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- Dr. Pradip K. Bhattacharya, Medical Superintendent, Chirayu Medical College & Hospital, Bhopal.
**Indian COVID-19 Risk Score, Comorbidities and Mortality**

Shashank R Joshi

Human Coronavirus (popularly version two of SARS-CoV2) is a RNA virus which possibly accidentally jumped via unknown intermediate from a probable bat source in Wuhan, Hubei province of China which is the ground zero of the pandemic. The original human host patient (index case) of the pandemic still remains elusive and crucial for virologists and immunologists to generate correct strategy for vaccine or cure. The human Coronavirus are enveloped non-segmented positive sense RNA viruses belonging to the genus *Betacoronavirus* of the subfamily *Orthocoronavirinae*. The virus is at the center of a ‘perfect storm’ in a pandemic has virtually halted planet earth and connected the world digitally like never before. Unfortunately mathematicians and modelers have suddenly erupted instead of microbiologists and public health specialists generating numbers often alarmist based on unknown denominators and creating numbers which appear unrealistic. Covid 19 the disease caused by corona virus is a simple viral infection which most humans will overcome by their own immunity but a small percentage (possibly 3 to 6%) will succumb to the virus due to a cytokine storm especially in a vulnerable population.

The case fatality rate or mortality of covid 19 is linked to this vulnerability and vulnerable groups and the urgent need to develop Indian vulnerability score to screen and identify this subset (Table 1). The key variables conferring vulnerabilities in the early stages of the Indian corona pandemic appear to be age (more than 55 not 65 like the world average, obesity (BMI >27), hypertension, diabetes, chronic heart / lung / renal / hepatic disease states, congenital or acquired immunodeficiency states, as well as individuals on long term immunosuppression or treatments including transplant recipients apart from pregnancy or children below 10). This score will need validation in the Indian context and will allow a risk stratification to conserve resources. Clearly this pandemic will push both central and state governments of India to move up from the minimal spending on health to a larger spend and build public health infrastructure under various "Ayushman Bharat" and related health schemes. The per capita spend for the GDP on health being one of the lowest in the world so a shift of budgetary allocation from Defence to defence of human health is clearly the need of the hour. Public health infrastructure and critical care will need to be revamped. India has both political and peoples will to battle this virus,its lockdown and its aftermath both economically and health wise.

The Indian Covid 19 risk score is designed for high risk stratification from a public health perspective to save lives. Early Indian data suggest Male gender, age >50-60 is showing mortality from states like Maharashtra unlike global 65 years of age. Hypertension, Diabetes, Obesity apart from chronic heart disease, chronic lung disease, chronic renal diseases have emerged as clear vulnerable populations at risk for death from the Indian data. India unfortunately has a high burden of NCDs especially Obesity, Hypertension, Diabetes and heart diseases apart from chronic kidney disease which will drive mortality. The virus host interactions which will drive mortality will be linked via this risk score and vulnerable population.

The human coronavirus SARS CoV2 is a typical large RNA virus. The classical virus dock via its spike S protein of the viral envelope to the angiotensinogen converting enzyme type 2 (ACE2) in the lungs and the gut. During the host virus membrane fusion the S protein is cleaved at S1/S2 boundary by human proteases and a spike fusion peptide is released for viral entry. The viral spike glycoprotein of SARS CoV2 interacts with the cell surface of ACE2 and the virus is internalised by endocytosis. The endocytic event upregulates the activity of ADAM metallopeptidase domain 17 (ADAM 17), which cleaves ACE 2 from cell membrane resulting of ACE 2 mediated protection setting the stage for pro inflamatory cytokines release in the circulation. The human proteases for S protein cleavage vary among different coronaviruses, which determine the epidemiological and pathological features of virus, including host range, tissue tropism, transmissibility and mortality. For instance, a variety of human proteases, such as trypsin, tryptase clara, human airway trypsin-like protease (HAT) and transmembrane protease serine 2 (TMPRSS2), are known to cleave and activate the S protein of SARS-CoV. These proteases are widely expressed in many important organs, which is critical reason for the systematic infection, serious pathogenicity and high mortality of SARS-CoV. The current SAR S CoV2 typically attaches via the Spike protein to the ACE 2 enzyme and TMPRSS2 protease play the crucial role in its tropism and expression. The spike protein has two subunits namely S1 which determines the cell tropism and S2 which mediates virus cell membrane fusion via HR1

---

Endocrinologist, Lilawati Hospital, Bhatia Hospital, Dean, Indian College of Physicians; Consultant Endocrinologist, Lilawati Hospital, Bhatia Hospital, Apollo Sugar Clinic, Mumbai, Maharashtra

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**Table 1: Indian COVID-19 risk score (vulnerability, mortality risk)**

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<tr>
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<tr>
<td>1. Age more than 55 years</td>
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<td>2. Male gender</td>
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<td>3. Hypertension</td>
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<td>4. Diabetes</td>
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<td>5. Obesity</td>
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<td>6. Chronic heart disease</td>
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<td>7. COPD or asthma or chronic lung disease</td>
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<tr>
<td>8. Chronic kidney or liver disease</td>
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<tr>
<td>9. Any congenital or acquired immunodeficient state</td>
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<tr>
<td>10. Any users of corticosteroid or immunosuppressants or transplant recipients</td>
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* Pregnancy or children below 10 years need attention"
and HR2. The TMPRSS2 which is a key protease in the ACE 2 may be androgen dependent. Androgen receptor activity has been considered a requirement for the transcription of the TMPRSS2 gene because no other known TMPRSS2 gene promoter has been described in humans to date. Theoretically, the hyperandrogenic phenotype might correlate with COVID-19 increased viral load, increased viral dissemination, and severity of lung involvement. This confers the male gender a disadvantage make them more vulnerable for SARS CoV2.

Currently the increase mortality due to the novel coronavirus is due to unopposed activation of the local renin angiotensin system (RAS) in the lungs and heart. People with underlying comorbidities the increased RAS will predispose them to cytokine storm. In these subjects ACE 2 is protective which is consumed by the SARS cov2 and there is unopposed action of Angiotensin 2 leading to a cascade of cytokine storm of Interlukins: IL6, IL1 and others. Human ACE 2 plays a key role in the pathogenesis of the cytokine storm. The Human ACE 2 and its receptors have several well know gene polymorphisms which are documented across ethnic groups. There are average of six genetic variants associated with higher ratios of ACE2 cells: rs233575 (A), rs714205 (G), rs1978124 (C), rs879922 (G), rs2048683 (G), rs1877752 (C) which confer population risk in many ethnic groups including Asian Indians. Human ACE 2 polymorphisms studies recently analysis the datasets have show there are susceptible as well as resistant which can confer vulnerability or susceptibility to the SARCOS cov2 and its pathogenesis and outcome. In fact currently there are several trials underway looking at recombinant soluble ACE 2 or ACE2 FC fusion protein can be used a decoy to the SARS cov2 binding. Also role of ACE inhibitors and Angiotensin Receptor blocker may paradoxically be protective and will need evidence base generation. The role of NSAIDS like Ibuprofen and Thiazolidiones (glatzone) which was also under scrutiny is now being relooked as being protective. The link of this pathway to mortality will be closed looked at as the pandemic evolves especially in the Indian high density clusters which are Insulin Resistant.

There is a link between COVID-19 and multiorgan failure may be dependent on the fact that most COVID-19 patients are complicated by pneumonia, which is known to be associated with early changes of clotting and platelet activation and artery dysfunction; these changes may implicate in thrombotic-related events such as myocardial infarction and ischemic stroke. Recent data showed that myocardial injury compatible with coronary ischemia may be detectable in SARS-CoV-2 patients and laboratory data exploring clotting system suggest the presence of a hypercoagulation state. The two phenotypes of Covid 19 lung are now well described namely Type L and Type H. The Type L being classically low elastance, low ventilation to perfusion ratio, low lung weight, low lung recruitability a typical interstitial lung edema and may worsen into P-SILI Patient–Self Inflicted Lung Injury (CT-Ground glass). These typically need High flow nasal ventilation or Non invasive ventilation. The type H patient is typically high elastance, high right to left shunt, high lung weight and high lung recruitability and progresses into severe ARDS (CT Bilateral infiltrates) which need classical mechanical ventilation. Prone position, Hypoxia, Oxygenation and novel strategies of oxygen delivery will be the key to Covid 19 lung as the pandemic emerges.

This issue has the first case series from Jaipur, Rajasthan which gives a clinical scenarios from India. The various hot spots and red zones in India like Mumbai, Pune, Amdavad, Delhi, Indore and others will soon emerge with their own clinical scenarios as ICMR and NIV will unravel sequences of the genomes of the strains of the viruses and their mutants from India. It is crucial to develop and generate Indian antibodies and develop indigenous kits to develop Immune defence and vaccine. Immunological and anti cytokine therapies will be also key especially IL6 blockers like Tocilizumab, Sarilumab, Ixilizumab etc Make in India will get a major push for diagnostics, treatments and vaccines from Indian research hubs supported by government agencies like ICMR and CSIR apart from the private sector. Indian strains of corona virus and their mutations will need data generation on terms of Virululence, survival in Indian environmental conditions like temperature, humidity as well as human host innate immunity in a BCG and Polio vaccinated Indian population apart from nutritional deficiencies of macronutrients (proteins), micronutrients and vitamins (like Vitamin D, C or zinc). The high burden of Insulin Resistance and Cardiometabolic Risk in Asian Indian population may confer a mortality risk and thus close vigilance in this subset. Currently even its mode of transmission is dual; droplet airborne possibly microdroplet or aerosol generating as well feacal needs better documentation but will lead to mandatory ‘Masking’ or covering of face, mouth and eyes in times to come as well as clean toilets across the entire Indian population as we will gradually unlock the country.

References


Clinical Profile of Covid-19 Infected Patients Admitted in a Tertiary Care Hospital in North India

Sudhir Bhandari, Abhishek Bhargava, Shrikant Sharma¹, Prakash Keshwani, Raman Sharma, Subrata Banerjee

Abstract

Background: The novel coronavirus (Covid-19) continues to wreak havoc across China, European countries, USA and now seems to gain a strong foothold in India. The aim of this report is to describe the clinical profiles of these Covid-19 infected patients admitted in Sawai Mansingh Hospital (S.M.S.), Jaipur ranging from their age, sex, travel history, clinical symptoms, laboratory evaluation, radiological characteristics, treatment provided along with common side effects and the final outcome. The described cases are one of the earliest cases of Covid-19 in the Indian subcontinent.

Methods: Epidemiological, clinical, laboratory, and radiological characteristics and treatment outcomes data were obtained with data collection forms from electronic medical records and history given by 21 Covid-19 infected patients admitted in S.M.S., Jaipur. Patients were tested for Covid-19 by real-time reverse transcription polymerase chain reaction (RT-PCR) assay of 2019-nCoV RNA.

Results and Discussion: During the course of this study 21 Covid-19 positive patients were admitted in S.M.S Hospital, Jaipur. Male patients constituted 66.66% of total patients and majority of the patients (80.90%) were below 60 years of age. Most of the patients (71.40%) were either foreigners or had a history of foreign travel suggesting that these cases were not community acquired except for 4 cases from textile producing district Bhilwara (known as Manchester of India), an epicenter of North India. Approximately 33.33% patients were completely asymptomatic and of those who were symptomatic cough was the most common symptom (85.71%) followed by fever (78.57%), myalgia (64.28%), headache (28.57%) and dyspnea (28.57%). Three patients (14.28%) had underlying comorbidity in the form of hypertension, diabetes mellitus, hypothyroidism, chronic kidney disease or coronary artery disease. 11 patients (52.38%) had lymphopenia in their hemogram during the course of admission. 3 patients (14.28%) had leucocytosis and 4 patients (19.04%) presented with thrombocytopenia. All 4 patients in the severe category had raised FDP, D-Dimer levels and they needed oxygen support. These patients had deranged liver functions and had elevated pro-calcitonin levels, serum ferritin levels and LDH levels. 1 out of the these 4 cases went into ARDS during the course of treatment. 10 patients yielded negative results for Covid-19. The mean duration from admission to getting 1st Covid-19 sample negative was 8.3 days. 18 patients (85.71%) are still under treatment.

Conclusion: Clinical investigations in initial Covid-19 patients in the Indian subcontinent reveal lymphopenia as predominant finding in hemogram. Patients with older age and associated comorbid conditions (COPD and diabetes) seem to have greater risk for lung injury thereby requiring oxygen support during the course of disease and these patients also had greater derangement in their biochemical profile.

Introduction

In December 2019 a new respiratory tract infecting agent emerged in Wuhan city of China, known as the coronavirus. It was later named Covid-19. Full-genome sequencing and phylogenetic analysis indicated that 2019-nCoV is a form of betacoronaviruses associated with human severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).¹ The 2019-nCoV has close similarity to bat coronaviruses, and it has been postulated that bats are the primary source. While the origin of the 2019-nCoV is still being investigated, current evidence suggests spread to humans occurred via transmission from wild animals illegally sold in the Huanan Seafood Wholesale Market.² It spread rapidly through China infecting more than 85,000 people. Within a few months it engulfed the Europe causing massive loss of life and property in Italy, Spain, France, Germany, UK and then USA. It is now set to gain a foothold in India which is the second most populous country of the world. As of now more than 650,000 people have been infected and 28,000 people have succumbed to the illness across the globe. The WHO declared Covid-19 a global pandemic on 11 th March 2020. Illness ranges in severity from asymptomatic or mild to severe; a significant proportion of patients with clinically evident infection develop severe disease. Mortality rate among diagnosed cases (case fatality rate) has a variable range; true overall mortality rate is uncertain, as the total number of cases (including undiagnosed persons with milder illness) is unknown.³ Before 3 rd March, India had 3 cases of coronavirus in Kerala all of which were treated and discharged. On 3 rd March, India’s 4 th case was diagnosed in the state of Rajasthan and it was later found that this patient had infected 17 other Italians who were on a tour to India. Within this period 21 Covid-19 infected patients were admitted in

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Sawai Mansingh Hospital, Jaipur. The objective of this paper is to describe the clinical profiles of these patients ranging from their age, sex, travel history, clinical symptoms, laboratory evaluation, radiological characteristics and treatment provided along with common side effects and outcome.

**Study Design**

All consecutive patients with confirmed Covid-19 infection admitted to S.M.S Hospital, Jaipur from 1st March upto submission of paper, were enrolled. Oral consent was obtained from patients. The clinical outcomes (i.e., discharges, mortality, and length of stay) were monitored upto submission of paper.

**Data Collection**

The medical records of patients were analyzed by the research team of the Department of Medicine, SMS Hospital, Jaipur. Epidemiological, clinical, laboratory, and radiological characteristics and treatment and outcomes data were obtained with data collection forms from electronic medical records and history given by patients. All data was reviewed by internal medicine specialists. Information recorded included demographic data, medical history, exposure history, underlying comorbidities, symptoms, signs, laboratory findings; chest computed tomographic (CT) scans, and treatment measures (antiviral therapy, Anti-retroviral therapy, anti-malarial therapy, respiratory support). Berlin definition was used to define ARDS.

**Real-Time Reverse Transcription Polymerase Chain Reaction (RT-PCR) Assay for Covid-19**

Throat swab samples were collected for extracting 2019-nCoV RNA from patients suspected of having 2019-nCoV infection and were placed into a collection tube containing virus transport medium (VTM) for extraction of total RNA. This process was tried to be completed in minimum possible time. Optimum amount of cell lysates were transferred into a collection tube and were later centrifugated. The suspension was used for RT-PCR assay of 2019-nCoVRNA. This diagnostic criterion was based on the recommendation by the National Institute of Virology (Pune).

**Selected Case Profiles**

**Case 1:** A 67 year old male, chronic smoker (40 pack years), resident of Italy presented to S.M.S Hospital with chief complaints of fever, cough and shortness of breath. He was started on a combination therapy of Tab chloroquine, Tab Lopinavir + Ritonavir and Cap Oseltamivir along with appropriate antibiotics when his report came positive for Covid-19. He was able to maintain saturation on Non-invasive BiPaP form of ventilation for 19 days but due to progression into ARDS (Figure 1), he was later intubated. He became corona negative on 12th day of his hospitalization and was referred to other hospital as per request of Italian embassy.

**Case 2:** An 85 year old male, known case of Type 2 Diabetes mellitus, Coronary Artery Disease, Hypothyroidism, Chronic Kidney Disease, Hypertension and had a travel history to Dubai presented with fever and shortness of breath. He had bilateral pneumonitis (Figure 2) and was also diagnosed as a case of corona on 10th March 2020. He was started on same drug combination as Case 1 and he turned negative on 5th day of his treatment. Antibiotics were started according to culture sensitivity. He was discharged and advised home quarantine for 14 days and is doing well in follow up.

**Case 3:** A 24 year old male with history of travel to Spain presented with fever and myalgia. He had no shortness of breath. He developed chest pain on 4th day of his hospitalization. His ECG (Figure 3) was suggestive of Tall T waves and ST elevation, though Trop-T was normal.

**Case 4:** A 38 year old male, healthcare worker by occupation presented with fever and cough since 5 days. He is a physician in Bhilwara district of Rajasthan. He was diagnosed as a case of Covid-19 on 18th March 2020. His Chest Xray PA view was suggestive of bilateral pneumonitis and CT scan (Figure 4) was done outside before being admitted in S.M.S. Hospital, Jaipur. We relied more on serial chest Xray and clinical evaluation rather than
CT scan of chest as going for CT scan may have posed a risk to other patients.

