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Different Recent, New and Old Approaches Could Help us to Win the Game against SARS-COV-2

By Amro A. Amara

Abstract- SARS-COV-2 is a virus that has led to the death of a large number of persons, and caused a global endemic problem since December 2019. Vaccines have been prepared, and authorized in an argent way to survive lives. Any possible or known tactic has been used to prevent its spreading, treat infected individual, and to understand how it changes its structure to produce, in advance, a pre-made vaccine that could be used in an adequate time. Understanding their antigenIcity, mutation, adaptation, different types of the produced vaccines, its in cito interaction, and the like, are essential to win the battle. Humanity has been winning the battle against some more virulence viruses like smallpox (human virus), and the Rinderpest (animal virus) using strategies that could only describe nowadays as a "simple method.". This review is concerned with highlighting important issues concerning SARS-COV-2, and its vaccine(s), structure, epitopes, RNA, surface antigens, personalizing the individual different responses, the need for case-by-case treatments, and the like.

Keywords: *SARS-COV-2; treatment personalization; epitopes; vaccine; control strategies.*

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Amro A. Amara

Abstract- SARS-COV-2 is a virus that has led to the death of a large number of persons, and caused a global endemic problem since December 2019. Vaccines have been prepared, and authorized in an argent way to survive lives. Any possible or known tactic has been used to prevent its spreading, treat infected individual, and to understand how it changes its structure to produce, in advance, a pre-made vaccine that could be used in an adequate time. Understanding their antigenIcity, mutation, adaptation, different types of the produced vaccines, its in cito interaction, and the like, are essential to win the battle. Humanity has been winning the battle against some more virulence viruses like smallpox (human virus), and the Rinderpest (animal virus) using strategies that could only describe nowadays as a "simple method.". This review is concerned with highlighting important issues concerning SARS-COV-2, and its vaccine(s), structure, epitopes, RNA, surface antigens, personalizing the individual different responses, the need for case-by-case treatments, and the like. Additionally, it introduces some pro-posed strategies that have been extracted from the treating, and vaccine preparation for other viruses. Humanity should benefit from each single idea that could help in controlling of SARA-COV-2, and any other tactic that can be used to control any virus, which is the message of this review.

Keywords: SARS-COV-2; treatment personalization; epitopes; vaccine; control strategies.

I. Introduction

Respiration is the process of absorbing oxygen and expelling carbon dioxide. Respiration is a delicate, and vital process. A few minutes without oxygen can result in death or critical deterioration of the brain in a human. The majority of the oxygen in the body is bound to hemoglobin, which is made up of four iron-containing ring structures (hemes) that are chemically attached to a large protein (globin). Each iron atom can bind, and then release an oxygen molecule. Carbon dioxide transport in the blood is far more complicated (Klocke 2013). One of the serious attackers to the respiratory organ is the SARS virus. SARS refers to the severe acute respiratory syndrome, while SARS-CoV refers to severe acute respiratory syndrome coronavirus. Corona viruses (CoV) are the primary etiologic agents of the common cold. It causes outbreaks, and pandemics. In general, corona viruses cause disease in humans, other mammals, and birds. In humans, it causes respiratory, and intestinal disease. Severe acute respiratory syndrome (SARS), Middle East respiratory syndrome (MERS), and the recent rapidly progressing COVID-19 caused by SARS-CoV-2 are examples. SARS-Cov-1 has infected more than 8,000 people in 32 countries, and caused about 10% death (Cavanagh and Britton 2008). SARSr-CoV refers to one of many viruses similar to SARS-CoV-1, and SARS-CoV-2. No other SARSr-CoV virus has infected humans or caused severe illness like SARS-CoV-1, and SARS-CoV-2. Bats are important reservoir hosts for many SARSr-CoV strains. Several strains have been identified in palm civet. More than 600 million COVID-19 cases, and 6.5 million fatalities have been reported globally as of August 31, 2022 (Low, Zabidi et al. 2022). To avoid confusion, it is recommended to use the numbers behind SARS-CoV to distinguish between the two important viruses SARS-CoV-1, and SARSr-CoV-2. The severe acute respiratory syndrome coronavirus SARS-CoV (old name) or SARS-CoV-1 (new name), is generated severe acute respiratory syndrome (SARS) epidemic in 2002-2004. The severe acute respiratory syndrome coronavirus virus 2 (SARS-CoV-2) is causing the ongoing COVID-19 pandemic. SARS virus's virions have a buoyant density of approximately 1.18 g ml-1 in sucrose (Cavanagh and Britton 2008). Corona viruses do not necessarily respect species barriers. The deadly spread of severe acute respiratory syndrome (SARS) coronavirus is reported among wildlife, and humans. As a group, corona viruses are not confined to specific organs. Target tissues could include the nervous, immune, renal, and re-productive systems, as well as many parts of the respiratory, and intestinal systems (Cavanagh and Britton 2008).

II. Vaccine

Kantarcioglu et al. (2022) reported that most vaccines made for SARS-CoV-2 (COVID-19) contain the viral spike protein. They are including whole virus vaccines, viral vector vaccines, RNA vaccines, DNA vaccines, and their hybrid forms. COVID-19 variants cause various pathological responses, some of which may be resistant to antibodies generated by current vaccines (Kantarcioglu, Iqbal et al. 2022). These vaccines have been tested on many subjects, including young children, immunocompromised patients, pregnant subjects, and other specialized groups (Kantarcioglu, Iqbal et al. 2022). Coronavirus-2 (SARS-CoV-2) main target organ is the lung. It can bind to the

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endothelial layer via angiotens in-converting enzyme 2 (ACE 2) receptors expressed on target cells. COVID-19 can affect almost any organ system (Chen, Zhou et al. 2020, Hu, Guo et al. 2020, Huang, Wang et al. 2020, Wu and McGoogan 2020, Zhou, Yang et al. 2020). Most symptoms are mild, with a significant subset developing severe diseases ranging from pneumonia, and acute respiratory distress syndrome (ARDS), and multiple organ failure (MOF) (Hu, Guo et al. 2020, V'kovski, Kratzel et al. 2020, Zhou, Yang et al. 2020, Kantarcioglu, Iqbal et al. 2022). The vaccine used has been ap-proved in emergency procedures. They are approved for emergency use (Kantarcioglu, Iqbal et al. 2022). Kantarcioglu et al. (2022) reported that only the Pfizer vaccine has been fully approved by the US FDA (2021) (Kantarcioglu, Iqbal et al. 2022). The vaccine can generate neutralizing antibodies (Kantarcioglu, Iqbal et al. 2022).

Triggering the spike proteins resulting in the formation of neutralizing anti-bodies, and T-cell responses (Kantarcioglu, Iqbal et al. 2022). Coronavirus-es share four structural proteins. They are 1) a high surface area glycoprotein (S about 1150–1450 amino acids); 2) a small envelope protein (E. about 100 amino acids, present in small amounts in virions); 3) integral membrane glycoprotein (M about 250 amino acids), and 4) a phosphorylated nucleocapsid protein (N about 500 amino acids). Group 2a viruses have an additional structural glycoprotein, the protein hemagglutinin esterase (HE; approximately 425 amino acids) (Cavanagh and Britton 2008).

The early studies on vaccines against the COVID-19 virus have targeted the viral spike (S) protein. Antibodies targeting M (membrane), and E (envelope) proteins have failed to neutralize the COVID-19 infection. The N (nucleocapsid) protein is highly immunogenic, and can elicit robust humoral, and cellular immune responses. The most interesting one is the viral spike (S) protein. The antibodies attach to the viral spike protein (S), and prevent it from binding to the human angiotensin-converting enzyme-2 receptor (ACE2 receptor). This enzyme is essential for the virus to enter the cell. Protein S is a fusion glycoprotein divided into two functionally distinct parts (S1, and S2). S1 is found on the surface of the virus, and contains the receptor-binding domain (RBD) which specifically binds to the host cell receptor. The S2 transmembrane domain contains the fusion peptide, which mediates the fusion of viral, and cell membranes (Sharma, Sultan et al. 2020, Lee, Kim et al. 2021, Kantarcioglu, Iqbal et al. 2022).

