Hypertension & CAD
when co-exist can attract complications...

In Hypertensives with symptomatic CAD

Telvas*\text{-}\text{beta}
Telmisartan & Metoprolol Succinate ER Tablets 25/50 mg

- Helps achieve target BP
- Offers end organ protection
- Helps reducing cardiovascular morbidity and mortality

The Alliance for Assured CV Protection
### The NO. 1 Choice of Experts

#### Allegra-M

**Rich evidence in Indian patients with proven clinical superiority vs other combinations**

<table>
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<td>Published safety data in Indian patients</td>
<td>9.6%</td>
<td>23.2%</td>
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#### Your trusted choice for managing Allergic Rhinitis

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**References**

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In Hypertensive Patients

Start with

\[\text{ONCE-A-DAY} \]

\[\text{Stamlo} \]
Amlodipine 2.5mg/5mg/10mg tab.

leader at heart

In Uncontrolled Hypertensives on monotherapy

Switch to

\[\text{ONCE-A-DAY} \]

\[\text{Stamlo-T} \]
Amlodipine 5 mg + Telmisartan 40 mg tabs

**Powerful & Consistent BP Control**

In Hypertensives with increased sympathetic drive

\[\text{ONCE-A-DAY} \]

\[\text{Stamlo Beta} \]
Amlodipine 5 mg + Atenolol 50 mg tablets

**Prompt and adequate BP control**

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An oral ribonucleoside analogue that potently inhibits replication of SARS-CoV-2. Oral broad-spectrum antiviral

The mechanism of action of molnupiravir is independent of mutations in the spike protein

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Mitigates the risk of progression to severe disease

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Timing of Transfer from ICU- Not Too Early, Not Too Late!

Trupti H Trivedi

Even as critical care has developed rapidly in the 21st century, need for ICU beds continues to rise all over country, more so as population in India is relatively young and there is significant burden of tropical infections, sepsis, trauma, poisonings and envenomations and recent rise in incidence of non-communicable diseases, such as diabetes, hypertension, coronary artery disease and cancer. India has approximately 10 hospital beds for 10,000 people, one third of global average. Proportion of ICU beds is expected to be 10% of total hospital beds, but at present we are nowhere near this mark.\(^1\) During current SARS-CoV-2 pandemic, the shortage of intensive care units was realized and many ICUs have been upgraded with help of donations and government initiatives. Country has mix of public hospitals run by government, tertiary hospitals attached to medical colleges and private hospitals run by trusts, society or corporate companies. As intensive care includes expensive equipments and technology, most of district hospitals do not have state of the art facilities and at times poor patients have to travel across states to get a bed in well equipped ICU in public hospitals, which offer free treatment through various funding schemes. As per recent estimation, 85% ICU beds in country are paying beds and very few patients have medical insurance, thus a single ICU admission in family can cause significant financial burden.

Culture of quality improvement has become standard in ICU care. These include care bundles for routine procedures like mechanical ventilation, and central venous catheter placement and sepsis management that involve ‘doing the simple things well’ to make patient care safer. Indian Society of Critical Care Medicine (ISCCM) has published list of quality indicators as guidelines for ICUs in India\(^2\) and included standardized (risk adjusted) mortality rate; morbidity parameters like iatrogenic pneumothorax, new onset acute renal failure, decubitus ulcers; operational parameters like length of stay in ICU, compliance protocols, ICU re-admission rates; errors and patient safety parameters; infection control and customer satisfaction. Most of these parameters are to ensure quality care, patient safety and optimal utilization of ICU facility. Effective admission and discharge criteria are needed to limit use of ICU beds for those who benefit from them most. In a multicenter, point-prevalence study of 4038 adult patients from 120 ICUs in India it was observed that self-paying patients, district hospitals ICUs, and inadequately equipped ICUs were independently associated with adverse outcome and discharge from ICU for terminally ill patients due to financial constrains is widely practiced and there is need to address legal, social, and other implications related to end-of-life care.\(^3\)

In this issue of journal, Vijoy Kumar Jha et al have published epidemiology of ICU readmission at Command Hospital Air Force Bangalore.\(^4\) Over a period of 3 years out of 2538 patients transferred to wards from ICU, 198 had to be readmitted in ICU during same hospital admission (7.8%). Of these, majority were readmitted within 48 hours of ICU discharge and with same diagnosis as index admission, due to cardiac, respiratory or neurological deterioration or worsening of sepsis. Mortality in readmitted patients was higher (31%) than overall ICU mortality of 14%. The bed occupancy of the ICU was 87.62% and the average length of stay in the ICU was 4.28 days during study period. Details of condition, severity score of readmitted patients at initial ICU discharge was not available as it was a retrospective study and limited data was available from Hospital Information System. Authors have recommended use of stability and workload index for transfer (SWIFT) score and good hand over practice in addition to clinical and biochemical parameter check at ICU discharge to prevent readmission.

Usually, ICU physicians use their clinical judgement to decide timing of transferring patient out to general ward or step down unit. This decision is influenced by multiple factors – condition of patient, need for beds in ICU, facilities and availability of beds in step down unit, presence of limitation of medical treatment (LOMT) order, and financial constrains. It is observed that there is an optimal timing for patients to be shifted out of the ICU, with an increasing risk of subsequent death if patients leave the ICU either too early or too late.\(^5\) While too early transfer increases risk of re-admission and subsequent death, delayed transfer can lead to increase risk of ICU complications and nosocomial infections. Appropriate place for post ICU care is also important. Very few hospitals have high dependency units with comparable level of equipments and nursing care in India, and patients are usually transferred to general wards or nursing homes from ICU. While Western literature reports high long term mortality, a poor quality of life after ICU discharge,\(^6\) in India the scenario is different and quality of life is as good as in general population,\(^7\) as mean age of ICU patients is less and admissions are mainly due to reversible condition and patients tend to have less co-morbid conditions. Hence improving quality of ICU care is even more important in India.

Typical rates of readmission to ICU have a wide range from 1.2-14.5% of live ICU discharges. ISCCM has recommended 4-6% as benchmark for ICU re-admission to be used as quality control.\(^8\) There is no doubt that patients readmitted in ICU tend to have higher mortality, length of stay in ICU and more utilization of organ support systems. Factors
Determining need for re-admission include severity and nature of disease at index admission, clinical parameters of patient at time of ICU discharge, facilities and level of care available at step down unit and if any LOMT orders are given. Many readmissions to ICU are not avoidable. These are due to progression in natural history of patient’s disease or development of new indication for ICU care. Such admissions tend to be after 72 hours of ICU discharge. Premature discharge, inadequate care in step down unit, adverse drug reactions, complications of procedure and nosocomial infections are important preventable causes of re-admission to ICU. Preventing readmissions to ICU has the potential to reduce readmissions to ICU has the potential to prevent longer ICU stay and ICU mortality when measured at ICU admission, it is not useful to predict ICU readmission when measured at ICU discharge. Stability and Workload Index for Transfer (SWIFT) score is specifically developed to predict readmission risk to the ICU at time of ICU discharge. SWIFT consists of five different parameters: mode of ICU admission, length of ICU stay, respiratory parameters (PaO2/FiO2 ratio and PaCO2) and neurological status. Modified SWIFT includes renal function. SWIFT score of >15 is associated with higher readmission rate in medical and surgical ICU patients. Critical care resources are limited and expensive. The appropriate utilization of ICU services is a complex challenge. Out of every 100 patients discharge from ICU, 4 to 6 get readmitted during same hospital admission and another 5 to 7 die in wards due to LOMT orders. Readmitted patients have longer duration of ICU stay, more dependence on organ support system and are at increased risk of death. There are opportunities to identify patients at risk for readmission and tackle preventable factors at time of ICU discharge, involve relatives in decision making and give instructions to step down unit taking care of these patients to prevent readmissions. Though ICU readmission rate has been considered a quality indicator for ICU performance, aiming for a zero readmission rate will lead to a defensive approach by ICU team, leading to unnecessary long duration of stay and increased risk of nosocomial infections and deprive ICU care to more critical and deserving patients in resource limited setting.