**Results**

**Demographics, clinical features and laboratory findings**

A total of 21 patients diagnosed as Covid-19 were included in this study with 4 patients not maintaining oxygen saturation on room air and needed oxygen support and rest 17 patients who did not require oxygen support. The median age for all patients was 43.5 years ranging from 2 to 85 years and the majority (80.90 %) of them were below 60 years of age (Table 1).

CT scan – Multifocal patchy peripheral and sub pleural area of air space ground glass opacities in both lung parenchyma, involving posterior segments of both upper lobes, lingular segment of left upper lobe, right middle lobe, superior and postero-basal segments of both lower lobes suggestive of viral pneumonitis.

**Table 1: Patient’s Comorbidities and Symptoms**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>All patients (n=21)</th>
<th>ICU Patients (n=4)</th>
<th>No ICU care (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.5(2.0-85.0)</td>
<td>61.0(37.0-65.0)</td>
<td>36.0(2.0-70.0)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>14 (66.66%)</td>
<td>4 (100%)</td>
<td>10 (58.8%)</td>
</tr>
<tr>
<td>Women</td>
<td>7 (33.33%)</td>
<td>0</td>
<td>7 (41.1%)</td>
</tr>
<tr>
<td>Smoker</td>
<td>1 (4.76%)</td>
<td>1 (25%)</td>
<td>0</td>
</tr>
<tr>
<td>Signs and symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>11 (52.38%)</td>
<td>4 (100%)</td>
<td>7 (38.88%)</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (57.1%)</td>
<td>4 (100%)</td>
<td>8 (47.0%)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>9 (42.85%)</td>
<td>4 (100%)</td>
<td>5 (29.41%)</td>
</tr>
<tr>
<td>Sputum production</td>
<td>5 (23.80%)</td>
<td>2 (50%)</td>
<td>3 (14.28%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (19.04%)</td>
<td>0</td>
<td>4 (19.04%)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 (38.0%)</td>
<td>3 (75%)</td>
<td>5 (29.41%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>4 (19.04%)</td>
<td>4 (100%)</td>
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</table>

**Table 2: Comorbidities**

<table>
<thead>
<tr>
<th>Comorbidities</th>
<th>No. of Patients (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>2 (9.5%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3 (14.28%)</td>
</tr>
<tr>
<td>Cardiovascular Disease</td>
<td>1 (4.7%)</td>
</tr>
<tr>
<td>COPD</td>
<td>1 (4.7%)</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>2 (9.5%)</td>
</tr>
</tbody>
</table>

history of foreign travel except and four patients (19.04%) who were residents of Bhilwara and one from Ramganj, Jaipur (Table 3).

Four patients (19.04%) of the total needed oxygen support (Table 3). 10 patients (47.61%) were given Lopinavir + Ritonavir combination where as 5 patients (50%) turned Covid-19 negative with mean duration of first negative sample after commencing treatment was 8.3 days. All patients who were given Lopinavir + Ritonavir developed either gastritis or diarrhea. None of them developed QT prolongation. 11 patients (52.38%) were given oselatmivir of which 5 patients (45.45%) turned negative. 18 patients (85.71%) were given chloroquine. Diarrhoea was the most common side effect reported among patients (38%). One young patient developed long T wave in ECG (Figure 3) with slight transient asymptomatic dip in blood pressure but with normal 2D echo and serial quantitative Trop-T. 1 post-corona, 2 samples negative patient was shifted to another hospital as per request of Italian Embassy for the management of ARDS and residual illness, remaining 2 post-corona patients with 2 negative samples were discharged. 18 patients (71.42%) are still under treatment.

Five patients (23.80%) of total had lung infiltrates and rest had normal x rays. The HRCT chest of 2 patients could be done and it was suggestive of bilateral multiple ground glass opacities with predominantly peripheral predisposition. Serial X ray and close monitoring of oxygen saturation with ABG / pulse oximeter was done to monitor development of ARDS.

12 patients (57.14%) had lymphopenia in their hemogram (Table 4) during the course of admission. 3 patients (14.28%) had leucocytosis. 5 patients (23.81%) presented with thrombocytopenia. 4 patients (19.04%) had leucopenia and 2 patients (9.5%) had eosinopenia. Three patients (14.28%) had lymphopenia with thrombocytopenia. Nine out of 14 male patients had lymphopenia.
(64.28%) while only 2 female patients (28.57%) demonstrated lymphopenia. Seven patients (33.33%) had completely normal hemogram. Six patients (28.57%) had derangement in the liver function tests. Three patients (14.28%) had a deranged lipid profile in the form of hypertriglyceridemia.

**Special comments for severe cases**

4 patients (19.04%) needed oxygen support and all of them were male. 3 out of these patients had one or the other co-morbidity in the form of diabetes (50%), hypertension (50%), hypothyroidism (50%) or COPD (25%). 3 of the patients in the severe category belonged to the healthcare workers. Median age was 61 years in this group as compared to 36 years in those who did not require oxygen support. All 4 patients had leucocytosis, 2 patients had thrombocytopenia during the course of hospital stay and all of them also suffered with deranged liver functions and elevation in serum bilirubin levels. Elevated pro-calcitonin levels, serum ferritin levels, LDH levels, FDP and D-Dimer levels were found in all 4 patients with oxygen support. 1 out of these 4 (25%) went into ARDS during the course of treatment.

**Discussion**

This study included 21 Covid-19 affected patients with the median age being 43.5 years, which is a decade younger than that reported by Wang et al\(^1\) (56.0 years), Chen et al\(^2\) (55.5 years) and closest to that in Huang et al\(^3\) (49.0 years). Most of the patients requiring oxygen support were above 55 years of age, thus demonstrating that elder patients were more likely to have lung injury and require ventilator support. Patients requiring oxygen support were more likely to have underlying comorbidities (75%) including either of diabetes, hypertension, COPD or hypothyroidism.

Most of the patients having Covid-19 were male (66.66%) which was similar to that reported by Huang et al and Chen et al which show 73.0% male predominance but higher than that reported by Wang et al (54.3%). This male predominance may have happened due to increased foreign travel by males for occupational or educational purposes. Only 1 (4.76%) patient in our study had COPD as educational purposes. Only 1 (4.76%) patient in our study had COPD as hypertensive (50%), hypothyroidism (50%) or COPD (25%).

3 patients (14.28%) had a deranged lipid profile in the form of hypertriglyceridemia. (64.28%) while only 2 female patients (28.57%) demonstrated lymphopenia. Seven patients (33.33%) had completely normal hemogram. Six patients (28.57%) had derangement in the liver function tests. Three patients (14.28%) had a deranged lipid profile in the form of hypertriglyceridemia.

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Table 4: Laboratory Evaluation Of Patients

<table>
<thead>
<tr>
<th>Age/ Sex</th>
<th>Hemogram</th>
<th>Raised SGOT / SGPT</th>
<th>Raised Pro-calciton</th>
<th>Raised CRP</th>
<th>Raised Ferritin</th>
<th>Raised LDH</th>
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<th>Age/ Sex</th>
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textile producing district Bhilwara, an epicenter of North India with maximum number of community acquired cases in India from a single district.

In our study cough was the most common symptom present in our patients (85.71%) followed by fever (78.57%) which was in contrast to that reported in Huang et al and Wang et al where fever was the most common symptom found (91.7%) and Guan et al (87.9%). 7 of our patients (33.33%) presented with lymphopenia which is lesser than reported by Zhang J et al (75.4%). Some patients also presented with lymphopenia with thrombocytopenia (14.28%). Lymphopenia was much more commonly seen in male patients (64.28%) as compared to females (28.57%). All patients requiring oxygen support, presented with lymphopenia indicating, that occurrence of lymphopenia can be used as a marker of prognosis. The laboratory evaluation of patients requiring oxygen support to maintain saturation demonstrated deranged liver function tests and elevated levels of pro-calcitonin, LDH, ferritin, FDP and D-Dimer levels which were significantly higher than in patients who did not require oxygen support.

HRCT chest of patients demonstrated predilection for peripheral lung fields in the form of patchy ground glass opacities.

Limitations

Our study has some limitations. We studied early cases of the Indian subcontinent. Although a different disease but earlier experience of H1N1 pandemic helped us in infrastructural management and treatment. Various treatment guidelines and testing protocols were revised during the study duration.

Conclusion

This study showed variable range of presentation. Asymptomatic patients during the course of disease despite being Covid-19 positive pose a great epidemiological risk to the society as they can spread the infection unrestrictedly and shall be strictly isolated. Lymphopenia in hemogram and raised markers like pro-calcitonin, ferritin, FDP and D-Dimer do help in prognosis. Old age and comorbidity is associated with poor prognosis.

Conflict of Interest

None of the authors have conflict of interest.

References

Infections in Systemic Lupus Erythematosus

Anjali G Rajadhyaksha¹, Kunal Jobanputra²*

Abstract

Objectives: Infections are a major cause of morbidity and mortality in patients of Systemic Lupus erythematosus (SLE). We therefore aimed to determine the spectrum of infections in patients of SLE, find a correlation between various disease parameters and the severity and outcome of infections and to compare the outcome between different modalities of immunosuppressive therapy.

Methods: A cross-sectional study was carried out by including all the diagnosed patients of Systemic lupus erythematosus (based on SLICC criteria¹) aged 12 years and above who developed infections during the study period of 18 months. Immunocompromised patients because of coexisting diseases like diabetes, retroviral disease and cancer patients on immunosuppression were excluded. 139 cases of infections were identified in 104 patients of SLE during the study period.

Results: 92 patients had one episode of infection, 19 patients had two episodes and 3 patients contracted infections thrice during the study period. The mean age of the sample population was 29.45 ± 7.9 years. 21-30 years age group constituted 51.75% (59/114) of the patients. 61/139 infections (44%) were bacterial, 22/139 (16%) fungal, 20/139 (14%) viral and 4/139 (3%) parasitic. Tuberculosis was the most common infection (40/139, 28.78%). Lower respiratory tract was the most common site of infections found in the study (37/139, 26.62%). 75/139 (54%) were major infections. 50% tuberculous infections were extrapulmonary. The mean duration of SLE until the time of infection was 35.84 ± 53.80 months. SLE Disease Activity Index (SLEDAI) was ≥ 5 in 92.09% of cases. End organ damage was found in 82.7% (115 cases) and amongst them, renal lupus was found in 110/115 cases. No association was found between end organ damage and severity or outcome of infections. In 89 cases patients were on prednisolone alone, in 29 cases patients were additionally on Cyclophosphamide or had received it in the past, and in 15 cases Mycophenolate mofetil (MMF) with prednisolone while in 6 cases all the three drugs had been given at some point of time. Tuberculosis was the most common infection amongst all the groups. The mean daily dose of prednisolone was 19.62 ± 16.04 mg/day. The mean cumulative steroid dose in patients of our study was 9165.76 ± 7833.72 mg. Central nervous system infections occurred more in patients who had received Cyclophosphamide (p = 0.01). Five deaths occurred due to life threatening infections and all of them were either on high dose prednisolone or on cytotoxic drugs (Cyclophosphamide/Mycophenolate mofetil [MMF]). There was no association between treatment modality and severity and outcome of infection.

Conclusion: SLE patients are predisposed to various minor as well as life-threatening infections. It is essential to prevent infections by screening, reducing exposure to sources or contacts of infection and minimizing the exposure to immunosuppressive agents while controlling disease activity.

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease affecting mainly the females of reproductive age group. With improved diagnosis and immunosuppressive treatment, the pattern of leading causes of mortality in SLE has shifted from intrinsic disease to infectious complications. Patients are predisposed to myriad of infections owing to immunosuppressive treatment, immune dysregulation and genetic factors.² Here, we investigate the etiology, clinical characteristics and factors associated with development of infections and its outcome with various modalities of immunosuppressive therapy.

Patients and Methods

A cross-sectional study was carried out after ethics committee approval and written informed consent from the subjects. We identified all the diagnosed patients of Systemic lupus erythematosus (based on SLICC criteria¹) in the wards and following up in outpatient department at our tertiary care hospital. All SLE patients (aged 12 years and above) who developed infections during the 18 months of our study period were included. Patients who were immunocompromised because of coexisting diseases like diabetes, retroviral disease and cancer patients on immunosuppression were excluded.

A total of 139 episodes of infections were noted in 114 patients of SLE during the study period. Detailed history taking and physical examination were done. Infections were diagnosed by clinical features, laboratory tests and imaging, and were confirmed by cultures, histopathological examination and/or resolution after antibiotic therapy. We recorded the demographic data, clinical features and disease parameters of SLE at the time of diagnosis of infection. Patients were assessed for end organ damage of the kidneys, lung and central nervous system during any point of their disease course. Patients were considered to have active renal lupus if they had proteinuria of >0.5gram/24hours and...
The mean age of the sample population was 29.45 ± 7.9 years. 21-30 years age group constituted 51.75% (n=59) of the patients. 61 of 139 infections (44%) were bacterial, 22 (16%) fungal, 20 (14%) viral and 4 (3%) parasitic. The causative organism could not be found out in 32 infections (23%). Tuberculosis was the most common infection (40 of 139, 28.78%). Lower respiratory tract was the most common site of infections found in the study (37 of 139, 26.62%), followed by skin (35 cases) and systemic infections (31 cases). However, mucocutaneous infections together constituted the largest group (31.65% of all infections). 75 cases of infections (54%) required admission and/or intravenous antibiotics and were considered major infections, while 64 infections (46%) were treated on outpatient basis (minor infections). 20 (50%) tuberculous infections were extrapulmonary, 14 (35%) were pulmonary, while 6 (15%) were disseminated. 7/40 (17.5%) cases of tuberculosis had past history of the same. Of the 14 cases of Pulmonary tuberculosis, 10 (71%) were sputum positive including one case of Multidrug resistant disease. Most common sites of affection of extrapulmonary tuberculosis were cervical lymph nodes (6 cases), followed by mediastinal lymph nodes abdominal tuberculosis and pleura (5 cases each).

The mean duration of SLE until the time of infection was 35.84 ± 53.80 months. Disease activity was moderate [SLEDAI score 6-10] in 69 cases (49.64%), while SLEDAI was high [>10] in 59 cases (42.45%). There was no statistically significant difference between SLEDAI scores of patients with major and minor infections (p = 0.22). End organ damage was found in 82.7% (115 cases) and amongst them, renal lupus was found in 110 cases, lung involvement in 18 cases and CNS involvement in 3 cases. Active renal lupus was present in 65 cases, while in 45 cases it was in remission. Fisher’s exact test did not show any association between end organ damage and infections of a particular system. Also, no association was found between the presence of end organ damage and severity of infections (p = 0.96).

All of the patients were on at least prednisolone. In 89 cases patients were on prednisolone alone, in 29 cases patients were additionally on Cyclophosphamide or had received it in the past, and in 15 cases Mycophenolate mofetil (MMF) with prednisolone while in 6 cases all the three drugs had been given at some point of time. Tuberculosis was the most common infection amongst all the groups. The mean daily dose of prednisolone was 19.62 ± 16.04 mg/day. It was higher for major infections but the difference was not statistically significant (p value = 0.81). The mean cumulative steroid dose in patients of our study was 9165.76 ± 7833.72 mg. The mean cumulative dose of cyclophosphamide in patients who received the drug was 11.01 ± 7.25 g. No association was found between cyclophosphamide and occurrence of major infections (p = 0.32). Also, there was no association between treatment with Cyclophosphamide in the preceding six months and occurrence of major infections (p = 0.12). The mean cumulative dose of MMF was 505.73 ± 386.87 g. Except for central nervous system infections which occurred more in patients who had received Cyclophosphamide (p = 0.01), there was no association between the modality of treatment with any particular type of infection (p = 0.09).

Five of 114 patients succumbed to infections, three deaths occurred due to ventilator associated pneumonia, while one each due to sepsis and disseminated tuberculosis. The mean duration of SLE until the time of death was 16.40 ± 11.13 months. All the patients had previous or existing renal lupus. The median SLEDAI score in patients who died was 9 while the same in discharged patients was 13, but the difference was not significant (p = 0.23). There was no association between treatment modality and outcome of infection. Two of five patients were on Mycophenolate mofetil while one was on quarterly cyclophosphamide. The other two were on high dose steroids (1mg/kg/day). Thus, all five of them were either on high dose prednisolone or on cytotoxic drugs (Cyclophosphamide/ Mycophenolate mofetil). The mean cumulative doses of all three immunosuppressants among the deceased group was lesser than among the patients who were treated of infection as lethal infections occurred earlier during the disease course, but the difference was statistically non-significant.

### Discussion

Systemic lupus erythematosus is a multisystemic autoimmune disease
marked by fluctuations in disease activity, which makes the course of the disease unpredictable and prognosis variable. Earlier the survival rate which was 50 % at 4 years, has improved to 85-90% at 10 years due to early detection of organ involvement, diagnosis and treatment options including immunosuppressive agents and renal replacement therapy. The pattern of leading causes of death in SLE has shifted from those due to intrinsic disease to infectious complications. Many factors related to the genetics, immunity, disease activity and immunosuppression contribute to occurrence of infection in SLE patients.

