD, MSc, FASA[1]

[1]Department of Anesthesiology, Children's National Medical Center

Midazolam premedication is widely used before general anesthesia, but remains controversial due to its paradoxical side effects, including over sedation, decreased blood pressure, and respiratory depression. Patients with obstructive sleep apnea (OSA) are at particularly high risk for upper airway collapse as result of worsened obstruction of the pharynx after administration of sedatives, anesthetics, and analgesics.[1] While professional guidelines, including those from American Society of Anesthesiologists, provide direction regarding the perioperative management of OSA patients, focusing on general risks of respiratory depression and airway collapse with sedatives and opioids, specific guidance with regards to midazolam on emergence and recovery time in pediatric patients with moderate to severe OSA undergoing tonsillectomy and adenoidectomy (T&A) is limited.[2] We hypothesized that preoperative midazolam may increase emergence and discharge times in pediatric patients with OSA after T&A.

We conducted a retrospective chart review of patients at Children's National Health System who underwent T&A between July 2014 and December 2015. Patients who received midazolam were compared to patients who did not receive midazolam. Demographic data included age, gender, apnea-hypopnea score, body

Characteristics	Midazolam		P value
	No (n=387)	Yes (n=83)	
Age, mean (SD)	3.7 (1.4)	3.4 (1.4)	0.14
Weight, mean (SD)	17.4 (7.8)	16.5 (6.3)	0.31
BMI, mean (SD)	16.9 (3.9)	16.8 (3.9)	0.88
Gender			
Male	212 (54.8%)	51 (61.4%)	0.27
Female	175 (45.2%)	32 (38.6%)	
Race			
African Am./Black	187 (48.4%)	29 (34.9%)	0.16
Caucasian	66 (17.1%)	18 (21.7%)	
Hispanic/Latino	92 (23.8%)	24 (28.9%)	
Other	41 (10.6%)	12 (14.5%)	
Awake or Deep			
Awake	68 (17.6%)	11 (13.3%)	0.34
Deep	319 (82.4%)	72 (86.7%)	
ASA score			
1	56 (14.5%)	14 (16.9%)	0.41
2	295 (76.4%)	65 (78.3%)	
3	35 (9.1%)	4 (4.8%)	

*P values were obtained from t-test for continuous data, and Chi-square test for categorical data

TABLE 1: Demographic characteristics by midazolam status

Continued on p. 58

Group	Mean emergence time (95% CI), min*	Difference (95% CI), min	P value	Mean discharge time (95% CI), min*	Difference (95% CI), min	P value
No Midazolam	45.1 (39.9, 50.2)	5.2 (-7.1, 17.4)	0.41	115.8 (108.8, 122.9)	10.1 (-6.7, 26.8)	0.24
Midazolam	50.3 (39.2, 61.4)			125.9 (110.7, 141.1)		

TABLE 2: Emergence time, discharge time between Midazolam vs. No Midazolam group

Continued from p. 57

mass index, diagnosis, American Society of Anesthesiologists physical status classification score, length of surgery, and medications administered for anesthesia and recovery. Data endpoints included emergence and discharge times, perioperative desaturations, postoperative apneic episodes and delirium. Baseline demographic characteristics were compared using unpaired t-test for continuous data and Chi-square test for categorical data. Emergence and discharge times were compared using multiple linear regression, adjusting for predefined potential confounding factors.

There were no significant differences in demographic characteristics between the Midzolam (n=83) and No Midazolam (n=387) groups. Likewise, there were no significant difference in emergence or discharge times between these two groups. After adjusting for all potential confounders (surgery duration, dexmedetomidine and fentanyl doses adjusted to weight, and awake or deep tracheal extubation status), emergence time was 5.2 minutes (95% CI: -7.1, 17.4) longer in the Midazolam group (50.3 minutes, 95% CI: 39.2, 61.4) compared to the No Midazolam group (45.1 minutes, 95% CI: 39.9, 50.2). This association was not statistically significant (P= 0.41). After adjusting for potential confounders (surgery duration, dexmedetomidine and fentanyl doses dose adjusted to weight), discharge time was 10.1 minutes (95% CI: -6.7, 26.8) longer in the Midazolam group (125.9 minutes, 95% CI: 110.7, 141.1) compared to the No Midazolam group (115.8 minutes, 95% CI: 108.8, 122.9). This association was not statistically significant (P= 0.24).