References

Oral Rivaroxaban in the Prophylaxis of COVID-19 Induced Coagulopathy

Dhiraj Kumar1, Vaishnavi Kaimaparambil3*, Sheeba Chandralekha2, Janvi Lalchandani3

Abstract

Background: Preliminary data highlights the importance of anticoagulation therapy in the prevention and treatment of thromboembolism in SARS CoV-2 infection. There is insufficient data comparing the safety and efficacy of direct oral anticoagulants (DOACs) and subcutaneous enoxaparin in the prophylactic management of COVID-19 associated thromboembolic disease, particularly in mild to moderate cases of COVID-19 infection.

Objectives: The study was designed to investigate the efficacy of oral rivaroxaban as a prophylactic anticoagulant in mild to moderate SARS CoV-2 infection.

Methods: In this randomized, open-label, prospective superiority trial involving hospitalized patients with confirmed mild or moderate COVID-19 disease without known thromboembolism, we assigned 230 patients to receive either once-daily oral rivaroxaban (10mg or 15mg) or once-daily subcutaneous enoxaparin (40mg or 60mg) for a median duration of 8 days. The primary outcome was a composite of all major, clinically relevant haemorrhagic and thrombotic events.

Results: The primary efficacy outcome occurred in 4 of 115 patients in the rivaroxaban group (3.5%) versus 16 of 113 patients in the enoxaparin group (14.2%) (hazard ratio 0.207, 95% confidence interval [CI], 0.069 to 0.621, P=0.005). Adverse events developed in 4.3% of patients in the study group and 12.4% in the enoxaparin group (hazard ratio 0.328; 95% CI, 0.118 to 0.910; P=0.032). Major bleeding was seen in 1 patient (0.9%) in the rivaroxaban group and 3 patients (2.7%) in the enoxaparin group.

Conclusions: Rivaroxaban alone was superior to enoxaparin for the prophylactic management of coagulopathy associated with mild to moderate SARS CoV-2 infection.

Introduction

The Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is a global, rapidly emerging virus that causes the coronavirus disease 2019 (COVID-19).1 The disease has impacted nations and resulted in considerable morbidity and mortality, as well as economic and infrastructural collapse. As of 30th March 2021, there are 128,540,982 confirmed cases and over 2,500,000 deaths.2

Recent observations suggest that respiratory failure in COVID-19 is not driven by the development of acute respiratory distress syndrome (ARDS) alone. Even though infection is a well-known trigger for venous thromboembolism (VTE),3-5 microvascular thrombotic processes may play an important role in progression of disease in COVID-19.6

Heparin has been the treatment of choice in the management of thromboembolism in numerous disease states.7 Enoxaparin was the first low molecular weight heparin to be approved by the U.S Food and Drug Administration in 1993 for the management of venous thromboembolism.8 Studies conducted over the last ten years have shown consistent efficacy and safety of DOACs (direct oral anticoagulants) in prophylaxis and treatment of DVT (deep vein thrombosis),9 non-valvular atrial fibrillation10 and cancer-associated venous thromboembolism.11 The ROXANE trial (Oral Rivaroxaban versus subcutaneous enoxaparin [Clexane™] in the prophylaxis of COVID-19 induced coagulopathy) was designed to investigate the utility of rivaroxaban alone for management of coagulopathy in mild to moderate COVID-19 infection, as compared to enoxaparin.

Methods

Study Design and Oversight

We conducted a single-centre, randomized, open-label, prospective trial comparing the efficacy and safety of rivaroxaban with that of subcutaneous enoxaparin for the management of venous thromboembolism for those diagnosed with mild or moderate COVID-19 infection at Sevenhills Hospital Dedicated COVID Hospital, Mumbai. The protocol (available in the Supplementary Material) was approved by the institutional ethics committee at the participating institution. Informed consent was obtained and documented from all the patients. Trial was registered with Clinical Trials Registry – India.

The first two authors wrote the first draft of the manuscript and contributed to subsequent versions, made the decision to submit the manuscript for publication, and hereby vouch for the accuracy and completeness of the data and for the fidelity of the study protocol.

Patients

All consenting, in-hospital patients were eligible if they were between 25 to 75 years of age with objectively
confirmed evidence (RT-PCR) of mild or moderate COVID-19 disease. Dosing regimens for rivaroxaban and enoxaparin were as per local protocols and emerging evidence. This included prophylactic to intermediate dosing strategies – enoxaparin 40 mg or 60 mg SC and rivaroxaban 10 mg or 15 mg PO OD - for both treatment arms, given the patients had symptomatic mild or moderate disease. The CHA$_2$DS$_2$VASc scoring system was utilised to objectively stratify risk profile of patients. Patients with a mild CT-severity index were given anticoagulation (10mg rivaroxaban or 40mg enoxaparin) if CHA$_2$DS$_2$VASc score was ≥2 if female, ≥1 if male, D-dimer levels >500 nanograms per millilitre or had previous history of malignancy, deep vein thrombosis (DVT), systemic embolism or ischemic events. All patients with a moderate CT-severity index were treated with anticoagulants (15 mg rivaroxaban or 60mg enoxaparin) considering the increased risk of coagulopathy and progression of disease in accordance with local guidelines. A full list of inclusion and exclusion criteria is provided in the Supplementary Material.

Randomisation

Patients were allocated in a 1:1 ratio using computer-generated randomization to receive oral rivaroxaban and subcutaneous enoxaparin. Recruitment of participants was continued until 1st November 2020. The intended duration of administration of the drug was for the duration of hospital stay, as decided by the investigating team.

Outcome Measures

The primary outcome was a composite of all major, clinically relevant haemorrhagic and thrombotic events. The primary efficacy endpoints were progression of disease requiring treatment escalation, including need for (i) supplemental oxygen, (ii) need for high-flow oxygen devices or non-invasive ventilation, (iii) invasive mechanical ventilation and/or extracorporeal membrane oxygenation (ECMO); transfer to intensive care; the incidence of radiologically confirmed new or recurrent DVT or PE in the patients during their period of stay in the hospital; stroke and systemic embolism; myocardial infarction; death from vascular causes; and all-cause death. The definitions of the efficacy outcomes are provided in the Supplementary Material.

The primary safety endpoint was bleeding, including major and clinically relevant non-major bleeding. Major bleeding was defined as overt bleeding in a critical site (e.g. intracranial, intraspinal, intraarticular, intrahepatic, intrapericardial), associated with a fall in haemoglobin of 2 grams per decilitre or more, leading to transfusion of 2 or more units of packed red blood cells or whole blood. Clinically relevant non-major bleeding was defined as overt bleeding not meeting the criteria for major bleeding but associated with medical intervention, unscheduled contact (visit or telephone call) with a physician, (temporary) cessation of study treatment, or associated with any other discomfort such as pain, or impairment of activities of daily life. (Further details regarding the criteria are provided in the Supplementary Material). As a part of monitoring anticoagulant therapy, bleeding risk was stratified using the HAS-BLED scoring system; ≤3 was considered as having low bleeding risk.