The WHO reported that 296 candidate vaccines against COVID-19 had been developed, 112 in clinical trials, and 184 in preclinical trials (WHO. 2021). Vac-cines developed include attenuated or inactivated whole virus vaccines, replicating/non-replicating virus vector vaccines, DNA, and mRNA-based vaccines, and recombinant or modified protein (subunit protein, virus-like particles) (Chung, Beiss et al. 2020, Sharma, Sultan et al. 2020, Lee, Kim et al. 2021, Kantarcioglu, Iqbal et al. 2022). Mutations in protein S genes, particularly in RBD coding regions, are of utmost importance. Mutations in the S RBD protein- coding regions may be variants with increased rates of transmission, severity, mortality, and reduced susceptibility to monoclonal or polyclonal antibodies produced in response to infection or vaccination, and fraud in the diagnosis of the virus (Singh, Pandit et al. 2021). There are many considerations for people with special health conditions, such as pregnant women (Juan et al., 2020), and immunocompromised patients (Wang, Berger, & Xu, 2021). In general, vaccinating people with specific health problems is still under study. See Kantarcioglu et al., (2022), and the references therein for details (Kantarcioglu, Iqbal et al. 2022).

The innate immune system function as the first line of the host defines against SARS-CoV-2. Innate immune responses limit viral entry. It interferes with its essential replication pathways including translation and assembly. It helps to identify, and remove infected cells, coordinates, and accelerates the development of adaptive immunity. Cell surface, endosomal, and cytosolic pattern recognition receptors (PRRs) respond to pathogen-associated molecular patterns (PAMPs). They trigger inflammatory responses, and programmed cell death. In general, in-nate immunity limits viral infection, and promote clearance. However, excessive immune activation can lead to systemic inflammation, and severe disease. One should highlight that, acquiring common cold viruses, moderate corona virus, or even other reparatory virus infections naturally will build immunity that will react in less severity against CoV variants. In response to innate immune-dependent viral clearance mechanisms, Coronaviruses (CoVs) have evolved evasion strategies to limit host control, and enhance replication, and transmission (Blanco-Melo, Nilsson-Payant et al. 2020, Konno, Kimura et al. 2020, Li, Liao et al. 2020, Burke, St Clair et al. 2021, Diamond and Kanneganti 2022).

A primary function of the innate immune system is the inflammatory response. CoVs have developed several evasion strategies to counteract these host defenses. SARS-CoV-2 can evade antiviral innate immune responses by reducing IFN levels. Patients with mild, and moderate COVID-19 have low levels of IFNs type I, and III in their serum (Blanco-Melo, Nilsson-Payant et al. 2020, Diamond and Kanneganti 2022). SARS-CoV-2 infection limits IFN type I, and III production at post-transcriptional levels. SARS-CoV-2 prevents the release of mRNA from transcription sites, and/or triggers degrading transcripts in the nucleus (Blanco-Melo, Nilsson-Payant et al. 2020, Diamond and Kanneganti 2022). SARS-CoV-2 also encodes several proteins that disrupt RLR sensing pathways, and IFN induction, signaling, or effector functions. SARS-CoV-2 ORF9b, N

and M proteins can inhibit the expression of IFN-β, and pro-inflammatory cytokines by interfering with RIG-I, and MDA5 pathways. ORF9b also able to block the TLR3–TRIF pathway (Chen, Xiao et al. 2020, Han, Zhuang et al. 2020, Li, Liao et al. 2020, Ebinger, Fert-Bober et al. 2021, Sui, Zhao et al. 2021, Diamond and Kanneganti 2022). There are many other mechanisms involved in the evasion of the innate immune system. To fraud the existing or, the produced antibodies the virus simply mutates the target site(s). The SARS-CoV-2 virus has mutated dramatically, with increased transmissibility, and virulence. This natural selection is based on mutations common to RNA viruses that are beneficial in terms of replication, host immune evasion mechanisms, and transmission of the virus (Lauring and Hodcroft 2021). The multiple mutations encompassing the epsilon variant demonstrate the independent convergent changes in severe acute respiratory syndrome coronavirus (SARS-CoV-2), with its spike protein mutation L452R in Delta (L452R), kappa (L452R), and Lambda (L452Q) is present. Variants (Plummer, Contreras et al.). SARS-CoV-2 with mutations are defined as variants. A variant of concern (VOC) denotes a variant with increased transmissibility, and severity, a significant decrease in neutralizing antibodies produced in response to vaccination/previous infection, or reduced efficacy of vaccines/treatment. Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Omicron (B.1.1.529). The Omicron variant has a high risk of immune evasion. Therefore, a potential reduction in neutralization by post-vaccination sera may facilitate spread (Chen, Hsu et al. 2022, Wu, Zhou et al. 2022). SARS-CoV-2 non-structural proteins also contribute to host immune evasion (Low, Zabidi et al. 2022).

SARS-CoV-2 is the causative agent behind the ongoing COVID-19 pandemic. This virus is a cumulative outcome of mutations (new variants). The major five VOCs are Alpha (B.1.1.7), Beta (B.1.315), Gamma (P.1), Delta (B.1.617.2), and Omicron (B.1.1.529, and BA lineages). Omicron itself has >100 subvariants at present, among which BA.1 (21K), BA.2 (21L), BA.4 (22A), BA.5 (22B), and BA.2.12.1 (22C) are the dominant ones (Hossain, Akter et al. 2022).

III. Epitopes

Vaccine-induced protection against SARS-CoV-2 is mainly based on humoral responses. Total antibody titers (against the viral spike RBD), and half-maximal neutralization titers (NT50s) (using pseudotyped or live viruses) have been used for the evaluations (Mulligan, Lyke et al. 2020, Walsh, Frenck et al. 2020, Ebinger, Fert-Bober et al. 2021, Müller, Andrée et al. 2021). Antibodies induced by the vaccine or found in the sera of patients share common binding epitopes. Aluminum adjuvant enhances the immune response induced by the vaccine. A single vaccine dose might elicit a high level of virus-neutralizing activity. The toxicology studies in the non-human primates confirmed vaccine safety. The vaccination protected in non-human primates against an in vivo challenge with SARS-CoV-2 (Yang, Wang et al. 2020). The epitope profiling in RBD-based antigens of SARS-CoV2 revealed the critical antigenic determinants, including three immunodominant epitopes. They are: 1) a highly conserved epitope (350VYAWN354) exposed on the surface of the viral spike protein trimer, 2) a variable epitope among different virus strains (473YQAGSTP479) found in the receptor binding motif (RBM), and 3) a highly conserved cryptic cross-reactive epitope (407VRQIAP412) shared by RBD of SARS-CoV-2, and SARS-CoV (Jiang, Zhang et al. 2021). These data can elucidate the humoral immune responses to the viral spike protein RBD, and enable the development of new anti-SARS-CoV-2 vaccines (El-Baky and Amara 2022).

IV. Epitope in mRNA Vaccines

With the appearance of SARS-CoV-2 variants that harbor mutations in critical epitopes, the risk of eroding adaptive immunity elicited by either vaccination or prior infection as a result of this antigenic evolution increased. The identified epitopes in the COVID-19 mRNA vaccine may form the basis for further research on immune escape, viral variants, and the design of vaccine, and therapy. Mutation panel assays targeting the viral variants of concern demonstrated that the epitope variety induced by the mRNA vaccine is rich in breadth, and thus, can grant resistance against viral evolutionary escapes of the future, which represents an ad-vantage of vaccine-induced immunity. mRNA vaccination against SARS-CoV-2 elicited antibodies targeting viral spike RBD that have a broader distribution across RBD than natural infection-induced antibodies, which seem to offer more resistance against future SARS-CoV-2 evolutionary escapes (El-Baky and Amara 2022).