Premedication with midazolam was not associated with a prolonged emergence or discharge time or with a higher incidence of complications after anesthesia for T&A in patients with OSA. These data can help to further characterize the best perioperative management strategies in pediatric patients with OSA undergoing T&A.

REFERENCES:

1. Francis A, Eltaki K, Bash T, Cortes S, et al. The safety of preoperative sedation in children with sleep disordered breathing. Int. J. Pediatr. Otorhinolaryngol. 2006; 70(9):1517-21.

2. American Society of Anesthesiologists: Practice guidelines for the perioperative management of patients with obstructive sleep apnea: A updated report by the American Society of Anesthesiologists Task Force on Perioperative Management of Patients with Obstructive Sleep Apnea. Anesthesiology 2014; 120:268–86.

Neurodevelopmental Screening in Premature Infants Undergoing Patent Ductus Arteriosus (PDA) Ligation

Jung Huh, MSII
CO-AUTHOR: Melissa A. Peace, MSIII
ADVISOR: Pamela Mudd, MD[1,2]

[1]The George Washington University, School of Medicine and Health Sciences
[2]Children's National Hospital

Indomethacin		Post-operative neurological findings (IVH, PLV, ventriculomegaly, RI values)				
N = 54		Better	Mixed	Same	Worse	Missing
Yes	n = 17	8 (47.1%)	0 (0.0%)	7 (41.2%)	0 (0.0%)	2 (11.8%)
No	n = 37	15 (40.5%)	3 (8.1%)	9 (24.3%)	4 (10.8%)	6 (16.2%)

TABLE 1: Pre-operative indomethacin treatment and post-operative neurological findings

Patent Ductus Arteriosus (PDA) is a congenital heart defect that affects about half of preterm infants born before 32 weeks of gestation. When pharmacotherapy with cyclooxygenase inhibitors like indomethacin is unsuccessful or contraindicated, patients must undergo surgical ligation of ductus arteriosus.[1] However, surgical ligation is significantly associated with neurodevelopmental impairment (NDI) at two years of age.[2] Examples of NDI range from cerebral palsy to compromised vision, hearing, posture, language, cognition, socialization, and coordination. In addition, patients who underwent secondary surgical ligation demonstrated higher NDI compared to those who received indomethacin treatment alone.[1]

Neurological findings leading to motor and cognitive delay in preterm infants include intraventricular hemorrhage (IVH), periventricular leukomalacia (PVL), ventriculomegaly, and hydrocephalus. Severity of the first three presentations can be determined via different grading systems based on head ultrasounds (HUS) and magnetic resonance imaging (MRI). Importantly, the higher the IVH or PVL grade, the higher the risk for ventriculomegaly as well as nonoptimal neurodevelopment. Furthermore, a progressive elevation in intracranial pressure (ICP) seen in hydrocephalus demonstrates a strong correlation with increased resistive index (RI) values of anterior cerebral artery (ACA), which is measured via Dopper.[3] In fact, infants with PDA exhibited higher RI values than those without PDA. But among those who received surgical ligation, there was no significant difference between pre- and post-operative RI values.[4]

Our objectives were to determine the clinical compliance with pre-operative indomethacin treatment as well as post-operative neurodevelopmental screening and consultations. Given that the risk for NDI is higher with surgical ligation, an understanding of the current screening methodology is needed for improvement of care.

A three-year retrospective chart review of premature infants who received PDA ligation at Children's National Hospital was performed. Information regarding pre-operative indomethacin use and post-operative consultations in neurology, child development, and physician medicine and rehabilitation (PM&R) were extracted from the charts. Neurological imaging data from HUS, Doppler, and MRI were re-evaluated for IVH, PVL, cerebellar hemorrhage, ventricular dilation, and RI values. Standard statistical methodology was applied.

[P]ost-operative consultations and screening measurements revealed that a majority of patients who underwent PDA ligation present with symptoms concerning for poor neurodevelopmental outcomes.

Fifty-four patients were identified (27M/27F; mean [SD] gestational age 25.2 [2.74] weeks). Of these patients, all seven infants (13.0%), who demonstrated worse or mixed postoperative findings in terms of RI values and ventriculomegaly, had not received indomethacin prior to surgical ligation (primary ligation) (Table 1). In two of

Continued on p. 60

Continued from p. 59

those patients, indomethacin was contraindicated because of evolving IVH and/or coagulopathy. Additionally, 32 infants (59.3%) received postoperative consultations in child development, neurology and/or PM&R; the other 22 infants did not have them on file. Out of the 32 cases, 29 infants (90.6%) exhibited developmental delay and/or neurological abnormalities on their first visits. Only three patients (9.4%) developed normally across all domains and lacked any significant neurological abnormalities after PDA ligation (Table 2).