Surveillance and Follow-Up

During the study, one patient was lost to follow-up (discharged against medical advice). As an unconnected and independent treatment strategy, patients in both intervention groups who showed disease progression and/or eligible as per local and institutional treatment guidelines were discharged on prophylactic rivaroxaban (10mg once daily) for 15 days. All patients who were discharged with prophylactic oral anticoagulation were instructed to report to the centre if they had any symptoms of haemorrhagic or thrombotic events. These results are reported separately and have not been included in the primary analysis. (Refer to Supplementary Material)

Statistical Analysis

The study was aimed to test the hypothesis that rivaroxaban would be superior to subcutaneous enoxaparin in the primary efficacy outcome in mild to moderate COVID-19 infection. Assuming a 30% incidence of composite outcome in the enoxaparin group and an effect size (absolute risk reduction) of 15% in the primary composite outcome, we expected to enrol at least 300 participants for the study to provide a power of 80% (two-sided alpha level [α], 0.05). A total of 230 patients were enrolled by the end of the target study period, given the ethical commendations dictated by the IEC and limited participation during the peak of the pandemic. (Refer to Supplementary Material)

The primary efficacy analysis was conducted by the investigating team on an intention-to-treat basis with the use of a Cox proportional-hazards model to analyse the time until the first event of the primary trial outcome during the treatment period. The evaluation of the primary outcome was done by considering the time from randomization until the first episode of thrombotic or haemorrhagic event or progression of disease (primary trial outcome); the total duration of hospital stay was used if neither a thrombotic nor haemorrhagic event occurred within the study period (censored time). The primary efficacy data set (intention-to-treat population) and safety data set consisted of all the patients who had undergone randomization and received at least one dose of a trial drug. Bleeding events were included in the analysis if they occurred during treatment or within 48 hours after the last dose of a study drug. All patients who were event-free at the end of the hospital stay were censored. Kaplan–Meier curves were generated to display the distribution of events over time (Figure 2). All data were handled solely by the principal investigators of the trial and analysed by the investigating team with the use of IBM SPSS software (Build 1.0.0 1447).

Results

Patients

Through 1st August 2020 to 1st November 2020, 230 patients were enrolled - 115 received rivaroxaban and 113 received subcutaneous enoxaparin at a dedicated COVID-19 Hospital in Mumbai, India (Figure 1). The characteristics of enrolled participants were similar at baseline (Table 1).

In the rivaroxaban treatment arm, a total of 65 patients received 10mg once daily and 50 patients received a dose of 15mg once daily. Among those receiving subcutaneous enoxaparin, 62 patients received a dose of 40mg daily, and 51 patients received a dose...
Fig. 1: Enrolment and outcomes

of 60mg daily.

Treatment and Follow-Up

In the enoxaparin group, the median duration of enoxaparin treatment was 8 days (interquartile range [IQR], 6 to 10 days). Compliance was measured systematically by recording the actual number of doses taken (as monitored by investigators on individual case record forms) and total doses that were to be administered as part of treatment regimen. Average adherence to therapy was above 90% in the rivaroxaban group and above 85% of patients in the enoxaparin group. Patients on rivaroxaban received the drug for a median duration of 8 days (IQR, 6 to 10 days).

Clinical Outcomes

The clinical outcomes and treatment characteristics are shown in (Table 2). The intention-to-treat analysis indicated the primary efficacy outcome occurred in 4 patients (3.5%) in the rivaroxaban group as compared to 16 patients (14.2%) in the enoxaparin group, for a hazard ratio of 0.207 (95% confidence interval [CI], 0.069 to 0.621; P = 0.005).

One patient receiving 15mg rivaroxaban daily and three patients in the enoxaparin group (1 on 40mg subcutaneous LMWH and 2 patients on 60mg subcutaneous LMWH) required admission to intensive care during course of treatment. The rate of patients requiring transfer to intensive care due to suspected or confirmed pulmonary embolism or cardiorespiratory failure were 0.9% (1 of 115 patients) in the rivaroxaban group and 2.7% (3 of 113 patients) in the enoxaparin therapy group (P = 0.304).

The safety outcome occurred in 5 patients (4.3%) in the study group and 14 patients (12.4%) in the enoxaparin therapy group (P = 0.032) (hazard ratio 0.328; 95% CI, 0.118 to 0.910). Out of this, major bleeding, including systemic bleeding, non-fatal bleeding leading to fall in haemoglobin more than 2 grams per deciliter, requiring interruption or discontinuation of therapy was observed in 1 patient (0.9%) in the rivaroxaban group and 3 patients (2.7%) (P = 0.304) in the enoxaparin group.2 The clinically relevant non-major bleeding primarily included large subcutaneous haematomas, intramuscular haematomas, rectal blood loss and epistaxis.

Discussion

A total of 230 consenting patients were enrolled at Sevenhills Dedicated COVID Hospital, Mumbai in this study during the period of pandemic between August 2020 and November 2020. Due to the rapidly evolving and poorly understood nature of the disease itself, the inclusion criteria were designed to ensure the study population was representative of patients with COVID-19 in the real-world setting.

