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Research and Ethics during the COVID-19 Pandemic

Thatte UM1, Gogtay NJ2

Public health emergencies such as the COVID-19 pandemic demand that research be done as an ethical imperative so that therapeutic and preventative options that are unique to the pandemic can be offered quickly and with an evidence base to the general public at large. This research however must be tempered by the fact that there exists scientific uncertainty, social and institutional disruption, and an overall climate of fear and distrust during these times.1 In addition, research should be done in a manner that does not impede response efforts.1 This editorial draws from several existing and current guidelines,1-5 that address research ethics during a pandemic and places them in the context of the evolving pandemic in India.

General Ethical Issues to consider while designing research studies in COVID-19: Remember that essentially nothing changes and that the patients’ safety, welfare and dignity remains paramount and forms the basis for all guidance documents. There are however, some specific aspects that need to be addressed while designing and conducting research in times of COVID19 as outlined below.

Benefit risk assessment: The proposal from the Principal Investigator [PI] must be designed in such a way that the benefits accruing from the research outweigh the risks. Although this will be reviewed by the Ethics Committee (EC), the PI must identify the risks and benefits of the research after a careful literature review. For drug interventions, this becomes doubly important as most drug interventions are “repurposed” – that is are available for use in other conditions and someone may want to try that drug in COVID19 e.g. lopinavir/ritonavir available for treatment of HIV and being now used for the current pandemic. A small paragraph in the protocol explaining how the risks are justified vis à vis the benefits always helps in a faster review from the EC with fewer questions and a quicker approval. We must consider not only physical harms but also the social risks, psychological harms and discomforts.1 It is important to note here that in view of the fact that the disease is new and there is a dearth of, as also, constantly evolving information, it is often difficult to predict all risks or even any potential benefits at the outset. It is a good practice to incorporate a dynamic benefit risk assessment several times during the conduct of the trial including an interim analysis6 for futility or utility into the trial design to assist in taking these informed decisions as the trial progresses. These reviews should be performed by an appropriately constituted Data Safety Monitoring Board (DSMB).7 It is also important to remember that recommendations8 made early in the course of the pandemic [for example the use of Hydroxychloroquine for prophylaxis by the Indian Council of Medical Research] may later evolve as more evidence accrues.9,10

Privacy and Confidentiality: Any research on COVID-19 infection may be highly sensitive in nature. There is a lot of scope for stigmatization, discrimination, and violence against the treating physician and the participant while conducting the research. It is very important for the researcher to plan carefully how the confidentiality of the research related data will be maintained and more importantly the privacy of the research participant. This is most important during publication and taking consent of the participant to publish any data especially photographs (even anonymised) must be taken à priori. Any results seen during the course of the study must not be discussed with the media or more importantly put out on social media before the study is complete. This runs the risk of handing out false hope to an already anxious population. Special care must be taken not to share sensitive data [for example X-rays, blood reports or CT scan reports that have identifiers] as these are private data of the patient and doing so violates the patients’ privacy.

Community Engagement: In this pandemic, it is very important to engage with the community to improve public trust, help improve design and conduct studies that are responsive to the community’s health needs. Research should also include interventions like social distancing, use of sanitising measures or masks for example that often get less attention relative to drug measures. Failure to build and maintain community trust during the process of research design and implementation, or when disclosing preliminary results, will not only impede study recruitment and completion but may also undermine the uptake of any interventions proven to be efficacious. Engaging with affected communities before, during, and after a study is essential to build and maintain trust. Wherever possible, community representatives (e.g. community advisory board) should be involved in conceptualization, review, research, and dissemination of results in such settings. The EC should insist on an à priori agreement between researchers and sponsors regarding post-research access to successful interventions and benefit sharing if relevant. One of the aspects that is being explored are the Controlled Human Infection Models (CHIMs) for COVID19 and these raise exciting and the prospect for fast-tracking vaccine development. However, the ethical challenges surrounding them need considerable attention.11

Dissemination of results: We are living in an era of “pre-prints”/online ahead of print that may not be peer reviewed are freely available in the public domain as was the case with the use of Hydroxychloroquine [HCQ] in combination with azithromycin[posted on medRxiv on 11th May 2020]. The paper was subsequently withdrawn by the authors who have now asked for it not be cited.12 The physician

1 Professor and Head, 2 Professor, Dept. of Clinical Pharmacology, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra
community thus must not base any policy decisions as well as individual patient care decisions on non-peer reviewed material.

Storage of Biological Material: In COVID-19, samples may be in the form of expectorated sputum, endotracheal aspirate, or Broncho alveolar lavage (BAL) besides other body fluids, such as blood, plasma, dried blood spots, urine, stool, tissues, and organs. These are likely to be prospectively collected or stored. At the point of writing this editorial, there is considerable discussion on the testing for antibodies and the choice of kits. Stored samples are important as they can be used to establish prevalence of antibodies in populations and guide studies on the use of convalescent plasma. In future these studies can also inform vaccine development. All safeguards must be utilised for storage of infectious samples. It is important to have clarity on custodianship, mandatory to obtain approval of the EC/governance committee, appropriate written consent (including broad consent\(^1\)), maintain individual confidentiality and privacy.

Public health and socio behavioural research: While public interest is focused on drug research in an attempt to find a cure, the physician community needs to also remember the importance of public health and socio-behavioural research. If any such research is planned, it is very important to consult the relevant chapters in the ICMR Bioethics Guidelines.\(^2\)

Regulatory decisions: During the pandemic, Monitored Emergency Use of Unregistered and Experimental Interventions (MEURI)\(^3\) may be approved with the following precautions: Thoroug scientific review followed by an ethics review, oversight by a local EC, use of GMP products, making accessible rescue medicines/supportive treatment, meticulous documentation of therapeutic processes including adverse events, fast track research and possible sharing of peer reviewed data on safety and efficacy for further research. The consent process is important and must be carried out with care, community engagement and ensuring fair distribution of scarce resources.

Ethics Committees – In resource constrained settings like ours, there is always a tension between the maximum recommended and minimum essential requirements to conduct a good trial.\(^5\) ECs therefore have added responsibilities and one of the most important challenges they have to face is that of providing ethics review in time sensitive circumstances- the need for immediate action to contain an infectious disease outbreak may make it impossible to adhere to the usual timeframes for research ethics review. The EC must adapt its SOPs in time, without undermining any of the substantive protections that ethics review is designed to provide. On-line meetings, more frequent meetings, online circulation of project related documents are some of the specific efforts an EC can take to save time.

What then is the take home message? It is important to design and conduct locally relevant research as, especially in infectious diseases, local factors influence the course of the disease and the consequent outcomes. The climate of fear and desperation during a pandemic where only uncertainty looms on the horizon, the prevailing atmosphere can make it difficult for all clinical research stakeholders like ethics committees, prospective participants, investigators and even regulators to engage in an objective assessment of the risks and benefits of research participation. In an environment where large numbers of individuals become sick and die, any potential intervention may be perceived to be better than nothing, regardless of the risks and potential benefits (or lack thereof). Regulators and ECs that approve research protocols or any emergency authorization should ensure that clinical trials are initiated only when there is a reasonable scientific basis to believe that the experimental intervention is likely to be safe and efficacious, and that the risks have been minimized to the extent reasonably possible. Informed consent is another key aspect that investigators should focus upon as it is important to remember that there exists a specific vulnerability of potential participants who are in quarantine or isolation and cut off from their families and who may feel powerless to decline an invitation to participate in research or make decisions without adequate support systems that would otherwise exist. Finally, all stakeholders – pharmaceutical companies, contract research organizations, investigators, ethics committees, and the regulator should understand that these are extraordinary times that often demand extraordinary measures and out of box thinking which may include among other things approval for compassionate use of drugs or a clinical trial waiver [Remdesivir being one example] based on data generated outside the country,\(^6,7\) off label use of drugs by clinicians with a clear understanding of benefits and risks, understanding participant vulnerability and involving the participant and the community at large in the decision making process and an openness to use therapies from complementary and alternative systems of medicine [for example using immunity boosters recommended by the Ministry of AYUSH].\(^8\) Only then will be able to offer hope to the most important stakeholder in clinical research- the patient.

References

Characteristics, Treatment Outcomes and Role of Hydroxychloroquine among 522 COVID-19 hospitalized patients in Jaipur City: An Epidemioclinical Study

Sudhir Bhandari†*, Ajeet Singh†, Raman Sharma†, Govind Rankawat††, S. Banerjee†, Vishal Gupta†, Amitabh Dube‡, Shivankan Kakkar‡, Shrikant Sharma†, Prakash Keswani†, Abhishek Agrawal†, Amit Tak‡, CL Nawal†

Abstract

Purpose: The present study was undertaken to investigate epidemiological distribution, clinical manifestation, co morbidity status, treatment strategy and case fatality index of emerging COVID-19 infection at SMS Medical College Hospital, Jaipur, Rajasthan. It also evaluated efficacy of hydroxychloroquine (HCQ) in treatment of patients and risk of serious adverse outcomes in patients with COVID-19 in relation to their co morbidity status.

Materials and methods: In an attempt to provide extensive information pertaining to epidemiological and clinical characteristics of COVID-19, the present study was undertaken on 522 patients. The patients were COVID-19 confirmed positive by genomic analysis through Reverse Transcriptase Polymerase Chain Reaction (RT-PCR) at SMS Medical College and Attached Hospitals, Jaipur. The indoor admitted patient’s information inclusive of demographic profile (age, sex, nationality, residence), date of confirmation for positive COVID-19 case, travel/ exposure history, date of recovery/ death, clinical features, co morbidities and treatment plan was recorded. A serial follow-up of recovered patients to evaluate infective period of the disease was also part of the study.

Results: A total of 522 patients of laboratory confirmed COVID-19 test by RT-PCR at SMS Hospitals, Jaipur were assessed. Among the confirmed cases, most of patients were young adult in the age group with mean age of 35.42 years. 22.41% patients were below 20 years of age, majority of patients (58.80%) were in the age range of 21 to 50 years and only 18.79% patient population was in the age range of above 50 years. Females (39.08%) were affected less than males (60.91%) with an average sex ratio of female: male being 0.64. Out of the total analyzed patients, only 24.32% patients were symptomatic, among them fever (55.90%), cough (52.75%), sore throat (49.60%) and shortness of breath (46.45%) were the most common presenting clinical manifestations while a few patients also had symptoms of headache (26.77%), chest pain (6.29%) and other symptoms (7.87%) like pain abdomen, fatigue, joints pain, altered sensorium etc. Most of symptomatic patients belonging to older age group. An average of 40.40% patient population of above 50 years of age, were symptomatic while none of the patients below 10 years of age were symptomatic. 13.98% patients had some or the other underlying co morbidity disease. The most prevalent co morbidity was hypertension (42.46%) followed by Diabetes mellitus (39.72%), Old k-chest (20.54%), COPD/ Bronchial Asthma (16.43%), Coronary artery disease (13.69%), Chronic kidney disease (13.69%) and Valvular heart disease (6.84%) distributed in co morbid patients of COVID-19. 60.27% of patient population with underlying co morbidity conditions were more prone to develop symptomatology complex as compared to that observed in patients with no co morbidity (18.42%). 116 patients had recovered with effective treatment till the date of data analysis. Time of recovery was counted from the date of positive report to 1st negative report of oropharyngeal sample by RT-PCR for COVID-19 with an average recovery time of 8.15 days. 23.27% patients recovered within 5 days, while 52.58% patients took about 6-10 days, 23.27% patients took 11-15 days and remaining 0.86% took more than 16 days to recover. In the present study 15 patients had died till analysis of data, among the deceased, 73.33% were above 50 year of age with a male preponderance (66.6%). Interestingly, all deceased (100%) had presented with clinical manifestations of COVID-19 and all had underlying multiple co morbidity conditions. Majority of patients had early mortality after admission to hospital with two third death account in initial three days. Asymptomatic patients (cases) treated with HCQ recovered early (average recovery time =5.4 days) compared to asymptomatic patients who did not receive any treatment (control group) and had longer recovery time (average recovery time =7.6 days).

Conclusion: The varied spectra of COVID-19 mostly affects young adult age group (third to fifth decades of life). Interestingly, early age group was also affected in significant proportion when compared with similar data from other countries. It was observed that male population seemed to be was more prone to getting infected. Majority of COVID-19 positive patients (nearly three-
fourth) were asymptomatic (mostly in young age range) at the time of diagnosis, which poses a major challenge for healthcare workers. Fever, cough, sore throat, shortness of breath were major symptoms that could be detected in such COVID-19 patients. Symptomatic clinical manifestations were more common in old age population. Infectivity was higher in patients that had underlying co-morbid disease, especially in patients with multiple co-morbid conditions. Symptomatic presentation of COVID-19 was observed to be higher in patients with co-morbid disease. Average recovery time from COVID-19 was 8 days with effective treatment. Mortality in COVID-19 was higher in old age population, male gender, symptomatic and co-morbid patients as compared to other similarly matched group. Most of mortality was noted within first few days of admission, suggestive of early mortality due to the primary disease process. Treatment with HCQ had early recovery without effectively influencing the overall mortality.

**Introduction**

Since November 2019, the rapid outbreak of coronavirus disease 2019 (COVID-19), which arose from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, has become a public health emergency of international concern. COVID-19 has contributed to an enormous adverse impact globally. Infection by COVID-19 can result in a range of clinical outcomes, from asymptomatic to severe life-threatening course or death. Characterization of epidemiological, clinical, co-morbid features with recovery and mortality of COVID-19 is crucial for development and implementation of effective control strategies and management protocol. If well tracked and monitored early in its time-course, early characterization of an emerging pathogen provides a unique opportunity to understand its transmission, natural history, and effectiveness of screening, though plausibility of making such assumptions relating to time course and geographic locales become far-fetched when the pathogen has spread-over with full tensity. Based on current epidemiological investigation, the incubation period of COVID-19 seems to be 1–14 days, mostly 3–7 days. COVID-19 is contagious during its latency period. It is highly transmissible in humans, especially in the elderly and people with underlying diseases. As per literature median age of patients is 47–59 years with around 41.9–45.7% of patient population being of female gender. The clinical manifestations of COVID-19 are heterogeneous with fever, cough, sore throat, shortness of breath, headache, fatigue, abdominal discomfort being the predominant features. On admission, many patients have reported as having at least one co-morbidity with diabetes, hypertension, and cardiovascular and cerebrovascular diseases being most commonly reported conditions. Similar with influenza, Severe Acute Respiratory Syndrome coronavirus (SARS-CoV)⁶ and Middle East Respiratory Syndrome coronavirus (MERS-CoV),⁷ COVID-19 more readily predisposes to respiratory failure and death in susceptible patients. Recovery and mortality of patients from COVID-19 is influenced by their respiratory system involvement and other systemic manifestations. In the present study clinical data of 522 patients admitted to SMS Medical College Hospital, Jaipur, Rajasthan with laboratory-confirmed COVID-19 test were analyzed with the objective being to evaluate epidemiological characteristics, clinical features, co-morbidity status and outcome of COVID-19 with its prognostic and diagnostic correlation and implications.

**Method**

**Study Design:** The present descriptive, retrospective analysis was done on COVID-19 positive patients admitted to S.M.S. Medical College Hospital, Jaipur, Rajasthan from last week of February, 2020 to April 20, 2020, when COVID-19 was declared a public health emergency of pandemic proportions and subsequently formal screening and diagnostic investigations for SARS-CoV-2 was initiated throughout India. The privacy and confidentiality of patients was observed as per norms.

**Data Collection**

After collection of all required data and careful medical chart review, the clinical data of laboratory-confirmed 522 hospitalized patients till 20th April 2020 was compiled and tabulated. The diagnosis of COVID-19 was made based on the World Health Organization interim guidance, wherein confirmed cases denoted were patients whose RT-PCR assay findings for nasal and pharyngeal swab specimens were positive. The epidemiological data (age, sex, residence) was recorded and clinical data, inclusive of recent exposure history, clinical symptoms and signs, co-morbidities, was obtained. The admitted patients were serially followed up for their symptomatology complex, with recovery of patients being confirmed with first negative oropharyngeal or nasopharyngeal sample by RT-PCR for COVID-19. This concept was based on seroconversion in COVID-19 patients. The primary endpoint of the study was a composite measure which consisted with negativity of first COVID-19 sample or death of patient.

COVID-19 positive patients were treated with Lopinavir/Ritonavir, Hydroxychloroquine (HCQ), Azithromycin and symptomatically accordingly.

**Variables:** The patient characteristics were collected at baseline and confirmed cases were diagnosed based on positive viral nucleic acid test result on throat swab samples. The variables evaluated included age and gender distribution, clinical manifestations, co-morbid status, recovery trending in terms of time and resolution of symptoms, death of patients and their correlation with each other and were categorized for analysis and necessary preventive and curative protocol was initiated. Age distribution graphs were constructed and sex ratio (i.e., male: female [M:F] ratio) was calculated. The clinical profile of COVID-19 positive patients was evaluated in terms of percentage prevalence in relation to age group of patients. Co-morbid status of patients was documented as percentage prevalence of COVID-19 in such patients and its correlation with symptomatic presentation and mortality of patients. Recovery of patients was analyzed as time duration of date of positive sample to first negative sample by RT-PCR for COVID-19. Mortality of patients was analyzed with respect to time duration from admission, age group and gender of deceased and association, if any, with symptomatic presentation and ante mortem co-morbidity. Treatment of patients was based on a rationale protocol.
of decreasing viral load. In the follow-up study of a total of 131 patients, severity of COVID-19 was segregated into critically ill, severely ill, mildly ill and asymptomatic category (8). The patients were treated according to their severity and divided into (1) Group A for critically ill patients treated with Lopinavir and Ritonavir, (2) Group B for severely ill patients treated with HCQ and Azithromycin, (3) Group C for mildly ill patients treated with HCQ alone, (4) Group D for asymptomatic patients treated with HCQ alone and (5) Group E for asymptomatic patients without any proposed definitive treatment (HCQ not received by this group due to some contraindication or refusal by patients/attender). To study effect of HCQ on prognosis of patients, asymptomatic COVID-19 positive patients were further subdivided into two categories, with and without HCQ, into Group D and Group E considered as Case and Control respectively for this study.

The Rationale of Putative Definitive Management Protocol of COVID-19

SARS-CoV-2 is a virus belonging to coronavirus family and has a propensity to access pulmonary portal via angiotensin converting enzyme receptor 2 (ACE2) or basigin mediated entry and has four structural proteins namely S (spike), E (envelope), M (membrane) and N (nucleocapsid). The entry of virus is also facilitated by proteases of host cells. Considering the entry of virus and its initiation into host cell through proteases, the concept of designing a definitive management protocol primarily targeting the entry point and protease facilitator was evolved. Subsequently, use of antiretroviral drugs Lopinavir and Ritonavir, approved for use in patients afflicted with Human Immunodeficiency Virus (HIV), as protease inhibitors (moreover documentation of genome similarity of SARS-CoV-2 HIV) and that of HCQ as its inhibitory action on respiratory angiotensin converting enzyme receptor (ACE2), the portal and receptor of entry of SARS-CoV-2. The macrolide azithromycin was included as part of management protocol due to its inhibitory action on protein biosynthesis, anti-inflammatory, anti-cytokine actions and presentation with different invasion inhibitory activity.

Statistical analysis

The present hospital based, observational descriptive study conducted on 522 COVID-19 patients at SMS Medical College Hospital, Jaipur to investigate epidemiological distribution, clinical manifestation, co morbid status, treatment strategy and case fatality index of emerging COVID-19 infection at SMS Medical College Hospital, Jaipur, Rajasthan. The efficacy of hydroxychloroquine (HCQ) in treatment of patients and risk of serious adverse outcomes in patients with COVID-19 in relation to their co morbid status was also undertaken. The descriptive statistics for quantitative data was expressed as mean and standard deviation and qualitative data was expressed as proportions.

Results

Serial data from COVID-19 positive patients were collected, evaluated, interpreted and correlated with each other and with clinico-epidemiological variables of age, sex, clinical features, co morbidity, recovery and mortality.

A total of 522 laboratory confirmed COVID-19 patients by RT-PCR admitted at SMS Medical College Hospital, Jaipur, Rajasthan till 20th April 2020, were assessed. Among the confirmed cases, most of patients were young adult in the age group with mean age of 35.42 years. 22.41% patients were below 20 years of age, majority of patients (58.80%) were in the age range of 20 to 50 years and only 18.79% patient population was in the age range of above 50 years. Proportional distribution of patients according to age group was found as 0-10 year 0.665 (95% CI = 0.046-0.09), 10-20 year 0.159 (95% CI = 0.129-0.193), 20-30 year 0.257 (95% CI = 0.22-0.296), 30-40 year 0.192 (95% CI = 0.159-0.228), 40-50 year 0.14 (95% CI = 0.111-0.173), 50-60 year 0.098 (95% CI = 0.074-0.126), 60-70 year 0.063 (95% CI = 0.044-0.088), 70-80 year 0.015 (95% CI = 0.007-0.03), Above 80 year 0.011 (95% CI = 0.004-0.025)(Figure 1). Females (39.08% (95 % CI = 34.9% - 43.4%)) were affected less than males (60.91% (95 % CI = 56.36% - 65.1%)) with an average sex ratio of female: male being 0.64.