Female to male ratio in our study was 15:1. The mean age of the patients was 29.45 ± 7.9 years with 51.75% of patients belonging to the age group of 21 – 30 years. The mean duration of SLE in these patients was 35.8 ± 53.8 months. In a Brazilian retrospective study, the mean age of patients was 39.15 years ± 11.65 years. The median time since onset of disease was 87 months (IQR 60 to 132 months). While in an Indian study, there was a female to male preponderance of 8 :1. 52.7% of patients had single episode of infection. 54% cases of infections were major while the rest were managed on outpatient basis. In a study conducted by Gladman et al., 58 % of patients had single episode of infection while 42 % had more than one infection episodes. In another study by Duffy et al., 43 % were major infections. In our study, tuberculosis was the most common infection. Lower respiratory tract infections accounted for 26.6 % of infections, followed by infections of the skin (25.1 %). Mucocutaneous infections added up to make 31 % of the total infections found in the study. The above results are consistent with the findings of study by Bosch et al., in which skin and mucous membrane were the most common site of infections (16%). However, urinary tract was the second most common site (12.7%). The above mentioned Indian study showed urinary infections to be the most frequent (54%) followed by that of the respiratory system (16%). In contrast, our study had only 6.4 % of genitourinary tract infections. There was higher proportion of tuberculous infections in our study, perhaps accounted by the high prevalence of Tuberculosis in India. The incidence of TB in lupus patients varies from 150 to 2,450/100,000 patient-years. In our study, extrapulmonary tuberculosis was more common, with 50% of cases being extrapulmonary. In a study by Zhang et al., 31 of 42 patients (73.8 %) had extrapulmonary disease. 8 of them had hematogenous disseminated tuberculosis. In a retrospective analysis by Hou et al., extrapulmonary tuberculosis was found in 11 of 21 patients (52%). Extrapulmonary tuberculosis and serious hematogenous infection occur more often in SLE patients. Renal Lupus and past history of tuberculosis posed greater susceptibility to tuberculosis. The occurrence of tuberculosis in SLE has been found to have a correlation with higher dose of steroids and higher mean daily dose of prednisolone.

92.09 % of infection episodes in our study had SLEDAI score of ≥5 at the time of infection, signifying moderate to very high disease activity. Zonana et al. found that SLEDAI score of > 4 was an independent predictor of infection. However, there were conflicting findings in a study by Shanbag et al. SLEDAI scores at the time of mucocutaneous infections were lower than during other infections. Similarly, Borba et al. noted that most episodes of herpes zoster occurred during the periods of remission, while another study did not support this finding. Our study found no relation found between SLEDAI score with severity of infection or outcome of infection. A nested case control study by Irastorza et al. showed that SLEDAI score did not modify the risk of major infections in SLE patients.

An Egyptian study found that high CRP, consumed C3, disease activity and positive anti-dsDNA were independent risk factors for development of infection in SLE, but no such association was found in our study. There was no relation between presence of end organ damage and severity of infection. In the above nested case-control study, renal involvement was shown to have an association with occurrence of major infections by univariate analysis, but non-significant by multivariable analysis. Contrary to our study, Bosch et al and Zonanan et al. showed a significant association between renal lupus and occurrence of infections.

Bacterial infections were the most common with steroid usage followed by fungal and viral. The mean daily dose of prednisolone at the time of infections in our study was 19.62 mg/ day. It was greater than 10 mg/day for most of the types of infections. There was no relation between the mean dose of prednisolone and severity of infections. In the study by Irastorza, the median dose of prednisolone was 7.5mg/day in patients who had major infections as compared to 2.5 mg/day in those without. Each 10mg/day increase in prednisolone dose multiplied the risk of developing infection by 11 times. The risk of infection increased with higher doses and longer duration of treatment, although a specific threshold below which it can be considered safe has not been determined. The cumulative dose of prednisolone ranged from 6443 mg to 14945 mg. (Mean 9165 mg). Toronto lupus cohort showed that prednisolone dosage equivalent to 20 mg for 30 days was a significant factor for infection and use of steroids was associated with infections by multivariate analysis (OR 3.0, CI 1.15-9.31). In a study among elderly SLE patients (Age > 50 years), treatment with a cumulative dose higher than 4.5 g of steroids led to life-threatening infections.

The mean cumulative dose of Cyclophosphamide in patients who received the drug was 11.01 ± 7.25 g. We found that infections of the central nervous system were significantly associated with treatment with Cyclophosphamide (p value = 0.01) while other infections did not show a significant association with the same. However, Duran-Barragan et al. and Zonana et al. showed that cyclophosphamide is associated with urinary tract infections and with herpes zoster. Treatment with MMF was not found to be associated with occurrence of any of the infections. The proportion of viral infections with Mycophenolate in our study was lesser than with steroids or Cyclophosphamide. In a cohort study by Subedi et al, Mycophenolate mofetil was found to have increased risk of bacterial infections but not viral infection. The Egyptian prospective cohort study showed a highly significant increased
risk of infection with cyclophosphamide but not with Mycophenolate mofetil. However, our study did not find relation between treatment modality with any particular type of infection or its severity. Also no relation was found between usage of more than one immunosuppressive agent during the disease course and development of multiple infections.

In our study, 4 deaths occurred due to critical infections like ventilator associated pneumonia and sepsis while one patient died of disseminated tuberculosis. A US study found out that mortality risks were higher among patients who developed opportunistic infections, sepsis and those who required mechanical ventilation. Though the lethal infections occurred earlier during the disease course, we did not find any significant difference in the disease activity in the deceased group as compared to those who were treated of infection, similar to Hellamnn et al. Also, all deceased patients were on high dose prednisolone or cytotoxic drugs and had renal lupus. There was a strong correlation found between death from infection and use of steroids and cytotoxic drugs in the preceding three months. Goldblatt et al. also found that majority of the patients who died of infections were on high dose prednisolone plus at least one immunosuppressant drug and were more likely to have renal involvement. There was no relation between cumulative dose of various immunosuppressive drugs and outcome of infection. Further studies can be designed with healthy controls and SLE patients without infections to study the risk factors associated with infections in Indian patients.

References

Dysphagia in Parkinsonism: Prevalence, Predictors and Correlation with Severity of Illness

Yogesh Shilimkar¹, Charulata Londhe²*, Uma Sundar³, Pramod Darole²

Abstract

Introduction: Dysphagia is frequently present in Parkinsonian syndromes and is associated with increased morbidity and mortality. Early identification of swallowing dysfunction is critical to minimize complications like aspiration pneumonia and malnutrition. Published prevalence rates for dysphagia in Parkinsonian syndromes vary widely with a very few studies from India. In this study we aimed to determine prevalence of dysphagia in Parkinson’s disease and other Parkinson plus syndromes; to correlate it with severity of underlying illness and to determine the factors predicting dysphagia in patients of Parkinson’s disease.

Methods: It was a prospective observational study performed over 18 months in the neurology clinic of tertiary care public teaching hospital in Mumbai. All patients of Parkinson’s disease (PD) diagnosed by UKPDS criteria and all patients of Parkinson-plus syndromes diagnosed clinically were included in the study serially. Patients with cognitive dysfunction (MMSE <24) and those having other neurological or non-neurological causes of dysphagia were excluded from the study. Swallowing dysfunction was assessed by MASA scoring sheet. Disease severity of PD was assessed by modified Hoehn and Yahr scale. Peripheral oxygen desaturation after swallowing water was monitored by pulse-oxymetry; as a bedside test for micro-aspiration. The data was tabulated and analyzed.

Results: 70 patients were included in the study including 63 with PD, 5 with PSP and 2 with MSA. Dysphagia was present in 40 (57.4%). 27 had mild; 12 had moderate and 1 had severe dysphagia. In Parkinson’s disease dysphagia was significantly associated with following predicting factors: age > 65 years, disease duration > 3 years, modified Hoehn and Yahr scale > 2 and MMSE < 27 (p< 0.001 for all). By multiple logistic regression analysis, the duration of disease and MMSE score were the independent predictors for dysphagia in Parkinson’s disease. Severity of dysphagia directly correlated with severity of underlying disease demonstrated by decreasing MASA score with rising Hoehn and Yahr stage.

Conclusions: Prevalence of dysphagia in Parkinsonian syndromes was overall 57.14%; being 55.16% in Parkinson’s disease. Prevalence and severity of dysphagia showed direct correlation with severity of Parkinson’s disease. Duration of disease and cognitive dysfunction are the independent predictors of dysphagia in Parkinson’s disease.

Introduction

Parkinsonism is a syndrome characterized by bradykinesia, rigidity and tremors. Parkinson’s disease (PD) is the most common form affecting substantia nigra (approximately 75%). Parkinson-plus syndromes are associated with more widespread neurodegeneration. They are Multisystem atrophy, Progressive supranuclear palsy and cortical- basal degeneration.

Dysphagia is frequently present in Parkinsonian syndromes. It may lead to complications like aspiration pneumonia, malnutrition and also affects intake of medications. More than 80% of patients of Parkinsonism develop dysphagia some time during the course of illness.1 Any or all of oral, pharyngeal and esophageal stages of deglutition may be affected. Despite its high prevalence dysphagia is often overlooked and underdiagnosed in Parkinsonian patients.2 Patients themselves may be unaware of swallowing impairment until late stages. It is important to detect signs of dysphagia during clinical evaluation of patients with Parkinsonism. The treatment is in the form of optimization of dose and timing of dopaminergic medications and referral to speech language therapist for swallowing techniques.

The various methods to assess swallowing function include clinical assessment, fiberoptic endoscopy, videofluoroscopy and manometry.1 In this study we aimed to determine the prevalence of dysphagia in Parkinsonian syndromes; to correlate swallowing dysfunction with severity of disease and to determine predictors of dysphagia in Parkinson’s disease.

Methodology

It was a prospective observational study performed in the Neurology clinic of a tertiary care public teaching hospital in Mumbai over a period of 18 months. Approval from the institutional ethics committee was obtained. The patients with Parkinson’s disease diagnosed by UKPDS criteria2 or Parkinson plus syndrome diagnosed clinically were included in the study serially. Sample size was 70. Patients with cognitive impairment (MMSE score<24) or having any other cause for dysphagia were excluded from the study. Following data were recorded in each patient:

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demographic data, symptoms, CNS examination, diagnosis of Parkinsonian syndrome, duration of disease, severity of disease in Parkinson’s disease by modified Hoehn and Yahr scale,³ MMSE score, signs and symptoms of aspiration pneumonia. Swallowing assessment was done by using Mann Assessment of Swallowing Ability scoring sheet (MASA).7,8 Dysphagia was classified into mild, moderate and severe grades as per the scores. Risk of micro-aspiration was checked by bedside assessment method.9 Patient was given 150 ml of water to swallow under supervision. Peripheral oxygen saturation was measured by pulse oxymetry before and after swallowing. Drop in peripheral oxygen saturation >2% after swallowing was considered as positive indicator of micro-aspiration.

MASA was designed as a clinical assessment tool for neurological oropharyngeal dysphagia. It can be applied to patients of stroke, Parkinson’s disease, amyotrophic lateral sclerosis or head injury. It is a 24- item tool with maximum score of 200. Dysphagia can be graded into mild (score 168-177), moderate (139-167), severe (score<138) and no dysphagia (178-200).s

The modified Hoehn and Yahr scale is used for assessing severity of PD.

### Results

Seventy patients were included in the study; 45 males and 25 females; 63 were P.D. and 7 were P.D. plus syndromes. The age was ranging from 42 to 88 years with mean age of 65.16 years. Swallowing dysfunction was present in 40 patients with prevalence of 57.14%. As per MASA score 27 had mild dysphagia; 12 had moderate dysphagia and one patient had severe dysphagia. Prevalence of dysphagia in our study is shown in Figure 1. Of 63 patients with PD, 35 had some degree of dysphagia (23 mild, 11 moderate and 1 had severe dysphagia). Of 5 patients with PSP 4 had swallowing dysfunction (3 mild and 1 moderate). Of 2 patients with MSA one had mild dysphagia. Subgroup analysis of MSA and PSP patients was not done as number of patients were less.

Among P. D. patients (n=63) the mean age was significantly higher in patients with swallowing dysfunction (68.74 ± 9.16) than patients without swallowing dysfunction (61 ± 5.08). (p=0.0004) There were no significant gender differences in the prevalence of dysphagia. Mean MMSE score was significantly lower among patients with dysphagia (25.43 ± 1.14) than patients without dysphagia (27.71 ± 1.16) p=0.0001. The mean disease duration in patients with dysphagia (3.91 ± 1.53 years) was significantly greater than in patients without dysphagia (2 ± 0.69) (p<0.0001). Mean modified Hoehn and Yahr score was significantly higher in patients with dysphagia (2.8 ± 0.2) than in patients without dysphagia (1.52 ± 0.42) (p< 0.0001). As the duration of disease and the stage of PD increased the MASA score decreased as shown in Figures 2 and 3. Thus, the prevalence as well as severity of dysphagia rises with increasing severity of PD. The Table 1 summarizes clinical characteristics of 2 study groups i.e. Parkinson’s disease patients with or without dysphagia.

Statistical analysis using chi-square test showed significant association between presence of dysphagia in P. D. and following patient parameters: Age >=65 years, MMSE<27, modified Hoehn and Yahr scale >2 and duration of symptoms >=3 years (Tables 2, 3, 4, 5). By multiple logistic regression analysis, the duration of disease (p=0.03, OR 4.56, 95% CI 1.135-18.30) and MMSE score (p=0.04, OR 0.40, 95% CI 0.165-0.980) were found to be the independent predictors for dysphagia in P. D. patients.

The bedside test of oxygen desaturation after swallowing water was positive for micro-aspiration in 10 patients with swallowing dysfunction.
Dysphagia includes alteration of swallowing process in any of oral, pharyngeal or esophageal stages. Dysphagia in Parkinsonism is asymptomatic till advanced stages and may remain undetected in early stages or till complications arise. It has been estimated that PD patients have a 3.8 times increased risk of developing aspiration pneumonia as compared to general population. Aspiration pneumonia is a major cause of hospitalization and death in patients with Parkinsonism. The pathophysiology of dysphagia includes defective basal ganglia control on medullary deglutatory motor centers. Bradykinesia, rigidity and involuntary movements interfere with swallowing. There is slowness in bolus formation, bolus propulsion, presence of drooling, presence of oral residue; all indicating oral stage dysfunction. During pharyngeal stage there may be delay and reduction in airway closure, reduction in movements of hyoid and presence of pharyngeal residue. The respiratory-swallowing coordination may be impaired along with absent or delayed effective cough. In addition to motor alterations the impairment of cognitive and sensory functions also interferes with swallowing. Oropharyngeal somatic sensation, taste and smell sensations are also altered in patients with PD. Leopold et al demonstrated by videofluoroscopy methods at least one or more abnormalities of laryngeal movements in 95% patients with Parkinsonism. The prevalence of dysphagia in our study population was 57.14% (55% in P. D.). The published prevalence rates of dysphagia in Parkinsonism vary from 11-81%. Such wide variation may be due to study populations with different stages of disease and different methods used to assess swallowing function. We could not compare the prevalence of dysphagia among various Parkinsonian syndromes as the number of patients in the Parkinson plus group was less.

Patients with dysphagia were older (> 65 years age), with more advanced disease (modified Hoehn and Yahr scale > 2), and greater duration of disease (> 3 years) and with mild cognitive dysfunction (MMSE score < 27). Similar findings were reported by Clarke et al., Kanna and Bhanu et al and Kim et al. Miller et al has reported the latency of approximately 10 years for symptomatic dysphagia and aspiration. In our study the mean duration of disease in patients with dysphagia was 3.62 years (ranging from 1 to 6 years). We could identify presence of mild asymptomatic dysphagia using clinical tests. Dysphagia is also associated with abnormal cough reflex and abnormal voluntary cough. Mari et al demonstrated that cough on swallowing water is predictive of presence of dysphagia and risk of aspiration. Peripheral oxygen desaturation > 2% after drinking water is also predictive of aspiration. This test is quick, easy and can be performed in OPD or bedside. However, it is positive only in moderate or severe dysphagia by MASA score and is negative in mild dysphagia. Risk of aspiration is higher in advanced stage of PD as demonstrated by higher modified Hoehn and Yahr stage in patients with positive bedside oxygen desaturation test.

Our study had certain limitations. Sample size for PD plus syndromes was small. Swallowing function was assessed by clinical methods due to financial and other constraints. Being a cross-sectional study, the patients were not followed up for the assessment of swallowing function over longer time and for the effects of therapeutic interventions. Further studies are required for the same.

**Conclusion**

Dysphagia is present in a significant proportion of patients with Parkinsonism. The assessment of swallowing function should be a part of clinical assessment of patients with Parkinsonism. Swallowing dysfunction may be suspected in patients with advanced PD (modified Hoehn and Yahr scale > 2), with longer duration of disease (> 3 years), advanced age (> 65 years), lower MMSE scores (< 27).