Table 1: Demographic and Clinical Characteristics of the Patients

<table>
<thead>
<tr>
<th>Characteristics of patients</th>
<th>Rivaroxaban (N=115)</th>
<th>Standard therapy (N=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age – yr.</td>
<td>51.5</td>
<td>54</td>
</tr>
<tr>
<td>Male sex – no. (%)</td>
<td>71 (58.2)</td>
<td>68 (60.2)</td>
</tr>
<tr>
<td>Weight – no.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50kg</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>50-100kg</td>
<td>92</td>
<td>103</td>
</tr>
<tr>
<td>&gt;100kg</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Liver function within normal limits at time of randomisation – no.</td>
<td>114</td>
<td>113</td>
</tr>
<tr>
<td>Creatinine levels within normal limits at time of randomisation – no.</td>
<td>115</td>
<td>111</td>
</tr>
<tr>
<td>CHADS2 Score ≥2 – no. (%)</td>
<td>51 (49.0)</td>
<td>53 (51.0)</td>
</tr>
<tr>
<td>HAS-BLED score ≤3</td>
<td>112</td>
<td>111</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Pre-existing conditions ≤1</td>
<td>88</td>
<td>80</td>
</tr>
<tr>
<td>≥2</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32</td>
<td>29</td>
</tr>
<tr>
<td>Clinical condition on admission Sinus tachycardia</td>
<td>39</td>
<td>39</td>
</tr>
<tr>
<td>SpO2 90%&lt; x ≤94%</td>
<td>20</td>
<td>22</td>
</tr>
<tr>
<td>≥95%</td>
<td>95</td>
<td>91</td>
</tr>
<tr>
<td>Diagnostic methods</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spiral computed tomography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>43</td>
<td>36</td>
</tr>
<tr>
<td>Moderate</td>
<td>41</td>
<td>48</td>
</tr>
<tr>
<td>Pulmonary angiography</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>D-dimer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Raised (&gt;500ng/ml)</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Normal (&lt;499ng/ml)</td>
<td>79</td>
<td>76</td>
</tr>
<tr>
<td>Inflammatory markers (inc. CRP, IL-6, Ferritin, LDH)</td>
<td>87</td>
<td>100</td>
</tr>
<tr>
<td>Raised</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Normal</td>
<td>28</td>
<td>13</td>
</tr>
<tr>
<td>Pre-randomisation treatment with antplatelet or anticoagulant – no. (%)</td>
<td>115</td>
<td>113</td>
</tr>
<tr>
<td>At least one dose of study drug received – no.</td>
<td>115</td>
<td>113</td>
</tr>
<tr>
<td>Dosing regimen</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40mg SC QD LMWH</td>
<td>-</td>
<td>62</td>
</tr>
<tr>
<td>60mg SC QD LMWH</td>
<td>-</td>
<td>51</td>
</tr>
<tr>
<td>10mg PO OD Rivaroxaban</td>
<td>65</td>
<td>-</td>
</tr>
<tr>
<td>15mg PO OD Rivaroxaban</td>
<td>50</td>
<td>-</td>
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</table>
Table 2: Clinical Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban (N=115)</th>
<th>Standard therapy (N=113)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of treatment – days</td>
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<td></td>
</tr>
<tr>
<td>Median</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Interquartile range</td>
<td>4</td>
<td>4</td>
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<tr>
<td>Mean study treatment duration – days</td>
<td>8.4</td>
<td>8.7</td>
</tr>
<tr>
<td>Average compliance (%)</td>
<td>90.1</td>
<td>87.3</td>
</tr>
<tr>
<td>Loss to follow-up</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intention-to-treat population — no. of patients</td>
<td>115</td>
<td>113</td>
</tr>
<tr>
<td>Progression of disease (requiring treatment escalation, worsening of oxygen saturation ≤90% on room air, ICU transfer, cardiorespiratory failure) – no. (%)</td>
<td>4 (3.8)</td>
<td>16 (14.2)</td>
</tr>
<tr>
<td><strong>Venous thromboembolism</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of first recurrent venous thromboembolism — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal pulmonary embolism</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death in which pulmonary embolism could not be ruled out</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonfatal pulmonary embolism</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse event — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any event emerging during treatment</td>
<td>5 (4.3)</td>
<td>14 (12.4)</td>
</tr>
<tr>
<td>Any serious event emerging during treatment</td>
<td>0</td>
<td>5 (4.4)</td>
</tr>
<tr>
<td>Any event resulting in permanent discontinuation of study drug</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Any event leading to or prolonging hospitalization</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Fatal (retroperitoneal, intracranial, gastrointestinal)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Other nonfatal episode in a critical site</td>
<td>1 (0.9)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Associated with a fall in haemoglobin of ≥2 g/dl, transfusion of ≥2 units, or both</td>
<td>1 (0.9)</td>
<td>3 (2.7)</td>
</tr>
<tr>
<td>Death or ICU transfer needed during intended treatment period — no. (%)</td>
<td></td>
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<tr>
<td>Pulmonary embolism or pulmonary embolism not ruled out</td>
<td>0</td>
<td>1 (0.9)</td>
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<tr>
<td>Bleeding</td>
<td>0</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
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<td>0</td>
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<tr>
<td>Ischemic stroke</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Other cardiac disorder or respiratory failure</td>
<td>1 (0.9)</td>
<td>2 (1.8)</td>
</tr>
<tr>
<td>Progression of disease plus major bleeding events – no. (%)</td>
<td>9 (7.8)</td>
<td>30 (26.5)</td>
</tr>
</tbody>
</table>

Appendix Table S1: Events in Post-discharge Prophylaxis

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Total no. of patients</th>
<th>Mean duration of therapy – days</th>
<th>Average Compliance (%)</th>
<th>Adverse Events – no. (%)</th>
<th>Any event during course of treatment</th>
<th>Any serious event emerging during treatment</th>
<th>Any event leading to permanent discontinuation of drug</th>
<th>Any event leading to hospitalization</th>
<th>Acute Coronary Events</th>
<th>Systemic Embolism</th>
<th>Cerebrovascular Event</th>
<th>Death due to Vascular Cause</th>
<th>Death due to Non-Vascular Cause</th>
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</thead>
<tbody>
<tr>
<td>Venous thromboembolism</td>
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<td>Type of first recurrent venous thromboembolism</td>
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<tr>
<td>Fatal pulmonary embolism</td>
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<td>Death in which pulmonary embolism could not be ruled out</td>
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<td>Nonfatal pulmonary embolism</td>
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<td>Safety</td>
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<td>Adverse event — no. (%)</td>
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<td>Any event emerging during treatment</td>
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<td>Any serious event emerging during treatment</td>
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<tr>
<td>Any event resulting in permanent discontinuation of study drug</td>
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<tr>
<td>Any event leading to or prolonging hospitalization</td>
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<td></td>
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<tr>
<td>Fatal (retroperitoneal, intracranial, gastrointestinal)</td>
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<td>Other nonfatal episode in a critical site</td>
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<tr>
<td>Associated with a fall in haemoglobin of ≥2 g/dl, transfusion of ≥2 units, or both</td>
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In patients diagnosed with mild and moderate SARS CoV-2 infection, anticoagulation with oral rivaroxaban alone had improved efficacy as compared to subcutaneous enoxaparin in the prevention of COVID-19 associated coagulopathy. During the period of treatment in-hospital, the intention-to-treat analysis indicated that 7.8% of patients in the rivaroxaban group and 26.5% of patients in the enoxaparin therapy group had a composite outcome of thrombotic or haemorrhagic event. Safety outcome (as described previously) occurred in 4.3% patients in the rivaroxaban group and 12.4% in the enoxaparin group. Out of this, major bleeding occurred in 0.9% of patients in the rivaroxaban group and 2.7% of patients in the enoxaparin group. The drug offered a relative risk reduction of over 70% in the rivaroxaban group and reduced the absolute risk of reaching trial endpoint by 18%. Prophylactic therapy with rivaroxaban prevented an adverse outcome for every 5 patients treated over a median duration of 8 days.

While devising the inclusion criteria for the study, we used the CHA₂DS₂-VASc scoring system to triage patients at risk of progression of disease. This scoring system had the advantage of having components that were found to increase risk of severe COVID-19 disease, including age, comorbidities such as hypertension, diabetes mellitus, stroke, and vascular disease. In the recent months, this scoring system has been modified and validated as a useful tool in stratifying patients with COVID-19 pneumonia (Gunduz R et al; Quisi A et al, Cetinkal G et al).

Our data suggests that rivaroxaban has a statistically superior benefit-risk
adherence, ease of use, and improved trial are promising, and increased discharge can be seamlessly continued post-
Additionally, direct oral anticoagulants to moderate COVID-19 infection. The trial indicates that rivaroxaban is safe, effective, and practical in the management of disease, as shown in emerging evidence around the world.