In conclusion, the retrospective chart review demonstrated a potential correlation between the lack of preoperative indomethacin treatment and worse or mixed neurological findings after PDA ligation. Additionally, post-operative consultations and screening measurements revealed that a majority of patients who underwent PDA ligation present with symptoms concerning for poor neurodevelopmental outcomes. Although preterm infants selected for surgical ligation may have a higher pre-ligation risk for NDI,[1] the reported prevalence of neurodevelopmental abnormalities may also be underestimated due to the lack of post-operative screening and follow-ups. Thus, the study highlights the need for a better neurodevelopmental screening protocol for preterm infants receiving PDA ligation.

First postoperative consultations (child development, neurology, PM&R) n = 32	
Developmental delay ± neurological abnormalities	29 (90.6%)
Normal development without neurological abnormalities	3 (9.4%)

TABLE 2: Neurodevelopmental findings based on first post-operative consultations

REFERENCES:

1. Weisz DE, More K, McNamara, PJ, et al. PDA ligation and health outcomes: A Meta-analysis. Pediatrics. 2014; 133(4).
2. Bourgoin L, Cipierre C, Hauet, Q, et al. Neurodevelopmental outcome at 2 years of age according to patent ductus arteriosus management in very preterm infants. Neonatology. 2016; 109:139-146.
3. Domer RA, Burton, VJ, Allen MC, et al. Preterm neuroimaging and neurodevelopmental outcome: a focus on intraventricular hemorrhage, post-hemorrhagic hydrocephalus, and associated brain injury. J Perinatol. 2018; 38(11):1431-1443.
4. Ecury-Goossen GM, Raets, MMA, Camfferman, FA, et al. Resistive indices of cerebral arteries in very preterm infants: values throughout stay in the neonatal intensive care unit and impact of patent ductus arteriosus. Pediatr Radiol. 2016;46:1291-1300.

Cold Atmospheric Plasma Induced Cell Activation in the Treatment of Glioblastoma Multiforme

Andrea L. Klein, MSII
CO-AUTHORS:
Dayun Yan, PhD[1]
and Eda Gjika, PhD[1]
ADVISORS:
Jonathan H. Sherman, MD[2] and
Michael Keidar, PhD[1]

[1]The George Washington University School of Engineering and Applied Science
[2]The George Washington University School of Medicine and Health Sciences

Glioblastoma multiforme (GBM) is the most common and aggressive primary central nervous system (CNS) neoplasm in adults. Diagnosis with GBM confers a dismal prognosis due to four main characteristics of the malignancy: (1) extensive proliferative, angiogenic, migrative, and invasive capabilities that result in an incredibly tolerable tissue, (2) microinvasion limiting the ability to perform gross total surgical resection, (3) a heterogeneous cell population that responds differentially to treatment within the same mass, and (4) downregulation of the immune system in the tumor microenvironment, enabling immune evasion. The current standard of care for the treatment of GBM includes a combination of radiation therapy, surgical resection, and medical management (temozolomide/TMZ at initial presentation and bevacizumab at recurrence). With a median post-diagnosis survival time of 15–16 months in patients receiving multifaceted treatment (chemotherapy, radiation, and surgery), any innovation with the potential to either independently target or synergistically improve other, currently available treatment modalities for GBM is of great interest to neuro-oncology providers and patients.