V. Some Proposed Strategies

a) *Proposed approach No. (1;): Activate the immune system with similar viruses (e.g., smallpox)*

The concept of using similar safe virus to vaccines against another virulence one is well known to the immunologist. Close, safe viruses could satisfy the demand for protecting against dangerous ones by activating the immune system, and producing antibodies that could neutralize them. Perhaps the most famous example is smallpox. The modern vaccine technology starts with simple observation, which has been well known among farmers but less explained until a physician explains it. The milkmaid which has been infected in their hand by cowpox is known that she becomes protected against smallpox. She has been happy because her face will be beautiful. She starts to

song, and a physician hears this song "I shall never have smallpox for I have had cowpox. I shall never have an ugly pockmarked face." The cow's name is "Blossom". The physician started to investigate the case, and then he concluded that the infection with cowpox will protect against smallpox. He made manual infection from arm to arm by the cow lymph node (Amara 2016). In similar thinking, recently Fage et al. (202 2) reported that the existence of SARS-CoV-2 with other viruses that infect the respiratory organ could help in its control (Fage, Hénaut et al. 2022). Because of the small number of co-infection cases reported since the start of the pandemic, the types of interactions between SARS-CoV-2, and other respiratory viruses are poorly understood. During concurrent infection, SARS-CoV-2 interferes with RSV-A2 replication but not A(H1N1)pdm09 replication. They are both respiratory viruses. Prior infection with A(H1N1)pdm09 reduces SARS-CoV-2 replication. According to Fage et al. (2022) the mechanism involved in the viral interference between SARS-CoV-2, and A(H1N1)pdm09 is mediated by the production of interferon (Fage, Hénaut et al. 2022). This approach, which, has been an old tactic and has been used since smallpox (treated by cowpox).

b) *Proposed approach No. (2): Attenuating the virus strain (e.g., Rabies)*

Pierre-Victor Galtier (1846-1908) a veterinarian, a student of Chauveau at the Lyons veterinary school (France). He demonstrated rabies to be an affectionateness of the nervous system, with a variable incubation period. In 1879, he evoked that laboratory dogs could be replaced by rabbits. In 1881, and 1882, Louis Pasteur, and his students Charles Chamberland, Emile Roux, and Louis Thuillier entered the fray. They modified Galtier's technique by inoculating nervous tissue from a rabid animal directly into the brain after trephination. By successive passages in dogs, they obtained a virus of maximal virulence coupled. The process was a with fixed incubation period of around ten days. To attenuate the virus virulence they, changing that host species. That has achieved indirectly by passages through rabbits. Emile Roux made up the selected attenuation procedure. It consisted of suspending the spinal cord of a rabid rabbit in a flask, in a warm dry atmosphere, as a process for slow desiccation. Using animals as alive propagating medium, Pasteur, and his group succeeded in producing 'attenuated viruses of different strengths'. A standardized range of viruses have been prepared and used to prepare a vaccine (Habel 1956, Lombard, Pastoret et al. 2007, Amara 2016). One should observe that the attenuated virus is used as a vaccine in the time of the activity of the virulence virus.

c) *Proposed approach No. (3): Use partially fragmented virus (e.g., Rinderpest)*

Rinderpest is a fatal disease has been known since time immemorial in Europe, and Central Asia with mortality range from 90 to 100%. Rinderpest or the Cattle plague (also steppe murrain) caused by Rinderpest virus (group V ((-) ssRNA. It comprises among the great historical besets that cause destroyed human farm animals (Barrett, Pastoret et al., Pastoret and Jones 2004, Amara 2016). Robert Koch is the owner of the first publication of the practical method of immunizing cattle against the Rinderpest infections. He injects the uninfected animal with the bile of the animal that died by the Rinderpest, and after that with the serum of an immunized animal. After many trails, from the different researchers, Robert Koch, doing work in South Africa, recommended that cows could be saved by subcutaneous injection of blood serum, from immunized animals, and bile, from an infected animal. This unsafe formula has been shortly substituted by the employ of immune serum, and later on by mixing of immune serum, and virulent virus. Afterward, the method has been improved by consecutive passages of the bovine virus through goats, which enabled Edwards to produce a compromised vaccine in India in the 1920s. Runs with inactivated vaccines as well occurred. Afterward, the successful isolation of the virus in cell culture led to the in vitro developing of a weakened strain, and from this the production of a safe, and highly efficient vaccine (Mortellaro and Ricciardi-Castagnoli 2011, Bento, Staats et al. 2015, Amara 2016).

d) *Proposed approach No. (4): Virus ghost preparation using H2O2 (e.g., Newcastle virus)*

Evacuating viruses from their genomic material, and keeping their 3D structure unattached is a new approach. Newcastle virus has been prepared as a ghost virus by its evacuation from its RNA using H2O2 in concentration has given the name "bio-critical concentration" while it is the concentration, which has been used to evacuate E. coli. Few studies have been conducted on this promising approach. The unique point is that a cocktail of the viruses are expected to satisfy the demand of the immune system to confer correct immunization can be applied into H2O2 bio-critical concentration to turn them to virus ghosts. Interestingly, the first simple study to evacuate the Newcastle virus has recommended the use of H2O2 as a virus deactivator, that has been recommended by many authors. H2O2 is a potent active chemical compound that can oxidize/degrade cell macromolecules, including the genomic DNA, RNA, and plasmids. The idea is to calculate the H2O2 concentration that could degrade the genetic material (even after time) but keep the virus 3D structure including its surface antigen, in the correct form. This approach has been used to evacuate, viruses, bacteria,

yeast, and filamentous fungi as well as the mushrooms spore (anthers chemical compounds are included) (Amara 2013, Amara 2014, Amara, Neama et al. 2014, El-Baky 2014, Amara 2015, Amara 2015, Abd El-Baky, Sharaf et al. 2018, Abd El-Baky, Sharaf et al. 2018).

e) *Proposed approach No. (5): Probiotics that produce antiviral compounds*

H2O2 exhibits antimicrobial activity against yeast, Gram-positive, and Gram-negative bacteria (Suskovich, Kos et al. 2010). Some beneficial microbes produce H2O2 under aerobic conditions of growth. They release it into the environment to protect themselves (Daeschel 1989). Among the other postulated pro-biotic mechanisms engaged in host protection or amelioration of viral respiratory diseases, the significant roles are reported to: reinforce, and protect the mucosal barrier; to stimulate forming antimicrobial compounds (e.g., H2O2) (Balta, Butucel et al. 2021).

Probiotics, prebiotics, phytobiotics, and natural antimicrobials, including their metabolites, have received significant attention, mainly due to the SARS-CoV-2 pandemic, and are continuously tested for their ability to inhibit viruses, and pre-vent their pathogenic impact on the host (Aguila, Lontok et al. 2020, Baud, Dimopoulou Agri et al. 2020, Lee, Choi et al. 2021)

A recent clinical trial conducted demonstrated that oral bacteriotherapy ad-ministration of a mixed probiotic formulation in COVID-19 hospitalized patients reduced the risk of respiratory failure by approximately 8-folds, improved gut symptomology, and promoted the disappearance of diarrhea in all the subjects within seven days (Aarti, Martina et al. 2020, Azagra-Boronat, Massot-Cladera et al. 2020, d'Ettorre, Ceccarelli et al. 2020, Lopez-Santamarina, Lamas et al. 2021).

VI. Future Prospective

It is becomes clear that even with the massive development in the science, and technology in different fields that, we still know much less. A virus that could not replicate, seen only under high magnification using the electron microscope, could pain us a lot. Even so, it is also proving that the world has become a big village. A respective amount of basic science becomes available for every person. The transfer of knowledge is so fast. Many respective institutions, and organizations that get the responsibility, companies that produce the different vaccines, and political makers that take the designs. So, what could be introduced in the future? There is a need for epitopes, and antigens databases, more fast protocol for personalizing the treatments, and more funds for the research and the researchers. There is a need for collecting experts worldwide in groups to exchange knowledge. In fact, there is a need to link the scientific institutions with the industry in a correct way that does not waste the time of the scientists or the money of the companies. The physical control of the movement, and the personal contacts, hygiene, the contact with the animals, particularly the wild animals, the patients' living conditions in the hospitals, and the like, should be revaluated, and readjusted.

VII. Conclusions

This review is concerned with highlighting the most crucial point concerning SARA-COV-2, its nomenclature system, structure, antigenicity, epitopes, variants, different developed vaccines, the response of the personae with health issues, some strategies that succeeded with other viruses, some in natural treatments (e.g., probiotics), some points about the role of the innate immunity, and new idea for virus evacuation (virus ghost). The review gives the message for searching inside, and outside the immunity box. The simple introduced tactic might help in cases such that the vaccines production did not satisfy the global demand, in case of emergency or natural catastrophe, and the like.