### References


### Table 2: Association of dysphagia with patient’s age in Parkinson’s disease

<table>
<thead>
<tr>
<th>Age &gt;=65 years</th>
<th>Dysphagia present</th>
<th>Dysphagia absent</th>
<th>(p&lt;0.0001)</th>
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</thead>
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<tr>
<td>27</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>21</td>
<td></td>
<td></td>
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</table>

### Table 3: Association of dysphagia with MMSE score in Parkinson’s disease

<table>
<thead>
<tr>
<th>MMSE &gt;=27</th>
<th>Dysphagia present</th>
<th>Dysphagia absent</th>
<th>(p&lt;0.0001)</th>
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<tr>
<td>6</td>
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<td>29</td>
<td>4</td>
<td></td>
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</table>

### Table 4: Association of dysphagia with severity of Parkinson’s disease assessed by modified Hoehn and Yahr score

<table>
<thead>
<tr>
<th>HandY score</th>
<th>Dysphagia present</th>
<th>Dysphagia absent</th>
<th>(p&lt;0.0001)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;= 2</td>
<td>23</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>&lt; 2</td>
<td>12</td>
<td>25</td>
<td></td>
</tr>
</tbody>
</table>

### Table 5: Association of dysphagia with duration of Parkinson’s disease

<table>
<thead>
<tr>
<th>Duration &gt;= 3 years</th>
<th>Dysphagia present</th>
<th>Dysphagia absent</th>
<th>(p&lt;0.0001)</th>
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</thead>
<tbody>
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<td>30</td>
<td>7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration &lt; 3 years</td>
<td>5</td>
<td>21</td>
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</tbody>
</table>

### Table 6: Association of presence of dysphagia by MASA score with positive bedside test for micro-aspiration in Parkinsonian syndromes

<table>
<thead>
<tr>
<th>Bedside test positive</th>
<th>Bedside test negative</th>
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</thead>
<tbody>
<tr>
<td>Mild / No dysphagia</td>
<td>0</td>
</tr>
<tr>
<td>Moderate / severe dysphagia</td>
<td>10</td>
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</tbody>
</table>
Prevalence and Antibiogram of Urinary Tract Infections in Renal Transplant Recipients at a Tertiary Care Hospital in North India

Isra Halim1, Neeraj Goel2, Ashwani Gupta3, Chand Wattal4*

Abstract

Introduction: Although, urinary tract infections (UTI) remain the most common cause of mortality and morbidity in renal allograft recipients, there is scarce data from India on the etiology and antibiogram of UTI post kidney transplantation. Therefore, the current study was undertaken to evaluate the prevalence, etiology and the antibiogram of pathogens causing UTI in this cohort.

Methods: Renal allograft recipients enrolled during the study period were screened for UTI by standard microscopy and routine culture on the day of admission and subsequently every 3rd day post-surgery till discharge. If UTI was present, the etiological agent and its antibiogram were recorded along with the demographic details of the patients.

Results: The prevalence of UTI post-transplantation at our centre was 30%. *Escherichia coli* and *Klebsiella pneumoniae* were the most common organisms isolated in 42% and 39% cases, respectively. Majority of patients developed UTI on Day 6 (36.6%) and Day 9 (36.6%) post-transplant. Our study revealed a high percentage of resistance to commonly used 1st and 2nd line antibiotics like third generation cephalosporins (96.6%), fluoroquinolones (96.6%), and aminoglycosides (56.7%) and carbapenems (55.2%).

Conclusion: Considering the high prevalence of UTI and antibiotic resistance rates in kidney transplant patients in our study, there is an urgent need for developing hospital based local antibiogram for appropriate management of UTI. Fosfomycin as an empirical therapy might be a useful choice for adequate coverage of potential pathogens at our centre. Further multi-centric studies on a larger sample size are recommended from India for formulating antibiotic policy.

Introduction

Urinary tract infections (UTI) remain a common cause of mortality and morbidity post renal transplant. It is well-documented that renal transplant recipients are more likely to develop an episode of UTI as opposed to the general population. The reported prevalence of UTI in renal recipients in the past decade ranges between 13 to 80% across various studies. The Spanish Network for the study of Infection in Transplantation (RESITRA) described an incidence of UTI of 0.45 episodes per 1000 transplantation days among 2052 renal transplant patients followed for 3 years. Urinary tract infection in renal transplant patients constitute of approximately 40-50% of all infectious complications in the post-transplant period.

The established risk factors for acquiring a UTI in kidney transplant patients are urinary bladder catheterization, cadaveric kidney transplant, abnormalities of the native kidney or the allograft (such as vesico ureteral reflux), rejection episodes, and use of immunosuppressive drugs, gender, age, invasive urological maneuvers, as well as hospitalization itself.

With the emergence of Multi drug resistant organisms (MDROs), especially in gram negative bacteria, management of patients with UTI...
post transplantation is becoming exceedingly difficult. Therefore, knowledge of etiology of UTI and local antibiogram of the pathogens in kidney transplant patients is imperative for early diagnosis of UTI and its management to minimize rejection episodes.

Data from India on UTI prevalence, etiology and antibiogram in post renal transplant patients is scarce. In recent years, a few studies from North and South India on UTI in kidney transplant patients have reported a considerably high prevalence of UTI in renal transplant patients. This study aims to assess the prevalence of UTI, its etiology and antibiogram in renal transplant patients.

Materials and Methods

This was a hospital based retrospective as well as prospective observational study conducted at Sir Ganga Ram Hospital, a 675 bedded tertiary care hospital. The study involved the department of Clinical Microbiology & Immunology and Department of Nephrology. The study included 100 consecutive pediatric and adult patients, who had undergone renal transplantation during the 6 month study period. Chronic kidney disease (CKD) patients admitted for renal transplant surgery but failing to undergo transplant surgery due to medical/surgical complications were excluded from the study.

Methods

Baseline demographics of all patients including age, sex, type of donor—whether cadaveric or live were recorded. The patients were screened for UTI on the day of admission (Day 0) and subsequently every 3rd day till discharge by performing routine microscopy and urine culture. A positive urine culture (bacterial growth of ≥ 10^5 cfu/ml) in the presence of significant pyuria (pus cells ≥ 10/μl) was defined as UTI. Phenotypic identification of organisms till species level was done using MALDI-TOF MS (Biomerieux Marcy l’Étoile, France). Antibiotic susceptibility testing (AST) was performed using automated systems VITEK 2 systems (Biomerieux Marcy l’Étoile, France) and interpreted according to Clinical and Laboratory Standards Institute (CLSI) interpretative guidelines. The day of the UTI was recorded to assess the time of development of UTI post-transplantation.

Statistical analysis

Data collected in a predesigned performa was entered in MS EXCEL Software. Data including demographic details of study cases and variables pertaining to the details of UTI episodes if any, viz. the time of infection from the day of transplant, the etiology of UTI and the antibiotic susceptibility results of the organisms were documented. Descriptive statistics were analyzed using SPSS software version 17.0. Continuous variables were presented as mean ± SD. Categorical variables were expressed as frequencies and percentages. The Pearson’s chi-square test was used to determine if there is a relationship between two categorical variables. P<0.05 was considered statistically significant.

Ethical clearance

The study was approved by the Institutional ethics Committee (Reference letter number: EC/10/18/1417) prior to the start of the study.

Results

Demographic data

A total of 100 patients (males: n=87, females: n= 13) undergoing renal allograft transplant were included in the study. The overall prevalence of UTI among the study population was observed to be 30%. The mean age of the study population was 39.4 years, ranging between 12 to 67 years. The prevalence of UTI was maximum in the age group between 26 years to 50 years (56%), while it was 19 % and 25 % in the age groups between 0 to 25 years and 50 to 75 years, respectively, and was not significantly associated with UTI (p= 0.305). The percentage of males and females developing UTI post kidney transplant was observed as 29.9% (26/87) and 30.8% (4/13), respectively (p =1.00). The overall length of stay (LOS) of patients ranged from 10 days to 50 days with an average of 16.8 days. In patients developing UTI, the LOS was 18.3 ± 4.4 days against 7.4 days ranging between 6 to 21 days. Patients developed UTI between 3 to 18 days post renal transplant (Mean= 6.7 days). The majority of UTIs occurred on Day 6 (36.6%) and Day 9 (36.6%) post-transplant.

A total of 31 microorganisms were isolated from the 30 patients, as 1 patient had poly microbial infection due to Enterococci spp. and Candida spp. Out of these 31 organisms, 28 (90.3%) were by gram negative bacteria (GNB),
2 (6.4%) were by gram positive cocci (GPC) and 1 (3.2%) by Candida spp. E.coli was the most common organism isolated in 13/31 (42%) cases followed by Klebsiella pneumoniae in 12/31 (39%) cases (Figure 1).

Figure 2 shows the AST pattern of the 28 enterobacteriaceae isolated in our study. A high percentage of resistance to the commonly used 1st and 2nd line antibiotics were observed in enterobacteriaceae in our study as: Ceftriaxone (96.6%), Ciprofloxacin (96.6%), Amikacin (58.7%), Piperacillin-tazobactam (62.1%) and Meropenem (55.2%). We also observed 10% resistance to colistin in enterobacteriaceae (Figure 2).

Discussion

UTI has been observed as the most common bacterial infection post renal transplantation.6 Once thought of as a benign pathologic process, UTI has emerged as a potential threat to the function and survival of the graft kidney in renal allograft recipients.

In the present study, we report a prevalence of 31% UTI among renal allograft recipients. A comparable prevalence of 33% and 33.3% have been reported in previous studies by Shirazi et al., and Gondos et al., respectively.12,13 Studies across the world, including Mexico, Brazil, Libya and those conducted in the African-American belt also report such high prevalence of UTI in this susceptible cohort.14 In India, previous studies from New Delhi and Telangana reported a prevalence of 32.86% and 41.9% UTI post transplantation.15,19 The high prevalence of UTI in kidney transplant patients in various studies could be explained due to the use of high dose immunosuppressive agents, surgical trauma and the presence of post-operative indwelling catheters and ureteric stents.

The mean age of our study population was 39 years. Mohan et al., reported a similar age of transplant patients in their study (32.4 years ± 10.2 years).15 In contrast, data from the West particularly America and Europe shows higher mean age of population in kidney transplant patients (Mean= 54 years).16 The younger mean age group of kidney transplant patients in our study could be due to higher prevalence of uncontrolled diabetes mellitus and hypertension in the Indian population as compared to Western countries.17 In our study we did not observe a significant association between gender and UTI post kidney transplantation which is in concordance with other studies.12,13

The etiology of UTI is varied in different hospital settings but the current data suggest UTI due to GNB remains the leading cause of UTI,6 similar to the results of our study (Fig1). In our study, E.coli (39%) and Klebsiella pneumoniae (42%) were the leading causes of UTI. Comparable results were reported in a study by Menegueti et al., conducted on 1,847 urine cultures from kidney transplant patients. Klebsiella pneumoniae (36%) and E.coli (20%) were most frequent pathogens causing UTI in their study.7 In contrast, a recent study from New Delhi reported higher rates of UTI due to E.coli (72.46%) post renal transplantation surgery.8 E.coli and Klebsiella being a major component of fecal flora are most likely introduced into the urinary tract through catheterization, thereby resulting in frequent UTIs due to these organisms.

UTI in renal allograft recipients are usually hospital acquired infections as they are acquired after 48 hours of hospital admission. Our study showed high rates of UTI due to Multidrug resistant organisms (MDROs). ESBL producing Enterobacteriaceae and carbapenem resistant Enterobacteriaceae (CRE) rates were observed as 96.6 % and 55.2%, respectively, in our study. Another Indian study conducted on renal allograft recipients in 2014 reported rates of 46.6% and 33.3% ESBL and CRE producing pathogens, respectively.15 Similarly, Origuen et al., compared patients between 2002 and 2004 with another cohort between 2011 and 2013 and observed the progressive increase in MDR pathogens and ESBL producers from 43.9% to 67.8% and 6.6% to 26.1%, respectively.18 The rate of CRE (1-3%) reported in Western data is low compared to that reported from India.19 The possible reason for high rates of MDROs in our study may be attributed to high prescription of antibiotics at our centre (189 Daily Defined Doses/100 bed days).20 Our hospital being a referral tertiary care centre with a dedicated kidney, liver and bone marrow transplant units has admissions of critical patients often with high case mix index (CMI)21 who require higher prescription of antibiotics which may contribute to the emergence of MDROs.22 In our study population, the patients received an average of 7.4 days of empirical antibiotics before developing UTI. In a large study of over 1500 kidney transplant recipients by Yuan et al, use of broad-spectrum antibiotics for 5 days or more within 1 month before UTIs was associated with more frequent UTIs due to MDROs.23

UTI in kidney transplant patients due to MDROs like ESBL and CRE have shown to result in impaired graft function or graft loss and increased length of stay. UTI by CRE may warrant escalation of antibiotic therapy by polymyxins as the last resort antibiotics. However, colistin administration in this cohort is fraught with complications due to its nephrotoxicity. Nephrotoxicity associated with colistin (43-60%) in kidney transplant patients is potentiated by the use of concomitant nephrotoxic agents, like calcineurin inhibitors. CRE are often susceptible to fosfomycin24 and thus fosfomycin maybe an attractive antibiotic therapy in UTI due to CRE, while it poses challenges for its sensitivity testing. At our centre cefuroxime is often used as an empirical treatment of UTI before urine culture and sensitivity results are available. The antibiotic of our study suggests that this may be inappropriate in the current situation due to high prevalence of MDROs and requires urgent revision of antibiotic policy. We recommend the use of fosfomycin as an empirical therapy for UTI for adequate coverage of potential pathogens and escalate or de-escalate as quickly as possible based on susceptibility results. Similarly, Bader et al also suggest the use of higher antibiotics like aminoglycosides and colistin as alternatives in MDR Gram-negative UTIs in their study population based on their local antibiotic.25

Although our study results provides an important insight to the prevalence and antibiogram of UTI in kidney transplant patients at our centre but interpretation and extrapolation of our study results is limited by the small sample size of our study. Therefore, multi centric studies on a large population cohort may be required to formulate antibiotic guidelines for the early and appropriate treatment of UTI.
References


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Metformin Hydrochloride 500 mg SR + Glimpiride 2 mg

In uncontrolled T2DM, STEP UP with Glycomet®-GP 3
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*Data on file

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Lactate-free AARC ACLF Score (LaFAS) – A Simple User-friendly Score is the Best Prognostic Marker for Patients with Alcohol Induced ACLF in Western Indian Population in a Non-transplant Resource-limited Setting

Shamshersingh G Chauhan1, Alisha Chaubal2, Kailash Kolhe1, Harshad Khairnar1, Mamata Lotlikar1, Swapnil Walke1, Vipul Chaudhari1, Meghraj Ingle3, Vikas Pandey2, Akash Shukla4*

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Received: 12.02.2019; Accepted: 12.09.2019

Abstract

Introduction: Acute-on-Chronic liver failure (ACLF) is a disease with a distinct spectrum of liver injury, with a rapid downhill course Here we describe three new scores – Albumin Bilirubin Index (ALBI), platelet albumin bilirubin index (PALBI) &Lactate-free AARC ACLF score (LaFAS), in predicting short-term mortality in patients with alcohol induced ACLF when compared to standard validated scores.

Methods: Consecutive patients diagnosed as alcohol induced ACLF as per the APASL 2014 definition were included in the study. Standard scores – MELD, MELD-Na, Maddrey’s discriminant function, CLIF-OF & CLIF-C ACLF scores, APACHE II, ALBI, PALBI and LaFAS were calculated. The endpoints of the study were to predict short term mortality in alcohol induced ACLF patients using ALBI, PALBI and LaFAS and finding the cut-offs of these new scores and comparing it with standard validated scores.

Results: 67 patients were studied with 97% being male. Mean age was 45.78 ± 8.15 years. 44 patients died. The cut-offs, area under the ROC curve; sensitivity& specificity, positive and negative predictive values of the new prognostication scores were, respectively: ALBI (-0.57; 0.948; 90.9% & 82.6%; 77.69% & 93.15%), LaFAS (7; 0.968; 95.5% & 96.7%; 95.075 & 96.99%), PALBI (-0.28; 0.59; 61.4% & 52.2%; 46.13% & 66.98%). LaFAS and ALBI outnumbered the valid prognostic scores in predicting short-term mortality. PALBI underperformed when compared to all other scores.

Conclusion: Thus incorporating albumin and bilirubin in a mathematical equation (for ALBI) or combining it with creatinine & grade of hepatic encephalopathy (for LaFAS) would help in prognosticate the patients with ACLF on admission in a resource limited setting thus enabling them to be transferred to a transplant center.

Introduction

Acute-on-Chronic liver failure (ACLF) is a disease with a distinct spectrum of liver injury, with a rapid downhill course, unless urgent intervention is not taken into action. Thus to prognosticate these patients becomes an important issue. Various scores are available to stage ACLF and guide urgent management. These include the Model for End Stage liver disease (MELD) and its extension, the MELD-Na, the Chronic liver failure (CLIF) consortium ACLF score, Acute Physiology and Chronic Health Evaluation II score (APACHE II). These scores are cumbersome and predict mortality only when extra-hepatic failure is present. Alcohol is the most common cause of ACLF in our country with the per capita consumption on a steady rise. Alcoholic hepatitis is a spectrum of disease ranging from an indolent elevation of transaminases to ACLF.

Albumin-Bilirubin Index (ALBI) combines serum albumin and bilirubin in a mathematical equation. This helps in assessing the severity of liver dysfunction. It has been studied to predict mortality in patients with hepatocellular carcinoma (HCC) and to prognosticate patients with primary biliary cirrhosis. It has been tested in Hepatitis B induced ACLF where it has predicted mortality as accurate as the MELD score and better than the Child-Turcotte Pugh (CTP) score.

Platelet-Albumin-Bilirubin Index (PALBI) is similar to ALBI but incorporates platelet count as a marker of portal hypertension, has been found better than Child-Turcotte-Pugh (CTP) score in predicting survival in patients undergoing transarterial chemoembolization for hepatocellular carcinoma.