In the present study a total of 522 patients were analyzed and among them only 127 patients (24.32% (95% CI = 19.6 – 26.9)) were symptomatic while remaining 395 patients (75.68% (95% CI = 73.0 – 80.2)) had no clinical manifestations at presentation. In symptomatic patients, fever (55.90%), cough (52.75%), sore throat (49.60%) and shortness of breath (46.45%) were most common presenting clinical manifestations while few patients also presented with headache (26.77%), chest pain (6.29%) and other non-specific symptoms (7.87%) like pain abdomen, fatigue, joints pain, altered sensorium, etc. Symptomatic presentation in COVID-19 was also dependent on age profile of patients with most of symptomatic patients (40.40%) being in old age group of above 50 years, while none of patients of below 10 years of age were symptomatic (Figure 2). In the study population 73 patients (13.98% (95% CI = 11.1 – 17.2%)] had underlying co morbid disease. Multiple co morbid disease was more prevalent (57.53%)
among co morbid population. The most prevalent co morbidity observed in the sample population co morbid patients of COVID-19 was hypertension (42.46%) followed by Diabetes mellitus (39.72%), Old k-chest (20.54%), COPD/ Bronchial Asthma (16.43%), Coronary artery disease (13.69%), Chronic kidney disease (13.69%) and Valvular heat disease (6.84%), while co morbid disease percent distribution in whole sample population was noted as 5.93% for HTN, 5.55% for T2DM, 2.87% for Old k-chest, 2.29% for COPD/Bronchial Asthma, 1.91% for CKD, 1.91% for CAD-LVF and 0.95% for RHD-MS-MR (Figure 3). COVID-19 patients who had underlying co morbid conditions were more prone to develop symptomatic disease (60.27%) as compared to that observed in such patients with no co morbid conditions (18.42%). In the present study 116 patients recovered with effective treatment at the time of data analysis. Time duration needed for recovery was assessed as time elapsed between date of positive report to 1st negative report of oropharyngeal/nasopharyngeal sample by RT-PCR for COVID-19. An average recovery time of 8.15 days was observed. 23.27% patients recovered within 5 days, while 52.58% patients took 6-10 days, 23.27% patients took 11-15 days and remaining 0.86% took more than 16 days to recover. In the present study 15 patients succumbed to life and died due to COVID related illness, among the deceased 73.33% were above 50 years of age with a male preponderance (66.6%). Interestingly all deceased (100%) presented with clinical manifestation of COVID-19 and all had underlying multiple co morbid conditions (Table 1). Majority of patients had early mortality after admission in the Hospital and accounted for 13.33% of death on first day of admission, 40% of mortality was observed on second day, 13.33% on third day, 13.33% on fourth day, 6.66% on fifth day and 13.33% mortality was observed after sixth day of admission (Figure 4). In the follow-up study of a total 131 patients were categorized by severity of disease into critically ill, severely ill, mildly ill and asymptomatic patients of COVID-19. Patients treated according to their severity were categorized as (1) Group A inclusive of critically ill patients treated with Lopinavir and Ritonavir, (2) Group B included severely ill patients treated with HCQ and Azithromycin, (3) Group C had mildly ill patients treated with HCQ alone, (4) Group D was inclusive of asymptomatic patients treated with HCQ alone and (5) Group E included asymptomatic patients receiving only symptomatic and no proposed definitive treatment (HCQ not received by this group due to some contraindication or refusal by patients/attender). To see effect of HCQ on prognosis of patients, asymptomatic COVID-19 positive patients were divided into two categories on the basis of treatment that was categorized as Group D and Group E considered as Case and Control respectively for this study. In the present study, Group A had 9 patients, Group B had 16 patients, Group C had 25 patients, Group D had 44 patients and Group E had 37 patients and among them percentage recovered patients were 44.44%, 64.70%, 93.93%, 97.50% and 96.85% for each group, respectively (Figure 5) with an average recovery time of 16.1 Day, 14.3 Day, 10.1 Day, 5.4 Day, 7.6 Day, respectively for each group. Asymptomatic patients (case) treated with HCQ recovered early (average recovery time = 5.4 days) as compared to that observed in asymptomatic patients who did not receive any specific proposed treatment (control group) and had longer recovery time (average recovery time =7.6 days). The difference of percentage of recovered patients in the two groups categorized as case and control was not statistically significant (Table 2).

Discussion

The dread and specter of COVID-19 made its first appearance in Wuhan, China and it has spread like wildfire out and across precincts of China and across the globe with a pace that has taken everyone by surprise. Confirmed cases of COVID-19 is being reported from all corners of the world and subsequently World Health Organization (WHO) officially declared COVID-19 a pandemic on March 11, 2020.15 Research is underway to understand more about transmissibility, severity, and other features associated with COVID-19.16 The virus, SARS-CoV-2, of COVID-19 has been found to have higher levels of transmissibility with higher potential of pandemicity, as the effective reproductive number (R) of COVID-19 (2.9) is estimated to be higher than the reported effective reproduction number (R) of SARS (1.77) at this early stage.17 The SARS-related coronaviruses are covered by spike proteins that contain a variable
Table 1: Epidemiology, time duration, Clinical features and comorbidity of deceased (in 15 COVID-19 related deaths in Hospital setup)

<table>
<thead>
<tr>
<th>S. No.</th>
<th>Age (year)</th>
<th>Sex</th>
<th>Contact history</th>
<th>Date of admission</th>
<th>Date of death</th>
<th>Outcome</th>
<th>Clinical manifestation</th>
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<tr>
<td>1</td>
<td>85</td>
<td>M</td>
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<td>01.04.2020</td>
<td>02.04.2020</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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<td>09.04.2020</td>
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<td>-</td>
</tr>
<tr>
<td>4</td>
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<td>-</td>
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<tr>
<td>5</td>
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<td>15.04.2020</td>
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<tr>
<td>6</td>
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<tr>
<td>7</td>
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<td>Yes</td>
<td>11.04.2020</td>
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<tr>
<td>8</td>
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<td>-</td>
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<tr>
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<td>76</td>
<td>M</td>
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<td>13.04.2020</td>
<td>17.04.2020</td>
<td>DEATH</td>
<td>-</td>
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<td>10</td>
<td>22</td>
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<td>Yes</td>
<td>14.04.2020</td>
<td>17.04.2020</td>
<td>DEATH</td>
<td>-</td>
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<tr>
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<td>F</td>
<td>Yes</td>
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<td>12</td>
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<td>M</td>
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<td>17.04.2020</td>
<td>18.04.2020</td>
<td>DEATH</td>
<td>-</td>
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<td>13.04.2020</td>
<td>18.04.2020</td>
<td>DEATH</td>
<td>-</td>
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<td>17.04.2020</td>
<td>17.04.2020</td>
<td>DEATH</td>
<td>-</td>
</tr>
<tr>
<td>15</td>
<td>62</td>
<td>M</td>
<td>Yes</td>
<td>18.04.2020</td>
<td>19.04.2020</td>
<td>DEATH</td>
<td>-</td>
</tr>
</tbody>
</table>

In symptomatic patients, fever and cough were the most common presenting features, followed by sore throat, shortness of breath and headache while few patients also presented with chest pain and non-respiratory symptoms like pain abdomen, fatigue, joints pain, altered sensorium, etc. Symptomatic presentation in COVID-19 was also dependent on age profile of patients with most of symptomatic patients (about 40-40%) falling in the age range above 50 years of age, while none of patients below 10 years of age were symptomatic. The pediatric age group poses a real challenge for community in terms of adherence to preventive measures.
It was observed in the present study co morbidities have a tangible impact on clinical characteristics and course in COVID-19 positive patients. It has been observed that COVID-19 patients have circulatory and endocrine co morbidities. Patients with at least one or more co morbidity have been reported with poor clinical outcomes. Notwithstanding the commonness of circulatory and endocrine co morbidities, patients with COVID-19 rarely have co morbid respiratory diseases (particularly COPD). In the present study population 13.98% patients had underlying co morbid disease with multiple co morbid diseases being more prevalent. The most prevalent co morbidity observed in present study was hypertension followed by Diabetes mellitus, Old k-cough, COPD/ Bronchial Asthma, Coronary artery disease, Chronic kidney disease and Valvular heat disease. Nearly about 60% COVID-19 patients who had underlying co morbid conditions developed symptomatic disease while only 18% non-co morbid patients developed symptomatic disease.

In follow-up series of COVID-19 patients, it was observed that most of patients recovered while few patients succumbed to the disease process with an average recovery to mortality ratio in given time period being 7.33. The recovery time of COVID patients was variable and it was observed to be dependent on patients’ age, sex, clinical presentation and underlying co morbid condition. The first seroconversion of first negative report of COVID-19 by RT-PCR defined overall healthcare burden with average hospital stay duration and concomitant appointment of healthcare personnel. In COVID-19 related deaths, major concern was ageing population of above 50 years with a predilection for male gender, necessitating the need to prioritize such a population cohort in order to minimize fatality rates of COVID-19. Interestingly all deceased present had clinical manifestations of COVID-19 and underlying multiple co morbid conditions. It was observed that fatalities in COVID-19, when they occur, are rapid and swift and take place early within few days of hospital admission. It was also observed that patient recovery rates were lowest in critically ill patients and highest in asymptomatic patients. As for efficacy of HCQ in asymptomatic COVID-19, the proportion of recovered asymptomatic patients who were on HCQ was slightly higher than those of control group (asymptomatic COVID-19 positive patients without any treatment). Recovery duration was maximum for critically ill patients followed by severely ill, mild symptomatic, asymptomatic without treatment and asymptomatic on HCQ in decreasing order.

**Conclusion**

It could be concluded that spectrum of COVID-19 mostly affects young adult age group (third to fifth decades of life), a finding that contrasts with documentations from other countries. The percentage of male gender to be afflicted with COVID-19 was more. Majority of patients (nearly three-
fourth) of COVID-19 disease were asymptomatic at the time of diagnosis and presentation. Symptomatic presentation was more common in old age population. Infection was higher in patients who had underlying co morbid diseases especially with multiple co morbid diseases. The average recovery time from COVID-19 was 8 days with effective treatment. Mortality in COVID-19 was higher in old age population, male gender, symptomatic and in patients with co-existing co morbid conditions. Most of mortality was noted within in few days of admission suggestive of early mortality due to primary disease. The recovery percentage was lowest with recovery duration being maximum in critically ill patients and the opposite trend was observed in asymptomatic patients on HCQ treatment. It was observed that putative definitive management protocol with HCQ enhances the chances of early recovery, modulating the overall mortality profile of COVID-19.

Limitations
The limitations of this study include its small sample population size with lack of complete follow-up. Ethical approval: Approval was not required.

Author contributions: S. Bhandari, A. Singh and G. Rankawat formulated the research questions, designed the study, developed the preliminary search strategy, and drafted the manuscript; S. Bhandari, G. Rankawat, R. Sharma refined the search strategy by conducting iterative database queries and incorporating new search terms; G. Rankawat, A. Dube, S. Kakkar, A. Talk, V. Gupta, S. Sharma collected and analysed data; S. Bhandari and A. Singh, A. Agrawal conducted the quality assessment. All authors critically reviewed the manuscript for relevant intellectual content. All authors have read and approved the final version of the manuscript.

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Availability of data and materials: The data that support the findings of this study are available from the corresponding author [Dr. Govind Rankawat, Email ID: govindranksr@gmail.com], upon reasonable request.

Declaration of competing interest: All authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential.

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References
A Prospective Validation Survey to Assess Usage of Premix Insulins in Management of Diabetes with Respect to the Recommendations Enlisted in Indian Guidelines

Sanjay Kalra, Rakesh Sahay, Mangesh Tiwaskar, Gagan Priya, Sambit Das, Ganapathi Bantwal

Abstract

Objective: Widely used in the management of diabetes, the premix insulin therapy is influenced by several patient preferences and physician choices. The present survey aims to provide specific recommendations based on published data for appropriate management of T2DM with premix insulins.

Methods: We administered an online questionnaire where the respondent physicians were requested to go-through the published India specific and international guidelines before the survey. The respondents were requested to answer the electronic survey based on their clinical experiences with patients having diabetes.

Results: Overall, 1408 doctors participated in the survey. Majority of physicians preferred a premix insulin regimen for initiation. Short-term therapy with premix insulins in insulin-naive T2DM patients with symptomatic hyperglycemia and/or glucotoxicity was strongly recommended by 40.7% physicians. Initiation of insulin early in the course of T2DM was recommended by 58.7% of physicians in cases where glycemic goals were not achieved by non-insulin drugs. Premix insulin analogues were preferred over human premix insulins by more than half of participating physicians (52.2%). Premix insulin analogues were preferred over basal insulins by 49.8% of physicians. Nearly half (44.5%) of the physicians recommended initiation of twice daily premix analogues over once daily basal insulins to achieve recommended glycemic targets. Around forty two percent (41.9%) physicians strongly believed that twice daily/thrice daily premix insulin analogues provide comparable glycemic control and safety to basal plus regimen with additional benefit of simplicity. During Ramadan premix insulin analogues were recommended over human premix by 46.5% physicians in view of improved safety and flexibility of dosing.

Summary: Majority of Indian physicians concur with the recommendations of INCG 2017 guidelines. Premix insulins were preferred for insulin initiation. IDegAsp was preferred over other premix insulins by majority of physicians. Twice daily premix insulins were recommended for intensification.

Introduction

Diabetes is a chronic disease and a growing challenge around the world including India. According to International Federation of Diabetes (IDF), approximately 9% of adults were estimated to have diabetes worldwide.1 Nearly 80% of the total adult patients with diabetes are from low- or middle-income countries.2 India is the second largest country with adult diabetic population of 72.9 million and reported approximately one million deaths due to diabetes in the year 2017. It is further predicted that the number of adults with diabetes will increase to more than 640 million by 2040.1

Type 2 diabetes mellitus (T2DM) is a metabolic disorder characterized by decline in β cell function, and optimization of glycemic control is the key factor in management of T2DM. By the time of diagnosis of T2DM, 50% of beta cells are already non-functional in majority of the cases.3 The Diabcare India 2011 study has shown that majority of patients with diabetes remain sub-optimally controlled and only around 19.7% of people with type 2 diabetes have a good glycemic control in India. The average HbA1c of T2DM patients in India is almost 2% higher than the ADA recommended target.7 T2DM is associated with a 2 to 3-fold increase in cardiovascular disease. Specific diabetic complications like renal failure, blindness and amputations in these patients can decrease the quality of life and substantially reduce the life expectancy.3,5

At diagnosis and in the initial phase, lifestyle modifications are recommended with metformin generally prescribed as monotherapy. Later on, when lifestyle changes and monotherapy fail to control blood glucose, the current practice is to progress to a combination of oral therapies in an effort to achieve the glycemic target.6 As the disease progresses, oral combination therapy may not be effective to maintain glucose control and triple oral therapy or insulin may be needed. As monotherapy, most diabetes medications can reduce HbA1c levels by 0.5 - 2.0%, except insulin, which can reduce HbA1c by more than 3%.7 Among all the treatment options available, Insulins provide...
the maximum reduction in HbA1c followed by lifestyle modifications, sulfonylureas and metformin.8,9

Premix insulins are combination of basal and rapid acting insulin preparations, facilitating management of both fasting and postprandial hyperglycemia. Premix insulin formulations available in Indian markets are: conventional premix formulations (Biphasic Human Insulin (BHI) 30/70, 50/50), analogue premix formulations (Lispro 25/75, Lispro 50/50, BIAsp 50/50, BIAsp 30/70) and insulin co-formulation (IDegAsp 30/70).10 A recent retrospective survey-based study, evidenced higher usage of premix insulin (68.5%) in Indian patients.11

Indian National Consensus Group (INCG) considered premix insulin as a realistic treatment choice in all stages of diabetes. Subsequently, INCG published national evidence-based consensus guidelines in 2009 for initiation and intensification of premix insulin therapy in India, which were later updated in 2014 and 2017 (Table1).10,12,13 American Diabetes Association (ADA) recognised the importance of premix insulin in its recently published “Clinical Practice Recommendations-ADA 2019”.6

Despite evidence supporting the early initiation of insulin to achieve optimal glycemic control, substantial proportion of patients do not achieve glycemic targets as they fail to intensify insulin therapy. Many patients and physicians are reluctant to begin insulin therapy due to weight gain, hypoglycemia and changes in lifestyle. Although several guidelines have been published for the management of T2DM, due to the non-applicability of these guidelines in Indian scenario, they cannot be widely used in Indian clinical practice. The present survey aims to provide specific recommendations based on published data for appropriate management of T2DM.

### Methods

This was a prospective online validation survey in which the respondents were requested to go through the published premix insulin analogues during the study. The respondents were requested to answer the electronic survey based on their clinical experiences with patients having diabetes.

### Study sample

A total of 1675 certified physicians all over India were approached purposely through email as respondents. Out of all the physicians contacted, 1408 participated in the study. Physicians carefully read the consent form, signed it and then after reading the India specific guidelines, provided their feedback in the survey questionnaire.

### Questionnaire

The present survey was conducted to facilitate and draw the attention of physicians towards optimal positioning of insulin therapies in routine care of T2DM. The questionnaire consisted of 40 questions; the first 10 questions were general statements about satisfaction level of patients and physicians as reported by physicians themselves. Rest of the 30 questions were based on 2017 INCG guidelines. The 2017 INCG guidelines are divided into seven models which are 1) initiation of premix insulin at diagnosis, 2) initiation of once daily premix insulins/co-formulations, 3) initiation of twice daily premix insulins/co-formulations, 4) intensification with twice/thrice daily premix insulins/co-formulations, 5) premix insulins in gestational diabetes mellitus (GDM), 6) premix insulins in T1DM and 7) premix insulins during Ramadan.

### Statistical analysis

The survey results were stratified on basis of Indian premix consensus published in 2017. Continuous variables were summarized with the descriptive statistics n (number of observations), mean and standard deviation, median, minimum and maximum values. Categorical data was summarized through numbers and percentages. All

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**Table 1: Premix insulin initiation and intensification – National guidelines**

<table>
<thead>
<tr>
<th>Initiative</th>
<th>INCG 2009</th>
<th>INCG 2013</th>
<th>INCG 2017</th>
</tr>
</thead>
<tbody>
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<td>Initiation</td>
<td>Premix insulin 10 U OD either in the morning (AM) or in the night (PM);</td>
<td>If after 3 months OAD treatment</td>
<td>Premix insulin analogues to be preferred over basal insulins (10 U pre-breakfast or pre-dinner).</td>
</tr>
<tr>
<td></td>
<td>Titrated BiAsp 30 OD or BID to achieve FPG &lt;110 mg/dL</td>
<td></td>
<td>IDegAsp to be preferred over premix insulin analogues</td>
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<tr>
<td></td>
<td>Night (PM) or morning (AM) dose needs to be titrated based upon pre-breakfast or pre-dinner blood glucose</td>
<td>If premix insulin OD failed to achieve HbA1c &lt;7 and had PPG excursions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intensify to BID premix analogues. Split the once daily dose into equal breakfast and dinner doses</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>When intensifying from BID to TID consider adding 2-6 U or 10% of total daily premix insulin dose before lunch which may require down titration of morning dose (2 to 4 U)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Twice daily IDegAsp can be recommended over premix analogues in view of superior fasting glucose control and lower risk of major and nocturnal hypoglycemia</td>
</tr>
<tr>
<td>Intensification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intensification</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GDM</td>
<td>Premixed insulin dose to be considered over premixed human insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premixed insulin dose to be adjusted on an individual basis</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Premixed insulin analogues to be considered over premixed human insulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BiAsp can be initiated at 6 U OD before breakfast and titrated to achieve FPG 90-120 mg/dL and mean plasma glucose not less than 86 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>BID BiAsp can be considered based on individual requirements.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

BiAsp=Biphasic insulin aspart; BID=Twice daily; BHI=Biphasic human insulin; BMI=Body mass index; HbA1c=Acetylated haemoglobin; IDegAsp=Insulin Degludec/insulin Aspart; OAD=Oral anti diabetics; GDM=Gestational Diabetes mellitus
enrolled physicians were considered for the analysis and summary reports.

The percentage of physicians, who were strongly in agreement with premix insulin consensus 2017, were analysed by calculating the percentage of response category of ≥8 from 1 to 10.

**Results**

Majority of physicians preferred a premix insulin regimen for initiation. Nearly 26.37% physicians preferred a twice daily insulin regimen and 18.18% preferred once daily insulin regimen (Table 2). The most common reasons for delay in insulin treatment were fear of injection followed by lack of appreciation of insulin therapy and patient’s embarrassment in injecting themselves in public (Table 3).

Table 4 summarizes the general information taken by physicians from patients. Nearly 85% of patients agreed to initiate the suggested therapy in less than 20 minutes of interaction with physicians. Most patients were successful in taking premix basal/or bolus insulin as prescribed (96.3%), exercising regularly (85.7%) and testing blood glucose levels as recommended (85.2%). However, only 57% patients were able to manage their weight. More than 90% of patients were satisfied with the overall insulin treatment (97.6%), safety of insulin treatment with respect to hypoglycemic events (93.9%), simplicity of insulin treatments (97.2%) and ability to control blood glucose levels (97.5%).

**Table 2: Summary of proportion of patients falling in different profiles during the survey period Overall (N = 1408)**

<table>
<thead>
<tr>
<th>Profile/statistic</th>
<th>Responses</th>
<th>Proportion of patients who fall into the below profiles as per to the physicians</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initiation at diagnosis</td>
<td>1293</td>
<td>12.90%</td>
</tr>
<tr>
<td>Initiation once daily</td>
<td>1332</td>
<td>18.18%</td>
</tr>
<tr>
<td>Initiation twice daily</td>
<td>1369</td>
<td>26.37%</td>
</tr>
<tr>
<td>Intensification with twice daily</td>
<td>1326</td>
<td>17.16%</td>
</tr>
<tr>
<td>Intensification with thrice daily</td>
<td>1211</td>
<td>6.67%</td>
</tr>
<tr>
<td>Premix insulin during Ramadan</td>
<td>1186</td>
<td>5.94%</td>
</tr>
<tr>
<td>Premix insulin use in Type 1 DM</td>
<td>1197</td>
<td>6.59%</td>
</tr>
<tr>
<td>Premix insulin use during pregnancy</td>
<td>1198</td>
<td>6.18%</td>
</tr>
</tbody>
</table>

**Table 3: Summary of most common reasons for delay in Insulin Treatment**

<table>
<thead>
<tr>
<th>Category, n (%)</th>
<th>Rank 1</th>
<th>Rank 2</th>
<th>Rank 3</th>
<th>Rank 4</th>
<th>Rank 5</th>
<th>Mean Rank</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients feel embarrassed injecting</td>
<td>198(14.06%)</td>
<td>343(24.36%)</td>
<td>385(27.34%)</td>
<td>297(21.09%)</td>
<td>185(13.14%)</td>
<td>3.05</td>
</tr>
<tr>
<td>Fear of weight gain</td>
<td>62 (4.40%)</td>
<td>131(9.30%)</td>
<td>153(10.87%)</td>
<td>435(30.89%)</td>
<td>627(44.53%)</td>
<td>1.98</td>
</tr>
<tr>
<td>Fear of Injection</td>
<td>908(64.49%)</td>
<td>244(17.33%)</td>
<td>145(10.30%)</td>
<td>61(4.33%)</td>
<td>50 (3.55%)</td>
<td>4.35</td>
</tr>
<tr>
<td>Lack of appreciation of insulin therapy in diabetes</td>
<td>162(11.51%)</td>
<td>414(29.40%)</td>
<td>379(26.92%)</td>
<td>249(17.68%)</td>
<td>204(14.49%)</td>
<td>3.06</td>
</tr>
<tr>
<td>Fear of hypoglycemia</td>
<td>78 (5.54%)</td>
<td>276(19.60%)</td>
<td>346(24.57%)</td>
<td>366(25.99%)</td>
<td>342(24.29%)</td>
<td>2.56</td>
</tr>
</tbody>
</table>

**Note**: Percentages were calculated using the non-missing count as denominator.

**General Note**: The most common reasons: Patients felt embarrassed injecting themselves in public, Fear of weight gain, Fear of Injection, Lack of appreciation of insulin therapy in diabetes, Fear of hypoglycaemia were rated from 1 to 5 for delay in treatment.

Mean rank was computed as below:

The actual ranks i.e. 1, 2, 3, 4, 5 were reversed in the opposite direction. The actual ranks were scored as rank 1 as 5, rank 2 as 4, rank 3 as 3, rank 4 as 2, rank 1 as 5. On the basis of the scores given mean rank was computed.

When asked to the physicians, when they would prefer using Degludec/Aspart (IDegAsp), 61.5% responded that it can be used at initiation as well as intensification. Occurrence of hypoglycemic events (98.9%) and maintaining HbA1c (97.8%) were the major concerns of physicians during the treatment of T2DM. In this survey the data supported that more than ninety percent of physicians (98.01%) were concerned about the experience of major or nocturnal hypoglycemic event. More than half (53%) of physicians considered premix insulin as substitute to basal plus therapy.