Table of Abbreviations

ARDS	acute respiratory distress syndrome
GEBRI	Genetic Engineering and Biotechnology Research Institute
MERS	Middle East respiratory syndrome
MOF	multiple organ failure
PAMP	pathogen-associated molecular patterns
PRR	pattern recognition receptors
RBM	receptor binding motif
SARS	Severe acute respiratory syndrome
VOC	variant of concern

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The Utility of Point-Of-Care-Ultrasound in Primary Care

By Hector R. Diaz Aguila, Anselmo Abdo Cuza, Orlando Valdes Suarez & Mercedes veliz Sanchez

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Introduction- The antecedent of ultrasound goes back to the 1940s after World War II when the prospect of ultrasound in medical practices was developed. In 1951 (1), the workshop of Douglas Howry, a radiologist, and his collaborators, Bliss and Posakony make possible the creation of a two-dimensional ultrasound scanner. Since also, ultrasound has elaborated over the occasions to approach a really useful tool in clinical radiology (2). The denomination of ultrasound at the point of care(Point of Care Ultrasound, POCUS) remodeled the paradigm of the ultrasound test carried out by imaging specialists or cardiologists defined by the descriptive pattern of the organs and carried out in certain time and places, to turn an extension of the physical examination (examination, palpation, percussion, auscultation and insonation) (3). Multi-organ clinical ultrasound must be achieved by the attending physician in any care setting(from home to an intensive care unit or operating room).

Keywords: general practice, family medicine, primary care, point-of-care testing, ultrasonography. echography.

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The Utility of Point-Of-Care-Ultrasound in Primary Care

Hector R. Diaz Aguila [α], Anselmo Abdo Cuza [σ], Orlando Valdes Suarez [ρ] & Mercedes veliz Sanchez [ω]

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I. Introduction

The antecedent of ultrasound goes back to the 1940s after World War II when the prospect of ultrasound in medical practices was developed. In 1951 (1), the workshop of Douglas Howry, a radiologist, and his collaborators, Bliss and Posakony make possible the creation of a two-dimensional ultrasound scanner. Since also, ultrasound has elaborated over the occasions to approach a really useful tool in clinical radiology (2). The denomination of ultrasound at the point of care(Point of Care Ultrasound, POCUS) remodeled the paradigm of the ultrasound test carried out by imaging specialists or cardiologists defined by the descriptive pattern of the organs and carried out in certain time and places, to turn an extension of the physical examination (examination, palpation, percussion, auscultation and insonation) (3). Multi-organ clinical ultrasound must be achieved by the attending physician in any care setting(from home to an intensive care unit or operating room).

II. What is Pocus?

The study, further than descriptive, has to respond clinical questions with binary answers(yes or not), it can be reiterated to valuate actions and ease the performance of invasive procedures like as venous catheterizations, pleurocentesis, pericardiocentesis, and others. POCUS is defined by the American College of Emergency Physicians(ACEP) as the use of ultrasound, at the patient bedside, for help in opinion, reanimation, procedural guidance or monitoring (2). POCUS is a secure and efficient form of imaging that benefit judgment and companion medical proceedings. During the coronavirus complaint 2019(COVID- 19) epidemic, POCUS was applied to predict the clinical resultants and antedate ICU admission or the need for supplemental oxygen administration (4).

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Nowadays, ultrasound equipment has approach more compact, advanced quality, and more affordable, facilitating the growth of POCUS which can readily be accomplished and interpreted by the clinician at the case's bedside. POCUS can be hugged as a substantial tool by a General Practitioner (GP) in medical practice and helps reduce health care expenses. Point- of- care ultrasound (POCUS), or bedside ultrasound, has been called the “visual stethoscope” of the 21st Century (5).

Primary Care is the base of health care in medical practice; it represents the first contact with GPs for cases asking for medical care. Using POCUS in primary health care settings has downgraded costs and transcended the quality of care gave by trained GPs who can efficiently apply it as a hasty bedside peculiar tool (6).

The use of ultrasound is quickly growing fashion ability in all areas including Emergency Department, Surgical or Intensive Care Units (ICU). Not only, it's fast, non-invasive and reasonable but also transportable facilities can be freely performed bedside without exposure to radiations, therefore, framing it ideal to use in unstable patient (7).

POCUS is an ultrasound exam that's accomplished at the bedside, and it's interpreted directly by the clinician, thus, POCUS is a potent adjunct to clinical appraisement. The certitude of the believable opinion that's judged from the medical history, and physical examination can be attested by the data supplied using POCUS, also POCUS can be an effective tool for attending patients and for proceeding guidance (8). Although the main goal of POCUS is slightly distinct between intensivists and GPs, the qualification to recognize and resuscitate critically ill cases is a tracing particularity in both specialties.

III. POCUS in Primary Care

Point of care ultrasound (POCUS) has grown an acquainted practice in prehospital care over the latest 10 years (9). Point of care ultrasound (PoCUS) is a fruitful, reasonable, secure, and mobile imaging modality that can be particularly applicable in resource-limited settings. For critically ill cases, similar as those with thoracoabdominal trauma, cardiac arrest, respiratory distress, chestpain, or shock.

Bedside multi-organ POCUS is now really applied as an adjunct that provides data to guide

clinical decision-making during all phases of diagnostic exercises.

Clinical ultrasound is a skillfulness which requires frequent execution in order to preserve mastership. An ultrasound workout program must thus contain a network which allows for the sustainment of axes beyond introductory training and proctoring (10). Once qualified, there's no minimal number of ultrasound examinations that can warrant sustained mastership, thus GPs should attempt to regularly carry out every procedure. Skill sustainment requires all the operations the provider is able to carry out, be a habitual part of the clinician's practice, with trainings assessed semi-annually (11).

The GPs consider POCUS to be kindly ready to use, not too time consuming, and of great value to the practice. In fact, POCUS can help diminish the charges of health care.

Main indications of POCUS in Primary Care (12):

I. Lungs

a) Pulmonary edema
b) Pneumonia
c) Pneumothorax
d) Asthma or Chronic Obstructive Pulmonary Disease

II. Cardiac

a) Left ventricular form and function
b) Left ventricular hypertrophy
c) Wall motion abnormalities
d) Pericardial fluid

III. Abdomen

a) Cholelitiasis
b) Nephrolithiasis
c) Appendicitis
d) Small bowel obstruction
e) Abnormal peristalsis
f) Intraperitoneally free fluid

IV. Obstetrics

a) Diagnosing and measurement of gestational age
b) Diagnosing suspicious ectopic pregnancy
c) Bleeding of the first trimester

V. Vascular

a) Diagnosing aneurism of abdominal aorta
b) Lower extremities venous thrombosis
c) Inferior vena cava diameter measurement
d) Ultrasound guided peripheral venous catheter

VI. Central nervous system

a) Cerebral hemodynamic pattern (and non-invasive ICP estimation) using spectral recording of the middle cerebral artery
b) Optic nerve sheath diameter measurement for assessing intracranial hypertension

VII. Musculoskeletal ultrasound

a) Detection of abscess and soft tissue infection
b) Soft tissue foreign bodies
c) Acute tendon trauma, join fluid, bone fractures.

VIII. US guided cardiac arrest

a) Evaluating the possible cause of cardiac arrest
b) Assessment the effectiveness of cardiac compressions
c) Verification of the effectiveness of lung ventilation

IV. Conclusion

Pont-of-Care-Ultrasound is an invaluable instrument for the medical care in Pre-hospital settings through which diagnoses of medical problems afflicting patients are made expeditiously.

It makes it easier to carry out differential diagnoses bedside the patient and therefore carry out a personalized medicine.

It favors the safe performance of invasive procedures and lowers the expenses of medical care.

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Addressing Inadequacy in the Quality of Palliative Care of Multiple Myeloma in Nigeria using Actionable Frameworks

By Ogbonna Collins Nwabuko, Innocent Ijezie Chukwuonye, Kingsley Akaba & Martin Anazodo Nnoli

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Abstract- *Background:* Nigeria ranks within the top eleven countries of the world with the least average life expectancy from birth. As a result, the middle-elderly population is fast eroding. The worse hit in this scenario is the palliative care of the elderly who is neglected due to poor social determinants of health occasioned by leadership failure. Multiple myeloma is a common haematological malignancy in the middle-elderly target population that requires palliative care. Unfortunately, the quality of palliative care of people living with multiple myeloma in Nigeria is low partly due to grossly inadequate annual health budget.

Aim: To improve the quality of palliative care of multiple myeloma in Nigeria using actionable quality improvement frameworks.