Given the difficulty of administering a parenteral agent such as enoxaparin, including patient discomfort, reduced levels of compliance (Haykal T, Zayed T, Deliwal S), and increased exposure of healthcare workers to infectious patients, the oral anticoagulant rivaroxaban is a promising alternative as evidence by our study. The trial indicates that rivaroxaban is safe, effective, and practical in the management of patients with mild to moderate COVID-19 infection. Additionally, direct oral anticoagulants can be seamlessly continued post-discharge, unlike their counterpart low molecular weight heparin that requires bridging over a period of several days. The findings of this trial are promising, and increased adherence, ease of use, and improved benefit-risk profile make this drug a clinically viable alternative for prevention of coagulopathy associated with SARS CoV-2 infection.

The rationale for use of anticoagulation in management of the SARS CoV-2 pandemic was discovered early in the pandemic, and has since, significantly changed disease outcomes. In the Tongji hospital in Wuhan, Tang et al. discovered that use of heparin reduced mortality in patients with severe COVID-19 infection.

In April 2020, Paranjape et al. at Mount Sinai Health System in New York City used various forms of anticoagulation in a large cohort of patients. The study concluded that anticoagulation was associated with lower in-hospital mortality, more specifically, prophylactic dose anticoagulation showed improved survival rates. However, our study observed progress of hospitalised patients in the ward which provided clearer association of anticoagulation use and progression of disease requiring intensive care.

The ACTION trial presented in the ACC 21 sessions discussed similar anticoagulation dosing strategies in the management of COVID-19 pneumonia. The study failed to show that therapeutic anticoagulation was beneficial as compared to prophylactic anticoagulation (Lopes et al).

The trial conducted by Albani et al. compared therapeutic versus prophylactic dosing regimens and revealed similar results (Filippo Albani et al).

In contrast to this, therapeutic dose anticoagulation in moderately ill patients with COVID-19 was found to increase probability of survival until discharge and reduced need for organ support. However, it was associated with significantly more major bleeding events as compared to prophylactic doses.

All above trials discuss the importance of clinically appropriate dosing regimens in the anticoagulation strategy employed in the management of COVID-19 infection. However, our study fundamentally differs in exploring the utility of oral anticoagulants as compared to parenteral anticoagulants. There is still insufficient data directly comparing efficacy of oral anticoagulation and parenteral anticoagulation in management of COVID-19 infection.

The main limitations of our study include the relatively small sample size. Lack of blinding and long-term follow up to shed light on continuing post-covid thromboembolic phenomenon create possible restrictions to the overall conclusion of the study. Subgroup analyses of dosing groups were inconclusive. A larger trial with adequate participants can further validate individual endpoints of this study. Given the ethical restrictions of this poorly understood infection and its global burden during the early phase of the pandemic, patients with severe COVID-19 infection could not be included, as dictated by the Institutional Ethics Committee (IEC). Further research on utility of oral anticoagulants in severe cases of COVID-19 infection can explore the efficacy of this class of drugs in varied stages of the infection.

Only 3 of 115 patients in the rivaroxaban group and 2 of 113 patients in the enoxaparin group were on antiplatelet therapy pre-randomization. However, whether this could have had implications on the overall effect of the intervention drug remains to be studied. Other direct oral anticoagulants (DOACs), such as apixaban and dabigatran, were not available to be included as potential interventions in the study. This could have provided a better insight into the efficacy of direct oral anticoagulants as a group in the
prophylactic management of COVID-19 associated coagulopathy. Our results are generally consistent with findings of anticoagulation dosing regimens in COVID-19 but provide additional, important insight into efficacy of DOACs in COVID-19 disease.

Our randomized controlled trial demonstrated that rivaroxaban as a single oral agent was not only as effective but superior in the prophylactic management of coagulopathy associated with SARS-CoV-2 infection. The relative ease of use and efficacy of rivaroxaban, supported by existing literature of its utility in several thromboembolic diseases, introduces a promising alternative in the management of an illness that continues to plague health care systems around the world.

Participating Institution
All authors were affiliated to the participating institution “Seven Hills Dedicated COVID Hospital (DCH)” in Mumbai, Maharashtra, India during the study.

Key Message and Statement
The protocol (available within the Supplementary Material) was approved by the institutional ethics committee at the participating institution. We have received no external funding or support for the work. All monetary support and resources were provided for by the institution which was under the Brihanmumbai Municipal Corporation as part of the group of major hospitals dedicated to managing the COVID-19 pandemic. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. The authors declare that they have no known competing financial interests or personal relationships that could have influenced the study and final publication.

Abbreviations List

References
8. The United States Food and Drugs Administration approves a generic enoxaparin. Ofosu, Frederick. s.l.: Clinical and Applied Thrombosis/Hemostasis, August 2010.
To Study Adverse Effect following Immunization (AEFI) and COVID-19 Infection amongst COVID-19 Vaccine Beneficiaries

Pawar Pradnya N1, Chavhan Smita S2, Jadhao Viplove F3, Adsul Balkrishna B4, Kumbhar Maharudra A5, Dhikale Prasad T6, Gokhale Chinmay N6, Ingale Aniket R7

Abstract
COVID-19 vaccines have been rolled out recently in several parts of the world. Little is known about the post-vaccination experience outside of clinical trial conditions. The aim of this study was to investigate the adverse effects and infection rate of vaccinated people in a community scenario. It will help to educate the public, dispel misinformation and reduce vaccine hesitancy.

Aim and Objectives: Assessing total beneficiaries of COVID-19 vaccination and finding among them COVID-19 infection and AEFI after vaccination.

Subject and Methods: Cross sectional Study at COVID-19 Vaccination centre at DCH in Mumbai, since 1st February 2021–31st July 2021, Data was collected by calling telephonically the registered beneficiaries in Vaccination Centre, data was collected and analysed in MS-excel sheet and SPSS using CHI-square test.

Results: 49.68% of the beneficiaries were from the age group of 45-60 years followed by >60 years age group (34.70%). 97.08% beneficiaries were from Mumbai. 3593(43.59%) had taken both the doses of COVID-19 vaccine while 4650(56.41%) had taken only first dose of COVID-19 vaccine. 360(4.44%) had contracted COVID-19 infection after vaccination. 88.71% had no AEFI after taking vaccine. 1.65% had mild AEFI and 9.63% had moderate AEFI.

Conclusion: Very few had contracted COVID-19 infection after vaccination. Out of all AEFI maximum were mild to moderate.

Introduction
The vaccination program has commenced in many countries worldwide, which is marked as a significant milestone in curbing the spread of the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), the causal agent of the corona virus disease 2019 (COVID-19) pandemic.1 Individuals who have been vaccinated are less inclined to be severely infected than those who have not received vaccines.2 These vaccines, which have received emergency authorisation from different regulatory bodies around the world, such as the Food and Drug Administration in the USA, have different mechanisms of delivery of antigens. Researchers have revealed that different vaccines have varied levels of efficacy, i.e., between 60% and 95%.3

Studying the clinical profile of those who got infected after receiving one or two doses of vaccine will give a clear indication as to the level of protection that a first dose and a second dose offered. If the first dose was enough to prevent serious disease and hospitalisation, then it should help the authorities decide whether covering as many people as possible with at least a single dose vaccine is the appropriate strategy for the State, it is pointed out.4 COVID-19 vaccines have been rolled out recently in several parts of the world. Although the protective efficacy is frequently discussed, little is known about the real-world post-vaccination experience outside of clinical trial conditions.2

The aim of this study was to investigate the adverse effects and infection rate of vaccinated people in a community scenario.

Knowledge about what to expect after vaccination will help educate the public, dispel misinformation and reduce vaccine hesitancy.