The percentage of physicians, who strongly agreed with premix insulin INCG consensus 2017 is in presented in Figures 1 and 2.

**Premix Insulin Initiation at Diagnosis (Consensus 1)**

Short-term therapy with premix insulins in insulin-naïve T2DM patients with symptomatic hyperglycemia and/or glucotoxicity was strongly recommended by 40.7% physicians. Premix insulin analogues were preferred...
was preferred over premix insulin analogues by 47.4% physicians.

**Once Daily Premix Insulins/Co-Formulations for Initiation (Consensus 2)**

Initiation of insulin early in the course of T2DM was recommended by 58.7% of physicians in cases where glycemic goals were not achieved by non-insulin drugs. Premix insulin analogues were preferred over basal insulins by 49.8% of physicians. In patients with higher PPG levels, IDegAsp was preferred over premix insulin analogues and basal insulins by many physicians (42.3%) for initiation of insulin therapy (10 U pre-breakfast or pre-dinner). 41.1% physicians recommended to titrate the insulin dose once or twice a week based on pre-meal value and recommended dose modification based on the lowest/mean value of the 3 most recent values.

**Twice/thrice Daily Premix Insulins/Co-Formulations for Initiation (Consensus 3)**

Nearly half (44.5%) of the physicians recommended initiation of twice daily premix analogues over once daily basal insulins to achieve recommended glycemic targets. Twice daily IDegAsp was recommended over premix insulins in view of lower risk of hypoglycemia and superior fasting glucose control by 48.8% physicians. A 6 units twice daily dosage was preferred for initiation by 38.1% physicians. Once/twice weekly dose titration schedule was recommended by 38.8% physicians using premeal value.

**Twice/thrice Daily Premix Insulins/Co-Formulations for Intensification (Consensus 4)**

Around forty two percent (41.9%) physicians strongly believed that twice daily/thrice daily premix insulin analogues provide comparable glycemic control and safety to basal plus regimen with additional benefit of simplicity. For intensification of premix insulin analogue regimen from once daily to twice daily, 37.2% physicians recommended to split once daily dose into equal breakfast and dinner doses for further titration. Intensification of premix analogue from twice daily to thrice daily was recommended by 37.4% physicians through addition of 2-6 U or 10% of total daily premix insulin dose before lunch. Thrice daily premix insulin analogue regimen and twice daily IDegAsp regimen were considered comparable with basal bolus by 35.7% and 43.1% physicians, respectively. Almost half of participating physicians

---

**Table 4: Summary of general information taken by physician from patients**

<table>
<thead>
<tr>
<th>Category, ( n (%) )</th>
<th>Overall (( N=1408 ))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average time spent to motivate patients to initiate insulin therapy with premix insulins</td>
<td></td>
</tr>
<tr>
<td>&lt;5 min</td>
<td>76 (5.4%)</td>
</tr>
<tr>
<td>5-10 min</td>
<td>601 (42.68%)</td>
</tr>
<tr>
<td>10-20 min</td>
<td>515 (36.58%)</td>
</tr>
<tr>
<td>20-30 min</td>
<td>171 (12.14%)</td>
</tr>
<tr>
<td>&gt;30 min</td>
<td>45 (3.20%)</td>
</tr>
<tr>
<td>Percentage of patients successful in different actions</td>
<td></td>
</tr>
<tr>
<td>Exercising regularly</td>
<td>1207 (87.72%)</td>
</tr>
<tr>
<td>Taking premix/basal or bolus insulin as prescribed</td>
<td>1336 (96.31%)</td>
</tr>
<tr>
<td>Adjusting insulin doses</td>
<td>1123 (79.75%)</td>
</tr>
<tr>
<td>Managing weights</td>
<td>804 (57.11%)</td>
</tr>
<tr>
<td>Testing blood glucose level as recommended</td>
<td>1199 (85.16%)</td>
</tr>
<tr>
<td>Percentage of patients satisfied with different insulin treatment options available today</td>
<td></td>
</tr>
<tr>
<td>Insulin treatment overall</td>
<td>1374 (97.59%)</td>
</tr>
<tr>
<td>Safety of insulin treatments in respect to hypoglycaemic events</td>
<td>1322 (93.89%)</td>
</tr>
<tr>
<td>Simplicity of insulin treatments</td>
<td>1340 (97.17%)</td>
</tr>
<tr>
<td>Ability to control blood glucose level</td>
<td>1379 (97.94%)</td>
</tr>
<tr>
<td>Control of blood glucose levels without increasing the risk of hypoglycaemia</td>
<td>1307 (92.38%)</td>
</tr>
<tr>
<td>Concern about patients experiencing a major or nocturnal hypoglycaemic event</td>
<td>1380 (98.01)</td>
</tr>
<tr>
<td>View of Physicians regarding insulin treatments</td>
<td></td>
</tr>
<tr>
<td>Primary focus on maintaining the majority of patients HbA1c levels</td>
<td>1377 (97.8%)</td>
</tr>
<tr>
<td>Primary focus on helping the majority of patients avoid hypoglycaemic events</td>
<td>1392 (98.86%)</td>
</tr>
<tr>
<td>Preference of using new premix co-formulation (Insulin Degludec/Aspart)</td>
<td></td>
</tr>
<tr>
<td>Initiation</td>
<td>221 (15.70%)</td>
</tr>
<tr>
<td>Intensification</td>
<td>289 (20.53%)</td>
</tr>
<tr>
<td>Both</td>
<td>866 (61.51%)</td>
</tr>
<tr>
<td>None of the above</td>
<td>32 (2.27%)</td>
</tr>
<tr>
<td>View of physician on premix insulin as substitute of other therapy as initiation</td>
<td></td>
</tr>
<tr>
<td>Basal only therapy</td>
<td>223 (15.84%)</td>
</tr>
<tr>
<td>Basal plus</td>
<td>745 (52.91%)</td>
</tr>
<tr>
<td>Human premix</td>
<td>214 (15.20%)</td>
</tr>
<tr>
<td>Other premix analog</td>
<td>175 (12.43%)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>51 (3.62%)</td>
</tr>
<tr>
<td>View of physician on premix insulin as substitute of other therapy at intensification</td>
<td></td>
</tr>
<tr>
<td>Basal</td>
<td>395 (28.05%)</td>
</tr>
<tr>
<td>Premix</td>
<td>473 (33.59%)</td>
</tr>
<tr>
<td>Basal bolus</td>
<td>459 (32.60%)</td>
</tr>
<tr>
<td>Not applicable</td>
<td>81 (5.75%)</td>
</tr>
</tbody>
</table>

Note: Percentages were calculated using the non-missing count as denominator.
(49.6%) strongly recommended twice daily IDegAsp over premix insulin analogues in view of superior fasting glucose control and lower risk of major and nocturnal hypoglycemia. However, 44.8% physicians recommended twice daily IDegAsp over premix analogues in cases where basal insulin analogues were inadequate for superior fasting glucose control. As per 42.6% physicians, recommended target for titration is pre-meal value of 80-130 mg/dL.

Premix Insulins in Gestational Diabetes (Consensus 5)

A strong agreement was reported by 31.7% of physicians for recommending premix analogues in GDM patients with high fasting plasma glucose values. A majority of participating physicians strongly believed that premix insulin analogues are generally more effective than human premix insulins in lowering postprandial glucose levels (38.9%) and overall safety and efficacy profiles were comparable to those of human premix insulin (41.3%). In GDM subjects, BIAsp was recommended for initiation at 6 U once daily before breakfast and titrated to achieve fasting blood glucose of 90-120 mg/dL and mean plasma glucose not less than 86 mg/dL by 34.6% physicians.

Premix Insulins in T1DM (Consensus 6)

For T1DM, 42.2% physicians strongly agreed that in patients with age more than 18 years where basal bolus is not feasible, biphasic insulin analogues are preferred over human premix insulins in view of their safety profile. Additionally, 38.1% physicians agreed that IDegAsp based regimen provides similar efficacy as compared to basal bolus therapy.

Premix Insulins during Ramadan (Consensus 7)

During Ramadan premix insulin analogues were recommended over human premix by 46.5% physicians in view of improved safety and flexibility of dosing. 42.1% physicians recommended once daily dose of premix insulins/co-formulations, to be administered at the time of breaking the fast and 42.3% physicians recommended twice daily premix insulin/co-formulations at usual pre-dinner dose at night meal with reduction in morning dose to 25-50%.

Discussion

Patients with T2DM report a progressive decline in the production of endogenous insulin from pancreatic β cells and they eventually need insulin therapy. However, initiating insulin at an early stage in course of diabetes is quite challenging for the physicians. Moreover, persons with diabetes are often worried about their condition and require continuous counselling from their treating physician. Linetzky et al reported a direct association between inadequate physician’s attention with poor insulin adherence and insufficient glycemic control in diabetic patients. Similarly, a higher score in patient-physician interaction domain was reported to be significantly associated with lower HbA1c values. Other factors like number of oral hypoglycemic agents used and type of insulin regimen taken also influence the glycemic control. Our study reported that a large patient population accepted insulin treatment within 20 minutes of discussion with the physician.

Short term intensive insulin therapy for newly diagnosed T2DM patients was reported beneficial in delaying disease progression. Additionally, the non-inferiority of coformulation insulin to BIAsp 30 was reported in many clinical trials. With coformulation insulins, there was a higher fasting plasma glucose reduction, lower total daily dose requirement and lower rates of overall confirmed, severe and nocturnal confirmed hypoglycemia. Multinational consensus published in 2018, recommends IDegAsp for initiation of insulin in drug-naive patients with symptoms of hyperglycemia, high carbohydrate diet, high HbA1c and high postprandial excursions. Similarly, in this survey, majority of participated physicians preferred coformulation IDegAsp over other premix insulin analogues and recommend IDegAsp for initiation and intensification of insulin treatment regimen. This survey depicts the percentage of physicians in agreement with the consensus statements of 2017 INCG guidelines for the use of premix insulins.

For initiation of insulin, multinational consensus recommends IDegAsp to insulin-naive patients with inadequate response to metformin, dual or triple oral therapy. Dose recommendations are, once daily or twice daily, depending on glycemic index, meal pattern and quantity. A starting daily dose of 10U or 0.1-0.2 U/Kg/Day is recommended, which may be adjusted with severity of hypoglycemia, weight of patient and meal patterns. The dose adjustment is recommended with 2-0-2 algorithm, addition of 2 U in case target fasting plasma glucose or post prandial glucose level is not achieved and reduction of 2 U in case of hypoglycaemia. In concordance with the above guidelines, in our survey majority of the physicians recommended premix insulins in patients with inadequate glycemic control with oral anti diabetics. Majority of the physicians preferred IDegAsp over premix insulin analogues for achieving recommended glycemic target at starting dose of 10 U. Dose titration was performed once/twice a week and was based on premeal plasma glucose value and dose modification was based on lower or mean value of premeal plasma glucose.

In T2DM patients, requiring basal plus therapy or basal bolus therapy for achieving their glycemic goals, premix insulin therapy was more convenient and equally advantageous regarding safety and efficacy. ADA recommends switching to twice daily premix insulin, if HbA1c is not controlled using basal insulin dose of 10U or 0.1-0.2 U/Kg/Day. The recommended starting dose is 2/3rd in the morning, 1/3rd in the evening for human insulins and two equal halves in morning and evening for analogue insulins. Dose calculation is based on the current basal dose with dose adjustment by 1-2 U or 10-15% once or twice weekly until glycemic targets are achieved. However, in present survey twice daily IDegAsp was recommended over premix in view of lower risk of hypoglycemia at a twice daily dose of 6U. Titration of dose is recommended once/twice weekly based on premeal value.

In GDM patients premix insulins provide a good treatment regimen with mealtime flexibility. Premix insulins BHI 30 and BIAsp 30 were reported to provide adequate glycemic control with fewer injections and reported safe in GDM patients. Our survey also evidenced preference of premix insulin and premix insulin analogues
over human insulins in GDM with view of flexibility of regimen.

Similar to T2DM, IDegAsp was reported to provide glycemic controls comparable to basal bolus therapy in T1DM patients.24 In multinational consensus IDegAsp is recommended in T1DM patients as Asp-Asp-IDegAsp regimen.25 In our survey many physicians strongly agreed that in patients with age more than 18 years where basal bolus is not feasible, biphasic insulin analogues can be preferred over human premix insulins in view of their safety profile.

Premix analogues are recommended in Ramdan owing to its flexibility with required modifications in the present survey. Treatment of patients with diabetes during long fasts requires a modification of insulin dose. In some patients, a larger insulin dose may be needed after a large evening meal.25 In multinational consensus, IDegAsp twice daily dose was recommended with usual pre-dinner dose at night and reduced morning dose by 25-50%.20

Conclusion

Majority of Indian physicians concur with the recommendations of INCG 2017 guidelines. Premix insulins were preferred for insulin initiation. IDegAsp was preferred over other premix insulins by majority of physicians. Twice daily premix insulins were recommended for intensification. The most common reasons for delay in insulin treatment were fear of injection followed by lack of appreciation of insulin therapy and patient’s embarrassment in injecting themselves in public. A lot needs to be done on educating the public on insulin use and training the physicians for adequate glycemic control without compromising the safety of patients. The strength of this survey is inclusion of large population and diverse geographical area. The limitations of this study are absence of respective patient’s questionnaires.

Acknowledgement

The authors thank Novo Nordisk India Pvt. Ltd. for supporting the conduct of the survey.

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Study of Beneficial Impact on Specific Biomarkers in Type 2 Diabetes During Ramadan Fasting (Unintentional Intermittent Fasting)

Rajiv Kovil1, Nida Shaikh2*

Abstract

Background: Fasting during the holy month of Ramadan is observed by Muslims worldwide as it accounts for one of the five pillars of the religion Islam. We speculate the fasts observed during the month of Ramadan to be unintentional intermittent fasts, which may have health benefits.

Objective: The study was attempted to know the alterations in biomarkers viz. body weight (BW), body mass index (BMI), serum glycated haemoglobin (HbA1c), systolic and diastolic blood pressure (SBP and DBP) due to Ramadan IF on type 2 diabetes (T2D) patients of western India.

Methods: A total 50 patients of T2D were selected for above-mentioned biomarkers assessment immediately before the starting of fast followed by after 45 days.

Results: The present results indicated the beneficial impact on intermittent fasting among patients (baseline versus followed up) by detecting the alterations of above-mentioned biomarkers. In overall results (n=50), the BW (Kg) and BMI (Kg/m²) values were significantly (P<0.001) decreased in followed-up patients (76.06 ± 15.41 and 27.45 ± 5.06) when compared to baseline value (77.26 ± 15.53 and 27.90 ± 5.11) while the level of HbA1c (mmol/mol) was also significantly (P<0.05) decreased in followed-up patients (7.62 ± 0.99) when compared to baseline value (7.90 ± 1.24). But no significant changes in the values of SBP and DBP were observed.

Conclusions: In conclusion, this observational study revealed the reduction of body weight, BMI and serum HbA1c levels probably due to IF for the T2D patients during the holy month of Ramadan. Moreover, the IF can be utilized as a therapy along with other pharmacological therapies. It is suggested future research work with other important biomarkers, which can be easier for T2D therapy.

Background

In the Ramadan fasting, healthy adult Muslims must fast from dawn to sunset during the holy month of Ramadan. The people restrict fluid intake, cigarette smoking, and medications. Ramadan fasting is a common form of time-restricted feeding as Intermittent Fasting (IF). It encompasses a major shift from normal eating patterns to exclusive night eating. This religious practice leads to health benefit and causes normal functioning of several biomarkers.1,9,10,14

The people restrict to calorific or low energy diet, specific food types, etc.26

In general, religious fasting depends upon continuous and intermittent and sometimes duration can vary from 1 to 200 days in which researchers observed the positive and negative health impacts 4,9,10,14,15,21,26,29,31,32 Several research work have been revealed that the religious fasting has beneficial effects on body weight and glycemia, cardiometabolic risk markers, etc.1,9,17,23,24,27

Among several intermittent fasting, the Ramadan fasting duration is for 30 days, which revealed beneficial impacts on several biomarkers. In earlier studies it was observed a significant weight reduction due to Ramadan fasting.28 It was also found a decreasing level of blood sugar, total cholesterol and other inflammatory markers viz. C-reactive protein, interleukin-6 and tumour necrosis factor-α, HbA1c, etc. due to Ramadan fasting.2,11,17,18,25,35

Among different glycaemic disorders, type 2 diabetes (T2D) is a well-known chronic disease, which is related to the epidemic of obesity that needs long-term medical therapy to prevent the development of its wide range of micro and macrovascular as well as neuropathic complications. These complications arise from the combination of resistance to insulin action, lower insulin secretion, and excessive or lower glucagon secretion.12 On the other hand, it was reported by Salti et al.29 that during the periods of fasting the risk factors in diabetics causing hypoglycaemia (sudden blood sugar lowering) and hyperglycaemia (sudden blood sugar increasing). It was suggested that people with diabetes who require insulin therapy are advised not to fast or who can fast appropriately monitor and adjust insulin delivery with the help of medical practitioner.27

Another therapy is well-established that patients with T2D treated with biguanides or sulfonylureas who were stable and did not show complication in progressive comorbid pathology.16,29 Khalil et al. mentioned that insulin delivery should be rescheduled as per change in meal timing during fasting in Ramadan. Studies have shown that fasting blood sugar and postprandial (after a meal) blood sugar is decreased.
among T2D patients during Ramadan. Overall glycaemic control appears to be improved during Ramadan.3,27,33

It was observed that major researchers have been found effect on individual biomarker or multiple markers such as body weight by using body mass index (BMI as Kg/m²) and glycaemic parameters such as fasting blood sugar (FBS as mg/dl) and/or post prandial sugar (PPS as mg/dl), glycated haemoglobin (HbA1c as mmol/mol), cardiometabolic risk markers as systolic blood pressure (SBP) and diastolic blood pressure (DBP) as mm/Hg, etc.1,9,17,23,24,27 but comparative study between BMI, HbA1c, SBP and DBP during the religious fasting of baseline versus follow-up in the patients of western India are lacking.

Objectives
The present study was attempted to detect the changes in biomarkers with special reference to body weight (Kg), BMI (Kg/m²), serum HbA1c (mmol/mol), SBP and DBP (mm/Hg) due to intermittent fasting during Ramadan on T2D patients of western India.

Methods
Recruitment of patients
Consecutive patients were enrolled when they visited for pre-Ramadan counselling. A total of 50 patients of age groups (21-80years) were selected of which 25 were males and 25 were females. All the patients were studied in Dr. Kovil’s Diabetes care Centre (Preventive Diabetes Centre and Diabetic Foot Clinic, Mumbai, India) during the study period of 45 days.

Inclusion criteria
In present work, the patients were enrolled fulfilling the inclusion criteria such as Type 2 DM, age less than 80 years, observing Ramadan Fasts.

Exclusion criteria
In the present study, the exclusion criteria were Chronic kidney disease (CKD), Type 1 DM, pregnant women, patients on multiple dose of insulin and >80 years of age.

Study design
A total 50 patients were recruited for the prospective observational study. All patients were subjected to detailed history followed by general and systematic examination. The patients were categorized into insulin taking group (n=15) and non-insulin taking group (n=35), and sulfonylurea (Su) treated group (n=30) non-sulfonylurea (non-Su) (DPP4 & Sglt2) treated groups (n=20). All the patients were selected for a baseline parameters body weight (Kg), BMI (Kg/m²), HbA1c (mmol/mol), SBP (mm/Hg) and DBP (mm/Hg) were estimated immediately before the starting of fast followed by after 45 days.

During the therapy as a part of Ramadan regime
All patients kept on background metformin therapy. Patients on insulin for once a day – insulin regime was kept at bedtime or pre-dinner. Patients on insulin twice a day – insulin regime was kept as 2/3rd in the evening and 1/3rd in the morning. Patients on sulfonylurea (Su) twice a day - the dose was reduced to 1/2 for morning and same (regular) dose for night. Patients on Sus once a day – morning dose shifted to before dinner. Patients on Dpp4 and Sglt2 – dose remained the same.

Biomarkers assessment
All patients were assessed for biomarkers 10 days before observing Ramadan fasts and 1 week after the month of Ramadan as end of study assessment (followed up). The parameter body weight or BW (Kg) was measured using ultrasonic body weight analyser in baseline and followed up patients. A Body Mass Index, or BMI, is a measurement was used to detect height and weight of a patient. The BMI was calculated by using formula as per CDC (26) for baseline as well as followed up patients. The estimation of HbA1c (mmol/mol) was done using ALERE AFFINIONTM which is a test based on spectral reflectance. The assay used here is boronate affinity. This parameter was estimated for baseline compared to followed up patients. The blood pressure was measured by using sphygmomanometer to detect SBP (mm/Hg) and DBP (mm/Hg) of studied patients for baseline compared to followed up.

Statistical analysis
The statistical analyses were done by using software (SPSS, version 20). The comparisons were expressed as number of patients and percentage of patients. All the variables were expressed as Mean ± Standard Deviation (M ± SD) and compared across the 2 groups Mann Whitney test and p value is <0.05 was considered as significant.

Results
The present results evaluated the impact on IF among patients (baseline versus followed up) of T2D by detecting the alterations of several biomarkers such as BMI (Kg/m²), serum HbA1c (mmol/mol), SBP and DBP (mm/Hg). In the gender distributions of patients, males 25 nos. (50.0%) and females 25 nos. (50.0%) were observed.

Among 50 patients of T2D, the BW (Kg) was significantly (P<0.001) decreased in the patients of followed up (76.06±15.41) when compared to baseline value (77.26±5.06) (Fig 1A). Among 50 patients of T2D, the BMI (Kg/m²) was decreased at a significant level (P<0.001) in the patients of followed up (27.45±5.06) when compared to baseline value (27.90±5.11) (Figure 1B). In case of serum biomarker as HbA1c (mmol/mol), in the patients of T2D, the level of HbA1c was significantly (P<0.05) slightly decreased in the patients of followed up (7.62±0.99) when compared to baseline value (7.90±1.24) (Figure 2).
In case of cardiac biomarker as SBP and DBP (mm/Hg), in the patients of T2D, the value of SBP and DBP did not show any change in the patients of followed up (121 and 80) when compared to baseline value (121 and 80) (Figure 3).

Table 1 describes the results for the patients of T2D on insulin therapy group and non-insulin therapy group in IF. For both baseline and followed-up BW (Kg), BMI (Kg/m²) and the level of HbA1c (mmol/mol) non-insulin therapy values were decreased without significant change when compared to insulin therapy values. The change in weight, BMI and HbA1c values did not observe any significant differences when compared to non-insulin and insulin in baseline and followed up groups.