Keywords: *multiple myeloma, palliative care, frameworks, quality, inequality, Nigeria.*

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Addressing Inadequacy in the Quality of Palliative Care of Multiple Myeloma in Nigeria using Actionable Frameworks

Ogbonna Collins Nwabuko [α], Innocent Ijezie Chukwuonye [σ], Kingsley Akaba [ρ] & Martin Anazodo Nnoli [ω]

Abstract- Background: Nigeria ranks within the top eleven countries of the world with the least average life expectancy from birth. As a result, the middle-elderly population is fast eroding. The worse hit in this scenario is the palliative care of the elderly who is neglected due to poor social determinants of health occasioned by leadership failure. Multiple myeloma is a common haematological malignancy in the middle-elderly target population that requires palliative care. Unfortunately, the quality of palliative care of people living with multiple myeloma in Nigeria is low partly due to grossly inadequate annual health budget.

Aim: To improve the quality of palliative care of multiple myeloma in Nigeria using actionable quality improvement frameworks.

Methodology: This was a systematic review and critical appraisal of palliative care of multiple myeloma in Nigeria and feasible frameworks that could improve quality of care. Three pairs of Medical Subject Headings (Multiple myeloma/Challenges in management in developing countries; Palliative care/Multiple myeloma; Palliative care/Quality assessment) were used as search strategy to demystify the research question. The issues of quality of palliative care of multiple myeloma were addressed from the perspectives of challenges of care of people living with multiple myeloma, methods of improving the quality of life of multiple myeloma patients in Nigeria, critical analysis of relevant quality areas, relevant structures and frameworks that could play key roles in mitigating healthcare needs of myeloma patients in Nigeria.

Results: The palliative care of multiple myeloma in Nigeria is grossly inadequate. The two major actionable quality improvement frameworks for palliative care of multiple myeloma are the Plan-Do-Study-Act- (PDSA) and Team-Based Outpatient Early Palliative Care (TO-EPC) frameworks. While PDSA model is more effective for quality improvement of health literacy, policy-making, health financing and diagnosis of multiple myeloma (preventive quality improvement), TO-EPC is more effective in the therapeutic intervention (curative quality improvement). Both are public health approaches of quality improvement in palliative care.

Conclusion: Palliative care of multiple myeloma in Nigeria is grossly inadequate and under-utilized when compared to their counterparts in high-income countries. There is a need to address these inequalities using actionable quality improvement frameworks such as PDSA- and TO-EPC conceptual frameworks which play integral roles in the preventive and curative arms of palliative care. To effectively carry out these functions, good governance, leadership competence and collaborative efforts are pre-requisites.

Keywords: *multiple myeloma, palliative care, frameworks, quality, inequality, Nigeria.*

Abbreviations: HIC: high-income country; LIC: low-income country; LMIC: low-middle-income country; MM: multiple myeloma; PC: palliative care; PCM: palliative care of multiple myeloma; PLMM/PLWMM: people living with multiple myeloma; QOL: quality of life.

I. Introduction

According 2019 Central Intelligence Agency (CIA) report, Nigeria ranks 214th in average life expectancy among the 224 member nations recognized by the United Nations with 54 years as the average number of years from birth.[1] This makes the country the 11th worst nation to live on earth with respect to average life expectancy from birth and disease burden. In addition, the high-income gap between the ruling class and ordinary citizen creates inequality in distribution of resources including access to Medicare, hence making the nation a non-egalitarian society.[2-3] The middle-elderly population is therefore, gradually going into extinction in Nigeria as a result of negligence and poor social determinants of health, which if properly managed could improve their quality-adjusted life years and average life expectancy from birth. These nuances are the fall-out of leadership failure. Leadership failure is the major contributor of low (inadequate) quality of palliative care in Nigeria and this has heavily impacted on survival outcome of hematological malignancies including such as MM.[4]

MM is a hematological malignancy due to monoclonal proliferation of long-lived plasma cells in the bone marrow leading to end-organ damages which include chronic bone pain, anaemia, orthopedic complications (i.e., pathological fracture), and chronic kidney failure (renal myeloma).[5] It is simply defined as cancer of the bone marrow which targets predominantly

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the middle-elderly population group (geriatric cancer). It is the second most common hematological malignancy of public health importance globally with a documented racial disparity for the blacks compared to their white counterparts.[6] MM is one of the hematological malignancies that requires adequate palliative care in order to improve the quality of life and survival intervals of the sufferers. Unfortunately, the quality of palliative care of people living with multiple myeloma in Nigeria is low due to grossly inadequate annual health budget.[7]

Palliative Care is a holistic intervention that improves the quality of life of people facing life-threatening illnesses through prevention and relief of their sufferings by means of risk identification, assessment and management of the conditions using approaches ranging from physical, socio-economic, psychological and legal in nature.[8] PC uses preventive and curative measures to improve QOL of the target population. The term ''holistic'' refers to a constellation of strategic approaches of intervention including physical, psychological, spiritual and social modes of attaining to the needs of the sufferers (i.e., PLMM) in order to improve their QOL. The term ''quality'' as used in this context connotes 'standard of care that is productive, effective, efficient and result-oriented' which is what differentiates level of PC in HICs from LICs and LMICs. The quality of PC is a predictive marker of activity and longevity (average life expectancy or survival outcome) of the sufferer. The higher the level of quality of PC, the higher the quality-adjusted life years and survival intervals. This disparity is evidenced by 5-years post-diagnosis survival interval of 7.6-15% for PLMM in Nigeria (a LMIC)[7,9] as against 50.7% in the United States of America, a HIC.[10] In all these, there is an interplay of leadership models, health economics, health governance and level (quality) of healthcare which invariably play key role in determining the QOL and life expectancy of PLMM in both transiting and developed countries.[11] These inequalities could be mitigated by implementation of the actionable PC models operable in HICs in transiting countries such as those found in sub-Saharan Africa.

This study aims to address the inequality in the QOPC of PLMM in Nigeria (a LMIC) using frameworks that can improve quality of PCMM.

II. Materials & Methods

This was a hybridized version of review and critical appraisal of evidence-based research publications on PCMM in Nigeria, LICs, LMICs and HICs and feasible framework that could improve the QOPC in the region.

Three pairs of medical subject headings (namely MM and Challenges in management in Developing countries; Palliative care and MM; and Palliative care and Quality Assurance) were used as search strategies in Medline, PubMed, Scopus, African journal online, CINAHL, Cochrane library and Google search engine for problem identification, comparative analysis and outcome evaluation of research questions.

The issues of quality of PCMM were addressed from the perspectives of challenges of care of PLWMM, methods of improving the QOL of PLWMM in NGA, critical analysis of relevant quality areas, relevant structures and frameworks that could play key roles in mitigating healthcare needs of PLMM in NGA. This paper presented a synthesis of the reviewed articles and the suggested interventions (frameworks) that could scale-up the quality of PCMM in a developing country such as Nigeria.

III. Results

There are 3 strategic challenges in managing MM in Nigeria and these are:

a) Poor awareness of the disease.
b) Inadequate modern facilities or equipment for disease diagnosis and assessment test.
c) Lack of novel therapeutic interventions.

The two arms of an ideal PC (namely the preventive and curative arms) are defective in Nigeria. These defects accounts for grossly inadequate and under-utilized PC in Nigeria and other LICs. The term ''inadequate'' as used in this context connotes poor- or low-quality care.

The identified pillars of preventive arm of PC that require quality improvement include:

Table 1: Pillars of Preventive Arm of PC

1. Education
2. Policy-making
3. Periodic Screening test/early detection (Diagnosis)
4. Funding

The proposed public health Model for improving this arm of PC is the Plan-Do-Study-Act (PDSA) Model.

Table 2: PSDA Model of QI of PCMM

MODEL	DESCRIPTION
Plan	Capacity building of Palliative Medicine via training and re-training of healthcare professional workforce in palliative care using 'catch them young' approach. Advocacy to government and donor agencies for support of palliative care medicine through funding or grants for procurement of equipment and execution of research projects in palliative care. There is a need for health insurance coverage for PLWMM. Establishment of center of excellence for management of MM; appropriation of adequate budgeting for MM care and research, Public health awareness campaign on MM and institutionalization of periodic MM screening test policy in health institutions.
Do	Strategic implementation and monitoring of performance indicators of Preventive PC (i.e., MM cancer registries, published list of healthcare professionals who received PC trainings over a given period, the number of grants received, lists of centers of excellence for MM care as evidenced by adherence to the guidelines for PCMM as follow-up.
Study	The observed impacts are recorded and data generated evaluated to test for quality improvement.
Act	Translating the outcome of data (result) into policy and useful frameworks for decision-making.