The APASL Asia Research Consortium ACLF consortium (AARC) has given a new score for prognostication of patients with ACLF known as the AARC ACLF score (Table 1). The variables included in it are serum lactate, serum total bilirubin, grade of hepatic encephalopathy and International normalized ratio [INR]. But many centers do not do serum lactate as a routine in their patients. Hence, a modification of the above score was devised, the Lactate-free AARC ACLF score (LaFAS) which was studied and presented in abstract form in patients with alcoholic liver disease with liver failure and compared with
Patients and Methods

Study Design

This study was a single center prospective observational study conducted at a non-transplant, tertiary center in Western India. Patients were enrolled between October 2017 to September 2018. The study protocol was reviewed and cleared by the institution’s ethical committee. ACLF was defined according to the APASL 2014 definition which stated that ACLF is an “acute hepatic insult manifesting as jaundice (bilirubin > 5 mg/dL) and coagulopathy (international normalized ratio [INR] > 1.5), complicated within 4 weeks by ascites and/or encephalopathy in a patient with previously diagnosed or undiagnosed chronic liver disease with a high 28-day mortality”.12 Alcoholic hepatitis was defined as a clinical syndrome with recent onset of jaundice and/or ascites in a patient with ongoing alcohol misuse.15 Severe alcoholic hepatitis was defined as modified Maddrey’s discriminant function (MDF) score more than 32. Active alcoholism was defined as 21 units per week for men and 14 units per week for women, not earlier than three months before admission.14 Liver biopsy was not done. Alcohol induced chronic liver disease was defined on terms of imaging showing nodular liver with evidence of portal hypertension on imaging and/or endoscopy.

Patients who had a significant alcohol use of >25 grams per day for along with diagnosis of ACLF according to the APASL 2014 definition were included in the study. Only patients who were ineligible to receive steroids due to either sepsis or gastrointestinal bleed or acute kidney injury were included in the study. Written informed consent was taken from patient or if they had any evidence of altered sensorium i.e. hepatic encephalopathy etc. the consent was taken from the relatives. The study was cleared by the institute’s ethics committee.

All patients who had acute insult apart from or along with alcohol like viral hepatitis [A, E, B, C], drugs and toxins etc., chronic liver disease apart from or along with alcohol, pregnancy related liver diseases, hepatocellular carcinoma and patients or relatives who failed to give consent were excluded from the study. The study was cleared by the institute’s ethics committee.

The prognostic scores were calculated on investigations based on investigations sent on day one of admission and were calculated as follows: ALBI score = −0.085 × (albuming/L) + 0.66 × lg (TBil μmol/L); MELD = 3.78 × Ln (TBil μmol/L) + 11.2 × Ln(INR) + 9.57 × Ln(creatinine mg/dL) + 6.4; MELD-Na = MELD + 1.32 × (137 – serum sodium) − 0.033 × MELD × (137 – serum Sodium)), where the minimum value for serum sodium was 120 mmol/L and the maximum was 135 mmol/L; modified Maddrey’s discriminant function (MDF) = [4.6 x (PT test - control) + Serum Total Bilirubin in mg/dL]; Chronic Liver Failure Consortium [CLIF] organ failure [OF] score was calculated and then incorporated into the CLIF-C ACLF score which was calculated as = 10 x [(0.33 × CLIF-OF +0.04 x Age +0.63 x Ln(WBC in 10^9 cells/L)-2] × APACHE II score; LaFAS; PALBI - (2.02 log10 Total Bilirubin) + (-0.37 log10 Total Bilirubin^2) + (−0.04 x albumin) + (−3.48 log10 platelets) + (1.01 log10 platelets^2)]

Sample size was calculated as 67 with power of study 0.90 with expected 15% dropout rate with type 1 error of 5% with a mortality assumption of 40%.

The primary endpoint of the study was to predict short term mortality in alcohol induced ACLF patients using ALBI, PALBI and LaFAS.

The secondary endpoint of the study was finding the cut-offs of these new scores and comparing it with standard validated scores.

Statistical analysis

In this study all the analysis was performed using 17.0 version of statistical software SPSS.

Descriptive Analysis

Continuous variables were summarized by using summary statistics (number of observations, mean and standard deviation) and categorical values by using frequencies and percentages. For all study cases during the hospital stay as per clinical discretion and post discharge they were followed up for three months thereon or until death during hospital. Post discharge, the blood investigations were done every two weekly until improvement was seen; defined as total bilirubin less than 5mg/dL and normalization of INR.

The AARC ACLF score

<table>
<thead>
<tr>
<th>Points</th>
<th>Total Bilirubin</th>
<th>Hepatic encephalopathy grade</th>
<th>INR</th>
<th>Lactate (mmol/L)</th>
<th>Creatinine (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>&lt;15</td>
<td>0</td>
<td>&lt;1.8</td>
<td>&lt;1.5</td>
<td>&lt;0.7</td>
</tr>
<tr>
<td>2</td>
<td>15-25</td>
<td>I-II</td>
<td>1.8-2.5</td>
<td>1.5-2.5</td>
<td>0.7-1.5</td>
</tr>
<tr>
<td>3</td>
<td>&gt;25</td>
<td>III-IV</td>
<td>&gt;2.5</td>
<td>&gt;2.5</td>
<td>&gt;1.5</td>
</tr>
</tbody>
</table>

CTP, MELD and, MELD-Na. The points allotted to them were the same as the original AARC score but with only exclusion of serum lactate. Maximum score being 12 and minimum being 3.

But to the best of our knowledge, there is no study that compares ALBI, PALBI or LaFAS as predictors for short-term mortality in patients with alcohol induced ACLF with standard, validated scores like CLIF-C ACLF, APACHE II, MELD and MELD Na in a non-transplant resource limited setting.
The majority of patients (97%) enrolled in the study. The mean age of the patients in our study was 45.78 ± 8.15 years. Hepatic encephalopathy was present in 40 patients with ACLF as per the CANONIC study, 20 on presentation, were ACLF grade 0 – 10 (14.9%), ACLF grade 1 – 20 (29.8%), ACLF grade 2 – 26 (38.8%), ACLF grade 3 - 11 (16.4%).

The baseline characteristics of the patients who survived versus who died are displayed in Table 3.

On univariate analysis it was shown that high total WBC counts, total bilirubin, INR, creatinine and low total serum proteins, serum albumin, bicarbonate, partial pressure of carbon dioxide in arterial blood and serum sodium were associated with significant mortality. Pulse rate, respiratory rate, mean arterial pressure, hematocrit, AST, ALT, alkaline phosphatase, serum potassium levels and arterial oxygenation were not significantly different in survivors and the dead, when calculated on admission.

The various prognostication scores in patients who died versus who survived, calculated using parameters sent on admission are displayed in Table 4.

The area under the ROC curve (Figure 2), of the various ACLF prognostication scores, calculated on admission, along with the cut-off values that predicted mortality at three months were: MELD (26; 0.863), MELD-Na (30; 0.878), APACHE II (14; 0.916), MDF (65; 0.896), CLIF-OF (09; 0.947), CLIF-C ACLF (45; 0.887), ALBI (-0.57; 0.948), LaFAS score(7; 0.968), PALBI(-0.28; 0.59). Thus it was shown that ALBI and LaFAS scored best amongst the others in predicting three-month mortality in patients with alcohol induced ACLF. PALBI was not found to be better than any of the standard scores in predicting mortality in our cohort of patients.

The sensitivities and specificities of the prognostication scores at their cut-offs have been depicted in Table 5. The LaFAS has the highest sensitivity and specificity amongst the scores in predicting mortality at 3 months with ALBI coming a close second followed by CLIF-OF. CLIF-OF had similar sensitivity compared to LaFAS but lower specificity.

Discussion

In this single prospective pilot study conducted at a non-transplant resource limited setting in western India, we compared three new scores – ALBI, LaFAS and PALBI with the valid prognostic scores, to predict mortality at three months. In our cohort, 65.7% of patients succumbed to the illness. High leukocyte count, high bilirubin, high creatinine and INR and low serum albumin were associated with high mortality in our set of patients. We also found out that in patients with alcohol-induced ACLF, LaFAS followed by ALBI predicted mortality better than the various prognostic scores. In our study, the cut-offs for the new scores to predict mortality: ALBI (≥ -0.57; Sensitivity – 90.9% and Specificity – 82.6%; positive predictive value – 77.69% and negative predictive value – 93.15%) and LaFAS (≥ 7; Sensitivity – 95.5% and Specificity – 96.7%; positive predictive value – 95.07% and negative predictive value – 96.99%).

Alcohol is the most common cause of ACLF across the globe20-23 and alcohol-related ACLF was found to have high mortality and poorer outcomes20-24 in some studies when compared to other causes of ACLF.20 Options to treat alcohol-related ACLF are limited. They include pentoxifylline, steroids, and nutritional supplementation. Liver transplant in such patients has shown to improve outcomes23 but many centers need a six-month abstinence period before it is feasible, something that cannot be possible in patients with ACLF. Thus, the need for urgent triage for these set of patients.

Various prognostic scores are available that require a host of clinical and biochemical parameters for...
calculation. Earlier MELD, MELD-Na, and CTP scores were used to assess the prognosis in patients suffering from ACLF. But because ACLF may be associated with multiple extra-hepatic organ failures, these scores don’t take them into account, thus impacting the prognostication of patients in this cohort. CLIF-OF is a complex score which takes into account multiple organ failures, namely - liver, kidney, brain, coagulation, circulation, and respiration with a 5-point range. These are based on expert opinion and not data. This lead to the development of CLIF-C ACLF score. Both these scores outperform the MELD, MELD-Na, and CTP scores in predicting mortality. APACHE II was devised by William Knass for prognosticating critically ill patients. It takes in to account a host of clinical and biochemical parameters with a range of 0-71. It has been studied in ACLF patients and has shown to be a better predictor of mortality than MELD, MELD-Na. 

The AARC ACLF score was devised using patients from the AARC ACLF consortium and was compared against the other validated scores. LaFAS has been studied and presented in an abstract form to predict mortality in patients with liver failure secondary to alcoholic liver disease but to the best of our knowledge, it has not been studied in patients with ACLF. ALBI has been studied in patients with Hepatitis B induced ACLF, where it was found as accurate as the MELD score. PALBI and ALBI together have been studied to predict mortality in patients undergoing transarterial chemoembolization for HCC. Addition of platelet count to ALBI leading to the formation of PALBI is taken as a surrogate marker for portal hypertension. This is the first study evaluating PALBI as a prognostic score for ACLF.

In our study, amongst the valid scores, APACHE II was found to have had the highest specificity and CLIF-OF, the highest sensitivity. CLIF C ACLF was found to be underperforming when compared to our new scores. The possible explanation would be that it was calculated on parameters based on admission and not between days 8-15, as advised, thus decreasing its predictive value in predicting mortality at three months. All the patients who were included in the study were steroid ineligible; hence treated with pentoxifylline and nutritional supplementation.

About 20-25,000 liver transplants are required per year in India, but by 2014, only about 1400 transplants were possible; most (80.7%) of which were live donor related. The cost of liver transplant ranges from 2.2-2.5 million Indian rupees. And less than 2% of transplants have been estimated to occur in the public setting. In the western zone of India, amongst the public sector hospitals, there is currently only one center for cadaver donor liver transplant and none for live donor liver transplant. Majority of patients that we cater to at our center are below the poverty line. Many hospitals in India, who serve this cohort of patient population, like ours, do not have a dedicated liver transplant team and a liver intensive care unit. Liver function tests (LFT), which incorporate transaminases, total bilirubin, serum proteins and albumin levels with INR, are usually the first investigation done in a patient suspected of having liver disease. Just incorporating albumin and bilirubin levels (for ALBI) in a mathematical equation or calculating a score or incorporating LFTs with the grade of encephalopathy and creatinine in LaFAS would help the primary treating physician in prognosticating the patient on admission and if possible, triage and early transfer to a liver unit for further management.

The strengths of our study are that we have validated two new scores in patients suffering from ACLF and have demonstrated their superiority when compared to the standard scores in predicting mortality.
There were few limitations in our study. First, it was a single center study and referral bias might have played a role in including sicker patients to the cohort; thus the high mortality in our cohort. Second, the scores were calculated on parameters based on the admission of the patients and not dynamically measured. Third, it was a pilot study thus the small sample size.

Conclusion

ALBI and LaFAS have been proven to predict mortality when compared to standard validated scores in patient with alcohol related ACLF. More studies with larger population cohort would be required to validate these scores.

References

A Prospective, Randomized, Interventional Study of Oral Iron Supplementation Comparing Daily Dose with Alternate Day Regimen Using Hepcidin as a Biomarker in Iron Deficiency Anemia

Sudhir Mehta1, Bhawani Shankar Sharma 2, Sandhya Gulati3, Nidhi Sharma4, Laxmi Kant Goyal5, Shaurya Mehta6*

Abstract
Aim: To assess effect of daily vis-a-vis alternate day oral iron therapy in terms of hemoglobin, reticulocyte hemoglobin equivalent (RET-He) and GI side effects using hepcidin as a biomarker

Methods: A hospital based randomized interventional two-arm analytical study was done among patients of IDA (20 in each group). The study population was divided into two groups by randomisation. Group 1 received oral iron supplements on alternate day and Group 2 received iron supplements daily. Hemoglobin, RET-He, Serum ferritin and Hepcidin level were assessed.

Results: On day 2nd, the rise in Hepcidin was not significant from base line in alternate day therapy group but was significantly increased in daily therapy group. On day 3, the rise in hepcidin was significant from base line in both the groups but the mean change in hepcidin was more in daily therapy group. RET-He began increasing on day 2nd in both the groups. In alternate day therapy group, the rise in RET-He was significant from base line from the day 2nd onwards while the rise in RET-He in daily therapy group was not significant even on day 3. In alternate day iron therapy group, the mean increase in hemoglobin on day 21th (1.58 ±0.53 gm/dl) was significantly more than mean increase among daily therapy (0.41 ± 0.25 gm/dl, P <0.05).

Nausea and metallic taste were reported more in daily therapy group.

Conclusion: Alternate day single tablet dosing schedule of oral iron therapy (60mg of elemental iron, ferrous sulfate) was more effective and better tolerated (gastrointestinal side effects) compared to daily supplementation in IDA.

Introduction
Iron deficiency is one of the most common nutrient deficiencies and a leading cause of anemia worldwide. Standard treatment of mild to moderate iron deficiency anemia (IDA) is oral iron therapy, divided in 3-4 iron tablets daily. The oral iron preparations are associated with gastro-intestinal (GI) side effects like metallic taste, nausea, flatulence, constipation, diarrhea, epigastric distress, vomiting, itching and black stools that stain clothes. The oral iron also has possible role in alteration of gut flora. Hepcidin plays a key role in iron homeostasis. Hepcidin is synthesized primarily in the liver and functions as an acute phase reactant to maintain homeostasis during fluctuation in plasma iron level by binding and inducing the degradation of ferroportin, which export iron from cell. In iron deficiency, the transcription of hepcidin is suppressed and gut iron absorption through divalent metal transporter 1(DMT1) is increased by the activation of hypoxia inducible factor2a. Hepcidin level has a strong direct correlation with serum level of ferritin. Alternate day oral iron therapy is found to be beneficial over daily oral iron therapy in terms of better iron absorption and lesser GI side effects. So, this study was undertaken to assess effect of daily vis-a-vis alternate day oral iron therapy in terms of hemoglobin, reticulocyte hemoglobin equivalent (RET-He) and GI side effects using hepcidin as a biomarker in view of lack of Indian data in this context.

Material and Methods
A hospital based randomized interventional two-arm analytical study was done in the Department of Medicine of Tertiary Care Hospital of Medical College. Initially, 50 patients of IDA (25 in each group) were recruited but in final analysis 40 IDA cases (20 in each group) remained due to either untimely attendance of the subjects or due to lost-to-follow up at 21st day. All patients with newly diagnosed & untreated mild to moderate iron deficiency anemia and above 18 years of age were recruited in the study after written informed consent and permission from institutional ethics committee. Patients with anemia other than iron deficiency (dimorphic anemia, vitamin B12 deficiency, folic acid deficiency, aplastic anemia, HIV-1 & HIV-2, malignancy, kidney disease, liver disorder, anemia of chronic disease, pregnancy, lactation, hemoglobinopathies), patients

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with severe IDA who required blood transfusion/parenteral iron therapy, patients on haematinsics supplementation within past 3 months of the recruitment in study were excluded from the study. Patients with any inflammatory disorder (excluded by CRP), malabsorption syndrome, bariatric surgery, taking proton pump inhibitors were also excluded from the study. The study population was divided into two groups by randomisation. Group 1 received oral iron supplements on alternate day and Group 2 received iron supplements daily (oral tablet ferrous sulphate 60mg, 2 hr. after meal).