Table 2 evaluates the results for the patients of T2D as non-sulfonylurea treated group (DPPIV and SGLT2) and Sulfonylurea treated group in IF. In case of baseline and followed-up BW (Kg) as well as BMI (Kg/m²), non-sus group values were decreased without significant change when compared to Sus group values. The baseline data for the level of HbA1c, it observed a decreasing trend at a significant level of P<0.005 for non-sus group value (7.33±1.27) when compared to Sus group value (8.27±1.09) while in the followed up data for HbA1c level, non-sus group value (7.18±0.85) was also decreased significantly (P<0.008) in comparison with sus group value (7.92±0.97). The change in weight and BMI values were observed a significant change at a level of P<0.001 when compared between non-sus group and Sus group. Change HbA1c value did not show any significant differences whether the patients were on sus or non-sus drug therapy when compared between non-sus and Sus of baseline and followed up groups separately.

**Discussion**

The present results clearly indicated the beneficial impact on IF of T2D patients. These important biomarkers such as BW, BMI and serum Hb1Ac level were significantly decreased (P<0.001 and P<0.05) in the followed-up patients in comparison with baseline value among the patients of T2D. But, cardiological parameters such as SBP and DBP were not varied between baseline and followed-up patients.

Generally, IF revealed low calorie restriction due to gap of 16:8 hrs diet intake. According to several researchers the IF is closely related for the improvement of cardiovascular and cerebrovascular functions, etc. 20,21,34 It was also known that reduced weight, waist circumference, HbA1c, etc. and risk of T2D due to the IF reported by many researchers. 3,21,30,34 The present
results for BW, similar observations were obtained that in the age groups of 18 to 58 years in which IF in Ramadan found statistically significant weight loss.17,18 Hypoglycaemia is a common disease and can easily be known by the occurrence of systolic blood pressure (SBP) in the amount of 140 mmHg and more, or diastolic blood pressure (DBP) of 90 mmHg or more. The present results revealed as such no changes in the cardiovascular markers in intermittent fasting of the T2D patients.6,34

The patients who are not using a SUS or insulin, the risk is lower for hypoglycaemia and it is not recommended additional glucose monitoring during fasting. In patients on a sulfonylurea or insulin (either alone or in combination with any other antidiabetic medication), the risk factor alone or in combination with any other antidiabetic medication), the risk factor about hypoglycaemia in intermittent antidiabetic medicines should be careful compared to patients on insulin therapy augmented by continuous glucose monitoring: An observational real-life study. Journal of The Association of Physicians of India ■ Vol. 68 ■ June 2020

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Conclusion
It is concluded from the present observational study that the overall reduction of body weight, BMI and serum HbA1c levels due to intermittent fasting (IF) during the holy month of Ramadan for the T2D patients is a suitable achievement in Western India. The present study observed significant reduction in weight, BMI and HbA1c values in patients on Non-Sulfonylurea (DPP4IV and SGLT2) drug therapy compared to patients on insulin therapy as well as Sulfonylurea therapy where there was non-significant reduction in weight, BMI and HbA1c values. Moreover, the T2D patients are under antidiabetic medicines should be careful about hypoglycaemia in intermittent fasting. It is suggested future research work with other important biomarkers, which can be easier for T2D therapy.
Observation on Treatment of Drug Resistant Kala-azar Patients with Fungizone in Patna, Bihar

CP Thakur¹, Kanisk Sinha²

Abstract

54 cases of drug resistant kala-azar patients, some cases were resistant to sodium stibogluconate, some to even single dose of ambisome and some to miltefosine came to us for treatment. All necessary investigations were done and splenic aspirations were positive for LD bodies. All these patients were treated with Fungizone at a dose of 1mg/kg body wt diluted with 5% glucose and given slowly in 4 hours. On the day 21st splenic aspiration was done and other necessary investigations were repeated. LD body was not found in any splenic aspirate except one case with HIV. Initially all the patients were divided into two groups, one group was fed adequate milk during their course of treatment and other group adequate amount of fish in their diet. The patients in both the groups were compared in the end. There was no difference between two groups regarding parasitological clearance. All the patients had parasitological cure except one patient with HIV. The weight of the patients improved in both groups. The patient with HIV needed 3 courses of anti kala-azar drug to become negative for parasites of kala-azar i.e LD body. That cases was given treatment for HIV also. The moment he became negative of kala-azar, he fled away.

Material and Method

54 patients of kala-azar who relapsed after treatment given in the different hospitals in Bihar came to us for treatment between 2015 and 2019.

36 such cases in 2015, 11 cases in 2016, 2 cases in 2017, 4 cases in 2018 and 1 cases in 2019 came to us for treatment. They had relapsed after taking a course of treatment given in different hospitals in different parts of Bihar.

2 patients in this group were treated with ambisome and 3 cases with miltefosine, an oral drug. All relapsed 54 patients were treated with Fungizone in our clinic. One patient was HIV positive. He was treated for kala-azar and HIV simultaneously.

These 54 patients were divided into two groups so far their diets were concerned, one group was given enough of milk in their diet and another group was given good amount of fish in their diet. The patients were allocated alternately to two groups- Milk group and Fish group.

Both the groups were treated with Fungizone at the dose of 1 mg / kg body

Introduction

Before the second world war kala-azar was endemic in Assam, Bengal (Now Bangladesh and west Bengal), Bihar, eastern Uttar Pradesh and some small area in Tamil Nadu where Donovan worked.¹ In those epidemics thousands of patients used to die. Massive spraying of DDT under the National Malaria Control programme possibly affected the prevalence of kala-azar in those affected areas and cases of kala-azar became negligible in Bihar,² Bengal and Assam and only some cases of post kala-azar dermal leishmaniasis were reported from those areas.³ Those probably acted as a reservoir of infection and gradually kala-azar cases increased.

The present epidemic of kala-azar which started in 1950’s remained a localized medical problem in 1950’s and early 1960’s. Then its incidence increased and death due to kala-azar also increased. The large number of deaths due to kala-azar caused panic in the society and also got critical reports in the news-papers. Then it drew the attention of the government of the state and the centre. But the epidemic kept on increasing and decreasing. Finally the central government took over the responsibility of treatment of patients. In this process of diagnosis and in-adequate treatment of the patients led to development of drug resistance in the patients to commonly used drugs. Bihar faced a very huge epidemic of kala-azar. The number of patients of kala-azar increased in Bihar. An epidemiological survey was done in 1977 in 4 worst affected districts of Bihar there were about 70,000 kala-azar patients with about 7% fatality from January to August 1977.⁴

The government had estimated the number of cases for whole Bihar might be on million up-to August 1977.⁵

Later the Government of India, Governments of Nepal and Bangladesh decided to eliminate kala-azar in their respective countries and thus from the Indian subcontinent. In India the governments at the centre and the states worked hard to eliminate kala-azar by 31st Dec. 2017, but it could not achieve the goal as Bihar and Jharkhand could not succeed in achieving the goal of one patient per 10,000 population. Kala-azar patients were given all facilities by the government department. During this period 54 drug resistant kala-azar patients who had relapsed came to us for their treatment. They came from different parts of Bihar and has been treated with different drugs used in the treatment of kala-azar during that period and not cured and relapsed.
wt. doing given slowly in transfusion in 5% glucose in 6 hours.

Both the groups were assessed on day 21 of their treatment for parasitological cure. The great precaution was taken to avoid any toxicity of the drug. Total and differential WBC count, Hb%, X-ray chest, bone marrow or splenic aspirations were done in each case before and after treatment. The search for parasites were done in the splenic aspirates after treatment. There were 43 males and 11 females in the study, the ratio between male and female was 3.9:1.

Age group of patients are given below.

<table>
<thead>
<tr>
<th>Age group</th>
<th>No of Patient</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 9</td>
<td>8</td>
</tr>
<tr>
<td>10 - 19</td>
<td>7</td>
</tr>
<tr>
<td>20 - 29</td>
<td>8</td>
</tr>
<tr>
<td>30 - 39</td>
<td>11</td>
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<tr>
<td>40 - 49</td>
<td>10</td>
</tr>
<tr>
<td>50 - 59</td>
<td>5</td>
</tr>
<tr>
<td>60 - 69</td>
<td>2</td>
</tr>
<tr>
<td>70 - 79</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>54 patients</td>
</tr>
</tbody>
</table>

Result

So far effect of milk and fish are concerned there was no difference between the two groups regarding general health of the patient. The health of the patients of both groups improved. All the patients were cured. The splenic aspirates of all patients on day 21 were negative except for LD body found in the patient whose blood was HIV positive. He required 3 courses of anti kala-azar drug for treatment for becoming negative and simultaneously becoming negative and simultaneously he was treated for HIV also.

But moment he became negative for kala-azar, he fled away and never returned again. Fish and milk helped the patients to regain their health, but there was no difference in other conditions. Because on day 21, 53 patients had their splenic aspirates negative for parasites. Only one patient that with HIV had parasites in splenic aspirates.

No patients relapsed except that gentleman who had HIV positive. He was given treatment for HIV along with treatment for kala-azar. He became negative after 3 courses of the drug. It was concluded that Fungizone was an effective anti leishmanial drug. If properly used all patients could be cured with this drug.

Discussion

Bihar has been abode of kala-azar since long for the last hundred years. We have faced this epidemic which started in 1950’s and reached its peak in 1970’s and since that it’s still continuing in Bihar inspite of the great efforts made by central and state governments.

We do not know why the kala-azar of Bihar and specially the central Bihar developed resistance to commonly used drug sodium stibogluconate. We tried drug Fungizone in the peak of epidemic in drug resistant kala-azar patients and cured all patients. So we used this drug to cure antimony resistant kala-azar patient. We thought it safe and effective but were fully aware of its toxicity and care required to prevent the toxicity of the drug.

Fungizone is an important anti leishmanial agent. It cured all patients who relapsed after cure with initial therapy with antimony or even ambisome or Miltefosine.

Besides this trial we have used fungizone in quite large number of patients of kala-azar as a first line drug during peak of the epidemic. So far I had not seen relapse with fungizone in kala-azar patients. We extensively used it when sodium antimony gluconate became ineffective. We even discontinued the drug for few days and started again but in this study we did not face any complication. Even those patients who relapsed after ambisome and miltefosine in this series were cured with Fungizone and they did not relapse after the cure. Fungizone is less expensive than ambisome. It is suggested that Fungizone could be safely used as a first line drug in the dose of 1mg/kg body wt for 20 days. But we were very careful about its toxicity. When patients complained some discomfort we discontinued the drug for few days and started again in the previous epidemic doses.

But in this series all the patients tolerated the drug very well except the HIV positive patient who required three courses of treatment for cure, all the patients were cured with one course of treatment. The diet of fish and milk did not have any effect on parasites but the health of the patients improved. This might be reason for good tolerance of the drug we cured patients who relapsed even after ambisome. But I thought the patient required more of the drug for cure not during this stage but later on. We cure some of the patients who relapsed after single dose of ambisome and gave them a two doses of the drug and all patients were cured. It was concluded that Fungizone could be used in drug resistant kala-azar patients, but used with full caution, and any toxicity should be tackled in early stage.

Conclusion

It was concluded that Fungizone could be safely used in the treatment of drug resistant kala-azar patients. It was given at a dose of 1 mg per kg body wt of Fungizone diluted in 5% glucose and given in four hours for 20 days. It cured all patients of kala-azar. This study was funded by Balaji Utthan Sansthan, Patna. A further study is required to find the exact cause and mechanism of unresponsiveness in kala-azar patients.

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Intrapleural Fibrinolytic Therapy in Loculated Pleural Effusions

MS Barthwal

Abstract
About 36% to 57% of bacterial pneumonias develop parapneumonic effusion. When the chest tube is correctly positioned as evidenced by postero-anterior and lateral chest radiographs and there is a significant amount of pleural fluid, the major reasons for failed drainage are multiple pleural space loculations or tube obstruction by thick and viscous fluid. The various modalities of treatment available for loculated pleural effusion are: saline flushes, placing one or more catheters in loculi under image guidance, video assisted thoracoscopic surgery (VATS), standard thoracotomy with drainage of empyema and decortication. The first two modalities are not so effective in improving drainage. The last two surgical modalities are more invasive, not easily available and, if available, are not affordable by majority of patients in the developing countries like India. The fibrinolytic agents, if used early in loculated pleural effusions, break loculations and early pleural peel thereby facilitating pleural space drainage.

Introduction
Pneumonia remains one of the commonest community and hospital acquired infection and as many as 36% to 57% of bacterial pneumonia develop parapneumonic effusion. To start with, parapneumonic effusion starts with exudative stage, which consists of clear, sterile fluid which resolves with antibiotics alone. In case of inappropriate and delayed initiation of antibiotics, the exudative stage progresses to fibrinopurulent stage where fluid becomes more viscous with development of loculations and in presence of continuing uncontrolled infection and non initiation of pleural space drainage, frank empyema with thick loculations and significant pleural thickening develops. Clinically, the three stages can be referred to as simple parapneumonic effusion, complicated parapneumonic effusion (CPE), empyema, tubercular effusion, traumatic hemothorax and malignant effusion. The various modalities of treatment available for loculated pleural effusion are: saline flushes, placing one or more catheters in loculi under image guidance, video assisted thoracoscopic surgery (VATS), standard thoracotomy with drainage of empyema and decortication. The first two modalities are not so effective in improving drainage. The last two surgical modalities are more invasive, not easily available and, if available, are not affordable by majority of patients in the developing countries like India. The fibrinolytic agents, if used early in loculated pleural effusions, break loculations and early pleural peel thereby facilitating pleural space drainage.

Background
Tillet and Sherry were the first ones to use fibrinolytic agents in 1949 in 23 patients who had loculated empyema or hemothorax. Their patients received intrapleural instillation of both streptokinase and streptodornase, which was extracted from concentrated filtrates of streptococi of Lancefield group C. There was significant improvement in drainage of pleural fluid. However, the initial enthusiasm waned because of significant systemic adverse effects in the form of fever, leukocytosis and general malaise. These side effects were due to immunological reaction caused by impurities in the preparation of agents. There was not much of use of this therapy until Bergh and colleagues in 1977 used purified streptokinase and reported significant improvement in 10 of 12 patients with empyema without the need for any major surgical intervention and without any significant adverse effects. In the ensuing three decades or so, there were numerous case series and randomized controlled trials using streptokinase (STK) and urokinase (UK) in complicated parapneumonic effusion and empyema with significant results. During last twenty years or so, the intrapleural streptokinase and urokinase have been used with encouraging results in our country.

However, the results of first multicenter, randomized, double blind study (MIST1) on utility of intrapleural fibrinolytics were found to be negative. In this study, 427 patients with pleural infection (either purulent pleural fluid or pleural fluid with a pH<7.20 with signs of infection) were randomized to receive either intrapleural streptokinase or placebo. There were no significant differences between the two groups in terms of mortality, need for surgery, radiographic outcome or length of hospital stay and the authors concluded that intrapleural streptokinase should generally be...
avoided in pleural infection. Although this was a large multicenter trial, yet it had some significant flaws in selection of primary outcomes and methodology as brought out by Heffner.17 Mortality in patients with parapneumonic effusions depends more upon the severity of underlying pneumonia, other co morbid conditions and age rather than facilitation of pleural space drainage with intrapleural fibrinolytics and it was rightly suggested that mortality should not be considered as primary outcome measure.17 Moreover significant number of patients in this trial was more than 60 years of age and majority of them had co morbid diseases, which could have contributed in increasing mortality and hospital stay. The patient population was heterogeneous in this study and radiological investigations like ultrasonography (USG) or computed tomography (CT) were not used to select patients with CPE or empyema with loculations without any significant pleural thickening, since this subgroup of patients is most likely to benefit from fibrinolytic therapy which breaks the loculations but possibly does not have any significant effect in liquefying pus.17 All randomized controlled trials, except for this multicenter trial, in spite of low number of patients and non-uniform selection criteria, have nevertheless shown that IPFT does facilitate the drainage of pleural fluid by breaking the loculations without any significant adverse effects. The Cochrane Database systemic review18 on IPFT in 2008 found that intrapleural fibrinolytic therapy conferred significant benefit in reducing the requirement for surgical intervention for patients in the early studies included in this review but not in the more recently published Maskell16 study. The reasons for this difference are uncertain. The review also found that in subgroup analysis the greatest benefit was in patients with loculated effusion but the data in this group was limited. Another meta-analysis by Wencheng Nie, et al19 found that intrapleural fibrinolysis with urokinase may be potentially effective in reducing the need for surgery, shortening the length of hospital stay without increasing the incidence of severe side effects.

**Administration of IPFT**

We have been using IPFT as a first line therapy since 1997 in lobulated effusions of various etiologies belonging to any age group with the sole aim of facilitating the drainage process with success criteria of radiological resolution and pleural space drainage thereby avoiding surgical intervention in responders. The non-responders are subjected to surgical intervention in the form of video-assisted thoracic surgery (VATS), if available or thoracotomy with decortications. The following stepwise approach is used in intrapleural fibrinolytic therapy (IPFT):

a. The drainage from intercostal tube or catheter should be less than 50 ml per day and the tube or catheter should be correctly positioned and is patent.

b. Imaging studies in the form of either ultrasonography (USG) or computed tomography (CT) are done to assess the site, size of loculations and the extent of associated pleural thickening. IPFT is indicated only in those cases where significant loculated pleural fluid is present and the chest tube or catheter is adequately positioned and patent.

c. STK/UK dosage schedule in adults is 2.5 lac IU of STK or 1 lac IU of UK given eight hourly for 3 doses. The dosage schedule of STK/UK in pediatric patients is as per age group. For STK: 6-12 years-100,000 IU, 1-6 years-50,000 IU and less than 1 year-25,000 IU. For UK: 6-12 years-50,000 IU, 1-6 years-25,000 IU and less than 1 year-10,000 IU. The dosage frequency is 8th hourly for three doses.

d. The drug is instilled though intercostal tube or pigtail catheter by dissolving in 50 ml of normal saline followed by flushing with 20 ml of normal saline (in pediatric patients the volume of fluid used is 20 ml followed by flushing with 10 ml saline). The tube or catheter is clamped for 2 hours after each dose. Three doses of STK/UK are considered as one cycle.

e. The criteria for successful outcome are the radiological resolution and volume of pleural fluid drained. The criteria used for radiological resolution are: maximum (normal or near normal chest radiograph), moderate (a clearance of 50 to 80% of pleural effusion), minimal (<50% clearance) and none (no change).20

f. Chest radiology and ultrasonography (USG) is initially done 48 hours after one cycle of STK/UK therapy and subsequently depending upon the response to therapy. The cumulative drainage is noted 48 hours after one cycle of STK/UK and also till the removal of chest tube.

g. Repeat fibrinolysis comprising of one more cycle of STK/UK is performed in cases who had more than 100 ml of cumulative drainage and minimal to moderate radiological improvement after 48 hours of initiation of fibrinolytic therapy.

h. Fibrinolytic therapy is discontinued if 48 hours after three doses of STK/UK, the cumulative drainage is less than 100 ml and there is no radiological improvement.

i. Responders to IPFT are defined as cases who had more than 500 ml of cumulative drainage and maximum radiological resolution after one or two cycles of IPFT. The rest of the cases are defined as non-responders.

**Predictors of Response to IPFT**

The early initiation of fibrinolytic therapy, before the development of severe pleural adhesions may lead to a more effective pleural drainage as has been demonstrated in an experimental study21 and in a study by Boures et al.7 The failure of IPFT is associated with pleural thickness >2 mm on CT scan which re-emphasizes the early initiation of IPFT.22

**Dosage Variation in India**

In India there has been a problem in using the daily or twice a day dosage schedule of intrapleural STK or UK, used in all studies from abroad, due to non-availability of STK or UK in the prescribed dosage. The minimum strength of STK freely available in India is 1,500,000 / 750,000 IU per vial. Once the vial is reconstituted, the solution can be stored only for eight hours at 2 to 8°C. By using intrapleural STK in the dosage of 250,000 IU eight hourly, two doses can be utilized thereby minimizing the wastage and at the same time maintaining its potency. Urokinase is available as 250,000/500,000 IU per vial in India and has been used in the dosage of 100,000 IU eight hourly for similar reasons. We had to adopt the eighth hourly schedule because of non-availability of requisite strength of STK or urokinase. However, in an experimental study23 it has been demonstrated that increasing dosing interval might in fact increase the efficacy of fibrinolytic therapy. The possible explanation for this is the presence of various protease inhibitors in the inflamed pleural...
space, which decease the half-life leading to shortening of proteolytic activity of STK/UK. Increasing the dosing frequency appears to prolong the half-life and thereby increasing proteolytic activity of STK/UK.  

**Choice of Fibrinolytic**

The various fibrinolytics used for IPFT are STK, UK and recombinant tissue plasminogen activator (t-PA). There are very few head to head trials comparing various fibrinolytics. In MIST2 trial, it was commented that using alteplase (recombinant t-PA) in place of STK along with deoxyribonuclease (DNase) might prove to be more effective. This comment does not seem to be convincing since no comparison between STK and alteplase was done in this trial and moreover, the better outcome in this trial was because of using alteplase with DNase. In a study of intrapleural fibrinolysis with UK versus alteplase in CPE and empyema, urokinase was found to be better than alteplase not because of more effective fibrinolysis but because of more complications of hemorrhage in alteplase group. Regarding the choice of fibrinolytic in our country, UK is a preferred cost effective option since STK is antigenic in nature and t-PA is steeply priced as compared to STK/UK.

Intrapleural fibrinolytic therapy has been used successfully in pediatric patients as reflected by various case reports and a randomized, control trial. IPFT has also been recommended as a first line of therapy in traumatic clotted hemothorax before proceeding to thoracotomy or pleural decortication.

**Adverse Effects**

Common side effects of IPFT are fever and chest pain, which is reported in less than 10% of patients. Major hemorrhage has been reported in a single case report after using 500,000 IU of STK with a dwell time of six hours. There have been isolated case report of ventricular fibrillation following UK. It is recommended that a single dose should not exceed 250,000 IU for STK and 100,000 IU for UK and dwell time should not be more than four hours. There is no significant activation of systemic fibrinolytic system even when a total dose of 1,500,000 IU given in a dose of 250,000 IU, 12 hourly and no monitoring of coagulation parameters is required.

**Contraindications**

Contraindications to IPFT are patients with bronchopleural fistula, major thoracic or abdominal surgery within two weeks, coagulation defects, and previous STK administration by any route.

**Combination of Fibrinolytic with DNase**

Tillet and Sherry used varidase in patients with loculated empyema and haemothorax, which was a combination of unpurified preparation of STK (fibrinolytic) and streptodornase (DNase), extracted from group `C' B-hemolytic streptococci. The use of this therapy was based on the hypothesis that purulent exudates contain almost equal proportion of fibrin and deoxyribonuclease nucleoprotein. Streptokinase or UK (fibrinolitics) liquefies fibrin and streptodornase (DNase) liquefies deoxyribonuclease nucleoprotein. As mentioned before, the results were good but further studies were abandoned because of adverse side effects. The efficacy of varidase has been demonstrated in an in vitro trial in which, thick empyema fluid from rabbits was incubated with STK or UK, there was no significant liquefaction of fluid. When the same fluid was incubated with varidase, the fluid was completely liquefied in 4 hours. Recombinant DNase has now replaced varidase. In a recent multicenter trial, a combination of intrapleural t-PA and DNase improved fluid drainage in patients with pleural infection and reduced the frequency of surgical referral and the duration of the hospital stay. Treatment with DNase alone or t-PA alone was ineffective.