The identified pillar of curative PC that requires quality improvement is therapeutic intervention (early treatment).

The Proposed Framework for Quality Improvement of Curative Arm of PCMM is the Team-based Early Palliative Care Conceptual Framework, TO-EPC (Figure 1). This is the current framework used in HIC where patients are referred palliative clinic by their attending physician. In TO-EPC, a longitudinal interdisciplinary collaborative care is given to patient by oncologist, family physician, community physician and other specialist depending on secondary problems associated with the disease. In addition, a follow-up care or visitation is extended to patient via the satellite home palliative care, acute palliative care unit and residential hospice or community palliative care unit.[12]

It operates on 4 principles (patient-led, family-centredness, attentive and flexible) of care under 4 domains (namely copping and support, symptom control, decision-making and future planning).

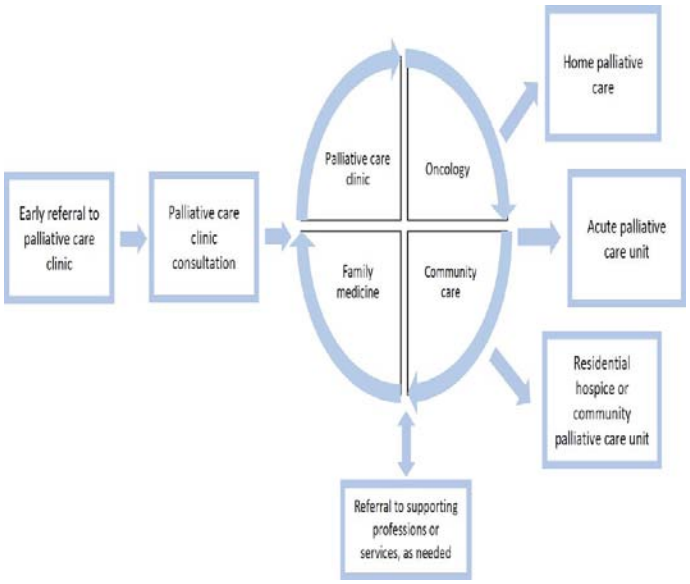

Figure 1: Team-based Outpatient Early Palliative Care Conceptual Framework[12]

IV. Discussion

This study has shown that an ideal PC uses preventive and curative measures to improve QOL of target population. The same principle is operative in the care of PLWMM. These two measures, also known as the arms of PC are mutually in-exclusive. Therefore, the quality improvement in level of PC must holistically address the two arms of PC to be effective. In order to improve PC, the World Health Organization (WHO) has proposed a model known as ''the WHO enhanced Public Health Approach Model for PC.'' This model operates on the premise that an effective level of PC must be founded on four pillars namely: appropriate policy, education, drug availability and strategic implementations.[13] This appears to be in keeping with the identified pillars of preventive arm of PC of MM which are grossly defective in Nigeria. There is a need to step-up the level of health literacy, policy-making processes, health financing and implementation strategies in the palliative care of people living with MM in Nigeria.[14] This may require application of other strategic leadership models for bringing about community and institutional change in the PCMM.[15]

To achieve a high level of quality of PC in any health organization therefore requires swinging into action the essential components of care. Quality improvement which is the gateway for transformational healthcare delivery requires a sustainable effort of healthcare stakeholders and it does not work in isolation but in synergy in association with quality assurance and quality management.[16]

The PSDA model and TO-EPC of MM are the strategic frameworks for achieve effective PC of PLWMM in Nigeria. While the PSDA model is more effective in the quality improvement of the diagnosis, education, funding, awareness creation and policy formulation, the TO-EPC takes care of definitive and supportive treatment of PLWMM. However, both frameworks in addition with the WHO enhanced PUBH approach model for palliative care are important in the comprehensive care of MM. These QI models (frameworks) should form integral part of the various components of comprehensive cancer care center in underserved setting including academic model providing access to healthcare. It is strongly believed that these actionable QI frameworks have the capacity to address the grossly inadequate quality care of MM in the middle-aged and geriatric populations which are gradually going into extinction in Nigeria and other sub-Saharan Africa regions.

However, actualization of actionable QI frameworks that could address the inadequate PCMM in Nigeria would be mirage without the key players coming together to embrace good governance, transformational leadership model and good health financing. The future healthcare leaders who must drive these operations must be visionary competent change agents who have the capacity and character to influence personal and institutional changes.[15]

V. Conclusion

The quality of PCMM in Nigeria is still grossly inadequate. There is a need to address the underlying causes which are primarily the defective preventive and curative arms of PC using actionable QI frameworks (namely the PDSA- and TO-EPC conceptual frameworks) and good health governance. This would require a healthcare-policy-driven government in order to be actualized. In all these, education, drug availability, funding, collaboration and strategic implementation of the policies are the tools to scale up the level of quality of PCMM, hence, improving survival outcome of

PLWMM in Nigeria (SDGs. 1 & 4). This approach serves as the WHO enhanced public health approach model for improving PC. This intervention is a strategic leadership approach to achieve United Nations sustainable developmental goal (SDG) 1 and 4.

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Author's Contributions

The authors contributed to the development of the study, data analysis, writing and revision of the article, and gave approval of the final version submitted for publication.

Disclaimers

The findings and conclusions of this article are solely the responsibility of the author and do not by any means represent the official position of the journal on the subject of discussion.

Conflict of Interest

The authors declared no conflicts of interest related to the authorship and publication of this article.

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Authors are advised to submit any mathematical equation using either MathJax, KaTeX, or LaTeX, or in a very high-quality image.

Tables, Figures, and Figure Legends

Tables: Tables should be cautiously designed, uncrowned, and include only essential data. Each must have an Arabic number, e.g., Table 4, a self-explanatory caption, and be on a separate sheet. Authors must submit tables in an editable format and not as images. References to these tables (if any) must be mentioned accurately.

Figures

Figures are supposed to be submitted as separate files. Always include a citation in the text for each figure using Arabic numbers, e.g., Fig. 4. Artwork must be submitted online in vector electronic form or by emailing it.

Preparation of Eletronic Figures for Publication

Although low-quality images are sufficient for review purposes, print publication requires high-quality images to prevent the final product being blurred or fuzzy. Submit (possibly by e-mail) EPS (line art) or TIFF (halftone/ photographs) files only. MS PowerPoint and Word Graphics are unsuitable for printed pictures. Avoid using pixel-oriented software. Scans (TIFF only) should have a resolution of at least 350 dpi (halftone) or 700 to 1100 dpi (line drawings). Please give the data for figures in black and white or submit a Color Work Agreement form. EPS files must be saved with fonts embedded (and with a TIFF preview, if possible).

For scanned images, the scanning resolution at final image size ought to be as follows to ensure good reproduction: line art: >650 dpi; halftones (including gel photographs): >350 dpi; figures containing both halftone and line images: >650 dpi.

Color charges: Authors are advised to pay the full cost for the reproduction of their color artwork. Hence, please note that if there is color artwork in your manuscript when it is accepted for publication, we would require you to complete and return a Color Work Agreement form before your paper can be published. Also, you can email your editor to remove the color fee after acceptance of the paper.

Tips for writing a good quality Medical Research Paper

1. Choosing the topic: In most cases, the topic is selected by the interests of the author, but it can also be suggested by the guides. You can have several topics, and then judge which you are most comfortable with. This may be done by asking several questions of yourself, like "Will I be able to carry out a search in this area? Will I find all necessary resources to accomplish the search? Will I be able to find all information in this field area?" If the answer to this type of question is "yes," then you ought to choose that topic. In most cases, you may have to conduct surveys and visit several places. Also, you might have to do a lot of work to find all the rises and falls of the various data on that subject. Sometimes, detailed information plays a vital role, instead of short information. Evaluators are human: The first thing to remember is that evaluators are also human beings. They are not only meant for rejecting a paper. They are here to evaluate your paper. So present your best aspect.

2. Think like evaluators: If you are in confusion or getting demotivated because your paper may not be accepted by the evaluators, then think, and try to evaluate your paper like an evaluator. Try to understand what an evaluator wants in your research paper, and you will automatically have your answer. Make blueprints of paper: The outline is the plan or framework that will help you to arrange your thoughts. It will make your paper logical. But remember that all points of your outline must be related to the topic you have chosen.