Aim and Objectives
1. To assess total beneficiaries of COVID-19 vaccination
2. To find COVID-19 infection after vaccination
   - To compare 1st and 2nd dose COVID-19 vaccine beneficiaries for Covid-19 infection
   - To study severity of infection after vaccination in beneficiaries with co-morbidities
3. To study AEFI after vaccination.

Subject and Methods
1. Study Design: Cross sectional study design
2. Study Setting: COVID-19 Vaccination centre at DCH in Mumbai, India run by MCGM
3. Study Duration: All patients with COVID-19 vaccination registered in centre since 1st February 2021–31st July 2021
4. Sample Size: Universal sample size
5. Inclusion Criteria: Those who had taken at least first dose and second dose of COVID-19 Vaccination
7. BIAS: Information bias

Data Collection: Data was collected by calling the registered beneficiaries in Vaccination Centre.
Data Entry and Analysis: Data was entered in MS Excel sheet with variables:

i) Age, ii) gender, iii) AEFI, iv) covid positive status v) co-morbidities,

Ethical Consideration: Study was approved by IEC of Seven Hills Hospital, Marol, Mumbai

Results

As of 20th September 2021 we had vaccinated Covishield doses 2, 21,570 (1st – 1, 56,353 and 2nd –65,217) and Covaxin doses 21,727 (1st - 10,670 and 2nd – 11,057)

Out of these an attempt was made to reach out 8243 beneficiaries.

Table 1: According to age

<table>
<thead>
<tr>
<th>AGE (yrs)</th>
<th>18 - 45</th>
<th>45 - 60</th>
<th>&gt;60</th>
<th>TOTAL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>839(17.67%)</td>
<td>236(49.78%)</td>
<td>1545(32.55%)</td>
<td>4747</td>
</tr>
<tr>
<td>Female</td>
<td>449(12.84%)</td>
<td>1732(49.54%)</td>
<td>1315(37.62%)</td>
<td>3496</td>
</tr>
<tr>
<td>Total</td>
<td>1288(15.62)</td>
<td>4095(49.68%)</td>
<td>2860(34.70%)</td>
<td>8243(100%)</td>
</tr>
</tbody>
</table>

Table 2: According to residence

<table>
<thead>
<tr>
<th>Residence</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mumbai</td>
<td>4591</td>
<td>3412</td>
<td>8003</td>
</tr>
<tr>
<td></td>
<td>(96.7%)</td>
<td>(97.5%)</td>
<td>(97.08%)</td>
</tr>
<tr>
<td>Out of Mumbai</td>
<td>156 (3.29%)</td>
<td>84 (2.40%)</td>
<td>240 (2.92%)</td>
</tr>
<tr>
<td>Total</td>
<td>4747</td>
<td>3496</td>
<td>8243 (100%)</td>
</tr>
</tbody>
</table>

Table 3: ii Dose Taken

<table>
<thead>
<tr>
<th>No. dose taken</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully vaccinated</td>
<td>1993</td>
<td>1600</td>
<td>3593</td>
</tr>
<tr>
<td>Partially vaccinated</td>
<td>2754</td>
<td>385</td>
<td>3139</td>
</tr>
<tr>
<td>Total</td>
<td>4747</td>
<td>3496</td>
<td>8243 (100%)</td>
</tr>
</tbody>
</table>

Table 4: Post vaccination Covid infection

<table>
<thead>
<tr>
<th>COVID status</th>
<th>Male</th>
<th>Female</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>COVID +VE</td>
<td>1993</td>
<td>1600</td>
<td>3593</td>
</tr>
<tr>
<td>COVID -VE</td>
<td>4722</td>
<td>3485</td>
<td>8207</td>
</tr>
<tr>
<td>Total</td>
<td>4747</td>
<td>3496</td>
<td>8243 (100%)</td>
</tr>
</tbody>
</table>

Table 4: Dose 2 taken and hospitalization

<table>
<thead>
<tr>
<th>Residence</th>
<th>Fully vaccinated</th>
<th>Partially vaccinated</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hospitalized</td>
<td>4 (30.77%)</td>
<td>10 (43.47%)</td>
<td>14</td>
</tr>
<tr>
<td>Not Hospitalized</td>
<td>9 (69.23%)</td>
<td>13 (56.52%)</td>
<td>22</td>
</tr>
<tr>
<td>Total</td>
<td>13 (56.11%)</td>
<td>23 (63.89%)</td>
<td>36</td>
</tr>
</tbody>
</table>

Table 5: AEPI developed post vaccination

<table>
<thead>
<tr>
<th>AEFI gender</th>
<th>NIL</th>
<th>Mild</th>
<th>Moderate</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>4222(57.73%)</td>
<td>77(36.61%)</td>
<td>448(6.19%)</td>
<td>4747</td>
</tr>
<tr>
<td>Female</td>
<td>3091(42.27%)</td>
<td>59(43.38%)</td>
<td>346(38.80%)</td>
<td>3496</td>
</tr>
<tr>
<td>Total</td>
<td>7313(88.71%)</td>
<td>136(1.65%)</td>
<td>794(9.63%)</td>
<td>8243(100%)</td>
</tr>
</tbody>
</table>

Not significant at p<0.05

36 (0.44%) had contracted COVID-19 infection after vaccination while others were unaffected. The result was not statistically significant at p-value < 0.05.

Table 4.1) The \( \chi^2 = 0.5645 \). The p-value is 0.452461

Not significant at p<0.05

Among 36 beneficiaries who became positive after taking COVID-19 vaccination 13 (36.11%) had taken their both the shots. Among 13 those required hospitalization were 4 and rest others required home treated (i.e. 69.23%). The result was statistically not significant with Chi-square value of 0.5645 and p-value 0.452461.

Table 4.2) The \( \chi^2 = 0.0584 \). The p-value is 0.808976

Not significant at p<0.05

Among 36 beneficiaries who became positive after taking COVID-19 vaccination 24 (66.67%) had co-morbidities (diabetes, hypertension, hypothyroid,). The result was not statistically significant with chi square value= 0.0584 and p-value= 0.808976.

The \( \chi^2 = 0.0259 \). The p-value is 0.872081

Not significant at p<0.05

The \( \chi^2 \) with Yates correction is 0.162. The p-value is 0.687288

Not significant at p<0.05

88.71% had no AEFI after taking vaccine. 1.65% had mild (redness, itching, and swelling on injection site) AEFI 9.63% had moderate AEFI (raise in BP, fever)

Only 1 patient had severe form of AEFI with development of Angioedema within 48 hrs of vaccination without any signs of stridor, respiratory distress or difficulty in deglutination which resolved with oral medication on same day of appearance

Discussion

Vaccines for SARS-COV-2 became available in December 2020. The development of an effective vaccine over a relatively short period of time required the coordinated efforts of multiple scientists, pharmaceutical companies, and government organizations.1

The Government of India (GOI) launched a nationwide vaccination drive in a phased manner based on 16th January 2021 for health care workers
initially and subsequently extending to frontline workers, and the higher-risk population at designated sites in two doses 28 days apart. We have studied, the response of people towards vaccination campaign and in our study, we have considered all the citizens who were registered or got vaccinated at our centre during the time interval of 26 January till July 2021. All the beneficiaries were contacted telephonically and were asked to respond to pre-filled questionnaires regarding their experience and feedback of vaccination at our centre. They were specifically asked for any side effect or adverse reaction to vaccination or any event of Covid symptoms or Covid positive status post vaccination. Total 8243 beneficiaries were registered for this study. Data was analysed on the basis of Age, gender, AEFI, Covid positive status, co-morbidities. Amongst the sample, 49.68% of the beneficiaries were from the age group of 45-60 years followed by >60 years age group (34.70%). Only 15.62% of the beneficiaries were from the age group of 18-45 years. Among which 37.58% were male and 42.42% were female; also 97.08% beneficiaries were from Mumbai and 2.92% were from out of Mumbai.