**Conclusion**

IPFT is a safe and cost effective option in the management of loculated effusions of varied etiologies. For a developing country like ours, this option must be exercised in eligible patients before subjecting them to costlier, not so easily accessible and more invasive surgical options.

**References**

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*IMS MAT Dec 2018. # AIOCD MAT Jan 2020
COVID-19: Striking a Balance between Health Care Provider Safety and Patient Care in the Indian Hospital Settings

Midhun Mohan N, Chandni Radhakrishnan, Indira P

Abstract
Background: The COVID-19 pandemic has taken its toll on the health care systems all over the world. The global shortage of resources has adversely affected the safety of healthcare personnel as well patients. This has forced the health care facilities to adopt various measures and improvisation in infection control practices, in addition to those in personnel protective equipments (PPEs) adapting to their need and their resources.

Objectives: To review the literature on the infection control practices in health care facilities against COVID-19 and put forward practical solutions, in addition to personnel protective equipments that may be adopted for health care personnel and patient safety in the Indian setting.

Conclusions: We are now amidst of COVID-19 pandemic and we need to focus on ‘Risk reduction as much as possible’. The facilities and resources should transform to meet the challenges within the shortest time frame. The concept of patient care needs to balance with the safety of the healthcare, patient and society. This is achievable only by a combination of engineering controls, administrative controls and PPEs. It involves a lot of committed team work while managing an outbreak like COVID - 19 attached with a lot of social stigma.

Introduction
The COVID-19 pandemic is here and is here to stay until a significant population in the community achieves immunity. Health Care Facilities differ in their capacity and capability and each of these facilities need to adopt strategies to manage the outbreak. This article is intended for all such facilities to continuously optimize their strategies, to manage their patients while keeping themselves safe.

The global shortage of Personnel Protective Equipments (PPEs) has forced the health care community to come up with many alternatives, including strategies like the extended use and reuse of PPEs. The safety offered by PPEs is highly dependent on the quality of the PPE, its fit, as well as its proper use. The rising number of Health Care Personnel (HCP) affected by the pandemic suggests that PPEs alone are not sufficient. The National Institute of Occupational Safety and Health (NIOSH) hierarchy of controls for workers safety considers PPEs as the least effective method of control compared to the other ones (Figure 1).

So PPEs should be considered as the basic requirement for HCP safety, the best method being a combination of controls.

Health Care Personnel (HCP) in this document refers to all the paid and unpaid persons, who provide their service in the health care setting and have the potential for direct or indirect exposure to patients or infectious materials.

‘Risk reduction as much as possible’ should be the axiom driving the Hospital Administration and the Health Care Personnel while managing COVID-19 patients. Elimination or substitution of the hazard is not possible at this phase of the pandemic until vaccines are developed or herd immunity is attained against the SARS CoV-2.
But engineering and administrative controls of varying levels can be implemented based on the capacity and capability of the health care facility and the phase of the epidemic at the local community.\textsuperscript{22,29,30}

The following measures - Engineering control and administrative control - must be considered by the health care facilities while planning and providing care for COVID-19 patients.

I. Engineering Controls - “Isolate People from the Hazard”:

The hazard here being COVID suspects and their activities including health-care interventions.\textsuperscript{16,22,31}

The measures include: Limiting Entry Points and Triaging; Physical barriers and cohorting; Heating Ventilation and Air Conditioning (HVAC) systems; and Airborne Infection Isolation Rooms (AIIRs).\textsuperscript{32}

1. Limiting Entry Points and Triaging: Hospitals should limit the number of patient entry points to one, preferably at the Emergency Department (ED). However health care facilities providing concurrent Out-Patient services at a distant location may provide a separate entry point. Each of these entry points should have a separate Triage point which screens all patients and their bystanders to identify COVID suspects.\textsuperscript{23,33}

Identifying and isolating the disease suspects is the most important step to prevent an outbreak of highly contagious disease like COVID-19 in a health-care facility during an epidemic.\textsuperscript{17} This has been evident from our previous experience during the Nipah outbreak.\textsuperscript{31} The screening should be based on the most recent National or State level guidelines that define a COVID suspect.\textsuperscript{3,5,24-37}

The entry point triage should be set up preferably outside the Hospital building or the Emergency Department where there is a lot of space and ventilation and the health care personnel should have appropriate PPEs.\textsuperscript{9,38} A different single entry point with screening facility should be provided for HCP entering the health care facility.\textsuperscript{17,32,35}

Once identified, COVID suspects should be safely transported to the isolation area with minimal contact to the non-essential healthcare workers or the public.\textsuperscript{32}

2. Physical barriers and Cohorting: Physical barriers are the best method to isolate COVID suspects from others.\textsuperscript{31} The area to be allotted for isolating COVID patients varies from isolation rooms to the entire hospital depending on the phase of the epidemic in the community, the number of COVID suspects expected to come to the facility and the capability of the health care facility.\textsuperscript{32}

Separate buildings or separate areas within the same building but with different entry and exit points or even isolation rooms within a common Emergency Department/wards can all be considered as physical barriers isolating COVID suspected patients from non-COVID patients.\textsuperscript{35,38} Separate triage points which prioritize patients based on their vitals should be provided in both the COVID area and the non-COVID area (Figure 2).

All patients with laboratory diagnosis of COVID-19 need to be isolated from the rest of the people. Independent isolation rooms with wash rooms would be the best choice, but if adequate number of rooms are not available, these patients may be cohorted to an isolation ward with 2 meter spacing between the beds if possible.\textsuperscript{32,35,39}

Within the group of COVID suspects itself there are \textit{true COVID suspects} who...
really have the SARS CoV-2 infection, but needs laboratory confirmation to diagnose; and false COVID suspects, who really don’t have the SARS CoV-2 infection, but meets the epidemiological or symptomatic criteria of a COVID suspect as per the existing guideline at that point of time (Figure 3).

Although it is impossible to differentiate the two categories without laboratory testing, it is important that these groups don’t come into contact with each other as much as possible to prevent nosocomial infection transmission. For this, isolation rooms with attached bathrooms for each of the COVID suspected patient is recommended. Isolation rooms are resource consuming, particularly for critically ill patients who require frequent monitoring and interventions. This includes engineering requirements like transparent walls and doors or CCTV for patient visualization; central monitoring systems; communication systems; and requirement of additional staff and equipments.

If adequate number of isolation rooms and resources are not available all COVID suspects may be cohorted to an isolation ward but with at least 2 meter distance between the beds and some sort of physical barrier between the beds such as curtains may be used to reduce the risk of droplet transmission and to provide privacy to the patient as needed (Figure 2). Even though 1 meter separation is adequate for preventing droplet transmission, 2 meter separation between the beds is recommended considering the work space required by the HCP while providing care. The available isolation rooms should be preferably provided to patients with more severe illness and those who are likely to require high risk aerosol generating procedures like high flow nasal cannula (HFNC), non-invasive ventilation (NIV) or tracheal intubation. Severe illness is strongly associated with high levels of virus production and higher risk of disease transmission. Necessary infection control practices should be adopted or modified to address all the surrounding areas including physical barriers and equipments used.

Similarly, within the group of non-COVID patients itself there are true non-COVID patients, who really don’t have the SARS CoV-2 infection and false non-COVID patients, who really have the SARS CoV-2 infection, but doesn’t meet the epidemiological or symptomatic criteria of a COVID suspect (Figure 3). The number of false non-COVID patients is going to be low in communities without local transmission of the disease. In places with community transmission, there is a higher risk of presymptomatic and asymptomatic COVID-19 patients to come into contact with others in the non COVID area when they come to the hospital for a non respiratory symptom or as a visitor with another patient. It is impossible to identify this group and isolate them at their initial presentation. Separate rooms or cubicles for all the non-suspect patients would be ideal to prevent infection transmission in the non-COVID area, but at least 2 meter distancing between beds and curtains between beds may be used if rooms are not available (Figure 2). Source control using a two layered surgical facemask if supplies are available or a cloth face-covering / mask for everyone entering the health care facility, regardless of symptoms should be instructed to address asymptomatic and presymptomatic transmission.

This additional care will mitigate the risk of transmission in diseases like COVID-19, where transmission can happen from asymptotics too. There should be specific emphasis on all standard precautions and infection control practices and must be regularly reinforced and audited.

3. Heating, Ventilation, and Air Conditioning (HVAC) Systems in Health-Care Facilities:

HVAC systems in health-care facilities are designed not just to maintain a comfortable indoor air temperature, humidity and control odors. HVAC systems appropriately designed can remove contaminated air; facilitate air handling requirements to protect susceptible staff and patients from airborne health-care associated pathogens; and minimize the risk of transmission of airborne pathogens from infected patients.

The engineering controls used in HVAC systems to contain or prevent the spread of airborne contaminants centers on:

a. General ventilation,

b. Local exhaust ventilation for source control

c. Air cleaning.

These principles may be adopted according to the capability of each health-care facility to reduce airborne transmission.

a. General ventilation strategies to prevent airborne contamination encompasses:

i. dilution and removal of contaminants via well-mixed air distribution of filtered air;

ii. directing contaminants towards exhaust registers and grilles via uniform, non-mixed airflow patterns;

iii. ventilation rates for virus removal ≥12 Air Changes per Hour (ACH). This is the minimum ventilation rate estimated to reduce the probability of infection in an enclosed room to less than 5% with an hour of exposure to an infectious source case;

iv. pressurization of individual spaces relative to all other spaces (see AIIRs section below); and

v. pressurization of the buildings relative to the outdoors and other attached buildings.

If the facility has a centralized HVAC system, there is a risk for airborne transmission from aerosols generated by COVID-19 patients as most of the health-care facilities generally use recirculated air. Choosing areas with separate HVAC systems for isolating COVID suspects from others would be ideal. If not possible use HEPA filters fixed into the HVAC system or even portable industrial grade HEPA units to decontaminate the recirculated air.

Decreased performance of the HVAC systems, improper installation, poor maintenance and filter inefficiencies can contribute to the spread of the health-care associated airborne infections. If the facility doesn’t have any centralized HVAC system, then choosing an area with a lot of natural cross ventilation would be optimal to control indoor air contamination of the virus. Controlled natural ventilation with fixed unrestricted openings on two sides, preferably on opposite sides that together constitute >20% of floor area, ensures that the air exchange rate is safely >12 ACH under all climatic conditions.

b. Local exhaust ventilation for source control: Control of the virus containing aerosol diffusion at the
source is the most effective way to maintain clean air. Air from rooms housing COVID suspects requiring high risk aerosol generating procedures should be separately exhausted to the outside without contaminating any other treatment area or pedestrian area or passed through a HEPA filter ± UVGI if recirculated.

Facilities having areas without central HVAC systems often use through the wall fan coil air conditioning units which serve only as recirculating units with low efficiency filters. If a patient room is equipped with this system alone, the room will not be suitable to be used as Airborne Infection Isolation Room as per guideline recommendations. But it may be utilized in resource limited settings for this purpose with certain modifications like providing additional local exhaust fans in the room with some compromise on the air conditioning.

c. Air cleaning: HEPA filters are at least 99.97% efficient for removing particles ≥0.3µm in diameter. But the maintenance costs associated with HEPA filters are high. They are usually fixed into the HVAC system; however, portable, industrial grade HEPA units are available that may be used. These units may be ultraviolet germicidal irradiation (UVGI) and activated carbon filtration. 29,32,45

Ultraviolet Germicidal Irradiation (UVGI) has been shown to be effective in reducing the transmission of airborne viral infections in hospitals. But because the clinical effectiveness may vary and of the potential carcinogenic and cataractogenic effects of conventional UVC light sources, UVGI is not recommended as a substitute for HEPA filtration, local exhaust of air to the outside, or negative pressure. 45,46 Far-UVC light (222-nm) at very low dose-rate may be used as a supplemental air cleaning measure.

4. Airborne Infection Isolation Rooms (AIIRs): Airborne infection isolation rooms are constructed using the above mentioned engineering controls of the HVAC systems to reduce airborne transmission. The salient features of AIIRs are 29,45,55,56

<table>
<thead>
<tr>
<th>Engineering Characteristics</th>
<th>AIIRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressurization</td>
<td>Negative Pressure rooms with ≥2.5 Pa pressure differentials and an analog/digital differential pressure monitoring system</td>
</tr>
<tr>
<td>Air changes per hour (ACH)</td>
<td>≥12 ACH</td>
</tr>
</tbody>
</table>

- **If recirculation of air into the centralized HVAC system cannot be prevented, install HEPA filters ± UVGI in the exhaust duct leading from the room to the general ventilation. If ventilation rates ≥12 ACH cannot be achieved, UVGI may be placed in the room.** 29,45,51
- COVID-19 patients who require high risk aerosol generating procedures should be managed in AIIRs. 29,35,45 If AIIRs are already not available in the health-care facility, rooms may be converted to meet at least some of the standards of AIIRs with the help of hospital engineers. Even simple exhaust fans that direct the air from the room to the outside atmosphere without contaminating any treatment areas or pedestrian areas can reduce room air contamination. 20,32 If the room doesn't have a centralized HVAC system and the facility is not able to provide local exhausts, the room isolating COVID suspects should be kept closed during aerosol generating procedures and cleaned after one hour of the procedure.

II. Administrative Controls - “Changing the Way People Work”

The measures includes: limiting the number of people getting exposed; limiting the exposure time of Health-Care Personnel; reduce aerosol generation and diffusion; continuous training of HCPs; good communication practices; proper decontamination and disinfection; and psycho-social and medical support.

1. Limiting the number of people getting exposed:

   a. **Limiting the Public:** measures include reducing or stopping elective surgeries/services based on the role of the health-care facility in managing the outbreak in the community; reducing or stopping out-patient services; providing telemedicine consultation; and limiting bystanders/visitors to health-care facilities.

   b. **Alternative care plan must be adopted for chronic conditions like psychiatric illness, epilepsy and non communicable diseases.** The system should adopt practices so that the non COVID care is not compromised and planning should be done ensuring patient and care giver safety.

   b. **Limiting the number of Health-Care Personnel (HCPs) getting exposed:** minimal number of HCPs required for providing the essential services in the health-care facility should be coming to the facility. The work force may be divided into 3 as shown in the Figure. 4

   The number of Health-Care Personnel in each group and the frequency of their rotations depend on the work load in the COVID and the non-COVID areas of the Hospital. The HCPs who are aged >65 years, with comorbidities or other risk factors like immune suppressed states or are pregnant may be allotted to work in the non COVID area or kept in the reserve group. Team work and sharing of work load within a group can help to reduce the number of personnel required in the COVID as well as the non-COVID group reducing the number of personnel getting exposed to the risk at any particular time.

2. Limiting the exposure time of HCPs to COVID suspects:

Although this is dependent on the condition of the patient, some generalized measures include:

   a. **Standardization of processes and ensuring adherence of all HCPs to these processes by using checklists and frequent auditing at different levels can help to reduce time, errors and provide uniform care.** 39,40 While designing these processes, the principle to follow during a disaster is to “provide the greatest good for the greatest number of people” rather than the best possible care to each patient.

   b. **Preparation of personnel and equipment:** discussion of the roles and responsibilities of the HCPs; condition of the patient; and back up plans if any difficulty arises, should be done outside the room for any time requiring high risk procedure, particularly aerosol generating procedure like intubation. In skill based needs, the trained man power must be utilized and these are not the areas for training new skills. The procedure, especially aerosol generating procedures must be completed at the shortest time. The HCP with adequate expertise should preferably do the procedure. Consider
bundling activities to minimize the number of times the patient’s room is entered (eg. Check vital signs during medication administration).5,12,34

c. Use of Technology like CCTV camera systems; central monitoring systems; two-way communication systems including visual communication; remotely controlled and centrally monitored infusion/syringe pumps;64 virtual critical care;65 and telemedicine66-68 for patient examination, monitoring and treatment can reduce the need for HCP exposure to the patient. Long lines for the pumps and long tubes for the ventilators with appropriate engineering measures can facilitate placement of these equipments outside the patient’s room for control by HCP without exposing themselves to the patient. Simple and non expensive robots can be used in some facilities as a substitution for HCP to do regular tasks like delivering food, oral medications, ventilation procedures.4,73,76-78

3. Reduce aerosol generation and diffusion: Hypoxemia has been one of the major indications for hospitalization during the COVID-19 pandemic and oxygen supplementation is a key element in managing such patients.5,69,70 All forms of oxygen supplementation are associated with some form of aerosol generation.71 This increases the risk for nosocomial infection transmission among Health Care Personnel (HCP) and other patients in the Emergency Departments and the Intensive Care Units.21

The risk of aerosol generation increases as the flow rate of oxygen supplementation increases. High risk aerosol generating procedures include high flow nasal oxygen therapy (HFNOT), non invasive ventilation (NIV), bag-mask ventilation, tracheal intubation, airway suctioning, bronchoscopy and cardiopulmonary resuscitation (CPR).72 Many of the aerosols generating procedures are life saving interventions, for which there are no alternatives at present.35 So appropriate modifications have to be made to reduce aerosol generation and diffusion, in addition to performing them in airborne infection isolation room while instituting these therapies.71,73-79

a. Low flow technique: The lowest oxygen flow rate that can achieve reasonable oxygen saturation should be used.73

b. Physical barriers: Surgical mask may be provided to the patient and placed over the nasal cannula and under the face mask while providing oxygen using these interfaces. An aerosol box or a clear plastic sheet may be tented over the patients head and upper body to reduce aerosol diffusion during intubation.75,80 A plastic sheet may be placed over the patient’s upper body including head while doing CPR.74

c. Rapid Sequence Intubation (RSI): Although the act of intubation is associated with the greatest risk of aerosol generation; once intubated, is considered safer method of oxygenation and ventilation compared to NIV or HFNOT. RSI with higher paralytic dose should be used to ensure apnea, prevent coughing and higher rate of first pass success during intubation.72,75

d. Viral filters meeting appropriate standards must be used for filtration of the expired air during any positive pressure ventilation procedures.4,73,76-78

e. Non vented interface for NIV: A non vented mask with viral filter attached to it should be used while providing non invasive ventilation with a mechanical ventilator and a double limb circuit. Similar interface with an additional expiratory port distal to the viral filter should be used if a BPAP machine with a single limb circuit is being used for the same.73,78

f. Closed suction systems should be used rather than open suctioning once intubated.

4. Continuous Training of HCP: Many of the health care personnel may be required to work outside of their regular working environment during this pandemic and these can open doors to errors that can harm the HCP as well as the patients. Ongoing training programs are a must for capacity building, to prevent errors and to increase the confidence of the HCP during this pandemic. In situ simulation exercises; mock drills; just in time training sessions; educational videos; online lectures and demonstration classes; and even debriefing sessions after a procedure can all be used for this and this must be a continuous process.73,81-84,76,77,85

5. Good Communication Practices:

is going to be challenging during the chaotic environment of an outbreak. It is crucial to ensure that the decisions taken by the health-care facility administration is communicated to the HCP working on the floor on a daily basis and the problems faced by the HCP are reported to the authorities. The health-care facilities have to be constantly updated about the local as well as the national guidelines, protocols and SOPs related to the outbreak by the Government. Adequate and timely communication to the patient and their relatives is also very important in situations where we provide isolation facility for care.

6. Decontamination

of equipments and the health-care facility surfaces as well as the proper disposition of the hazardous material should be ensured by the infection control team and the biomedical department.23,29,38

7. Psychosocial and Medical support:

Psychosocial support for all health care personnel (HCP), the COVID-19 suspects and their families is essential to get through the stressful phase of the pandemic and to manage the post traumatic stress disorder (PTSD) associated with the death of the patients or the dear ones. It helps to alleviate the fear as well as the social stigma associated with this contagious disease, as well as facilitates adherence to the infection control measures advocated to those in quarantine and isolation. A medical support team should be available in every institution and all health related issues of the HCP should be monitored and properly addressed by this team. Special attention should be taken by the health care system to provide adequate accommodation and quarantine facilities for the health care personnel who require them.86-89 The psycho social support to the health care
personnel, the patients and their family, and the volunteers involved must be a continuous process with appropriate timely interventions.

**Summary**

- **‘Risk reduction as much as possible’** for infection transmission prevention should be considered at every step while planning, preparing and fighting the COVID-19 pandemic.
- This is achievable by a combination of engineering controls, administrative controls and PPEs.
- Entry point screening triage and proper isolation of the COVID-19 suspects is the most effective engineering control for infection transmission prevention in the healthcare facility at this phase of the pandemic.
- Healthcare facilities at all levels need to adopt these measures according to their capability and the phase of the epidemic in their community. Improvisation rather than compromisation in measures to ensure healthcare personnel and patient safety is necessary as the pandemic takes its toll on all our resources.
- A highly contagious disease like COVID-19 with high human to human transmission is associated with a lot of stigmatization and requires a humane approach and care.

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Editor-in-chief API Textbook of Medicine

Nominations are invited from members of API for the post of “Editor-in-chief API Textbook of Medicine”

The nomination should be proposed and seconded by two members along with seven copies of the Biodata and should reach by 31st July 2020, to the Hon. General Secretary of API. Dr. Mangesh Tiwaskar, Unit No. 6 & 7, Turf Estate, Opp. Shakti Mill Compound, Off. Dr. E. Moses Road, Near Mahalaxmi Station West, Mumbai – 400011. Tel. No. 022 66663224, 24912218 Fax 2492063.

Dr. Mangesh Tiwaskar
Hon. General Secretary

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Dr. Mangesh Tiwaskar
Hon. General Secretary

*REVISION OF DATES LIKE AS PER GOVERNMENT NOTIFICATION DUE TO COVID 19
Hydroxychloroquine for COVID-19: What is our Current State of Knowledge?

Zarir F Udwadia1, Ketan N Malu2, Divyanshi Rana2, Shashank R Joshi3

Abstract

Chloroquine and Hydroxychloroquine are drugs which have been widely used in malaria and rheumatoid arthritis respectively for over 50 years. There was anecdotal evidence of their efficacy in the earlier SARS outbreak in 2003. This prompted physicians from across the world to use them in the present SARS-CoV-2 pandemic that is currently sweeping the globe, with 5 million people already infected to date. These drugs are already in widespread use for the treatment of COVID-19 in India, mainly because they are cheap and easily available, and because of the absence of any readily available alternative therapy. This timely review discusses the pre-clinical evidence, and data from the eight available clinical trials. We emphasise that careful monitoring for cardiac toxicity is required when these drugs are used. Finally, we conclude that current data does not allow us to recommend for or against the use of these drugs. Results of two large RCTs, one from the NIH and the other from WHO (Solidarity) are eagerly awaited before the role of these drugs in COVID-19 can be definitively established.

“Hydroxychloroquine and Azithromycin taken together have a real chance to be one of the biggest game changers in the history of medicine”

Donald Trump, President, USA

“The evidence is anecdotal. The president is talking about hope”.