3. Ask your guides: If you are having any difficulty with your research, then do not hesitate to share your difficulty with your guide (if you have one). They will surely help you out and resolve your doubts. If you can't clarify what exactly you require for your work, then ask your supervisor to help you with an alternative. He or she might also provide you with a list of essential readings.

4. Use of computer is recommended: As you are doing research in the field of medical research then this point is quite obvious. Use right software: Always use good quality software packages. If you are not capable of judging good software, then you can lose the quality of your paper unknowingly. There are various programs available to help you which you can get through the internet.

5. Use the internet for help: An excellent start for your paper is using Google. It is a wondrous search engine, where you can have your doubts resolved. You may also read some answers for the frequent question of how to write your research paper or find a model research paper. You can download books from the internet. If you have all the required books, place importance on reading, selecting, and analyzing the specified information. Then sketch out your research paper. Use big pictures: You may use encyclopedias like Wikipedia to get pictures with the best resolution. At Global Journals, you should strictly follow here.

6. Bookmarks are useful: When you read any book or magazine, you generally use bookmarks, right? It is a good habit which helps to not lose your continuity. You should always use bookmarks while searching on the internet also, which will make your search easier.

7. Revise what you wrote: When you write anything, always read it, summarize it, and then finalize it.

8. Make every effort: Make every effort to mention what you are going to write in your paper. That means always have a good start. Try to mention everything in the introduction—what is the need for a particular research paper. Polish your work with good writing skills and always give an evaluator what he wants. Make backups: When you are going to do any important thing like making a research paper, you should always have backup copies of it either on your computer or on paper. This protects you from losing any portion of your important data.

9. Produce good diagrams of your own: Always try to include good charts or diagrams in your paper to improve quality. Using several unnecessary diagrams will degrade the quality of your paper by creating a hodgepodge. So always try to include diagrams which were made by you to improve the readability of your paper. Use of direct quotes: When you do research relevant to literature, history, or current affairs, then use of quotes becomes essential, but if the study is relevant to science, use of quotes is not preferable.

10. Use proper verb tense: Use proper verb tenses in your paper. Use past tense to present those events that have happened. Use present tense to indicate events that are going on. Use future tense to indicate events that will happen in the future. Use of wrong tenses will confuse the evaluator. Avoid sentences that are incomplete.

11. Pick a good study spot: Always try to pick a spot for your research which is quiet. Not every spot is good for studying.

12. Know what you know: Always try to know what you know by making objectives, otherwise you will be confused and unable to achieve your target.

13. Use good grammar: Always use good grammar and words that will have a positive impact on the evaluator; use of good vocabulary does not mean using tough words which the evaluator has to find in a dictionary. Do not fragment sentences. Eliminate one-word sentences. Do not ever use a big word when a smaller one would suffice.

Verbs have to be in agreement with their subjects. In a research paper, do not start sentences with conjunctions or finish them with prepositions. When writing formally, it is advisable to never split an infinitive because someone will (wrongly) complain. Avoid clichés like a disease. Always shun irritating alliteration. Use language which is simple and straightforward. Put together a neat summary.

14. Arrangement of information: Each section of the main body should start with an opening sentence, and there should be a changeover at the end of the section. Give only valid and powerful arguments for your topic. You may also maintain your arguments with records.

15. Never start at the last minute: Always allow enough time for research work. Leaving everything to the last minute will degrade your paper and spoil your work.

16. Multitasking in research is not good: Doing several things at the same time is a bad habit in the case of research activity. Research is an area where everything has a particular time slot. Divide your research work into parts, and do a particular part in a particular time slot.

17. Never copy others' work: Never copy others' work and give it your name because if the evaluator has seen it anywhere, you will be in trouble. Take proper rest and food: No matter how many hours you spend on your research activity, if you are not taking care of your health, then all your efforts will have been in vain. For quality research, take proper rest and food.

18. Go to seminars: Attend seminars if the topic is relevant to your research area. Utilize all your resources.

19. Refresh your mind after intervals: Try to give your mind a rest by listening to soft music or sleeping in intervals. This will also improve your memory. Acquire colleagues: Always try to acquire colleagues. No matter how sharp you are, if you acquire colleagues, they can give you ideas which will be helpful to your research.

20. Think technically: Always think technically. If anything happens, search for its reasons, benefits, and demerits. Think and then print: When you go to print your paper, check that tables are not split, headings are not detached from their descriptions, and page sequence is maintained.

21. Adding unnecessary information: Do not add unnecessary information like "I have used MS Excel to draw graphs." Irrelevant and inappropriate material is superfluous. Foreign terminology and phrases are not apropos. One should never take a broad view. Analogy is like feathers on a snake. Use words properly, regardless of how others use them. Remove quotations. Puns are for kids, not grunt readers. Never oversimplify: When adding material to your research paper, never go for oversimplification; this will definitely irritate the evaluator. Be specific. Never use rhythmic redundancies. Contractions shouldn't be used in a research paper. Comparisons are as terrible as clichés. Give up ampersands, abbreviations, and so on. Remove commas that are not necessary. Parenthetical words should be between brackets or commas. Understatement is always the best way to put forward earth-shaking thoughts. Give a detailed literary review.

22. Report concluded results: Use concluded results. From raw data, filter the results, and then conclude your studies based on measurements and observations taken. An appropriate number of decimal places should be used. Parenthetical remarks are prohibited here. Proofread carefully at the final stage. At the end, give an outline to your arguments. Spot perspectives of further study of the subject. Justify your conclusion at the bottom sufficiently, which will probably include examples.

23. Upon conclusion: Once you have concluded your research, the next most important step is to present your findings. Presentation is extremely important as it is the definite medium though which your research is going to be in print for the rest of the crowd. Care should be taken to categorize your thoughts well and present them in a logical and neat manner. A good quality research paper format is essential because it serves to highlight your research paper and bring to light all necessary aspects of your research.

Informal Guidelines of Research Paper Writing

Key points to remember:

- Submit all work in its final form.
- Write your paper in the form which is presented in the guidelines using the template.
- Please note the criteria peer reviewers will use for grading the final paper.

Final points:

One purpose of organizing a research paper is to let people interpret your efforts selectively. The journal requires the following sections, submitted in the order listed, with each section starting on a new page:

The introduction: This will be compiled from reference matter and reflect the design processes or outline of basis that directed you to make a study. As you carry out the process of study, the method and process section will be constructed like that. The results segment will show related statistics in nearly sequential order and direct reviewers to similar intellectual paths throughout the data that you gathered to carry out your study.

The discussion section:

This will provide understanding of the data and projections as to the implications of the results. The use of good quality references throughout the paper will give the effort trustworthiness by representing an alertness to prior workings.

Writing a research paper is not an easy job, no matter how trouble-free the actual research or concept. Practice, excellent preparation, and controlled record-keeping are the only means to make straightforward progression.

General style:

Specific editorial column necessities for compliance of a manuscript will always take over from directions in these general guidelines.

To make a paper clear: Adhere to recommended page limits.

Mistakes to avoid:

- Insertion of a title at the foot of a page with subsequent text on the next page.
- Separating a table, chart, or figure—confine each to a single page.
- Submitting a manuscript with pages out of sequence.
- In every section of your document, use standard writing style, including articles ("a" and "the").
- Keep paying attention to the topic of the paper.
- Use paragraphs to split each significant point (excluding the abstract).
- Align the primary line of each section.
- Present your points in sound order.
- Use present tense to report well-accepted matters.
- Use past tense to describe specific results.
- Do not use familiar wording; don't address the reviewer directly. Don't use slang or superlatives.
- Avoid use of extra pictures—include only those figures essential to presenting results.

Title page:

Choose a revealing title. It should be short and include the name(s) and address(es) of all authors. It should not have acronyms or abbreviations or exceed two printed lines.

Abstract: This summary should be two hundred words or less. It should clearly and briefly explain the key findings reported in the manuscript and must have precise statistics. It should not have acronyms or abbreviations. It should be logical in itself. Do not cite references at this point.

An abstract is a brief, distinct paragraph summary of finished work or work in development. In a minute or less, a reviewer can be taught the foundation behind the study, common approaches to the problem, relevant results, and significant conclusions or new questions.