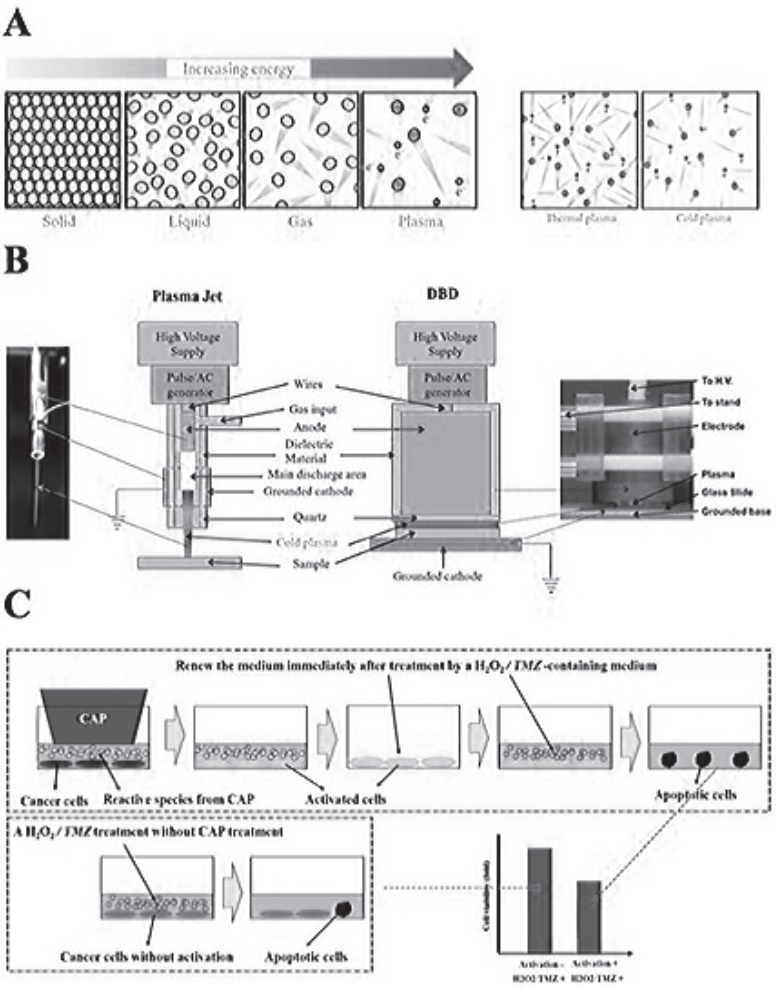


FIGURE 1: Cold Atmospheric Plasma and The Activation State
(a) Plasma is the fourth state of matter (b) Cold atmospheric plasma is generated by passing a carrying gas through high voltage to generate an array of emitted ionized particles. (c) Short treatment with cold atmospheric plasma sensitizes cancer cells to chemotherapy to generate an activation state.

Cold atmospheric plasma (CAP) is a high energy ionized state of matter (Figure 1A) that can be applied directly as a microjet or indirectly as an injection to tissue (figure 1B) as a means of immediately and selectively sensitizing cancer cells to chemotherapeutics.[1,5] The maximum threshold of sensitization, termed the "activation state", can be reached within 20 seconds of CAP treatment (Figure 1C). De-sensitization, however, takes five hours after CAP treatment.[2,3] By applying an electrical field to a carrying gas (usually helium

Continued on p. 62

Continued from p. 61

or argon), CAP is thought to exert its anti-cancer effects by generating reactive oxygen and nitrogen species that selectively damage neoplastic cells due to their pre-existing oxidative stress from high metabolic activity.[4]

In this study we demonstrate the existence of a CAP-induced activation state among human glioblastoma (U87) cells which confers increased sensitivity to TMZ and reactive species from H_2O_2 as quantified via cell viability.

Methods

The CAP device was designed and assembled in the Keidar lab at the George Washington University. This device used helium as the carrying gas at a flow rate of 8L / min. Electrodes were connected to a high voltage resonant transformer (8 kV peak to peak, 12.5 Hz). Optical emission spectroscopy was used to characterize the plasma. U87 cells were cultured in DMEM supplemented by 1% penicillin/streptomycin and 10% FBS. CAP was delivered to U87 cells in a 96-well plate for 1 minute in combination with 10 µM H_2O_2, 15 µM H_2O_2, 10 µM TMZ, or 50 µM TMZ in a total volume of 50 µL of media during treatment. Cell viability was measured by a standard MTT assay and the Cell Titer Glo 2.0 luminescent assay after three days of incubation.

Results

Direct treatment with CAP for 60 seconds sensitized U87 cells to treatment with TMZ at concentrations of 10 µM and 50 µM (Figure 2).