Anthony Fauci, Director, NIH

Chloroquine (CQ) is a widely used anti-malarial drug with immunomodulatory effects. Hydroxychloroquine (HCQ) is a more soluble and less toxic metabolite of chloroquine with fewer concerns about drug-drug interactions.1-2 The molecular mechanism of action of chloroquine and hydroxychloroquine has not been fully elucidated. As both drugs are affordable and widely available, there has been a growing interest in the use of these agents as potential treatments for Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2) till novel, specific treatments become available.

Levels of Evidence

1. Anecdotal: Doctors in Wuhan general Hospital made the intriguing observation that patients with SLE on HCQ did not seem to develop COVID-19. None of Wuhan hospital’s dermatology department’s 80 lupus patients were infected. They hypothesized that this may have been due to the long-term use of HCQ.3

2. In Vitro Studies: The cellular evidence of CQ and HCQ is based on the observation that they elevate the pH at the surface of the cell membrane and thus, inhibit the fusion of the virus to the cell membrane. They also inhibit nucleocapsid replication, glycosylation of viral proteins, virus assembly, new virus particle transport, and virus release thus achieving their antiviral effects.4 CQ inhibits SARS-CoV entry by changing the glycosylation of ACE2 receptor and spike protein.5 The in vitro study conducted after the SARS pandemic, caused by a very similar coronavirus (SARS-CoV-1)in 2005,6 demonstrated chloroquine to be effective in preventing the spread of SARS-CoV-1 in cell culture. Favourable inhibition of virus spread was observed when the cells were either treated with chloroquine prior to or after SARS-CoV-1 infection. Yao et al1 conducted a similar in vitro study for SARS-CoV-2. Using PBPK (physiologically based pharmacokinetic) modelling and simulation techniques the optimal dosing regimen for hydroxychloroquine was evaluated in in silico models. HCQ exhibited a higher in vitro antiviral effect compared to chloroquine when the drug was added prior to the viral challenge. They also established the optimal dose of HCQ [400mg BD on D1 followed by 200mg BD D2-5] and demonstrated it reached a good concentration in lung tissue. They concluded based on their in-vitro model that HCQ was able to achieve treatment efficacy with a good safety profile. Wang et al7 reported in vitro antiviral activity of CQ, with an EC50 (50% maximal effective concentration) of 1.13µM and an MOI (multiplicity of infection) of 0.05, and with high selectivity for SARS-CoV-2 rather than host cells.

CQ and HCQ also have a host of pleiotropic effects including anti-platelet activity,8 prevention of deep venous thrombosis9 and a mouse model of antiphospholipid syndrome demonstrating partial prevention of endothelial dysfunction by HCQ.10 These might prove significant with the emergence of case reports demonstrating coagulopathy and antiphospholipid antibodies in patients with COVID-19.

3. In Vivo Clinical Trials: The first

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Day 7 and 93% on Day 8. Virus cultures qPCR was noted, with 83% negative on all but two elderly patients. A rapid fall of hydroxychloroquine (200 mg daily for the remaining days (total treatment duration: 2 weeks or 3 weeks for mild/moderate or severe patients, respectively)). The negative conversion rate of SARS-CoV-2 among patients in the SOC plus HCQ group (85.4%) was similar to that of the SOC group (81.3%) within 28 day. The negative conversion time did not differ between SOC plus HCQ and SOC group (median, 8 days vs. 7 days; P=0.341). Compared to SOC alone, the addition of HCQ on SOC led to more rapid normalization of elevated baseline CRP (P=0.045) and recovery of baseline lymphocytopenia (P=0.547).

A more recent retrospective analysis of patients hospitalized with Covid-19 in the Veterans Health Administration medical centres across the United States analysed the associations between hydroxychloroquine and azithromycin (AZ) use and clinical outcomes14. The patients were categorized into three different groups based on the treatment received- HCQ (n=97), HCQ +AZ (n=113), or no HCQ (n=158). Compared to the no HCQ group (11.4%), there was a higher risk of death from any cause in the HCQ group (27.8%) (adjusted HR, 2.61; P=0.03) but not in the HCQ+AZ group (adjusted HR, 1.14; P=0.72). There was no significant difference in the risk of ventilation in either the HCQ group (adjusted HR, 1.43; P=0.48) or the HCQ+AZ group (adjusted HR, 0.43; P=0.09), compared to the no HCQ group.

These studies have highlighted the need for more robust clinical evidence before HCQ can be recommend in the treatment of SARS-CoV2 especially keeping in mind the potential side effects and drug interactions which it may lead to.

The recently published NIH guidelines for treatment of COVID-19 include the use of hydroxychloroquine and azithromycin for the treatment of COVID-19 with severe illness. However, the study was excluded from the Cochrane Library of Systematic Reviews and the Cochrane Collaboration because of methodological concerns.

### Table 1: Doses of HCQ used across different studies to date

<table>
<thead>
<tr>
<th>Study</th>
<th>HCQ dosing</th>
<th>Azithromycin dosing (if used)</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>In vitro study</td>
<td>Optimal dose recommended: 400 mg BD on Day 1 followed by 200 mg BD for next 4 days</td>
<td>_</td>
<td>Positive study</td>
</tr>
<tr>
<td>Initial Chinese study</td>
<td>200 mg BD for 5 days</td>
<td>_</td>
<td>Positive study</td>
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<tr>
<td>French study</td>
<td>200 mg TDS for 10 days</td>
<td>_</td>
<td>Positive study</td>
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<tr>
<td>MOHFW (Ministry of Health &amp; Family Welfare)</td>
<td>400 mg BD on Day 1 followed by 200 mg BD for next 4 days</td>
<td>500 mg OD for 5 days</td>
<td>Based on evidence available till 31st March, 2020</td>
</tr>
<tr>
<td>Chinese open labelled RCT</td>
<td>Loading dose: 1200 mg OD for 3 days</td>
<td>Maintenance dose: 800 mg OD for 2/3 weeks (mild-moderate/severe cases respectively)</td>
<td>Negative study</td>
</tr>
<tr>
<td>CloroCovid-19 trial (High vs low dose CQ)</td>
<td>High dose: 600 mg/day twice daily for 10 days</td>
<td>Low dose: 450 mg twice daily on 1st day and then once daily for four days</td>
<td>Recommendations against the use of high doses of CQ for severe SARS-CoV-2 because of safety concerns</td>
</tr>
<tr>
<td>SOLIDARITY trial</td>
<td>Loading dose: 800 mg BD (6 hours apart) on day1</td>
<td>Maintenance dose: 400 mg BD for 20 doses</td>
<td>Currently ongoing</td>
</tr>
</tbody>
</table>

Clinical evidence for the use of HCQ in the treatment of SARS-CoV-2 was reported in a news briefing by the Chinese Government. 62 COVID-19 positive patients with CT evidence of pneumonia hospitalised in Renmin hospital, Wuhan were included in this trial. The patients had mild to moderate illness and were admitted in the ward (none in the ICU), needing around 3 L / min nasal oxygen. It was a parallel group trial in which 31 of the 62 patients were computer randomised to receive HCQ 200 mg bid for 5 days. Other standard treatment was unchanged in the 2 groups. The treatment group showed an overall faster improvement in pneumonia on CT imaging (80% VS 54%). Crucially, none of the patients in the treatment group progressed to severe disease as opposed to 4 in the non HCQ group.

The second clinical study was a retrospective analysis published by Gautret and colleagues from Marseilles, France. In 80 hospitalized patients receiving a combination of hydroxychloroquine (200 mg of oral hydroxychloroquine sulphate, three times per day for ten days) and azithromycin (500mg on D1 followed by 250mg per day for the next four days), a clinical improvement was noticed in all but two elderly patients. A rapid fall of nasopharyngeal viral load tested by qPCR was noted, with 83% negative on Day 7 and 93% on Day 8. Virus cultures from patients’ respiratory samples were negative in 97.5% patients by Day 5 allowing a rapid discharge of these patients from contagious wards after a mean stay of 5 days. This study was critiqued by scientists around the world. Hulme and colleagues applied a Bayesian reanalysis of the paper and raised major concerns about the small size, the absence of a control limb, the fact that the physicians were not blinded, the obvious selection bias, and the inconsistently done PCR tests. Most glaringly, there had been 6 drop outs in the HCQ group (patients who had either died, needed ICU transfer, dropped out or had drug intolerance). These 6 results were surprisingly not included in the final analysis meaning Raoul “cured” only 100% of those patients who didn’t get sicker, die or leave the study! To our minds this was a deeply flawed study and the journal in which it was published took the highly unusual step of saying “it did not meet the society’s expected standards”.

Another multicentre, open-label, randomized, controlled trial conducted in China assessed the efficacy and safety of HCQ in adult patients with COVID-19. The patients were assigned in a 1:1 ratio to receive either standard of care (SOC) or SOC plus HCQ [loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily for the remaining days (total treatment duration: 2 weeks or 3 weeks for mild/moderate or severe patients, respectively)].
19 recommends against the use of hydroxychloroquine plus azithromycin outside of clinical trials because of the toxicity risk. It also mentions “insufficient clinical data to recommend either for or against using CQ or HCQ and if used, clinicians should monitor the patient for adverse effects especially prolonged QTc interval.”

A recently published study from New York examined the association between HCQ use and intubation or death in 1376 patients hospitalized at a large medical centre. They concluded that HCQ use was not associated with either a greatly lowered or increased risk of intubation or death stressing the need for further randomised controlled trials of HCQ in COVID-19 patients. The largest observational study, just published in JAMA20 also showed that in 1438 patients hospitalized in 25 hospitals in New York, the use of HCQ and/or azithromycin had no impact on in-hospital mortality.

SOLIDARITY TRIAL: “Solidarity” is an international clinical trial launched by the World Health Organization (WHO) to help find an effective treatment for COVID-19 which will compare four treatment options against standard of care and to assess their relative effectiveness against COVID-19. HCQ is one of the arms in this trial to be used in a loading dose of 800mg BD, 6 hours apart followed by a maintenance dose of 400mg BD for 20 doses. Enrolling patients in one single randomized trial will help facilitate the rapid worldwide comparison of unproven treatments. Indeed, this may prove the final answer on the efficacy if any of this drug.

Doses of HCQ to be used: There has been no uniformity in the dose of HCQ used with different dosing schedules in each trial. The doses that have been employed are summarised in Table 1.

Prophylaxis

Despite lack of data on prophylaxis, the Indian Council of Medical Research has already recommended HCQ as pre-exposure prophylaxis for frontline healthcare workers having “high-risk” contact with patients with suspected or confirmed COVID-19 (400 mg twice a day on Day 1, followed by 200 mg once weekly for next 7 weeks), and post-exposure prophylaxis for household and healthcare worker contacts of patients with confirmed COVID-19 (400 mg twice a day on Day 1, followed by 400mg once weekly for next 3 weeks). The evidence for this dosing schedule is not clear. Several trials exploring the use of CQ or HCQ for prophylaxis of COVID-19 in health care workers (HCWs) are underway, in particular a large trial in Oxford called COPCOV which is a randomised, placebo-controlled prophylaxis Study (COPCOV)21 using considerably higher doses of HCQ (a loading dose of 10 mg base/ kg followed 250mg chloroquine phosphate salt or 200mg of or hydroxychloroquine sulphate) to be taken daily for 3 months. It plans to recruit 40,000 HCWs and no definite conclusions on the utility of HCQ or chloroquine as a prophylactic agent can be drawn till this data is available. In addition, at present, there is no evidence to recommend mass prophylaxis at the population level.

Side Effects and Toxicity

The World Health Organization lists HCQ as an essential medicine.22 Majority of patients require no special caution except for patients with G6PD deficiency, diabetics and where significant drug interactions are likely. Long-term HCQ use can have adverse effects like cardiac arrhythmias (e.g., QT prolongation) and retinal damage.24 HCQ prevents the development of congenital heart block due to a potential inhibitory effect of type I interferon production and thus is safe in pregnant females.25,26 In the French study27 referred to earlier, patients receiving a combination of HCQ and azithromycin had only minor and rare side effects. Diarrhoea was the most common side effect, being seen in 4 of the 80 patients followed by nausea or vomiting (2/80) and blurred vision in one patient. In the trial conducted by Wei Tang et al,13 a significantly higher dose of HCQ (1200 mg as loading dose and 800 mg daily as the maintenance dose) was used. Adverse events were accordingly significantly higher, being reported in 21 patients (30%) in the HCQ group compared to just 7 patients (8.8%) reporting side effects in the SOC group (P=0.001). No patients reported serious adverse events in the SOC group whereas 2 patients reported serious adverse events due to disease progression and upper respiratory infection.

Toxicity seems to be dose related which was demonstrated in a randomized, phase Ib clinical trial conducted by Borba et al.20 They evaluated the effect of high doses (600 mg/day twice daily for 10 days) vs low doses (450 mg twice daily on 1st day and then once daily for four days) of chloroquine diphosphate as adjunctive therapy for patients hospitalized with SARS-Cov-2 Infection. They observed that 7 out of 37 patients in the high dosage group had QTc interval greater than 500 milliseconds as opposed to 4 in 36 patients in low dosage group. Ventricular tachycardia was seen in two patients in the high dosage group. Rhabdomyolysis developed in one patient which led to chloroquine discontinuation. These preliminary findings suggest that higher dosage of chloroquine should not be recommended for the treatment of severe COVID-19, especially among patients also receiving azithromycin and oseltamivir, because of safety concerns regarding QTc interval prolongation and increased lethality.

Chorin et al27 conducted a retrospective study in 84 COVID-19 patients treated with a combination of HCQ and azithromycin. Baseline ECG monitoring was done to rule out any QT prolongation. QTc prolonged maximally from baseline between days 3 and 4. 30% of patients showed an increase in QTc by greater than 40ms. In 11% of patients QTc increased to >500 ms, representing high risk group for arrhythmia [the QTc increased from a baseline average of 447 ± 30 ms to 527 ± 17 ms (P < 0.01)]. There were no torsades de pointes events recorded for any patients, including those with a severely prolonged QTc. QTc should be regularly followed in patients who are treated with HCQ/AZ, particularly in those with co-morbidities and in those who are treated with other QT-prolonging medications.28 Roden et al29 proposed mechanisms to minimize arrhythmia risk due to HCQ and Azithromycin use. They advised that if the baseline QTc interval is >500 msec or with known congenital long QT syndrome the drugs should be withheld and cardiac rhythm should be monitored. They also advised correction of hypokalaemia and hypomagnesemia. Recently a systematic review of 30 studies (28 ongoing) was published by Pacheo et al.30 This rapid systematic review identified two clinical studies (with available data), with limited
methodological quality, that evaluated the effects of hydroxychloroquine for COVID-19. They concluded that the efficacy and safety of HCQ and CQ in patients with COVID-19 is still uncertain and its routine use for this situation should not be recommended until the results of ongoing studies provide a proper assessment of their effects.

**Monitoring for Toxicity**

Mount Sinai Health System in their treatment guidelines for SARS-CoV-2 infection has recommended a baseline ECG before initiation of HCQ to rule out any QT prolongation and to check for any other drugs causing QT prolongation which might aggravate the risk. Based on the QTc interval their suggestions are mentioned in the figure below.

Mitra et al proposed an algorithm for management of QT prolongation in COVID-19 patients who were hospitalized. Both HCQ and azithromycin are known to cause QT prolongation and while using the combination the risk of Torsades de pointes (TdP) may increase. These drugs mainly act by blocking the hERG potassium channel. Drugs which act by blocking the late sodium current via blocking the INa-L channel (lidocaine and mexiletine) help to shorten the QT interval and suppress TdP. They suggested that the combination can be given in patients with prolonged QT interval by using late sodium channel blockers like lidocaine or mexiletine. They have also advised strict monitoring of serum electrolytes, heart rate and monitoring of QTc interval using ECG. A number of factors are known to contribute to increased risk of drug-induced TdP including female sex, structural heart disease, congenital long-QT syndromes, electrolyte disturbances, hepatic/renal failure and concomitant QT prolonging medications. The safety of QT prolonging medications may be maximized by close monitoring and optimization of these factors. A risk score has been derived and validated by Tisdale et al., for prediction of drug-associated QT prolongation among cardiac-care-unit-hospitalized patients. A Tisdale score of ≤ 6 predicts low risk, 7-10 medium risk, and ≥ 11 high risk of drug-associated QT prolongation.

Concerns regarding mortality risk, and the intensity of QT and arrhythmia monitoring should be considered in the context of several important mitigating factors: (a)The duration of use for these medications for COVID-19 infection is short (5 to 10 days for acute illness). (b) While QT-prolonging medication use has been associated with increased risk of death, this risk may be smaller than the potential benefit from treatment of COVID-19 for some patients. (c) There are large potential population-health benefits from hastening viral clearance of COVID-19. The U.S. Food and Drug Administration (FDA) on April 24, 2020 issued warnings about the use of hydroxychloroquine or chloroquine for treating COVID-19.

It warns general consumers to “not buy these medicines from online pharmacies without a prescription from your health care professional.” It also stresses that hydroxychloroquine and chloroquine “should be used for COVID-19 only where patients can be appropriately monitored in the hospital as required by the EUA or are enrolled in a clinical trial with appropriate screening and monitoring.”

**Conclusion**

HCQ was initially used extensively in most centres treating COVID-19 patients across the world. The rationale was that this was a cheap, widely available, relatively safe drug which could easily be administered orally. Whilst there is some in-vitro rationale for its use the data from the present clinical studies is not convincing enough for us to presently recommend this drug. Caution must be exercised when using it, with monitoring for potential cardiac toxicity. A Cochrane review of the available data is underway and the results of the large multi-centre SOLIDARTY trial which will include the use of HCQ across 150 sites is keenly awaited. The data from these larger, better designed RCTs are needed before we can make definite recommendations on the use of HCQ in the management of patients with COVID-19 infection. As available drug options are very limited at present, the medical community eagerly waits to learn if the current buzz around chloroquine and hydroxychloroquine proves to be hope or hype.

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Effective Patient-Physician Communication – A Concise Review

Aditya K Ghosh¹, Shashank Joshi², Amit Ghosh³

Abstract
Current medical care is heavily reliant on the use of evidence-based guidelines dealing with diagnosis and therapy. The burgeoning medical literature, easy availability of medical information in the social media and consumerism has increased the additional number of issues discussed during a patient physician meeting. Inability to satisfy the patient or their families due to poor communication skills of physicians remains an universal challenge all over the world. Poor patient physician communication decrease patient compliance to treatment strategies, poor patient satisfaction scores and on the extreme lead to violence directed to physicians. Most medical schools and residency programs have incorporated patient-physician’s communication skills in their curriculum. Similar opportunities to improve communication skills are available for practicing physicians. There are numerous tools that can be readily incorporated to improve the quality of patient physician communication. Communicating remotely with patients in the new era of COVID-19 using telehealth technology needs development of new skills that can be easily taught. Every physician need to periodically assess their own communication skills, and seek out conferences and learning opportunities within their hospitals, state, national or international medical community to continue learning and practicing new communication skills.

Introduction
Any approach on the topic on patient physician communication should start with understanding of the definition of the complex environment where the communications take place, i.e., healthcare, the uniqueness of medicine as a service industry and the expectations of the patient of their physicians. Healthcare is often defined as comprised healthcare systems and the various actions and policy within the system which improve health or well being.¹ A system based approach of assessing care includes looking at the structure of healthcare, examining the processes involved in giving actual care and the outcomes which results from the consequence of the interaction of the patient with the healthcare system. While excellent communication is involved in every step, it is most vital during the process of delivering care.

Medicine is a service industry however medical services are different from other services.² Unlike the ‘want’ services like telecommunication and entertainment industry, healthcare is a ‘need,’ service. Patient’s (consumer of medical service) are under considerable stress. Medical services are highly complex and technical and patients are at a considerable disadvantage due to the lack of knowledge on the disease. Most patients thereby have to trust their physician to be their care providers unequivocally.

In the healthcare environment, patients are challenged emotionally and go through physically grueling procedures and the stakes are usually high for patients. Errors in diagnosis, treatment plan or procedure can do great harm to the patient and worsen their quality of life. Hence most patients have to place an implicit trust on their physician. This makes patient seek physicians who possess high interpersonal qualities.

There has been considerable debate over years as what constitutes an ideal physician behavior? Based on a qualitative study of telephone interviews of 192 patients seen in the different medical specialties in Mayo Clinic Scottsdale, Arizona and Mayo Clinic Rochester, Minnesota between the years 2001 to 2002, the ideal physician was felt to be confident, empathetic, humane, personal, respectful, forthright, and thorough.² Physician behavior was felt to be as important as their technical skills and could reflect on patients first perception of physician competence. Emanuel and Dubler³ have suggested that the ideal physician-patient relationship includes 6 C’s- Choice, competence, communication, compassion, continuity and (no ) conflict of interest.

The processes of delivering care include interactions that occur between the patient and the healthcare system and comprises of (i) clinical care and (ii) interpersonal care¹. While clinical care involve the biomedical aspect of medicine and requires the physician to be skilled at diagnosing and treating the illness, interpersonal care require the interaction of the patient with the physician or other health care provider and require skills like communication, building trustful relationship, honesty, respect, integrity, empathy, and compassion.

In the present review we will focus on patient-physician communication with its challenges in clinical medicine especially in India and elsewhere. We will review the standard tools that can enhance patient physician communication in clinical practice and describe educational methods used in training of medical students and physicians in the area of patient physician communication. We highlight knowledge and skills required to communicate with patients using

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behind the tremendous advances in skills in physicians which seem to lag the slow progress of communications developed countries. However many physician communications abound in scope and opportunities of patient treatment options have increased the medicine and availability of newer technologies. Fossum and Arborelius identified the pattern of communication that they see the patient. Observation of students real-time in the locations where they spend time with patients. Physicians need to engage their patients’ stories and how the illness affected their patients’ lives. Active listening takes time but can yield essential clues about the patient’s health. Doctors are under tremendous pressure to be productive in patient’s health. Doctors are under tremendous pressure to be productive. Doctors are under tremendous pressure to be productive. Doctors are under tremendous pressure to be productive. Doctors are under tremendous pressure to be productive.

Many medical school and residency programs provide inadequate education on effective communication skills. Lot more time is devoted in teaching courses on advances in science and technology as well as learning evidence-based guidelines. In pre-clinical years students are able to spend time learning the curriculum as well as taking part in OSCE’s. However when students enter their clinical years communication skills are not addressed in the curriculum as well as taking part in OSCE’s. However when students enter their clinical years communication skills are not addressed in the curriculum as well as taking part in OSCE’s. However when students enter their clinical years communication skills are not addressed in the curriculum as well as taking part in OSCE’s. However when students enter their clinical years communication skills are not addressed in the curriculum as well as taking part in OSCE’s. However when students enter their clinical years communication skills are not addressed in the curriculum as well as taking part in OSCE’s. However when students enter their clinical years communication skills are not addressed in the curriculum as well as taking part in OSCE’s. However when students enter their clinical years communication skills are not addressed in the curriculum as well as taking part in OSCE’s.