From each study participants, detailed history was taken and thorough clinical examination was performed. After overnight fasting, 10 ml venous blood sample was drawn from left antecubital vein and sent for investigations including complete blood count, RET-He, iron indices, sugar, renal and liver function test, HIV-ELISA. For hepcidin assessment, samples were preserved at -20°C. The real time parameter of hemoglobinization, RET-He began increasing on day 2nd of start of iron therapy. RET-He was estimated by Sysmex XT 4000i automated hematology analyzer at base line, on day 2 and on day 3 of start of iron therapy. Hemoglobin was estimated by Sysmex XT 4000i automated hematology analyzer at base line, on day 2, day 3 and 21st day of start of iron therapy. RET-He was estimated by Sysmex XT 4000i automated hematology analyzer at base line, on day 2 and day 3 of start of iron therapy. Each patient was followed up and assessed for compliance, adverse effect including gastrointestinal symptoms up to 21st day after start of therapy. Serum ferritin was measured on IMMULITE 2000 Systems analyzer using a solid-phase, two-site chemiluminescent immunometric assay.

Statistical Analysis

Microsoft Excel® and SPSS® 20 for Windows® were used for data storage and analysis. The qualitative data were expressed in percentages and quantitative data were expressed as mean ± standard deviation. Student’s t test and Chi-Square test were used to determine statistical difference between variables. Results were considered significant if P < 0.05.

Results

At the baseline both groups were similar in terms of haemoglobin, serum ferritin, hepcidin and RET-He (P>0.05) (Table 1).

On day 2nd, the rise in Hepcidin was not significant from base line in alternate day therapy group but was significantly increased in daily therapy group. On day 3, the rise in hepcidin was significant from base line in both the groups but the mean change in hepcidin was more in daily therapy group as compared to alternate day therapy (Table 2A).

The real time parameter of hemoglobinization, RET-He began increasing on day 2nd in both the groups. In alternate day therapy group, the rise in RET-He was significant from base line from the day 2nd onwards while the rise in RET-He in daily therapy group was not significant even on day 3 (Table 2B).

In alternate day iron therapy group, the mean increase in hemoglobin...
on day 21st (1.58 ±0.53 gm/dl) was significantly more than mean increase among daily therapy (0.41 ± 0.25 gm/dl, P <0.05) (Table 2C).

Among the GI side effects, the frequency of constipation (1.5%) and epigastric distress (1.5%) were same in both therapy groups. Nausea and metallic taste were reported more by patients in daily therapy group. All these GI side effects were not significant statistically (P>0.05) (Figure 1).

Discussion

In this study, the effect of daily vis-a-vis alternate day oral iron therapy was evaluated in terms of hemoglobin, hepcidin level, reticuloocyte hemoglobin (RET-He) and GI side effects. It was found that alternate day oral iron therapy results in significant increment in hemoglobin along with lesser GI side effects compared to daily iron therapy.

Hepcidin is a regulator of iron metabolism. Hepcidin inhibits iron transport by binding to iron export channels “ferroportin” which are located on gut enterocytes and plasma membrane of RE cells. Plasma Hepcidin increases up to 24 hours after oral iron ingestion and it inhibit ferroportin channel, thus preventing gut iron absorption on the following day. So, iron absorption is much better in alternate day therapy compared to daily therapy which is reflected in significant rise in haemoglobin in the former group.

In previous report, among iron-depleted women, when daily oral iron therapy was given in divided doses, it increased serum hepcidin and reduced iron absorption. Alternate-day and single dose oral iron was found to optimize iron absorption in women.

In another study, among iron-depleted young women, morning oral iron acutely increases plasma hepcidin on the same day and 24 hours later. This increase in hepcidin was strongly associated with decreased absorption from the second iron dose, given 24 hours after the first. The oral iron therapy resulted in higher fractional absorption when dosages are spaced by 48 hours and increasing the interval between doses to >48 hours did not result in higher absorption than dosing at 48-hour intervals. So it can be concluded that the acute iron-induced increase in hepcidin influences iron absorption of successive daily iron doses. Thus the hepcidin levels were higher in daily dosing group compared to alternate dosing group. Our results are in echo with this study showing mean rise in hepcidin more in daily dosing group compared to alternate dosing group.

So, it can be concluded that among iron deficiency anemia, oral iron therapy given daily increases hepcidin in higher magnitude compared to alternate day oral iron. This increase in hepcidin results in decreased absorption from the second iron dose, given 24 hours after and lesser hemoglobinization which is reflected by less rise in RET-He. RET-He is a real time marker of iron incorporation in developing RBCs and this change can be seen as early as after 48 hours. So the increase in RET-He indicates augmented erythropoiesis after iron supplementation.

In our study, GI side effects were less frequent in alternate day oral iron therapy compared to daily oral iron therapy. Previous studies have also reported similar findings indicating that alternate day therapy is associated with less morbidity due to reduced gastrointestinal exposure to unabsorbed iron and ultimately improved tolerance of iron supplements. Plasma Hepcidin increases up to 24 hours after oral iron ingestion and it inhibit ferroportin channel thus preventing gut iron absorption on the following day. So, iron absorption is much better in alternate day therapy compared to daily iron therapy which is reflected in significant rise in haemoglobin in the former group.

Looking at this phenomenon, the gut toxicity of daily oral iron therapy can be explained by unabsorbed iron on the following day.

This study suggests to review the iron supplementation and treatment strategies for the prevention and control of iron deficiency anemia in populations with a high prevalence of iron-deficiency anemia.

Limitations

This study was limited to measure hepcidin only up to day 3. Patients with iron deficiency having severe anemia were not included who may respond differently to intravenous iron supplementation. The sample size was also a small one. Also, this study was a single center study conducted at a tertiary care referral hospital so the result may not imply on a general case.

However, this study makes a platform for larger multicentric study to substantiate the above hypothesis.

Conclusion

Alternate day single tablet dosing schedule of oral iron therapy (60mg of elemental iron, ferrous sulfate) was more effective and better tolerated (gastrointestinal side effects) compared to daily supplementation in correcting iron-deficiency anemia.

Acknowledgement

We are grateful to Dr. Y P Munjal Director PRF and Dr. GS Pangtey Jt. Secretary, PRF for their valuable and continuous guidance throughout the study.

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COVID 19: Diabetes and Obesity
API-ICP Recommendations

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Abstract
Diabetes and Obesity are major risk factors which confer vulnerability to Covid 19. Diabetes has immune defects which makes the individual susceptible to infections and covid 19 is no exception. Also covid 19 can cause pancreatic damage as well as stress hyperglycaemia in hospitals which may need Insulin. Among diabetes male gender, elderly, hypertension, heart disease and chronic renal disease are more vulbwdele to covid 19 and need strict supervision. Diabetes management in hospitalised situation merits early diabetes specific nutrition with Insulin. Adherence to lifestyle with self monitoring of blood glucose and adequate supply of Insulin and Oral antidiabetic agents is encouraged.

Basics
Novel Human corona virus (SARS-CoV2) or Human Corona Virus (HCoV), for the third time in last two decades has threatened to disrupt the planet earth. The earlier two outbreaks were in 2002 originating from china SARS with 8000 people affected and case fatality rate of 10 % and 2012 in Saudi Arabia MERS with 2000 people affected with a case fatality rate of 37 %.Both these corona viruses has been virtually conquered successfully. However the hardest evidence related to Diabetes came from Hong Kong during SARS epidemic which showed highest mortality even more than heart disease and cancer in people above 75 years of age. Diabetes clearly emerged in both these epemics of SARS and MERS a risk factor associated with poorer outcome especially in elderly and vulnerable population. Another interesting experimental work in transgenic mouse of a MERS model showed expression of DPP-4 receptor on the pulmonary alveolar cells. This model showed that MERS coronavirus binds to DPP IV receptor being domain of the pulmonary alveolar cells and may have contributed to the cytokine storm and higher mortality amongst diabetics. Possibly based on this model assumptions were made that diabetic get more pulmonary inflammation & infiltrates, more cytokine damage, weaker immune response and more severe disease. Even more we all know 5 to 15 % of the world population annually suffers from influenza or flu (millions contract it) and it causes in an excess of 300000 to 600000 pulmonary deaths. The current Human Corona virus SARS Cov2 is a zoonotic disease which came via bats possibly using Pangolins into humans. It caused COVID 19 as designated by WHO. Its origin was from Wuhan in China possibly the seafarers market there being the ground zero. It’s a beta RNA corona virus with spike glycoprotein which attaches to the ACE2 (Angiotensin Converting Enzyme) found in the pulmonary alveolar cells and possibly also the gut.

Clearly the vulnerable groups include Hypertension, Diabetes, Heart Disease, Lung diseases and any other immune compromised state. Our current focus is diabetes and obesity.

Diabetes and COVID 19

Incidence of infections is usually higher in patients with Diabetes compared to those without it. Diabetics also have more complications, more severe complications and death. Respiratory infections including tuberculosis are common in diabetics. Diabetics have clear cut compromised immune dysfunction. Diabetes and hyperglycemia leads to neutrophil dysfunction, poor chemotaxis, defective macrophage mononuclear function. There is also a deficiency of complement C4 in Diabetes, which is associated with Polymorphonuclear dysfunction and reduced cytokine response. Mononuclear cells and monocytes in Diabetics secrete less IL-1 and IL-6 and glycation would also reduce expression of class 1 MHC on surface of myeloid cells, impairing cell immunity. Decreased mobilization, chemo taxis, and phagocytic activity may occur in hyperglycemia and which may increase the susceptibility to oxidative stress in diabetes. Glycation of immunoglobulins in may be seen with poorer glycemic control (especially if the Hba1c is above 8 %) which harm the biological function of antibodies. In COVID 19 there is over activation of T-cells – leads to severe immune dysfunction. In severe COVID-19 patients had higher concentrations of pro-inflammatory cytokines. Therefore diabetes and hyperglycemic states especially with (a) Elderly above the age of 60 years (b) Hypertension (c) Obesity (d) Chronic heart or lung disease (e) Chronic kidney disease (f) Organ transplant (g) Patients on chronic immunosuppressive therapy (h) Acquired or genetic conditions of immunodeficiency - have a poor clinical as well as mortality outcomes. These vulnerable groups and comorbidities make COVID 19 cases get severe disease, cytokine storm, poorer response and death. Diabetics with complications and poorer glycemic control makes the virus survive longer and makes it more virulent. A new term called “Sugar-tension” as a twin epidemic of diabetes

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and hypertension will adversely alter the outcome possibly by 2 to 4 fold. Diabetic lungs in animal models, often have revealed augmented vascular permeability and collapsed alveolar epithelium.

**COVID 19 Dysglycemia - Hyperglycemia (Stress)**

COVID 19 can lead to a hypermetabolic state and lead to simple stress hyperglycemia which will alter outcomes. COVID 19 also can unmask latent diabetes especially in pre diabetics as well as predisposed cohorts. This can alter severity of pneumonia, ARDS, weaning of mechanical ventilation, the length of stay in ICU as well as short and early mortality. Often medications can also lead to iatrogenic dysglycemia .Many agents including corticosteroid as well as immune therapies can lead to hyperglycemia states leading to poorer outcomes. Also drugs like chloroquine, hydroxy chloroquine can lead to hypoglycemia which can also be severe. Chronic inflammation, pro-coagulant state; increase D dimer, immune dysfunction as well as direct virotrrophic effect of human coronavirus on pancreas cannot be ruled out. We will soon have data if a COVID 19 related pancreatopathy exists and autopsy data will give us clues which may also contribute to hyperglycemia or its worsening.

**Diabetes and COVID 19**

Types of Diabetes - Type 1, Type 2 or gestational or secondary, do not seem to be directly impacted by COVID 19. However Type 1 Diabetics below the age of 30 years, female gender have better outcomes compared to obese type 2 diabetics, males and elders race. Glucose control and glycemic variability adversely impact outcomes of COVID 19 diabetics. In asymptomatic or mild COVID diabetics, optimal glycemic control with diabetes specific nutrition (DSN), physical distancing, appropriate exercise with adequate 7 hour sleep and counseling is recommended with self-monitoring of blood glucose frequently to prevent peaks and valleys of glycaemia. Deaddiction from tobacco, smoking, alcohol as well as digital detoxification (zero screen time and mobile phone for 2 hours per day) is recommended. Hydration has to be individualized and optimal nutrition is recommended. Usually ACE inhibitors or Angiotensin Receptor Blockers, Thiazolidinediones, SGLT2 inhibitors may need to be used with extreme caution and pharmacovigilance and it is preferable to avoid starting them afresh. However the ACE inhibitors or ARBs verdict by many global guidelines is that they can be safe and even paradoxically protective. Ibuprofen and other NSAIDs may be avoided. Chloroquine (CQ) and Hydroxychloroquine (HCQ) can be good anti-inflammatory agents as option. CQ and HCQ are also adjuvants in diabetes but can cause hypoglycemia and need retinal evaluation, QT interval testing. They may have a role for prophylaxis is for healthcare worker and close contact as well a part of treatment regimens. Several Randomized trials are now being conducted on these trials which may answer this in a more definitive way.

**Management and Sick Day Regimen**

Management of diabetes - if glucose control is good: then continue same anti diabetic regimen. But if control is suboptimal then intensification with insulin may be needed as per requirement. However, if lockdown situation or access to the medications is an issue, the stricter diet, DSN-MNT, up titration of available drugs is recommended. Obesity can be associated with sleep apnea, reduced ventilatory function and surfactant dysfunction. In obese patients, continue diet, GLP-1 analogs, Orlistat as before unless injected by moderate to severe COVID or hospitalized. It is not wise to initiate aggressive weight losing measures during COVID19 infection. Avoid restrictive diet like keto diet or intermittent or prolonged fasting. No sudden change in pattern of diet or activity is advised. Yoga like Suryanamskar or simple Asana are recommended. Moderation is the key to success. COVID 19 is associated with hypoxia, hyper-catabolism and an overall catabolic state. Sarcopenia can aggravate it. Therefore 25-30 cals/kg/day intake with nutrient dense foods and 1.5-2 g protein/kg/day is recommended. For ICU or ventilated cases, early enteral Nutrition is recommended as early as 12 hours post ventilation and 24-36 hours in the ICU. A formula MNT or enteric formula with peptides may be needed. Disease specific enteral feeds like diabetic specific formulas or renal or hepatic specific diets are also useful. Blood pressure managements should be continued as per usual recommendations. Currently do not stop ACEi or ARB, though this needs individualization. If however, an anti-hypertensive drug has to be initiated or a regimen to be intensified, consider another class of drugs or agent.

When diabetics are ill, counter regulatory hormones like corticosteroids, catecholamines are released to fight the illness as a classical physiological response. These hormones can be triggered by any number of conditions, such as infections, cardiovascular ischaemic events, gastroenteritis, and dehydration causing Illnesses etc. This can cause wide fluctuations in the blood glucose levels and increased glycemic variability often leading to life threatening complications like Diabetic ketoacidosis, lactic acidosis and Hyperosmolar hyperglycemic states. Common cold or flu, including COVID-19 apart from Sore throat, Urinary tract infections, Bronchitis or pneumonia, gastroenteritis and diarrhea as well as Skin or genital infections such as abscesses (especially if these conditions are followed by a fever or high temperature) can cause hyperglycemia apart from corticosteroid therapy. Patients should be made aware of target glucose levels during an illness. They must be educated How to adjust medications, more frequent SMBG and ketone testing. They should be told to seek immediate emergency medical help if a) If they are not sure what to do b) If they vomit repeatedly (not able to hold down any food or drink for more than six hours), as they can quickly become very dehydrated c) If their blood glucose stays high (>250 mg /dl) for more than 24 hours or d) If they develop symptoms which could be indicative of developing diabetic ketoacidosis.

General guidelines to manage diabetes during an illness includes frequent blood glucose testing (SMBG). Following steps need to be taken, even if glucose levels are under control. Take diabetes medication as usual. Insulin treatment should never be stopped. Test blood glucose every four hours, and keep track of the results. Drink extra (calorie-free) fluid (except cardiac or renal or medical conditions
where fluids are restricted), and try to eat as normal. Allow patients to weigh themselves every day. Losing weight while eating normally can be a sign of high blood glucose. Also check body temperature every morning and evening and if fever is present may be a sign of infection. The control diabetes in children during illness should never be ignored though children have better outcomes in COVID 19 due to thymic humoral factors. General sick day diabetes management principles for children with diabetes are more frequent blood glucose and ketone (blood or urine) monitoring. The aim for a blood glucose levels should be between 70-180 mg/dL and blood ketones below 0.6 mmol/L when the child is ill. **NEVER STOP INSULIN.** If there is fever, insulin needs are usually higher. Monitor and maintain hydration with adequate salt and water balance. Treatment of underlying illness and symptoms (fever) is often needed. If, in a child with diabetes, fever or vomiting persists and/or weight loss continues suggesting worsening dehydration and potential circulatory compromise or fruity breath odor (acetone) persists or if there is a worsening or persistent elevated blood ketones >1.5 mmol/L or if urine ketones remain large despite extra insulin and hydration or if the child or adolescent is becoming exhausted, confused, hyperventilating (Kussmaul’s breathing), or has severe abdominal pain, urgent emergency medical or if possible specialist help should be taken or urgent hospitalization may be needed. The typical guidelines for T1DM patients remain same. **Remember: Insulin treatment should never be stopped.** The insulin dose may need to be increased and it might be necessary to take additional doses of fast-acting insulin to bring down the blood sugar levels. Blood glucose levels should be checked at least every four hours. Plenty of calorie-free fluids should be taken to avoid dehydration. Ideal blood sugar levels should be between 110-180 mg/dl and should be maintained. **Type 1 diabetics on Insulin pumps, if they have availability and access to pump care, should continue pump care or else under expert advice shift to basal bolus regimen with adequate insulin and SMBG supplies.**

**Global Recommendation for COVID 19 and Diabetes**

The AACE (American association of Clinical Endocrinologists) recommends to continue to take your prescribed medications. Refill prescriptions and be prepared with medications and testing supplies. Stay home as much as possible to reduce the risk of being exposed. Wash hands with soap and water regularly, for at least 20 seconds, especially before eating or drinking and after using the restroom and blowing nose, coughing or sneezing. Cover nose and mouth while coughing or sneezing with a tissue or a flexed elbow, then dispose the used tissue properly. Avoid touching eyes, mouth or nose if possible. If you get symptoms such as fever, cough, shortness of breath or wheezing, especially if you believe you may have been exposed to COVID-19 positive patient or live in or have recently traveled to an area with ongoing spread, call or see a health care professional immediately.