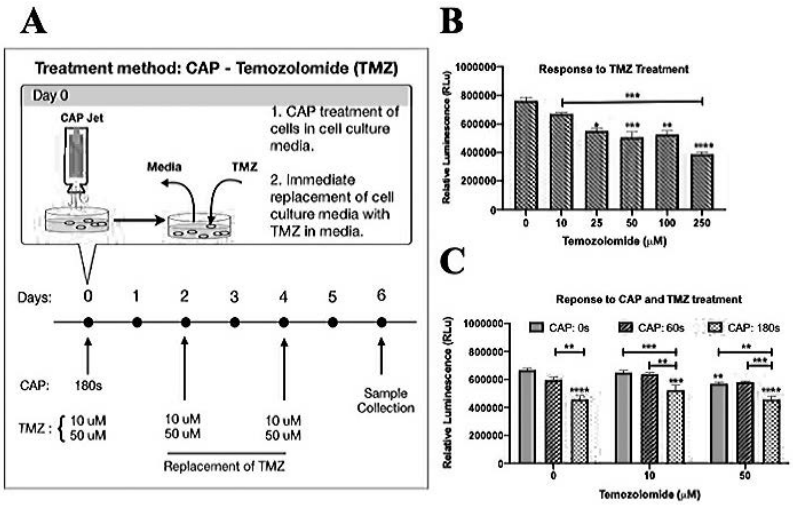


FIGURE 2: Cell Viability After Treatment in the Activation State
(a) Schematic of the experiment. Cell viability after treatment with (b) TMZ and (c) TMZ + CAP

Conclusions

Treatment of U87 cells with CAP produced an activation state that sensitized cells to treatment by H_2O_2 and TMZ. This drastic increase in cytotoxicity from a widely used drug provides encouraging evidence to support further research and the possible clinical application of CAP as an adjunct to existing therapy for GBM.

REFERENCES:

1. Chen Z, Simonyan H, Cheng X, et al. (2017). A Novel Micro Cold Atmospheric Plasma Device for Glioblastoma Both In Vitro and In Vivo.Cancers. 9(12), 61. doi: 10.3390/cancers9060061

2. Gjika E, Pal-Ghosh S, Tang A, et al. (2018). Adaptation of Operational Parameters of Cold Atmospheric Plasma for in Vitro Treatment of Cancer Cells. ACS Applied Materials & Interfaces. 10(11), 9269–9279. doi: 10.1021/acsami.7b18653

3. Yan D, Cui H, Zhu W, et al. (2017). The Specific Vulnerabilities of Cancer Cells to the Cold Atmospheric Plasma-Stimulated Solutions. Scientific Reports. 7(1). doi: 10.1038/s41598-017-04770-x

4. Yan D, Cui H, Zhu W, et al. (2017). The Strong Cell-based Hydrogen Peroxide Generation Triggered by Cold Atmospheric Plasma. Scientific Reports. 7(1). doi: 10.1038/s41598-017-11480-x

5. Yan D, Sherman JH, Keidar M. (2016). Cold atmospheric plasma, a novel promising anti-cancer treatment modality. Oncotarget. 8(9). doi: 10.18632/oncotarget.13304

Creation and Initial Assessment of a Low Cost, Easily Manufactured, Synthetic Fascia for Training

Steven Kurapaty, MSII

ADVISORS: Victor Moas, MD,[1] Peter Liacouras, PhD,[2] Stephen Goldman, PhD,[1] Spencer VanDecar, BS,[3] Brenton Franklin, MD,[3] Matthew Ritter, MD,[3] William Sweeney, MD,[3] and Jason Souza, MD[1]

1Walter Reed National Military Medical Center
2National Military Medical Center
3Uniformed Services University of the Health Sciences, Bethesda, MD

Few models to train fascial closure are currently available. Cadaveric or porcine fascia based training is not ideal due to significant inter-specimen variability, low supply, cost, and ethical concerns. We aimed to create an inexpensive and easily manufactured synthetic fascia suitable for simulation-based fascial closure training.

Methods

Synthetic fascia constructs were manufactured using combinations of various silicones and mesh materials. Constructs were biomechanically evaluated via tensile suture pull-through testing. Iterative testing provided direction for each fascia construct with the goal of achieving pull-through forces within 10N of the average strength of porcine fascia. Each construct was qualitatively assessed by the surgeon authors to optimize the tactile feel, suture drag, and thickness compared with human fascia. The construct with the best biomechanical profile was qualitatively evaluated by ten surgeons experienced in fascial closure. Respondents were instructed to create four 3cm incisions and grasp the fascia with a Kocher clamp and toothed forceps. Incisions were then closed with 2-0 polypropylene and 1 polydioxanone sutures, using both 1cm bites/1cm advancement and 5mm bites/5 mm advancement techniques.