In a study of videotaped interactions of patient physician communication, Fossum and Arborelius identified several components of a favorable patient centered consultation. These include for (i) the provider to be flexible, and (ii) being able to frequently move back and forth between discussion and communication with the patient’s problems keeping the patient’s expectation and concern into account. Consultations that included a steady, slow, sequential movement through the topics were associated with poor patient satisfaction as these did not involve patient’s input and there was a perception halfhearted attempt for a shared decision making. Patient centered interviews and patient physician communication

One the most common mistaken notion is that every physician is the skilled communicator. Most patients presume that a technical sound doctor is also an expert communicator. They are disappointed many times as a result of this assumption. Like most disciplines in medicine, excellent communication is a learned skill that is not intuitive though can be mastered with practice. The skill to be an effective communicator is a lifelong learning experience which needs continuous practice and improvement throughout the physician’s career. For most physicians good communication is also a good business practice.

From the patient’s perspective it is widely believed that patient centered communication is preferred over a physician centered communication style when it comes to history taking. Patient centered communication has a positive impact on several important outcomes like patient satisfaction, their adherence to treatment recommendations, and self-management of chronic diseases.

Patient centered communication increases the health providers understanding of patients individual needs, their values and perspectives, and allows them to give to the patient the information that they need for their own care, to build trust and understanding between the patient and the physician. This pattern of communication involves both verbal and nonverbal of physicians (e.g., posture, eye contact, vocal tone). Clinical outcomes in the management of diabetes, hypertension, and cancer are improved in patients who have had a chance to communicate the problems clearly by the physician using a patient centered communication style. Breakdown in communication is associated with increased likelihood that patient will initiate malpractice actions.

National Cancer Institute lists six fundamental functions of physician patient communication namely, (i) foster healing relationship, (ii) asking and exchanging information, (iii) responding to patients emotions, (iv) managing uncertainty, (v) making informed decision, and (vi) enabling patient self management.

Tools to improving medical communication skills

The common myths about doctor patient communication is that these skills are intuitive, innate, and automatically learned by more experience. Communication skills can be learnt and improved. Physicians need to devote time throughout their career as communication skill is a lifelong learning endeavor. Communication needs to be thoughtful and measured as words uttered in haste cannot be retracted and have an adverse effect on patients. What we say and how we communicate has a placebo effect (reduce anxiety) or nocebo effect (that is bad communication can increase pain and anxiety). Patient’s values their physician’s communication skills and consider them equal or greater than any cool technical skills. These also affect the patient’s ratings of the care they have received in hospital.

Many tools have emerged to aid in doctor patient communication.

A. The medical interview process can be conducted using the pneumonic GREAT, LAURS and VALUE technique.

i. GREAT : Greeting and Goals/ Rapport/ Evaluations, Expectations, Examination and Explanation/ Ask, Answer, Acknowledge/ Tacit agreement and Thanks.

ii. LAURS : Listening, Acceptance, Utilization of appropriate word, Reframing, and Suggestion.

iii. VALUE : Value family statements, Acknowledge emotions, Listen, Understand a patient as a person, Elicit questions. VALUE technique can help in shared decision-making.

B. Relationship building skills can be enhanced using PEARLS technique. PEARLS include Partnership for joint problem-solving, Empathetic understanding, Apologies for barriers to learners success, Respect for patients values and choices, Legitimation of feelings and intentions, and Support
for efforts at correction.

C. Patient centered interview could include the sentence ‘what else’ which would let the patient to express all the concerns rather than interrupting patients after the first statement

D. Assessing patients understanding of medical problem can be performed using the ‘Ask Tell Ask’ technique 12. The ‘ask tell ask’ method includes the following steps:

i. ASK the patient to describe the current understanding of the issue this will help the provider understand the patient’s level of knowledge, emotional status, and degree of education.

ii. TELL the patient in a simple language what you need to communicate regarding diagnosis, bad news, or treatment options while avoiding giving long lectures speak on easy language languages

iii. ASK the patient if she/he understood what you just said. This will give you an opportunity to check the patients understanding of her problem

E. When things are not clear-one effective technique that is used commonly when things are not clear or when you’re stuck is to ask for more information using ‘Tell me more!”

F. Communication tools used while responding to emotions - Use the pneumonic NURSE 13

i. N - Naming the emotion

ii. U - Understanding that the patient’s feelings are problems. This helps and building a relationship

iii. R - Respecting. Praise the patient for strength. This this can be a non-verbal response involving facial expression, touch or change in posture but could also be a verbal response acknowledging and respecting the patients emotions that shows empathy

iv. S - Supporting. Position can express concern, willingness to help, suggest statements about partnerships. Acknowledge patients efforts to cope

v. E - Exploring and asking the patient to elaborate on the emotion. This puts the physician in the patient’s position and to communicate that you understand their situation.

Empathy is different from sympathy which is a feeling of pity or concern from outside the patient’s position

G. One strategy of breaking bad news involves communication step summarized by the six step pneumonic SPIKES 14

SPIKES stands for Setting, Perception, Invitation, Knowledge, Empathy, Strategize 14. The six- step protocol for delivering SPIKES include:

i. Setting: plan ahead and have appropriate personal and family members present. Anticipate for possible patient reaction,

ii. Perceptions: as the patient what he or she has been told about the disease and audit the purpose of meeting. Correct any misconception

iii. Invitation find out how much the patient wants to know and how was your she would prefer to hear information

iv. Knowledge: gift patient the news use small sentences without medical jargon use pauses to address any emotion.

v. Empathy use empathetic statement to address emotions. Resist temptation to fix the situation.

vi. Strategize emphasize what can be done. Shift hope to achievable goals.

The key feature is maintaining hope is to support the patient through the grief and to re-orient them to what is more achievable. Understanding what is most important to the patient or what the patient is most afraid of when they are faced with the new medical reality helps the patient grasp their situation. An important aspect of communication with patient is advanced care planning, the process of finding out from the patient the future goals of care as disease worsens, and identifying a surrogate decision maker.

What is the patients coping style? Monitors versus Blunters

It is important to know your patient’s coping style. Are they monitors or blunters? Patients who have a problem focused coping style are called monitors, patient who use emotion focused coping’s are called blunters. 15

Monitors are more concerned and distressed about the risk for disease including cancer. They tend to scan and amplify worrisome cues in their health information and worry about threats and risk for a long period of time. They experience great anxiety about health risk and keep worrying about threatening information. While dealing with patients who are monitors it is important to provide them with detailed information about the health risk or this specific condition as well as strategy of managing and reducing the risk to decrease the anxiety.

On the other hand blunters do not seek for detailed information about the health risk of their medical condition. They become overwhelmed with health information. They find large quantity of information to be stressful specially if it includes statistics and risk factors and therefore blunt or block it from their conscious thought. Blunters may avoid medical screening procedure or choose not to engage in important health behaviors depending on how health information is presented and interpreted by them. Effective health messages presented to blunters should be short and succinct. Effective health messages presented to monitors should be clear and specific. Physicians should utilize non threatening language and explained the course of action in simple terms.

Can communication skills be taught?

1. Experiences with practicing Physicians: Communication skills can be taught to practicing physicians 16. A communications skill building course for physician has been conducted twice annually since 2004 in the Mayo Clinic Arizona. These courses where designed to increase physicians personal awareness as well as allow them to develop new communication and interpersonal skills. Satisfaction data from 3,561 patient surveys of 80 physicians who attended this course were analyzed. Patients who were seen by physicians who had completed the course reported a higher satisfaction rate as compared to the baseline scores of these physicians. There was also a 18% decrease in patient complaints. 15

The topics that were included in this course where, (i) active listening and reflection, (ii) eliciting and negotiating an agenda and (iii) relationship building. These topics were covered with a combination didactics and role-playing simulation. Participants shared challenging experiences and have opportunity to engage in role-play simulation, followed by facilitator guided debriefing. All participants offered their perspectives and strategies to each other when they encountered similar situations. Facilitators noted a increased spirit of continuous learning and improvement. Physicians where encouraged to incorporate the appropriate skills and behaviors which
they found more useful for the practice.

2. Experience with medical students: Medical students communication skills at the Mayo Medical School is assessed using a validated Interview Rubric comprising of 13 items. Each item under the category carry a score of 1–4 assessing the thoroughness of completion of each task under each category. The Interview Rubric is used to observe and provide feedback to medical students during history taking sessions of standardized patient’s.

The 13 categories of the Interview Rubric are:

1. **Introduction**: An effective introduction lessens the patient’s anxiety. The initial first few minutes of patient-physician interaction is very helpful informing a strong foundation,

2. **Eye contact with the patient**: The provider’s eyes should be at the same level with the patient’s eyes. A consistent engagement on the part of the provider is necessary as it shows good listening capability.

3. **Nonverbal communication**: Demonstration of emotions of physician (student) through nodding off the head, posture, body position, gives patient an impression that the provider is interested and empathetic.

4. **Listening**: Not being listened is a major source of patient to satisfaction. Good listening skills and essential for patient provider relationship.

5. **Questions**: Use simple language in asking questions from the patient instead of using complex medical jargon. Clarify rather than simplify the patient’s problems to help the student come to a diagnosis.

6. **Wait – time**: Allow enough time for the patient to answer one question before going to the next question. Giving inadequate time is disturbing to patient.

7. **Concern**: Showing genuine concern for patients problems and interest in every patient

8. **Organizations**: Interview should be conducted in an organized manner. It doesn’t mean that it should be rigid.

9. **Information gathering**: Establish a list of the patient’s agenda for the visit. Determine according to the time available and the urgency of the patient’s visit.

10. **Focus**: Interrupt the patient as little as possible. However a subtle control over the flow of the direction of the interview is important to facilitate the discussion.

11. **Empathy**: Ability to understand the patient’s feelings and put his/her feelings into words is essential in Medicine. Demonstrating empathy is essential part of effective communication.

12. **Awareness of unspoken issues**: Gently probing and reading between the lines when necessary can frequently allow the physician gain significant medical information hence watching the patients emotions and concerns that light below the surface of conversation is important

13. **Closure**: An appropriate closure to the interview is important. The physician needs to summarize what was discussed. It is necessary to ensure to the patient that there are no pending issues.

**Communication in Telehealth era: The COVID-19 experience**

The nature of the Coronavirus Disease 2019 (COVID-19) pandemic has forced the medical practice to evolve rapidly in order to adapt to the new requirements. One of the most notable adaptations recently has been the relationship between patient care and telemedicine has been one that has slowly evolved over the years. While in recent years, the practice of telehealth has been evolving slowly, it was still not considered plausible that telehealth could be practiced effectively. However, COVID-19 has forced that plausibility to quickly become a reality in order to safely practice social distancing and to deliver effective clinical care while avoiding unnecessary face to face exposures between doctors and their patients. Even whilst the kinks and drawbacks of telehealth are being discovered and worked through, the practice is being put to use by medical practitioners around the world.

Telehealth, also known as telemedicine, is defined as the dissemination of medical information that is conveyed through the medium of electronic communication. The modalities of this electronic communication comprise of a wide variety of resources including e-mail, video chat, phone calls, remote wireless monitoring, and mobile apps. Tucker, et. Al, in their seminal paper mentioned that there are three core levels at which telehealth is practiced: 1) Clinician to Clinician, 2) Clinician to Patient, and 3) Patient to Mobile Health Technology.

At each level, the tools that are utilized to practice telehealth and the services that most often utilize these tools are unique. For example, clinicians will communicate to each other via the use of e-mails and videos, especially in settings of Emergency trauma, ICU care, and surgical peer mentoring. In these settings, it is important for clinicians to be able to communicate via video in order to see examples and establish visual connection regarding the care that needs to be provided. Clinician to patient telehealth is practiced in the setting of care for chronic conditions, medication management, mental health, and counseling. In this setting, many modalities of telehealth utilized include remote wireless monitoring, as well as video chat and phone calls. In these settings, the connection outside of the clinic or hospital setting is important to cultivate via telehealth modalities, as it allows for patients to routinely follow up with their doctors without having to schedule multiple visits, which could discourage effective patient follow-up.

All three of this core telehealth settings (clinician-clinician, clinician-patient, and patient-mobile health technology) work together to guide patient care and management. Understanding the multiple avenues and opportunities to incorporate telehealth into medical care will help in developing systems that can serve as a powerful force in preventative medicine, improve patient care, and promote overall patient well-being.

As important as these benefits...
are, it is important to explore the drawbacks of telehealth practice as well. A thorough understanding of where telehealth can be seen as inferior to a proper visit to the clinic can help improve the overall experience of the Doctor-Patient relationship while conducting a Telehealth visit. Details of the critical components of effective telehealth visit are included in Table 1.

Effective communication with the patient can drastically improve the overall experience of telehealth practice by using the techniques GREAT and NURSE discussed before.

These drawbacks include: 1) set up, 2) skill set is foreign to many healthcare workers, not a developed skill set, 3) lack of management of the whole environment, 4) anxiety management (importance of building connection with patient, knowing how to position oneself in camera to not look down at patient) in conclusion patient physician communication is among the most essential lifelong skills for every physician. Every physician need to periodically assess their own communication skills, and seek out conferences and learning opportunities within their hospitals, state, national or international medical community to continue learning and practicing new communication skills. Every physician needs to be aware of their own communication styles and the prevalent culture within the community where they see their patients. Communication skills needs to be modified based on the subtle cultural variation that exists between different communities. Communicating remotely with patients in the new era of COVID-19 using telehealth technology needs development of new skills that can be easily taught. Mastering good communication skills could be one of the most satisfying personal achievements for every physician.

References


<table>
<thead>
<tr>
<th>Table 1: Critical components of an Effective Telehealth Visit</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>What is it</strong></td>
</tr>
<tr>
<td>Environment</td>
</tr>
<tr>
<td>I. Lighting</td>
</tr>
<tr>
<td>II. Background noise (either patient or doctor)</td>
</tr>
<tr>
<td>III. What is behind the physician in the background</td>
</tr>
<tr>
<td>Vocal variety</td>
</tr>
<tr>
<td>I. Tone while speaking</td>
</tr>
<tr>
<td>II. Clarity of voice</td>
</tr>
<tr>
<td>Confidentiality</td>
</tr>
<tr>
<td>Lag in response</td>
</tr>
<tr>
<td>Lack of immediacy moving from interview to executing management</td>
</tr>
<tr>
<td>Attitude to unfamiliarity</td>
</tr>
<tr>
<td>Equipment</td>
</tr>
<tr>
<td>I. Web Camera</td>
</tr>
<tr>
<td>II. Microphone</td>
</tr>
<tr>
<td>III. Internet connection</td>
</tr>
<tr>
<td>IV. Adjustable height to make sure webcam is at eye level</td>
</tr>
<tr>
<td>V. External lighting (optional)</td>
</tr>
</tbody>
</table>
| Appropriate assignment of purpose of telehealth visit | }

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API Guidelines on Immunizations during COVID-19 Pandemic

S Arulrhaj¹, Shashank R Joshi², Siddharth N Shah³, Mangesh Tiwaskar⁴, Milind Nadkar⁵, Agam Vora⁶

Scope

With the continued lockdown and other restrictions, the Medical professionals need guidance regarding immunization activities. It is in this context API is bringing out these guidelines.

• Continuation of immunization activities
• Prioritization of certain vaccines
• Precautions to be taken while immunizing during COVID-19 Pandemic

Background

The WHO declared COVID-19 as a Global Health Emergency in January 2020. It was declared a “Pandemic” on March 11, 2020. The Government of India declared a lockdown on March 22, 2020, which was initially for 21 days, ending on April 14, 2020, but was extended up to May 3, 2020 and further to May 17, 2020. The Ministry of Home Affairs has released guidelines to be followed during the lockdown on April 15, 2020. Since March 22, 2020 effective primary, secondary and tertiary care facilities have been minimal in view of the lockdown. The primary focus of public health has been in preparedness and containment of COVID-19 pandemic in the country and all other preventive health activities have been relegated to the background. Any flare of VPD will additionally burden the already stressed health care systems. The ministry of Home affairs in its guidelines dated April 15, 2020, has mentioned that Essential Medical Services be maintained during the lockdown. Clinics and Hospitals must continue providing Essential Medical services to non-COVID 19 patients.

Prevention (including immunizations) and management of communicable diseases is considered as an “Essential Medical service”.

It should be emphasized that “Immunization is a Core Health Service” that should be prioritized

Recommended Immunization schedule for adult individuals:

<table>
<thead>
<tr>
<th>Immunized</th>
<th>Not Immunized</th>
<th>Vaccine</th>
<th>Dose and Route</th>
<th>Brands</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPT</td>
<td>Between the ages of to 64 years A booster dose of Td vaccine once every 10 years till the age of 65 years</td>
<td>18-3 doses of Td vaccine; 2 Td doses are administered 4 weeks apart 3rd dose 6 to 12 months after the second dose</td>
<td>0.5 cc IM</td>
<td>Boostrix GSK Adacel –Sanofi Triple Ag Serum Institute</td>
</tr>
<tr>
<td>MMR</td>
<td>Not indicated</td>
<td>Single dose SC</td>
<td>Live vaccine</td>
<td>0.5cc SC</td>
</tr>
<tr>
<td>Influenza</td>
<td>For all especially high risk For all &gt; 65 years &lt; 65 years in those at risk</td>
<td>Every year</td>
<td>Every year</td>
<td>Inactivated</td>
</tr>
<tr>
<td>Pneumococcal (PCV13 and PPSV23)</td>
<td>Not indicated</td>
<td>PCV13 – 1 dose PPSV23 – 2 doses</td>
<td>PCV13 – Conjugate vaccine PPSV23 – Polysaccharide vaccine</td>
<td>0.5 cc IM</td>
</tr>
<tr>
<td>Varicella</td>
<td>For all who are not immune</td>
<td>Two doses administered 4 to 8 weeks apart</td>
<td>Attenuated live VZV (Oka Strain) in both 2.05 ml in deltoid area SC</td>
<td>Varilrix (Glaxo Smith Kline Biologicals) Okavax (Pasteur Merieux )Varibed MSD</td>
</tr>
<tr>
<td>Human Papilloma Virus</td>
<td>For adults who are already immunized booster dose is not needed if titles are adequate</td>
<td>In age group 9-14 years 2 doses are recommended at an interval of 6 months. For 15-26 years at 0.1 and 6 months</td>
<td>0.5 ml intramuscularly</td>
<td>GSK Cervarix-bivalent MSD Guardasil- 4 valent</td>
</tr>
<tr>
<td>Zoster</td>
<td>In &gt; 60 years</td>
<td>&gt; 60 years single dose</td>
<td>Live attenuated</td>
<td>0.65 ml subcutaneous in deltoid</td>
</tr>
</tbody>
</table>

¹President, The Association of Physicians of India; ²Dean, Indian College of Physicians; ³Director, Physician Research Foundation; ⁴Honorary General Secretary, The Association of Physicians of India; ⁵Honorary Editor Journal of The Association of Physicians of India; ⁶Member of Governing Body, The Association of Physicians of India

Received: 10.05.2020; Accepted: 18.05.2020
# Recommended Immunisation Schedule in special situations (routinely not used)

<table>
<thead>
<tr>
<th>Insert vaccines</th>
<th>Risk groups</th>
<th>Immunized</th>
<th>Not immunized</th>
<th>Vaccine</th>
<th>Dose or Route</th>
<th>Brands</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hepatitis B</td>
<td>At high risk</td>
<td>Not indicated</td>
<td>0.1, and 6 months if not immunized in childhood or if anti-HBs &lt; 20</td>
<td>Recombinant and plasma derived</td>
<td>Single dose child 10ug 20Ug adults</td>
<td>Shanvac B (Shanta biotech)</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>At risk</td>
<td>Single dose if high risk</td>
<td>2 doses at 6 months interval if not immunized in childhood</td>
<td>Inactivated</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Meningococcal</td>
<td>Not recommended routinely</td>
<td>High risk</td>
<td>Travelers and epidemic</td>
<td>Meningococcal conjugate (not for &lt; 2 years or &gt; 55 years)</td>
<td>0.5 cc SC &gt; 55 years 2 doses 1 month apart</td>
<td>Menactra (Sanofi)</td>
</tr>
<tr>
<td>Haemophilus influenzae</td>
<td>At risk</td>
<td>Single dose of HiB in high risk</td>
<td>Single dose of HiB in high risk</td>
<td>Antigen is polyribose phosphate or outer membrane protein and carrier is tetanus toxoid conjugate or diphtheria CRM protein</td>
<td>0.5 ml IM</td>
<td>Hiberix (GSK)</td>
</tr>
<tr>
<td>Rabies</td>
<td>Not routine as prophylaxis</td>
<td>Pre exposure for high risk</td>
<td>For those immunized 0, 3rd days no immunoglobulin</td>
<td>Pre exposure 0.7, and 28 days IM</td>
<td>Post exposure 0.3,7,14 and 28 days (90 days optional) with Rg ID 0.3,7 and 28 days over deltoid</td>
<td>HDCS PCECV Verorab(not for pre exposure)</td>
</tr>
<tr>
<td>Cholera</td>
<td>High risk patients</td>
<td>For high risk 2 separate doses 1 to 6 weeks apart for those aged over 6 years</td>
<td>For high risk 2 separate doses 1-6 weeks apart for those aged over 6 years</td>
<td>2 oral vaccines</td>
<td>2 separate doses</td>
<td>Dukoral (WC/ rBS) Recombinant B subunit</td>
</tr>
<tr>
<td>Typhoid</td>
<td>High risk Travellers or outbreak</td>
<td>If immunized booster every 3 years</td>
<td>3 doses of typhoid 23 a capsules / sachets are administered on alternate days Series repeated once in every 3 years as booster dose Vi vaccine single SG/ IM dose of 0.5 ml Revaccination every 3 years</td>
<td>2oral vaccines</td>
<td>2 separate doses</td>
<td>Dukoral (WC/ rBS) Recombinant B subunit</td>
</tr>
<tr>
<td>Varicella</td>
<td>Those who did not have chickenpox</td>
<td>For those already immunized in childhood booster doses are not needed if titres are adequate</td>
<td>Two doses administered 4 to 8 weeks apart</td>
<td>Attenuated live VZV (Oka strain) in both</td>
<td>2 doses 0.5 ml in deltoid area SC</td>
<td>Varilrix (GSK Biologicals) Okavax (Pasteur Merieux) varibed MSD Biovac chinese</td>
</tr>
<tr>
<td>Japanese encephalitis</td>
<td>Not routine</td>
<td>Single dose and booster dose may be given at 1 year</td>
<td>Mouse brain derived inactivated vaccine (NA) cell culture, live attenuated vaccine</td>
<td></td>
<td>0.5 ml SC Booster at 1 year</td>
<td>Chiron – old Protect Sanofi – immumax polio</td>
</tr>
<tr>
<td>Polio</td>
<td>Adults travelling to polio infected countries</td>
<td>Single dose of IPV/OPV spaced by 1 month</td>
<td>3 doses of IPV/OPV spaced by 1 month</td>
<td>Oral sabin IM killed salk</td>
<td>Live vaccine</td>
<td>Chiron – old Protect Sanofi – immumax polio Rotarix GSK RotaTeq MSD</td>
</tr>
</tbody>
</table>

for the prevention of communicable diseases and safeguarded for continuity during the COVID-19 pandemic, where feasible. Immunization delivery strategies may need to be adapted and should be conducted under safe conditions, without undue harm to health workers, caregivers and the community.