In our study, 3593(43.59%) had taken both the doses of COVID-19 vaccine while 4650(56.41%) had taken only first dose of COVID-19 vaccine.

During vaccination, 88.71% beneficiaries had developed no adverse reaction to vaccination, only 1.65% had mild (redness, itching, and swelling on injection site) AEFI 9.63% had moderate (redness, itching, and swelling on injection site) AEFI 9.63% had moderate (redness, itching, and swelling on injection site) AEFI 9.63% had moderate (redness, itching, and swelling on injection site) AEFI 9.63% had moderate (redness, itching, and swelling on injection site) AEFI 9.63% had moderate (redness, itching, and swelling on injection site) AEFI 9.63% had moderate (redness, itching, and swelling on injection site) AEFI 9.63% had moderate (redness, itching, and swelling on injection site) AEFI 9.63% had moderate. Symptoms of symptoms was 81% (3rd decade or 20-29 years), 80% (4th decade or 30-39 years), 68% (5th decade), 58% (6th decade), 45% (7th decade), 34% (8th decade) and 7% (9th decade, 80-90 years). Post-vaccination symptoms were more likely to be reported by women (74.7%) compared to men (58.6%) (p< 0.001). Among those who reported symptoms, 79% noticed them within the first 12 hours. 472 out of 5396 (8.7%) reported past history of COVID-19. Their symptom profile was not different to those who did not have a past history. In 90% cases, the symptoms were either milder than expected or meeting the expectation of the vaccine recipient. No serious events were reported. Symptoms were more common among younger individuals. As per Abohelwa M, Elmassry M, Abdelmalek J, et al all residents and fellows reported side effects after vaccination, including pain at the injection site (77; 100%), local redness (9; 11.6%), local swelling (13; 16.8%), fever (25; 32.5%), fatigue (25; 32.5%), chills (34; 44.1 %), headache (38; 49.4%), but no anaphylaxis or palpitations. No one reported severe incapacitating side effects.

A total of 195 people, i.e., 11.8%, suffered from COVID-19 confirmed by the test, while 83.3% (1385) did not suffer from it, and 72 people refrained from selecting the answer. However, based on the circumstances and symptoms, 18.5% (299) of people developed COVID-19, unconfirmed by the test, and 72.5% (1173) of people did not suspect COVID-19, but the asymptomatic transition of COVID-19 cannot be ruled out. When asked about the course of COVID-19, the answers were obtained that 74 people had an asymptomatic course, 325 people mild, 69 people moderate, and 1185 people did not suffer from COVID-19. A total of 468 suffered from COVID-19, which does not coincide with the responses to the previous question, i.e., people with a confirmed COVID-19 test result and confirmed based on symptoms and circumstances, i.e., 488 people. Assuming that 468 people suffered from COVID-19, it can be stated that as many as 28.3% of the respondents suffered from COVID-19.

According to Abohelwa M, Elmassry M, Abdelmalek J, Payne D etal one survey respondent tested positive for COVID-19, 8 days following the first vaccine dose and no respondents tested positive following the second dose of vaccine. According to J. Muthukrishnan, VasuVardhan et al. COVISHIELD has shown to reduce infections by 80-94%. In present study only 36(0.44%) had contracted COVID-19 infection after vaccination while others were unaffected.

**Conclusion**

1. Maximum beneficiaries were from the age group of 45-60 years followed by >60 years age group and then from the age group of 18-45 years.
2. Most of the beneficiaries were from Mumbai.
3. 43.59% had taken both the doses of COVID-19 vaccine while 56.41% had taken only first dose of COVID-19 vaccines. The result is statistically significant.
4. Very few had contracted COVID-19 infection after vaccination while others were unaffected.
5. As per the result both the doses of COVID-19 vaccine reduces the risk of hospitalization.
6. According to result the risk is more in those having co-morbidities although the result is not significant.
7. Out of all AEFI maximum were mild to moderate.

**References**

For risk reduction of Major adverse cardiac events (MACE) in CAD/PAD

Rivaroxaban 2.5 mg Tablets

The Vascular Dose for Polyvascular disease

an Expanded PAD indication for the Rivaroxaban Vascular Dose

ularization-lr-due-to-symptomatic-pad (Oct 11, 2021, 11:15)

# To reduce risk of major thrombotic vascular events in patients with PAD, including patients after recent lower extremity revascularization due to symptomatic PAD

CAD - Coronary Artery Disease      PAD - Peripheral Artery Disease
Clinical-epidemiological Profile of Coronavirus Disease 19 Associated Mucormycosis (CAM) and Relation with Zinc and Iron Levels

Ritu Karoli1*, Manish Raj Kulshreshtha2, Nikhil Gupta3, Mridu Singh3, Vikram Singh4, Shobhit Shakya3

Abstract

Introduction: Coronavirus disease associated mucormycosis (CAM), perturbed a lot by reaching to epidemic proportions particularly during the second wave of the pandemic.

Material and Methods: This was a retrospective, observational study of patients with COVID-19-associated mucormycosis admitted in April-May 2021 at a tertiary care teaching hospital. Demographic profile, clinical and laboratory parameters were recorded Multidisciplinary treatment including antifungals and surgical interventions were noted.

Results: This study included 98 patients of mucormycosis, diagnosed on the basis of clinical and radiological findings and later confirmed by microbiological investigations. Out of 98 patients, 72 had rhino orbital, 24 had rhino-orbital-cerebral and 2 had pulmonary mucormycosis. Twelve had coinfection of covid 19 while 86 had developed mucormycosis within 3 weeks.

Conclusion: CAM has posed as a continuum of challenges faced during the pandemic of covid 19. This rare and life threatening complication requires high index of suspicion for early diagnosis. Multidisciplinary involvement and timely interventions including antifungal pharmacotherapy, stringent glycemic control and surgical debridement can reduce the mortality. Mucormycosis is uniformly associated with low iron levels but role of zinc needs to be further studied.

Introduction

The Covid-19 symptom spectrum ranged from common clinical features that include fever, cough, fatigue, myalgia and pneumonia to involvement of many organ systems. It is associated with increased incidence of secondary bacterial and fungal infections.1 The fungal co-infections associated with COVID-19 have been reported last year too but it increased exponentially during the second wave. Mucormycosis is an uncommon but serious infection that complicates the course of severe COVID-19.2

In India, the prevalence of mucormycosis is already disproportionate high, approximately 0.14 cases per 1000 population, which is about 80 times the prevalence of mucormycosis in western countries.3

The prevalence of covid associated mucormycosis (CAM) was 0.27 per cent in patients managed in hospital wards and 1.6 per cent in patients managed in intensive care units.4

The prevailing second wave of COVID-19 created an upsurge in patients of mucormycosis. Indiscriminate use of steroids, antimicrobials, uncontrolled hyperglycemia and inadequate infection control in health care facilities have been implicated as risk factors of CAM5 but as a matter-of-fact exact cause is still speculative. Zinc supplement has remained an important component of treatment of covid 19 that might have served as supportive fuel for the growth of fungus. The link between iron metabolism in fungus and host is also of high relevance. Therefore, this study was planned to report the epidemiology, risk factors and clinical profile of mucormycosis and to investigate any relation with abnormal iron and zinc levels in patients admitted in the tertiary care teaching hospital situated in North India.