The Chinese guidelines say for the COVID-19 patients with diabetes, tailored therapeutic strategy and optimal goal of glucose control should be formulated based on clinical classification, coexisting comorbidities, age and other risk factors. Blood glucose should be controlled for all patients during hospitalization to monitor the progress of illness and avoid aggravation. During the 4-week follow-up period after discharge, blood glucose homeostasis should be maintained continuously and patients need to avoid getting exposed to other infectious diseases due to a lower immune response. The IDF (International Diabetes Federation) says older people and people with pre-existing medical conditions (such as diabetes, heart disease and asthma) appear to be more vulnerable to become severely ill with the COVID-19 virus. When people with diabetes develop a viral infection, it can be harder to treat due to fluctuations in blood glucose levels and, possibly, the presence of diabetes complications. There appears to be two reasons for this: Firstly, the immune system is compromised, making it harder to fight the virus and likely leading to a longer recovery period send secondly, and the virus may thrive in an environment of elevated blood glucose. The ADA (American Diabetes Association) is non-committal of the diabetes and COVID-19. People with diabetes do face a higher chance of experiencing serious complications from COVID-19. If diabetes is well-managed, the risk of getting severely sick from COVID-19 is about the same as the general population. COVID-19 is proving to be a more serious illness than seasonal flu, including people with diabetes. The risks are similar for people with type 1 and type 2 diabetes.

**Key Messages**

- Diabetes is a condition with significant immune dysfunction
- COVID-19 has also shown a component of immune dysfunction
- Diabetes patient with COVID-19 may have severe immune dysfunction leading to complications
- Diabetes is among the most common comorbidities observed in COVID-19 patients
- Diabetes has also been associated with severity of disease
- Diabetes (along with hypertension and coronary heart disease) needs to be assessed and managed in COVID-19 patients

**References**


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Guidance for Health Care Providers on Management of Cardiovascular Complications in Patients Suspected or Confirmed with COVID-19 Virus Infection

Thomas Alexander¹, Viji Samuel Thomson², Amit Malviya³, Bishav Mohan⁴, Gurpreet Singh Wander⁵, Harikrishnan S⁶, Sandeep Seth⁷, Sreenivas Reddy⁸, S Arulrhaj⁹, Siddharth Shah¹⁰, Shashank Joshi¹¹, Mangesh Tiwaskar¹², Milind Nadkar¹³, Kamlesh Tewary¹⁴

As cardiovascular health professionals, this guidance document has been brought out to help fellow physicians manage patients during the COVID-19 pandemic.

Introduction

The current coronavirus disease (COVID-19), a rapidly evolving pandemic, is a relatively unique infection unlike the earlier severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS) epidemics demonstrating a much greater infectivity though a lower case-fatality rate. The clinical manifestations are continuously being evaluated and management strategies rapidly evolving, including specific antiviral medications. This document summarises the current understanding of the cardiovascular complications of this infection and discusses the current pathophysiological mechanisms and management. However, it must be emphasised that a full understanding of the disease process is yet incomplete and as more information becomes available, this document will be updated to reflect new knowledge.

This document highlights the management of cardiovascular complications. However, detailed protocols for the diagnosis, triage, isolation, and management of COVID-19 patients with cardiovascular complications and/or cardiovascular patients with COVID-19 should be developed together with other medical specialties involved in management of these patients – intensivists, pulmonologists etc.

Scope of the Problem: The clinical manifestations of COVID-19 are dominated by respiratory symptoms followed by gastrointestinal symptoms; however, a significant percentage of patients have severe cardiovascular complications that can impact the course of the illness. In addition, some patients with underlying cardiovascular diseases (CVDs) show an increased mortality. Early case reports from the Chinese Centres for Disease Control indicate that patients with underlying comorbid conditions have an increased risk for contracting COVID-19 and have a worse prognosis. This is significantly worsened with increasing age. Depending on the report, between 25% and 50% of COVID-19 patients have pre-existing co-morbid conditions. Case fatality rates have varied significantly between countries and for different age groups. Estimates vary between 0.25% and 3%. Patients with comorbidities have higher mortality than the average population.

- Cancer: 5.6%
- Hypertension: 6.0%
- Chronic respiratory disease: 6.3%
- Diabetes: 7.3%
- Cardiovascular disease: 10.5%

Cardiac Manifestations of the Covid 19 Infection: Myocardial injury associated with the SARS-CoV-2 occurred in 5 of the first 41 patients diagnosed with COVID-19 in Wuhan, which mainly manifested as an increase in high-sensitivity cardiac troponin I (hs-cTnI) levels. The levels of biomarkers of myocardial injury were significantly higher in patients admitted to the ICU. Furthermore, more than 50% of patients who died demonstrated abnormally elevated Troponin levels.

About 90% of inpatients with pneumonia demonstrated elevated D-dimer concentrations indicative of heightened coagulopathy and manifested increased mortality.

Mechanisms of these effects include systemic pro-inflammatory cytokine responses that directly contribute to plaque rupture through local inflammation, induction of procoagulant factors and haemodynamic changes which predispose to ischaemia and thrombosis. In addition, among the confirmed cases of SARS-CoV-2 infection reported by the National Health Commission of China (NHC), some patients present with cardiovascular symptoms.

ACE2 is involved in heart function and has been identified as a functional receptor for coronaviruses, including SARS-CoV and SARS-CoV-2. SARS-CoV-2 invades alveolar epithelial cells, resulting in respiratory symptoms which are more severe in patients with coexisting cardiovascular diseases. This could be associated with increased secretion of ACE2 in these patients compared with healthy individuals. This has also led to concerns regarding the role of ACE-1 and ARB’s.

General Management and Specific subsets

Guideline-directed, medications given to cardiovascular disease (CVD)

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patients during a widespread outbreak is critical and these include statins, beta blockers, ACE inhibitors and anti-platelet agents.

Early identification and isolation of cardiovascular patients with COVID-19 symptoms from other patients is critically important. It is prudent to advise all cardiovascular patients of the potentially increased risk and to encourage additional, reasonable precautions in terms of infection control and social distancing. Acute viral infections have multiple short-term effects on the cardiovascular system:

- Increased risk of Acute coronary syndrome
- Myocarditis or worsening of previously stable LV dysfunction leading to heart failure
- Arrhythmias related to acute inflammation, ACS or LVF
- Shock

It is important to triage COVID-19 patients with underlying cardiovascular, diabetic, renal, respiratory or other comorbid conditions for prioritised treatment. In addition, careful thought should be given to manage specific subsets.

1. Myocarditis: It is important to note that recent reports suggest that acute cardiac injury is present in about 7% of patients with COVID-19 and may represent either type 2 MI or myocarditis. Importantly, myocarditis can be caused by direct infiltration of the virus but can also be secondary to severe hypoxia and the “cytokine storm” mounted in response to the systemic infection. Some of these manifestations might be, in part, attributable to metabolic disarray, hypoxia, neurohormonal or inflammatory stress.

Diagnosis of Myocarditis among COVID-19 patients is made by:

- Elevated troponin-I or T(Trop I/ Trop T)
- N-terminal brain natriuretic peptide (NTBNP) or BNP
- Sinus tachycardia and no ST segment elevation on electrocardiogram. Extensive QRS/ST-T wave changes predict poor prognosis
- Malignant tachyarrhythmias - ventricular tachycardia or fibrillation and AV blocks indicate extensive myocardial involvement and indicate prognosis
- Enlarged left ventricle with low left ventricular ejection fraction (LVEF) and global LV dysfunction on Echocardiography.

Management of myocarditis includes standard heart failure medications, ventilatory support and ECMO. Isolated case studies with prednisolone have shown benefit but is not recommended.

2. Acute Coronary Syndrome: Efforts should be made to try to differentiate between these Type 1 MIs vs. Type 2 acute coronary syndromes, with deferral of invasive management in the former, especially if the patient is hemodynamically stable. The classic symptoms and presentation of AMI may be overshadowed in the context of coronavirus infection, resulting in under or overdiagnosis.

Diagnosis of ACS should not be based only on elevated troponin levels since these can be significantly elevated in these patients even without ACS. A diagnosis should be based on:

- History
- Serial Troponin levels
- ECG
- Echocardiogram – to correlate with segmental wall motion abnormality
- Combined CT Coronary Angiogram (If feasible) at the time of routine CT scan being done for patient management.

Reperfusion therapy in ACS should take into consideration the clinical presentation, staff availability, risk involved for medical personnel and the availability of high dependency beds in a hospital. Patients with coronary artery disease and may be at particular risk as a result of coronary plaque rupture secondary to virally induced systemic inflammation, and

- Standard pharmacological therapy (aspirin, statins, beta-blockers, and angiotensin-converting enzyme inhibitors) should be continued or optimised in all these patients.
- Pro-coagulant effects of systemic inflammation may increase the likelihood of stent thrombosis and potent anti-platelet therapy may be advisable

Current recommendations for ACS management would include – For confirmed COVID 19 infections

- STEMI: Low risk STEMI patients, consider thrombolysis as the treatment of choice. Cardiac catheterisation should be considered only for rescue PCI.
- STEMI: High risk STEMI patients. The risks to the treating personnel should be considered before deciding on primary PCI. If PPE is available and the hospital cath lab personnel are well versed in its use, then consider primary PCI. In all other situations, thrombolysis should be the treatment of choice.
- NSTEMI/Unstable Angina: Conservative management

For patients with suspected COVID-19 infection presenting with ACS, the current recommendation is

- STEMI: Thrombolysis should be the reperfusion strategy of choice, like that in patients with confirmed COVID 19 cases (Preferably Tenecteplase or Reteplase)
- NSTEMI/Unstable Angina: Conservative management until the confirmatory test results are available.

Patients with COVID-19 can have significant thrombocytopenia. This should be considered when deciding the revascularisation strategy (Lippi et al. DOI: 10.1016/j.cca.2020.03.022)

3. Shock: The dominant clinical presentation of COVID-19 is acute respiratory illness, which may lead to ARDS and is manifested as hypoxemia and ground-glass opacities on CT scan. However, similar features may be seen in patients with cardiogenic pulmonary edema due to myocarditis, ACS or worsening of previous LV dysfunction. Therefore, it is important consider cardiogenic or mixed etiology as the cause of respiratory manifestations in COVID-19.

Preliminary studies suggest that older age, comorbidities (especially diabetes and cardiovascular disease including hypertension), lower lymphocyte count, higher D-dimer level, and possibly cardiac injury are risk factors to consider for cardiogenic origin.

In many clinical situations, Echocardiography and serum brain natriuretic peptide (BNP) can help clarify the diagnosis and help differentiate ARDS and cardiogenic shock.
Antiviral Therapy | Ribavirin | Lopinavir/Ritonavir | Chloroquine/Hydroxychloroquine
--- | --- | --- | ---
How it works | Inhibits replication of RNA and DNA viruses. | Lopinavir is a protease inhibitor; Ritonavir inhibits CYP3A metabolism increasing levels of lopinavir. | Alters endosomal pH required for virus/cell fusion. |
CV Drug Class Interactions | Anticoagulants, Antithrombotics | Antithrombotics | Antiarrhythmics |
CV Adverse Effects | Unknown | Altered cardiac conduction: QTc prolongation, high degree AV block, torsade de pointes | Direct myocardial toxicity vs. exacerbation of underlying cardiomopathy |

- Assess volume status
- Fluid resuscitation – restrictive rather than liberal and utilise crystalloids over colloids
- For adults with COVID-19 and shock, use Norepinephrine as the first-line vasoactive agent, followed by vasopressin or epinephrine.
- Titrate fluid/vasopressors to maintain MAP of 60-65mmHg
- Addition of Dobutamine should be considered in the presence of LV dysfunction and a MAP above 70mmHG.
- In refractory shock, steroids and ECMO may be considered.

Note: In patients with Corona virus infection there is marked lymphopenia and patient who succumbed to infection had very low lymphocyte counts. ECMO can result in reduction in some subsets of lymphocyte population. Hence lymphocyte counts should be closely monitored. In a small series of patients on ECMO the mortality reported was 83%. (Lancet Respir Med 2020; https://doi.org/10.1016/S22132600(20)30119-3)

4. Thromboembolic disease: There have been case reports of abnormal coagulation parameters in hospitalized patients with severe COVID-19 disease. In a multicentre retrospective cohort study from China, elevated D-dimer levels were strongly associated with inhospital mortality.

Endothelial dysfunction with concomitant vascular inflammation may contribute to the hypercoagulable state in such patients. In the setting of critically ill COVID-19 patients who demonstrate clinical deterioration as evidenced by hypoxia or hemodynamic instability, thromboembolic disease should be considered as an additional possibility and investigated with evaluation of D-dimer levels or venous doppler studies.

Case reports of COVID-19 infected patients show increased venous thromboembolism (VTE). Furthermore, in patients with severe infection, clots have been noted in the small vessels of all organs including lung, heart, liver and kidney. This could contribute to worsening of the clinical condition.

The optimal thromboprophylaxis regimen for patients hospitalized with COVID-19 related illness is not known and there is no data on the use of NOAC’s.

Current management strategies could include
- Unfractionated or LMW heparin
- Patients with recent stenting may benefit from intensification of the DAPT (substitute clopidogrel with Prasugrel/Ticagrelor)

5. Heart Failure: It is important to closely monitor patients for heart failure. This could result from myocarditis as well as HF exacerbation. New-onset atrial fibrillation as a cause for heart failure has also been reported.

The important management strategies include
- Guideline-directed medical therapy should be optimized in CVD patients. This includes the continuation of ACEI and ARB
- Optimise volume status with less aggressive fluid resuscitation for hypotension
- Atrial fibrillation to be managed medically or if hemodynamically unstable, cardioverted. For both AF and VT/VF, amiodarone can be used as per existing guidelines.

6. Systemic Hypertension: Following reports that systemic hypertension may be associated with increased risk of mortality in hospitalized COVID-19 infected subjects, there has been concern expressed regarding the potential adverse effects of angiotensin converting enzyme inhibitors (ACE-I) or Angiotensin Receptor Blockers (ARBs). The concern arises from the observation that, like the coronavirus causing SARS, the COVID-19 virus binds to a specific enzyme called ACE2 to infect cells, and ACE2 levels are increased following treatment with ACE-I and ARBs. This has resulted in some patients or their doctors inappropriately stopping these medications prescribed for hypertension or heart failure.

The safety concerns of ACE-I or ARB treatment in relation to COVID-19 does not have a sound scientific basis as of now. On the contrary, animal studies suggest that these medications might be protective against serious lung complications in patients with COVID-19 infection. Based on current data and in view of the overwhelming evidence of mortality reduction in cardiovascular diseases, ACE-I and ARB therapy should be initiated or maintained in patients irrespective of SARS-CoV2. Withdrawal of RAAS inhibition or a switch to alternate drugs at this point is not recommended.

7. Drug Therapy and COVID-19: Interactions and Cardiovascular Implications

The Indian Council of Medical Research (ICMR) has advised Hydroxychloroquine prophylaxis in health care workers involved in the care of suspected or confirmed COVID 19 infected patients and contacts of confirmed cases. Furthermore, HCQ is also one of the medications being evaluated as treatment in these patients. Since it is likely that there could be many patients on this medication a detailed table of drug interaction and precautions is also included.

8. Summary (Figure 1)

Safety of Medical Personnel and Catheterisation and Echocardiogram Laboratory Protocol

The cardiovascular care team (including physicians, nurses and technicians) may have limited training and experience with the
### Drug Interactions and Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Interactions and effects</th>
<th>Action to be considered</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Antibiotics and Macrolides (Azithromycin and others)</td>
<td>QT prolongation, arrhythmias</td>
<td>Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor</td>
</tr>
<tr>
<td>Quinolones (Ciprofloxacin and others)</td>
<td>QT prolongation, arrhythmias</td>
<td>Avoid co-prescription, if utmost essential assess basal QT by ECG and serially monitor</td>
</tr>
<tr>
<td>2. Anti-arrhythmic drugs (Amiodarone, disopyramide, procainamide, quinidine, amiodarone)</td>
<td>QT prolongation, arrhythmias</td>
<td>Avoid co-prescription, always weigh the risks and benefits and seek expert opinion if needed.</td>
</tr>
<tr>
<td>3. Anti-diabetic drugs including Insulin</td>
<td>HCQ lowers blood sugar levels.</td>
<td>May need to monitor blood sugar levels and may need to reduce dose of anti-diabetic drugs.</td>
</tr>
<tr>
<td>4. Betablockers (Metoprolol, carvedilol, bisoprolol)</td>
<td>HCQ increases drug levels of BB interfering with its metabolism at higher doses.</td>
<td>Can be continued, but this monitoring may be needed.</td>
</tr>
<tr>
<td>5. Digoxin</td>
<td>HCQ increases Digoxin levels at high doses.</td>
<td>Can be continued, but monitoring may be needed.</td>
</tr>
</tbody>
</table>

### Echocardiogram Laboratory

Specific recommendations for Echocardiograms would include

- Elective procedures to be postponed especially in patients with significant comorbidities. However, the decision making has to be individualised, considering the risk to the treating medical team versus the risk of delay in diagnosis or treatment.
- All catheterization laboratory personnel should use N95 masks and be trained in the proper techniques for donning and doffing of Personal protection equipment (PPE) including eye protection.
- Patients with known COVID-19 or suspected COVID-19 who are required to come to the catheterization laboratory, should wear an appropriate surgical mask. All members of the catheterization laboratory team should wear PPE.
- Intubation, suction, and active CPR can result in aerosolisation of respiratory secretions, thus increasing the exposure to medical personnel. The threshold to consider intubation in a patient suspected or confirmed COVID-19 patients are being treated should be at the discretion of the treating medical team.