Write your summary when your paper is completed because how can you write the summary of anything which is not yet written? Wealth of terminology is very essential in abstract. Use comprehensive sentences, and do not sacrifice readability for brevity; you can maintain it succinctly by phrasing sentences so that they provide more than a lone rationale. The author can at this moment go straight to shortening the outcome. Sum up the study with the subsequent elements in any summary. Try to limit the initial two items to no more than one line each.

Reason for writing the article—theory, overall issue, purpose.

- Fundamental goal.
- To-the-point depiction of the research.
- Consequences, including definite statistics—if the consequences are quantitative in nature, account for this; results of any numerical analysis should be reported. Significant conclusions or questions that emerge from the research.

Approach:

- Single section and succinct.
- An outline of the job done is always written in past tense.
- Concentrate on shortening results—limit background information to a verdict or two.
- Exact spelling, clarity of sentences and phrases, and appropriate reporting of quantities (proper units, important statistics) are just as significant in an abstract as they are anywhere else.

Introduction:

The introduction should "introduce" the manuscript. The reviewer should be presented with sufficient background information to be capable of comprehending and calculating the purpose of your study without having to refer to other works. The basis for the study should be offered. Give the most important references, but avoid making a comprehensive appraisal of the topic. Describe the problem visibly. If the problem is not acknowledged in a logical, reasonable way, the reviewer will give no attention to your results. Speak in common terms about techniques used to explain the problem, if needed, but do not present any particulars about the protocols here.

The following approach can create a valuable beginning:

- Explain the value (significance) of the study.
- Defend the model—why did you employ this particular system or method? What is its compensation? Remark upon its appropriateness from an abstract point of view as well as pointing out sensible reasons for using it.
- Present a justification. State your particular theory(-ies) or aim(s), and describe the logic that led you to choose them.
- Briefly explain the study's tentative purpose and how it meets the declared objectives.

Approach:

Use past tense except for when referring to recognized facts. After all, the manuscript will be submitted after the entire job is done. Sort out your thoughts; manufacture one key point for every section. If you make the four points listed above, you will need at least four paragraphs. Present surrounding information only when it is necessary to support a situation. The reviewer does not desire to read everything you know about a topic. Shape the theory specifically—do not take a broad view.

As always, give awareness to spelling, simplicity, and correctness of sentences and phrases.

Procedures (methods and materials):

This part is supposed to be the easiest to carve if you have good skills. A soundly written procedures segment allows a capable scientist to replicate your results. Present precise information about your supplies. The suppliers and clarity of reagents can be helpful bits of information. Present methods in sequential order, but linked methodologies can be grouped as a segment. Be concise when relating the protocols. Attempt to give the least amount of information that would permit another capable scientist to replicate your outcome, but be cautious that vital information is integrated. The use of subheadings is suggested and ought to be synchronized with the results section.

When a technique is used that has been well-described in another section, mention the specific item describing the way, but draw the basic principle while stating the situation. The purpose is to show all particular resources and broad procedures so that another person may use some or all of the methods in one more study or referee the scientific value of your work. It is not to be a step-by-step report of the whole thing you did, nor is a methods section a set of orders.

Materials:

Materials may be reported in part of a section or else they may be recognized along with your measures.

Methods:

- Report the method and not the particulars of each process that engaged the same methodology.
- Describe the method entirely.
- To be succinct, present methods under headings dedicated to specific dealings or groups of measures.
- Simplify—detail how procedures were completed, not how they were performed on a particular day.
- If well-known procedures were used, account for the procedure by name, possibly with a reference, and that's all.

Approach:

It is embarrassing to use vigorous voice when documenting methods without using first person, which would focus the reviewer's interest on the researcher rather than the job. As a result, when writing up the methods, most authors use third person passive voice.

Use standard style in this and every other part of the paper—avoid familiar lists, and use full sentences.

What to keep away from:

- Resources and methods are not a set of information.
- Skip all descriptive information and surroundings—save it for the argument.
- Leave out information that is immaterial to a third party.

Results:

The principle of a results segment is to present and demonstrate your conclusion. Create this part as entirely objective details of the outcome, and save all understanding for the discussion.

The page length of this segment is set by the sum and types of data to be reported. Use statistics and tables, if suitable, to present consequences most efficiently.

You must clearly differentiate material which would usually be incorporated in a study editorial from any unprocessed data or additional appendix matter that would not be available. In fact, such matters should not be submitted at all except if requested by the instructor.

Content:

- Sum up your conclusions in text and demonstrate them, if suitable, with figures and tables.
- In the manuscript, explain each of your consequences, and point the reader to remarks that are most appropriate.
- Present a background, such as by describing the question that was addressed by creation of an exacting study.
- Explain results of control experiments and give remarks that are not accessible in a prescribed figure or table, if appropriate.
- Examine your data, then prepare the analyzed (transformed) data in the form of a figure (graph), table, or manuscript.

What to stay away from:

- Do not discuss or infer your outcome, report surrounding information, or try to explain anything.
- Do not include raw data or intermediate calculations in a research manuscript.
- Do not present similar data more than once.
- A manuscript should complement any figures or tables, not duplicate information.
- Never confuse figures with tables—there is a difference.

Approach:

As always, use past tense when you submit your results, and put the whole thing in a reasonable order.

Put figures and tables, appropriately numbered, in order at the end of the report.

If you desire, you may place your figures and tables properly within the text of your results section.

Figures and tables:

If you put figures and tables at the end of some details, make certain that they are visibly distinguished from any attached appendix materials, such as raw facts. Whatever the position, each table must be titled, numbered one after the other, and include a heading. All figures and tables must be divided from the text.

Discussion:

The discussion is expected to be the trickiest segment to write. A lot of papers submitted to the journal are discarded based on problems with the discussion. There is no rule for how long an argument should be.

Position your understanding of the outcome visibly to lead the reviewer through your conclusions, and then finish the paper with a summing up of the implications of the study. The purpose here is to offer an understanding of your results and support all of your conclusions, using facts from your research and generally accepted information, if suitable. The implication of results should be fully described.

Infer your data in the conversation in suitable depth. This means that when you clarify an observable fact, you must explain mechanisms that may account for the observation. If your results vary from your prospect, make clear why that may have happened. If your results agree, then explain the theory that the proof supported. It is never suitable to just state that the data approved the prospect, and let it drop at that. Make a decision as to whether each premise is supported or discarded or if you cannot make a conclusion with assurance. Do not just dismiss a study or part of a study as "uncertain."

Research papers are not acknowledged if the work is imperfect. Draw what conclusions you can based upon the results that you have, and take care of the study as a finished work.

- You may propose future guidelines, such as how an experiment might be personalized to accomplish a new idea.
- Give details of all of your remarks as much as possible, focusing on mechanisms.
- Make a decision as to whether the tentative design sufficiently addressed the theory and whether or not it was correctly restricted. Try to present substitute explanations if they are sensible alternatives.
- One piece of research will not counter an overall question, so maintain the large picture in mind. Where do you go next? The best studies unlock new avenues of study. What questions remain?
- Recommendations for detailed papers will offer supplementary suggestions.

Approach:

When you refer to information, differentiate data generated by your own studies from other available information. Present work done by specific persons (including you) in past tense.

Describe generally acknowledged facts and main beliefs in present tense.

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Topics	Grades		
	A-B	**C-D**	**E-F**
Abstract	Clear and concise with appropriate content, Correct format. 200 words or below	Unclear summary and no specific data, Incorrect form Above 200 words	No specific data with ambiguous information Above 250 words
Introduction	Containing all background details with clear goal and appropriate details, flow specification, no grammar and spelling mistake, well organized sentence and paragraph, reference cited	Unclear and confusing data, appropriate format, grammar and spelling errors with unorganized matter	Out of place depth and content, hazy format
Methods and Procedures	Clear and to the point with well arranged paragraph, precision and accuracy of facts and figures, well organized subheads	Difficult to comprehend with embarrassed text, too much explanation but completed	Incorrect and unorganized structure with hazy meaning
Result	Well organized, Clear and specific, Correct units with precision, correct data, well structuring of paragraph, no grammar and spelling mistake	Complete and embarrassed text, difficult to comprehend	Irregular format with wrong facts and figures
Discussion	Well organized, meaningful specification, sound conclusion, logical and concise explanation, highly structured paragraph reference cited	Wordy, unclear conclusion, spurious	Conclusion is not cited, unorganized, difficult to comprehend
References	Complete and correct format, well organized	Beside the point, Incomplete	Wrong format and structuring

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