Characteristic	Similar to Human Fascia	Stronger pull-through force/ larger needle hole	Weaker pull-through force/ smaller needle hole
Needle hole enlargement	9	-	1
Suture-pull through	4	6	-
	Similar to Human Fascia	**Somewhat similar to Human Fascia**	**Not similar to Human Fascia**
Response to cutting	4	5	1
Tactile Feel (upon palpation)	-	7	3
Drag of needle	3	6	1
Grasping behavior (with Kocher clamps and forceps)	3	5	2

TABLE: Qualitative survey evaluating synthetic fascia characteristics (n= number of surgeons)

Results

The optimized synthetic fascia was created using a combination of silicone and powermesh with material cost for one 24x24cm sheet of $4.09 and a one-time cost for mold creation of $50. Manufacturing time for each fascial sheet was 20 minutes with a 16 hour curing time. 9/10 surgeons rated the construct as an acceptable teaching tool for abdominal fascial closures with only one respondent stating the construct felt "unnatural". The table below shows the breakdown of responses for each performance characteristic.

Conclusions

We describe a synthetic fascia construct that is inexpensive, easily manufactured, mimics the biomechanical profile of porcine fascia, and performs similar to human fascia as assessed by a group of experienced surgeons. Its use in simulation-based training should be encouraged and outcomes measured.

Development of a Customized 3D-Printed Cast for Treatment of Minimally Displaced Distal Radius Fractures in Pediatric Patients

Andrew Palosaari, MSII

ADVISOR:
Anuradha Dayal, MD[1,2]

[1]The George Washington University School of Medicine and Health Sciences
[2]Children's National Hospital Sheikh Zayed Institute for Pediatric Surgical Innovation

Distal radius fractures are the most common long bone fracture in the pediatric population and frequently require casting for treatment. Traditional casts are heavy, bulky, susceptible to water damage, and frequently lead to cutaneous and neurovascular complications. The incidence of cast-related skin complications is approximated to be 13.6 per 1,000 patients.[1] Current 3D laser scanning and printing technology enables physicians to take 3D images of a limb and create a customized, biocompatible cast that is lightweight, thin, and waterproof. Chen et al. have shown that 3D-printed casts of distal radius fractures have comparable clinical effectiveness compared to plaster casts.[2] Here we have developed a customized and biocompatible 3D-printed cast that can be used for treatment of minimally displaced distal radius fractures in pediatric patients.

Methods:

The forearm of a sample patient was scanned using the handheld Artec Eva Lite 3D scanner. The 3D image was uploaded into Geomagic and used to create a two-piece hollow-shell cast with computer assisted design (CAD). The files were then sent to Xometry®, a 3D-printing company, to be printed using MED610 biocompatible material (a durable polymer-based material approved by the FDA for prolonged skin contact). The cast was designed in two pieces to allow for easy placement on the forearm. Zip ties were used to enclose the cast around the forearm circumferentially. Holes were intentionally printed in the design to allow for facile evaporation of water and sweat.

FIGURE: A, the dorsal view of the 3D-printed cast. **B,** the lateral view of the 3D-printed cast.

Results:

A 3D-printed cast (Figure A and B) was printed on MED610 biocompatible material according to our specifications obtained from the Artec® Eva Lite 3D scanner. The thickness of the cast was 5 mm. The cast was offset from the skin of our sample patient by 1.75mm to allow for expected post-traumatic tissue edema and prevent compartment syndrome. Our sample patient wore this cast for two days (removed for showering and sleeping) and did not have any cutaneous or neurovascular complications.

Current 3D laser scanning and printing technology enables physicians to take 3D images of a limb and create a customized, biocompatible cast that is lightweight, thin, and waterproof.

Conclusions

In this work, we successfully developed a customized, biocompatible 3D-printed forearm

cast with the potential to treat minimally displaced radius fractures in orthopedic pediatric patients. Our future research will assess the clinical effectiveness and rate of cutaneous and neurovascular complications with the use of the cast compared to traditional casts in children aged 5 to 12 with minimally displaced radius fractures. These studies will provide a foundation for clinical trials to test the effectiveness of our 3D-printed casts in treating injuries requiring prolonged immobilization.

REFERENCES

1. DiFazio R, Vessey J, Zurakowski D, Hresko MT, Matheney T. Incidence of skin complications and associated charges in children treated with hip spica casts for femur fractures. J Pediatr Orthop. 2011;31: 17-22.
2. Chen Y, Lin H, Zhang X, Huang W, Shi L, Wang D. Application of 3D–printed and patient-specific cast for the treatment of distal radius fractures: initial experience. 3D Print Med. 2017;3:1-9.

Fusion

Fusion is the annual, student-run scientific journal of The George Washington University School of Medicine and Health Sciences William H. Beaumont Medical Research Honor Society.

Fusion was created to showcase medical student achievements in basic science and clinical research, clinical public health, medical education, and global health research. Submissions are requested from medical students annually in the fall.