### Conclusion

- COVID-19 infection is an evolving global pandemic with significant cardiovascular complications that require aggressive management and is prognostically important.
- Guideline directed management to be continued for pre-existing co-morbid conditions including CAD, systemic hypertension and heart failure.
- Acute complications include myocarditis, ACS, shock, heart failure and venous thromboembolic disease.
- Long-term cardiovascular effects are yet to be elucidated.
- Dedicated Echocardiogram machine within the isolation ward, where COVID 19 patients are being treated, would be preferable.
- Cardiac catheterisation procedures to be restricted to only emergency and life-saving situations.
- Sensitisation of the cardiac staff regarding the precautions in handling infected patients, adequate training and utilisation of PPE to be implemented for all medical personnel involved in the management of suspected or confirmed cases of COVID 19 infection.

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2. ACC CLINICAL BULLETIN COVID-19 Clinical Guidance For the CV Care Team. Dunnell Mullin, EWF; Science & Quality, American College of Cardiology’s bulleten.org.
Aspiration Pneumonitis

Arun VA¹, Rachana Warrier²

A 63 year old male, a smoker for 35 years, presented with complaints of hoarseness of voice and insidious onset progressive dysphagia to both solids and liquids of 3 months duration. Examination revealed cachexia and pallor but no lymphadenopathy. Indirect laryngoscopic examination revealed right vocal cord palsy with no vocal cord mass or growth. Oesophagastroduodenoscopy was planned but the scope could not be negotiated beyond the cricopharyngeal sphincter and a barium swallow was done. During the procedure he aspirated barium (approx 30 ml of 95% barium) in the rapid drinking phase and had paroxysms of cough and choking. The procedure was terminated and he was admitted and monitored in intensive unit for respiratory failure. Chest X-ray revealed barium in both the right and left main stem bronchi, outlining the bronchus intermedius, all four lower-lobe basal bronchi, and the segmental bronchi of both lower lobes (Figure 1). Patient did not show any respiratory distress in the next 48 hours and did not develop clinical features of aspiration pneumonia on follow up over 7 days. Nonetheless a computerised tomography contrast study of neck and chest done after 03 days to evaluate dysphagia and vocal cord palsy revealed carcinoma of cervical oesophagus extending from cricopharyngeal sphincter to second dorsal vertebra with invasion of trachea and distortion of glottis. Airspace opacities along with peribronchial cuffing was seen in the lateral and posterior basal segments of left lower lobe.

The aspiration of barium is a rare complication of contrast studies in gastroenterology. Barium sulfate is an inert material that does not usually cause chemical pneumonitis and, in cases in which this does occur, it is due to the simultaneous aspiration of gastric content or due to excipients added to barium meal.¹ The severity of the airflow obstruction will depend on the amount of contrast medium that enters the respiratory tract. If the amount is small, as highlighted here, there may be no symptomatic effects. Nevertheless, aspiration of large amounts of interferes with the gas exchange as barium occupies the alveolar space, leading to a shunt effect and altered ventilation/perfusion ratio with secondary respiratory failure, putting the patient’s life at risk. Review of literature also reports of cases with severe inflammatory reactions of the bronchial wall after the aspiration of contrast material leading to death.²³ Although it is common practice, the prophylactic use of antibiotics in patients in whom aspiration is suspected or witnessed is not recommended.¹⁴⁵ Management of such cases is essentially conservative.

References


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MEN Type I (Wermer Syndrome)

Gurdeep Kaur¹, Avinash Kulkarni², Sweta Banka², Rohitash Gurjari², Jeevraj Dhaka², Rajesh Prajapat²

Abstract
MEN I inherited as an autosomal dominant disorder leads to hyperplastic/neoplastic changes in parathyroid, pituitary and endocrine pancreas along with other characteristic tumours. Hyperparathyroidism is the most common manifestation of MEN I. Our case was a female patient aged 42 years who was diagnosed with parathyroid adenoma, coincident with pancreatic neoplasm and adrenal adenoma. Hyperparathyroidism was noted initially and hemiparathyroidectomy was performed. Though adrenal adenoma and pancreatic neoplasm were detected on CECT, patient was symptom free from them and thus steps were taken to treat the chief complaint of presentation which was multiple bone pains. Post-operatively patient’s serum Ca levels, serum PTH levels dropped drastically to normal ranges and there was remarkable improvement in complaints of patient. A multidisciplinary approach involving physicians, endocrinologists, oncologists, ENT surgeons and radiologists is pivotal for optimizing patient treatment. Treatment consists of surgery and drug therapy, often in association with radiotherapy or chemotherapy.

Introduction
MEN is characterised by a predilection for tumours involving 2 or more endocrine glands. Four major forms of MEN are recognised and are referred to as MEN types I-4. Each type of MEN is inherited as autosomal dominant syndrome or may occur sporadically i.e. without any family history. The diagnosis of MEN can be established in an individual by one of 3 criteria.

- Clinical features (2 or more of the associated tumours)
- Familial pattern in a first degree relative.
- Genetic analysis.

MEN I is also referred to as Wermer’s syndrome is characterised by the triad of tumours involving the parathyroids, pancreatic islets and anterior pituitary. In addition, adrenal cortical tumours, carcinoid tumours usually of the foregut, meningiomas, facial angiofibromas, collagenomas and lipomas may also occur in some patients with MEN I. The prevalence of MEN I is approximately 0.25% based on randomly chosen postmortem studies but is 1-18% among patients with primary hyperparathyroidism, 16-38% among patients with pancreatic islet tumours and <3% among patients with pituitary tumours. The disorder affects all age groups with reported age group range of 5-81 years. The clinical manifestations of MEN I are related to the sites of tumours and their hormonal products. In the absence of treatment, endocrine tumours are associated with an early mortality in patient with MEN I with approximately 50% probability of death by age of 50 years. The cause of death is usually a malignant tumour, often from a pancreatic neuroendocrine tumour (NET) or foregut carcinoid. In addition, the treatment outcomes of the patients with MEN I associated tumours are not as successful as these in patients with non MEN I tumours. This is because MEN I associated tumours with the exception of pituitary NETs, are usually multiple, making it difficult to achieve a surgical cure. Occult metastatic disease is also most prevalent in MEN I and the tumours may be larger, more aggressive and resistant to treatments.

Chromosomal location (11q13) is the most common mutated gene in MEN I.

Case Discussion
A 42 year old female patient came with complaints of multiple bone pains since past 6 months. Pain was of generalised type felt all over the bones and were not just in particular to joints. To begin with patient had only pain during exertion but it gradually progressed to state of pain even in rest. Patient also had associated complaints of generalised weakness and reduced appetite. She had no history of any difficulty in micturition, no history of recent fractures, no history of excess sweating, headache or pain abdomen. She had treatment history for pulmonary tuberculosis from 15 years back which was uneventful. Patient has operative history for dental cyst 5 years back. No h/o HTN, DM. Patient had family history of similar complaints depicted shortly in the pedigree charts (Figure 1).

1. Patient’s mother

![Pedigree of patients family of origin](image-url)
2. Elder sister
3. Elder brother

Her elder sister had similar complaints and was operated for parathyroid adenoma 16 years ago. Elder brother was also diagnosed as to be having hyperparathyroidism with diabetes mellitus.

Patient was anaemic on examination and rest GPE and systemic examination were normal. On initial evaluation she was pale weighing 40 kg with pulse rate 80/ min, blood pressure 120/90 mmHg with bony tenderness in lower limbs on deep pressure. Her Hb was 6 gm%, Serum Ca 15 mg/dl, alkaline phosphatase 415 U/L, Serum PTH levels were 1354 pg/ml, serum Vit D3 levels were normal, thyroid profile was normal, serum prolactin level was 15.11 (normal), all other routine biochemical investigation were normal. The chest radiograph revealed bilateral multiple foci of calcification (mottling) present all over the lung fields. Her CECT neck and abdomen (Figure 3) revealed heterogenous enhancing soft tissue density in right parathyroid (inferior) adenoma, right adrenal adenoma and neoplastic lesion in pancreatic body, multiple diffuse lytic lesions involving visualised skeletal system, pyramidal calcification in bilateral kidneys. Further MRI (Figure 2) neck revealed right inferior parathyroid adenoma. MRI brain study (Figures 4 and 5) was normal.

Patient was anaemic and had multiple bone pains thus tab cinacalcet, tab alendronate, analgesics were started and blood transfusion was done. Adequate hydration and analgesia was maintained.

Later on patient was operated for parathyroid adenoma (parathyroidectomy) under GA. Post operative serum PTH levels and serum Ca levels dropped to normal range drastically. There was remarkable improvement in pain also. The biopsy report revealed parathyroid adenoma.

Patient was followed up for 15 days and her complaints were drastically improved. Post operatively patient is still asymptomatic with no bone pains. Serum PTH levels are normal. In post operative follow up patient refuses to undergo further evaluation for the pancreatic mass and adrenal mass found on CECT abdomen.

Conclusion

Hyperparathyroidism and MEN are frequently underdiagnosed conditions. They should always be considered in patients with bone pains, recurrent renal calculi. Hypercalcemia in routine investigations should always prompt us for further work up to rule out hyperparathyroidism.

References

Invention of CT-Scan

Jayant Pai-Dhungat

We are nearing the 50th anniversary of first commercially available Computerized Axial Tomography or “CAT” Scanner which was created by British engineer Sir Godfrey Hounsfield (1924-2004) of EMI Laboratories in 1971. He co-invented the technology independently with physicist Dr. Allan Cormack (1919-1998) a South African American physicist. Both researchers were jointly awarded the 1979 Nobel Prize in Physiology or Medicine. Hounsfield was later knighted in 1981.

Before CT, radiographic images could be made with focal plane tomography based on simple principles of projective geometry which was first proposed by the Italian radiologist Alessandro Vellebona in 1930s, representing a single slice of the body on radiographic film (sectional radiography). During my Radiology posting (1969), I remember high X-ray tube rotating 180 degrees with its pivot point in focus to make patient’s sectional image appear sharper and other parts were fuzzed out. However, focal plane tomography remained unsatisfactory at producing images of soft tissues.

Decades of mathematical advances led to foundation of reconstruction method called Algebraic reconstruction technique which was later adopted with mathematical equations needed to convert the beam images into a 2D projection that one could actually visualize. Increased power and availability of computers in 1960s sparked research in computational tomographic images. While Hounsfield contributed in a more practical way, Cormack developed algorithms, equations and arrived at a schematic method independently.

Following the first clinical scan in 1971 (published in 1972), the patient with the suspected frontal lobe tumor was operated upon. The successful demonstration of CT’s worth led to further systems being installed in the UK by EMI. First CT scanner was installed in USA in 1973 at Mayo Clinic. By the end of the 1970s the importance of CT scanning in medicine became clear. The 1980s saw incremental development of CT scanner technology with: shorter scan times and increased matrix sizes, until by the late 1980s scan times were down to only 3 seconds and matrix sizes were up to 1024 x 1024. Spiral (continuous) scanning was introduced in the early 1990s and the development of multi-slice scanners with contrast, by the end of the century. CT scanner technology continued through the early years of 21st century; by 2005, 90% of PET scans were actually PET-CT fusion imaging scanners. Overall there has been improvements in speed, slice count, radiation dose and image quality. New generations CT scanner was developed in 2008 that could take images of beating hearts or coronary arteries in less than one second.

Modern imaging techniques no doubt have been invaluable in clinical practice. During our own lifetime procedures like painful Pneumoencephalography, bronchography, and percutaneous carotid angiography have all seen their demise. Patient management is revolutionized. However, these valuable modalities should not replace a good clinical evaluation of the patient, but be complimentary to it. Recent acronym published in BMJ by Richard Hayward- VOMIT (Victims Of Modern Imaging Technology) highlights over-reliance on sensitive imaging technologies in diagnoses; often without clinical rationale.
Prevalence and Risk Factors of Cardiac Autonomic Neuropathy in Diabetes Mellitus

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Sir,

Cardiac Autonomic Neuropathy (CAN) is a common form of diabetic autonomic neuropathy that encompasses damage to the autonomic nerve fibres that innervate the heart and blood vessels, resulting in abnormalities in heart rate control as well as central and peripheral vascular dynamics.1 Presence of CAN is responsible for silent myocardial infarction and sudden death in diabetics. We studied prevalence and risk factors of CAN in our diabetic patients.

70 patients, of more than 18 years of age, of either sex with Diabetes mellitus as defined by American Diabetes Association (ADA) criteria were included in study. Patients with documented heart disease and renal disease were excluded. Study was observational, cross sectional and was carried out for a period of one year. Detailed history was taken and general and systemic examination was done. The tests for autonomic cardiovascular function were performed as beside procedures as suggested by Ewing.2 Resting heart rate, heart rate response to valsalva manoeuvre, heart rate variation during deep breathing, blood pressure response to standing and to sustained hand grip were measured. Points of 0,0.5 and 1 was counted respectively for resting heart rate of <100, 100-110, >110, postural hypotension <20, 20-30, >30, Valsalva ratio >1.2, 1.2-1.0, <1.0, heart variability on deep breathing >15, 15-10, <10, increased diastolic BP during hand grip >15,15-10, <10. Points were added and grading of cardiovascular autonomic neuropathy was done into no, early and severe CAN for scores 0, 0-1.5, and >1.5 respectively as per criteria suggested by Ewing’s.

Among 70 patients of study group 36 (51%) had no CAN and 27 (39%) had early CAN and 7 (10%) had severe CAN. Prevalence of definite CAN was 49% in our study group. CAN was more prevalent in female diabetics. But the difference was not statistically significant. Mean age was 48.82 years, prevalence of CAN was seen more in 61-70 (64%) and 51-60 (59%) years of age. Prevalence of CAN was seen more in type 2 diabetes (53%) compared to type 1 diabetes (27%). But the difference was not statistically significant. Prevalence of definite CAN increased with increase in duration of diabetes which was statistically significant. (P value: 0.0001) Mean fasting blood sugar was 178.58 mg%, 245.44 mg%, 314.85 mg% respectively in patients with no CAN, early CAN and severe CAN. Significant statistical correlation was seen between glycaemic control and severity of CAN.

Prevalence of CAN increased with advancing age, increasing duration of diabetes and with uncontrolled diabetes. So detection of CAN at the earliest and strict glycaemic control is of upmost importance to prevent subsequent cardiovascular complications in diabetic patients.

References


Diabetic Retinopathy and Anemia: Is There a Treatable Nutritional element?

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Sir,

Diabetic retinopathy (DR) is the fifth leading cause of blindness across the globe. Anemia has been increasingly recognized as a risk factor for the occurrence and severity of DR.1,2 A total of 170 adults were enrolled into this cross-sectional study (males 93, females 77) from a tertiary care hospital, excluding renal failure, pregnancy and other ocular disorders. Patients with DR (n=85, males: 40, mean age: 57.26 ± 11.31 (SD) years were classified as Group 1, and those without DR (n=85, males: 53, mean age: 60.74 ± 13.00 (SD) years) as Group 2. The duration of diabetes 12.4 ± 7.6 (SD) years for Group 1 and 6.64 ± 4.48 (SD) years for Group 2. DR was classified as per ETDRS (Early Treatment Diabetic Retinopathy Study) and anemia with WHO definitions.

The mean Hb in patients in Group 1 was 10.4 ± 0.25 (SD) gm%, and in Group 2 was 12.70 ± 0.18 (SD) gm% (p=0.001). There were 67 patients with anemia, 56 in Group 1 and 11 in Group 2. There was a significant association between presence of anemia and that of DR (p=0.001). In Group 1, 28 (50%) (iron-24, B12- 3 and dual- 1) and in Group2, 6 (17.6%) had nutritional anemia (p=NS). In Group 1 the distribution was: iron deficiency 24, B12 3 and dual deficiency 1. Hematological variables (reticulocyte count, MCV, iron, total iron binding capacity, % saturation and serum B12 levels) did not show any significant difference groups. On logistic regression analysis, anemia and duration of diabetes emerged as predictors of DR, when hypertension, dyslipidemia, duration of diabetes, anemia, HbA1C, age, smoking and alcohol were analyzed (R² =0.306).

In conclusion this study reiterates the association between anemia and DR and highlights the presence of a nutritional element. This makes a case towards monitoring hemoglobin in patients with diabetes. Prospective studies with correction of anemia will elucidate the role treating anemia in DR.

Disclosure

This study was presented at the American Diabetes Association Annual Conference, Florida in July 2018.

References

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