**Immunizations during a Pandemic**

Due to reasons mentioned above, immunizations should be continued during COVID-19 Pandemic as immunization is an essential health activity.

**API Policy Decision during COVID 19 Pandemic**

Elderly about 50 years with Diabetes, COPD, Cardiac Disease, Kidney Disease must be recommended to have Influenza vaccine every year. We recommend this in our Routine Medical Practice.
During Pandemic of Covid Physicians must stress this Influenza vaccine. In fact the World Health Organization (WHO) during this Covid pandemic has mentioned that vaccination against respiratory illnesses (pneumococcal vaccine and Hib vaccine) is highly recommended to protect one’s health. Physician must advise parents to undertake the Immunization schedule to their children meticulously. There are lot of benefits coming out of BCG vaccine, Hepatitis vaccine and other viral vaccines. Evidences are in the

publication Physicians must take care of their Health by adapting to Adult Immunization Schedule to them, Family, Colleagues, and Healthcare workers.

References
Chest CT for Screening of COVID-19: Is it Feasible in Developing Countries?

Vineeta Ojha¹, Avinash Mani², Sanjeev Kumar³

CT has been proposed as a screening tool to detect COVID-19 cases owing to its high sensitivity when compared to RT-PCR.¹² However, this is to be taken with a pinch of salt.

Firstly, considering RT-PCR as the gold standard, 30% of the patients may have false positive findings on CT, denoting low positive predictive value as well as low specificity.¹ Also, it is worth noting that approximately 50% patients may have normal CT scan at initial presentation (0-2 days after symptom onset).² Hence, even patients with positive RT-PCR can also have a normal CT scan.

Secondly, the sterilization of CT machines is a daunting task requiring surface wipe-down with disinfectant as well as floor clean-up with dilute hypochlorite solution after the CT examination of a COVID patient.³ Most of the hospitals in the developing world in which COVID-19 is rapidly entering the stage of community transmission (Stage 3), cannot solely dedicate a CT machine only to test RT-PCR positive COVID-19 patients. Most of these hospitals have only one scanner and other critically ill patients might also require the same machine. There is always a risk of spreading the infection to these patients using the same scanner which is not properly sterilised. Moreover, many of the hospitals in low to middle income countries do not have an access to a CT scanner.

Finally, it is also to be noted that many of the COVID-19 patients are critically ill and transportation of these patients to the CT scanner for regular scanning is not only cumbersome, but also runs the risk of spreading the infection on the way to the scanner. Additionally, large scale use of CT can also increase the risk of radiation exposure to a large section of population.

Hence we conclude that even though CT might be a diagnostic tool with high sensitivity, RT-PCR still remains the standard diagnostic test for COVID-19, given the above mentioned drawbacks of CT. CT is recommended only in selected clinical situations for example, a COVID-19 patient with worsening respiratory status or at risk of progression or those with moderate – severe clinical features.⁴ It is especially pertinent in resource-poor settings in developing countries, where we are still preparing our best to tackle the surge in number of cases western countries are currently facing. According to the current literature, portable X-rays and ultrasounds could be more useful for diagnosis and follow up of lung abnormalities in COVID-19 patients, as it is easy to sterilize these equipments after each use and also minimizes the chances of cross-infection.⁷⁸

References

Rare Case of Congenitally Corrected TGA (CCTGA) presenting in 8th Decade

Donakonda Arun Kumar¹, Suresh Babu M²

Congenitally corrected transposition of the great arteries (CCTGA) is a rare form of congenital heart disease characterised by atrioventricular as well as ventriculoarterial discordance. The life expectancy of individuals with CCTGA is limited by the onset of the systemic ventricular failure. There have been only a few patients with CCTGA and age >50 years reported in literature.¹

We describe a 73 year-old man with CCTGA who was admitted to the hospital because of congestive heart failure. 2D Echocardiography done showed double discordance (AV and VA discordance), aorta was in the left and anterior to pulmonary artery, normal pulmonary and systemic venous drainage, depressed biventricular function with LVEF-30%, severe regurgitation of left and right AV valves, dilated LA, RA, RV suggestive of Congenital Heart Disease with Congenitally corrected TGA, with depressed biventricular function. Patient was treated with diuretics, cardiac medications and became symptomatically better.

Patients with CCTGA rarely survive to old age, CCTGA without associated intra cardiac defects is very rare. Fewer than 30 patients older than 40 years have been reported in the literature.² Our patient is one of the rare case survived up to this age. Much controversy exists regarding the ability of the morphological RV to support the systemic circulation In patients with CCTGA, who present as a naturally occurring model of this adaptation, systemic ventricular failure is the cause of death in more than 50%. A progressive deterioration of the systolic function of the systemic ventricle has also been described in patients without associated cardiac defects. First degree heart block, incomplete LBBB and increasing left (tricuspid) and right (mitral) atrioventricular valve regurgitation are known contributing factors.

Our patient presented with a profound deterioration in systemic ventricular systolic function. As there was no evidence for severe concomitant heart disease, the deterioration in systemic ventricular function may either be caused by long term maladaptation of the geometrically unfavourable RV shape or to the inability of the right coronary artery to supply the hypertrophied RV. Surprisingly, the limits of the RV adaptation to the systemic afterload seemed to be reached only at the age of 73 years.³

References

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Multiple Adhesions Diagnosed on $^{99m}$Tc-Nanocolloid Peritoneal Scintigraphy in a Patient with Previous Continuous Ambulatory Peritoneal Dialysis (CAPD)

Sandip Basu¹, Nandigam Santosh Kumar², Udaya Sekhar³

Herein, we present a 52 years old male, patient of end stage renal disease, who previously underwent CAPD and had developed 3 episodes of peritonitis and subsequently converted to hemodialysis, now presented with failure of multiple AV fistulas and planned for CAPD again. 13 mci of $^{99m}$Tc-nanocolloid diluted in 1.5 liters of peritoneal dialysate injected intraperitoneally through the peritoneal catheter under aseptic conditions and sequential anterior and posterior static images were acquired. Early preambulatory images demonstrated localized accumulation of tracer activity in sub-hepatic, umbilical and left iliac regions. Post-ambulatory and post-drainage static images demonstrated persistence of the uptake. No collection of tracer activity was observed in lateral aspects of the abdomen. Left pleuroperitoneal connection was also noted. X-ray chest revealed pleural effusion. Laparotomy was undertaken which revealed multiple peritoneal adhesions.

Peritoneal scintigraphy is safe, accurate and non-invasive way for diagnosing leaks in the peritoneal cavity along with diagnosing peritonitis, pleuropertoneal connections and possible adhesions before restarting CAPD. Some patients are able to return to CAPD after several episodes of peritonitis, a few others, unfortunately develop peritoneal adhesions may prevent catheter reinsertion, where peritoneal scintigraphy can provide valuable information in diagnosing adhesions.

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Received: 07.07.2017; Accepted: 09.10.2019
Coronary Cameral Fistula – A Rare Cause of Angina Pectoris in a Young Patient

Satyendra Kumar Sonkar¹, Anil Kumar²

Abstract
Coronary cameral fistula, a rare cause of angina pectoris in a young patient is of rare occurrence and is very sparsely reported. We present here a case of a 23 year old male with complaints of chest discomfort and breathlessness on exertion for 4 months. 2D Transthoracic echocardiography showed coronary cameral fistula opening into right atrium.

Introduction
Coronary cameral fistula results from an abnormal coronary artery system with abrupt terminations in the cardiac chambers. Anatomically, coronary arteries branch into capillaries and supply the myocardium. Embryologically, CAF seem to occur due to persistence of primitive intralabecular spaces. There are few reports mentioning coronary fistula opening into right atrium as a cause of angina pectoris. Owing to a very unique and almost uninform presentation, we considered this case with reporting.

Case Presentation
A 23 year old male presented in the medical emergency department with complaints of chest pain and breathlessness on exertion (NYHA class II/III) for 4 months. History of cough with minimal expectoration was present. No other significant medical and family history. On examination patient was afebrile, pulse rate 102 bpm, respiratory rate-26 breaths/min, and blood pressure 124/70 mmHg in right arm supine position. Systemic examination was unremarkable.

Differential Diagnosis
Patient was suspected to be a case of chronic respiratory disease like interstitial lung disease, pulmonary tuberculosis or stable angina, which could be attributable to anemia or structural heart disease and least likely coronary artery disease.

Investigations
Electrocardiogram was with in normal limits. Laboratory values showed Hb 10.3 g/dl, Hematocrit 34 %, WBC of 7.01 X10 9/L with 69 % neutrophils, Platelet count 110 X 10 9/L, Prothrombin time 17.2 second, Total serum bilirubin 0.73 mg/dL, with direct fraction 0.4 mg/dL, Serum Aspartate transaminase 10.8 IU/L, Serum Alkanine transaminase 10.9 IU/L, Serum Alkaline phosphatase 256.2 IU/L, Random blood sugar 84.9 gm/dl, S. urea 46.3 mg/dl, serum creatinine 0.93 mg/dl, Sputum for acid fast bacilli by Modified ZN method was negative. Chest skiagram posterioranterior view was normal. CECT (contrast enhanced computed tomography) Thorax shows evidence of irregular shaped small nodules in left curve zone, posterior segment and subpleural location. Rest of lung fields was normal. There was a filling defect in right atrium which required further echocardiographic correlation. 2 D transthoracic echocardiography shows a continuous flow of velocity 2 m/sec in right atrium signifying coronary cameral fistula along with a 2.7 X 1.8 cm. homogenous mass present in right atrium attached to lower inter atrial septum.

Treatment
After thorough investigations this patient was diagnosed as a case of coronary cameral fistula which was incidental finding. Patient was managed conservatively on beta blockers, nitrates and low dose aspirin.

Discussion
Coronary artery fistulas are rare congenital vascular anomalies of abnormal termination of coronary arteries and its incidence is 0.002%. In coronary cameral fistulas, coronary artery drains in cardiac chamber but when coronary artery abnormally communicate with a vein then it is called coronary arteriovenous fistula. Cardiac chambers (RV > RA >LV >LA) are involved in coronary cameral fistula and the major vessels like (pulmonary artery > coronary sinus> superior vena cava) in coronary arteriovenous fistula. Incidence of coronary cameral fistula varies from 0.08 -0.3 %, majority of them are incidently detected during transthoracic echocardiography or coronary angiography. The right coronary artery (55%) and left coronary artery (35%) are commonly involved in coronary artery fistula formation.

Clinical presentation varies on the basis of size, location, presentation of coronary steal phenomenon or amount of right –to-left shunt. Most coronary artery fistulae are small and usually do not cause any ischemic symptoms and excellent long-term prognosis. Large size CCF can present like angina, exertional dyspnea, palpitation, syncpe, myocardial infarction and rarely as endocarditis. Hemodynamically significant fistula with a left to right shunt may lead to congestive heart failure, pulmonary artery hypertension, and myocardial ischemia due to exertion induced coronary steal phenomenon.

In symptomatic patients of coronary artery fistula, fistula should be closed by either surgical or transcatheter approaches. Antiplatelet and antianginal drugs are required in proximally located moderate to large sized fistulae as well as for symptomatic relief from angina. Our patient was
managed conservatively as he denied from any surgical intervention and was discharged on anti-platelets and antianginal medications.

**Learning Points/Take Home Messages**

Coronary cameral fistula which itself is a rare entity, are usually asymptomatic but can present with angina, palpitation, signs of exercise related coronary insufficiency with normal ECG. It can also present with signs and symptoms of congestive heart failure with murmur. It can be a mimicor of atherosclerotic coronary artery disease.

**References**


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**Reversible Cardiovocal (Ortner’s) Syndrome in Dilated Cardiomyopathy - A Rare Presentation of a Common Disease**

**Anbarasan S¹, Vairakkani R¹, Chinnaiyan P², Indhumathi V³**

**Abstract**

Ortner’s syndrome is a rare cause of recurrent laryngeal nerve palsy due to cardiac causes. After the description of this syndrome by Ortner in patients with mitral stenosis, it was described by many authors in multiple other cardiac conditions. Here we present a case of Ortner’s syndrome in Dilated cardiomyopathy, which reverted completely after medical management of DCMP.

**Introduction**

Cardiovocal syndrome (Ortner’s Syndrome) was first described by Ortner, a Viennese physician in 1897 in patients with Mitral stenosis. Ortner attributed it to the enlarged left atrium compressing the left recurrent laryngeal nerve, resulting in hoarseness of voice. Since then many reports have been made about this rare syndrome in multiple other cardiovascular diseases. But the recurrent laryngeal nerve palsy resolving completely with medical management of the cardiovascular condition is not found in literature. Here we present this case of recurrent laryngeal nerve palsy due to Dilated cardiomyopathy which resolved completely with medical management of DCMP.

**Case Report**

A 65 years old male presented with insidious onset, gradually progressive dyspnea on exertion with history of paroxysmal nocturnal dyspnea for two months. He also had hoarseness of voice and non-productive cough, which was gradually worsening over the same duration. It was associated with swelling of legs and abdominal distension. There was no symptoms of upper respiratory tract infection, nasal regurgitation. He did not have chest pain, palpitations or syncope. History of reduced urine output was present and there was no early morning periorbital or facial puffiness. His past history revealed that he was a smoker amounting to 40 pack years and has quit a year back. There were no other comorbid illnesses including COPD, diabetes mellitus, hypertension or CAD.

Physical examination revealed that he was in congestive cardiac failure with elevated JVP, presence of S3 gallop, bilateral basal crackles with congestive hepatomegaly and ascites. Percussion over the second intercostal space in parasternal region revealed dull note on both sides suggesting the presence of enlarged pulmonay arteries.

His blood investigations revealed normocytic normochromic anaemia (Hb-9.8) with pre renal azotemia. Other blood investigations were unremarkable. ECG showed sinus tachycardia with heart rate of 108 per minute with no evidence of any ischemic changes. Chest radiography showed cardiomegaly with minimal pleural effusion in right. Two dimensional echocardiogram revealed dilation of all four chambers of heart with global hypokinesia with an ejection fraction of 30% (Figure 1). There were no regional wall motion abnormalities and pulmonary artery was dilated.

He was subjected to Indirect laryngoscopy for evaluation of hoarseness of voice which showed left vocal cord palsy (Figure 2). Considering his age and smoking history, a possibility of laryngeal malignancy or bronchogenic carcinoma was strongly considered. So he was subjected to bronchoscopy, which again revealed left vocal cord palsy and there was no evidence of any suspicious growth. Transbronchial biopsy and brachmovalveolar lavage were done. Both turned negative for any malignancy. HRCT of thorax was done and no evidence of bronchogenic carcinoma was found and it showed cardiomegaly with enlarged pulmonary arteries (Figure 3).

Patient was treated for dilated cardiomyopathy according to standard guidelines with loop diuretics, ACE inhibitors, beta blockers and aldosterone antagonists. Patient’s congestive symptoms improved. From

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day 6 of treatment his hoarseness of voice also began to improve and substantial improvement in voice was seen after two weeks. Indirect laryngoscopy was repeated which showed recovering vocal cord palsy. Patient was discharged with drugs to be continued in home. He came for follow up after two weeks and his voice was almost normal. Indirect laryngoscopy repeated at this time showed normally functioning vocal cords. So this case was diagnosed as idiopathic dilated cardiomyopathy with pulmonary artery dilation causing neuropraxia of left recurrent laryngeal nerve resulting in Ortner’s syndrome, which reverted back to normal on medical management of cardiomyopathy.

Discussion

Ortner’s Syndrome is a rare occurrence in Mitral stenosis patients with an estimated frequency of 0.25-0.5% in various case series. Left recurrent laryngeal nerve is preferentially involved because it descends into the thorax and hooks below the arch of aorta in between the pulmonary artery and the arch of aorta and posterior to ligamentum arteriosum and ascends up in the trachea-esophageal groove to supply the muscles of larynx. This course makes it vulnerable for involvement in cardiac diseases. Various structures surrounding the course of recurrent laryngeal nerve can cause compression resulting in cardiovocal syndrome. Cardiac conditions known to result in cardiovocal syndrome other than mitral stenosis includes Eisenmenger’s syndrome, patent ductus arteriosus, atrial septal defect, left ventricular failure and congenital heart disease.

Autopsy studies done by Fetterolf and Norris showed that the distance between the arch of aorta and pulmonary artery in aortic window is just 0.4 cm and they suggested that left recurrent laryngeal nerve gets compressed between these two structures and is responsible for vocal cord palsy. Recent studies suggest that compression of RLN between the dilated pulmonary artery and arch of aorta is a constant factor in almost all cardiovascular cases leading to vocal cord palsy.

In our case, the probable cause for the occurrence of cardiovocal syndrome seems to be the pulmonary artery dilation in addition to the enlarged left atrium. The distance between the arch of aorta and pulmonary artery was 0.67 cm in our patient.

In most cases of ortner’s syndrome, the vocal cord palsy either not improved or improved with surgery. We could not find any evidence in literature showing complete reversal of RLN palsy after medical management of the cardiac disease. This case is unique for its complete reversal of palsy with medical management.

Conclusion

This case is presented to highlight the occurrence of neuropaxia type of RLN palsy caused by cardiac diseases, in addition to permanent palsy and to emphasize the importance of cardiac evaluation in hoarseness of voice, when no other causes could be found.

References

Three times in the 21st century corona virus outbreaks have emerged from animal reservoirs to cause severe disease and global transmission concerns. SARS-I Cov (2002-04), MERS-Cov (Middle East Respiratory syndrome 2012 and current pandemic of novel corona virus Covid19 now named Corona virus Disease COVID-19 and labeled SARS-II.

Covid19 SARS-II emerged from the wet market of Wuhan, China in November 2019 and has since caused large scale pandemic so far affecting 3,780,623 people with 1,768 deaths and spreading over 185 countries till date (6/5/2020). India has presently 52,340 people with 1,768 deaths.

Clearly present Covid-SARS-II pandemic has brought much more devastation compared to SARS-I and other Corona infection. We have not seen such a pandemic sparked by a corona virus during our lifetimes. Current pandemic has not just been a public health crisis, but it has touched every sector in the society. It is much more infectious compared to SARS-I, given its long incubation period (up to 15 days) combined with air travel in initial months, Covid 19 became a “stealth” killer...

Covid19 is presumed, but not confirmed to have originated in bats, given a remarkable similarity to bat corona viruses which were the culprits of the two respiratory viral epidemics of the past two decades SARS-I started in China due to civets and raccoon dogs consumption which were later traced to natural hosts- horseshoe bats affected 2994 people killing 858 people in 2012. Camels seemed the source of infection in. MERS-Covid and this again was traced to Egyptian bats.

Rapidly advancing Covid-SARS-II menace is a huge challenge. Key moves are to detect and to protect. In the absence of vaccine, or treatment, social discipline, respiratory etiquettes, hand hygiene and lock down measures as is introduced in India since 25 March-20. During this outbreak we need to further increase the level of preparedness, alertness. Sharing of rapidly accumulating scientific information from the world is going to be a key factor during this outbreak. 30 vaccine formulations are in different stages of development and 4 drugs are being repurposed to treat covid patients in the trials. Learning from the experience and innovation from time to time can work wonders.

India has tapped into an unusual resource-its trains. Indian Railway has suspended its passenger trains after lockdown announcement from 25 March to contain the virus.

Railways have already begun to convert 5,000 train coaches into quarantine or isolation wards, which amount to 40,000 beds. And the railway ministry says it’s prepared to convert 15,000 more coaches into special wards and even ICU, s when necessary.

As lives vs. livelihood debate grips our world, strong political will combined with scientific information, appropriate public health action will ultimately determine the outcome of this pandemic.

In Ratan Tata’s words “it is the value of human motivation and determined effort that matter”.

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Hemoptysis as an Initial Presentation of COVID-19 - An Observation

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Sir,

Since the emergence of the novel corona virus in December 2019 in China, the virus has spread extensively in India as well. With increasing reach and number, this virus has become a global pandemic in no time. The common presenting signs and symptoms of the 2019 novel coronavirus (COVID-19) are fever, dry cough, shortness of breath, fatigue, and dyspnea. In view of the complications of COVID-19, the presenting symptom and radiological features of patients can be very atypical; hence early diagnosis remains a challenge.

We present a case of a 60-year-old Diabetic female, presented to the emergency department with a history of hemoptysis in a Tertiary care hospital in India. She reported having expectorated 3 to 4 times streaky amount of blood. She denied any other symptoms, breathlessness, chest pain or fever. Her vital parameters were Heart rate-100/min, Blood pressure- 110/70mm Hg, Respiratory rate- 30/min, Oxygen saturation-98% on room air. Systemic examination was essentially normal. Chest radiograph PA was done that was essentially normal.

She was admitted and received intravenous antibiotics (amoxycillin-clavulanic acid), inhaled oxygen, cough suppressants and intravenous tranexamic acid.

She denied any recent contact with an ongoing Covid-19 pandemic patient. The laboratory results were unremarkable upon admission. A High Resolution CT scan of the chest showed mosaic attenuation in both the lungs with interspersed areas of ground glass haziness and areas of air trapping (Figure 1). This patient was admitted with a provisional diagnosis of pulmonary infection or tuberculosis. Patient developed high grade fever in the emergency room while awaiting a bed in the intensive care unit. In view of the ongoing pandemic, a real time reverse-transcription-polymerase chain-reaction assay for Covid19 was done which eventually turned out to be positive. She was shifted to a designated facility and was managed conservatively with cough suppressants, antifibrinolytics and supportive care. The hemoptysis gradually decreased and the fever was relieved with symptomatic treatment and antiviral therapy according to the local Guidelines and Management for COVID-19.

Early recognition of Covid-19 infections remains a big challenge. The common signs and symptoms of COVID-19 infection at presentation include fever, cough, sore throat, breathlessness, fatigue or myalgia.¹,² Hemoptysis as a presenting symptom has been rarely reported worldwide; none have been cited in the limited literature from India.³ Hence, it is difficult to suspect COVID-19 infections especially without obvious contact exposure. The typical HRCT findings include ground glass opacities (GGO), mixed GGOs, or crazy-paving patterns, consolidation of the subpleural or peripheral regions of bilateral lung fields.⁴,⁵ It is really a challenge to diagnose COVID-19 infection from Ground glassing with with an isolated, non-peripheral distribution or mosaic attenuation with the only symptom of hemoptysis and without contact history. The first differential in consideration was a tubercular bronchiectasis upon admission.

The present case of COVID-19 pneumonia was likely caused by a distant contact of the viral infection, resulting in no traceable contact history. Furthermore, due to the complexity of the Covid-19 virus, the initial presenting symptom and imaging picture could also be atypical. Covid-19 pneumonia can present with atypical manifestations, such as hemoptysis on initial CT scans. This case demonstrates the complexity of the pathogenesis of the disease caused due to Covid-19 infection.

References


Fig. 1: HRCT thorax suggestive of mosaic attenuation with interspersed areas of ground glassing.
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