Methodology

This was a prospective study on the patients who were admitted in medicine wards of a tertiary care teaching hospital between 1st April 2021 to 30th July 2021. These patients were diagnosed to have mucormycosis on the basis of clinical and radiological findings and subsequently confirmed by microbiological investigations.

COVID 19 associated mucormycosis was defined as – if at the time of admission patients were tested positive for coronavirus infection or they had history of COVID 19 by identification of SARS-CoV-2 using reverse transcription polymerase chain reaction (RT-PCR) in nasopharyngeal swab.

Based on clinical parameters each patient was designated as mild, moderate and severe COVID 19 as per guidelines of Ministry of health and family welfare, government of India.6 Mild was defined as those with uncomplicated upper respiratory tract symptoms, no shortness of breath, hypoxemia or abnormal chest X-rays.

Moderate disease was defined as presence of clinical features of dyspnoea and/ or hypoxemia, fever,
Disease. All the findings and reports of patients to assess the extent of the orbits and brain were done in all tomography (CT)/Magnetic resonance performed were noted to determine the and neurological examinations, otorhinolaryngological, comprehensive ophthalmologic evaluations, medical treatment, and surgical interventions were similar to those in post covid state except prevalence of ICU admissions, presence of DKA and inflammatory mediators as shown in Table 1.

All the patients with mucormycosis had hyperglycemia at the time of admission. Sixty-six patients had past history of diabetes while rest were newly diagnosed. All the patients had glycosylated hemoglobin>7.5%. Diabetic keto acidosis was present in 12/98 patients who were treated with intravenous fluids, insulin and potassium chloride. Out of post covid 86 patients with mucormycosis, only 15 patients had history of hospitalization and hypoxemia for which supplemental oxygen therapy was given, while 31 patients had mild febrile illness and were treated at home. However, steroid therapy (dexamethasone, prednisolone or methyl prednisolone) was received by 58 patients for mean duration of 18±7 days.

The common presenting symptoms and signs were proptosis (90%), orbital pain (85%), headache (80%), facial pain (75%) conjunctival hyperemia or chemosis (70%), ptosis (70%), diplopia (65%), fixed and dilated pupil (63.6%), decreased visual acuity (63.6%), facial hypesthesia (50%), epistaxis (45%) and endophthalmitis (34.5%). Left eye was involved in 55% while right eye involvement was noted in 45% patients.

Paranasal sinuses were involved in all patients and 90% had multiple sinus involvement. Ethmoidal (72%), maxillary (65%), sphenoidal (43%) and frontal sinuses (23%) were involved in decreasing frequency.

Intracranial extension was evident in 24 patients. They presented with altered consciousness, seizures and hemiparesis. MRI brain suggested cavernous sinus thrombosis in 4 patients.

Laboratory parameters revealed significantly increased inflammatory markers including neutrophil lymphocyte ratio, hsCRP, ferritin and covid 19 illness while 4 had mild disease. Rest of the 86 had history of covid 19 within 3 weeks. The mean duration between RTPCR covid negative test and onset of symptoms of mucormycosis was 13±8 days. All the patients who had fungal coinfection had severe covid 19. Demographic features of patients who were diagnosed to have mucormycosisduring covid 19 illness were similar to those in post covid state except prevalence of ICU admissions, presence of DKA and inflammatory mediators as shown in Table 1.

Laboratory data consisted of complete blood count, liver and renal function test, examination of haemostasis parameters, inflammatory markers in form of high-sensitivity C-reactive protein (hsCRP), interleukin 6, lactate dehydrogenase and procalcitonin for presence of secondary bacterial infection. The normal reference range for the zinc concentration was considered 80–120 µg/dl. A zinc level <80 µg/dl was defined as ‘deficient while iron (60–180 µg/dl), ferritin (10–125 ng/ml) were considered normal, 80–125 ng/ml) were considered normal, .

Microbiological confirmation was obtained by microscopy for presence of fungal hyphae using potassium hydroxide mount. For fungal culture the samples were inoculated on Sabouraud dextrose agar. Tissue samples after debridement were submitted for histopathological analysis by using, periodic acid Schiff and Gomori methenamine silver stain.

Statistical analysis

A descriptive statistical analysis was performed for all variables using IBM SPSS Statistics version 21.0 (IBM Corp., Armonk, NY, USA), consisting of mean, standard deviation, percentage. Proportions and associations between characteristics of the study groups were compared by Fisher’s exact test. The Mann–Whitney U-test and t-test were used to compare continuous variables between the study groups. Multivariate logistic regression analysis was conducted to determine the odds ratio (OR) and 95% confidence intervals (95% CI) for the variables affecting mortality. Results were considered statistically significant when the p-value was <0.05.

Results

A total of 98 patients of mucormycosis were included in the study. Out of 98 patients, 72 had rhino orbital, 24 had rhino-orbital-cerebral and 2 had pulmonary mucormycosis whom bronchoalveolar lavage fluid confirmed presence of aseptate hyphae.

There was male preponderance noted in the study population. Mean age of the patients was 52±14 years. Majority were from rural areas. Out of 98, 12 patients were diagnosed to have covid 19 first and subsequently they developed symptoms of mucormycosis. Amongst them, 8 patients had severe

<table>
<thead>
<tr>
<th>Variable</th>
<th>Covid 19 coinfection (n=12)</th>
<th>Post covid (n=86)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>48±10</td>
<td>54±14</td>
<td>0.06</td>
</tr>
<tr>
<td>Male gender</td>
<td>7(58)</td>
<td>23(50)</td>
<td>0.12</td>
</tr>
<tr>
<td>ICU admission</td>
<td>4(33)</td>
<td>15(17)</td>
<td>0.01</td>
</tr>
<tr>
<td>Glucocorticoid therapy</td>
<td>8(67)</td>
<td>50(58)</td>
<td>0.88</td>
</tr>
<tr>
<td>Site of involvement</td>
<td>9(100)</td>
<td>63(100)</td>
<td>0.5</td>
</tr>
<tr>
<td>Rhino-orbital</td>
<td>3(25)</td>
<td>21(22)</td>
<td>0.8</td>
</tr>
<tr>
<td>Rhino-orbital-cerebral pulmonary</td>
<td>-</td>
<td>2(3)</td>
<td>0.06</td>
</tr>
<tr>
<td>Presence of DKA</td>
<td>1(8)</td>
<td>11(12)</td>
<td>0.23</td>
</tr>
</tbody>
</table>

Data is expressed as mean ± standard deviation, n(%)

Severely ill patients were defined as those with clinical signs of severe pneumonia plus one of the following: respiratory rate>30 breath/ min, severe respiratory distress and SpO2< 90% on room air; acute respiratory distress syndrome (ARDS); sepsis and septic shock or end organ damage.

Non Mucormycosis COVID 19(n=100) patients were also included in the study to serve as control group.

Exclusion criteria

1. Fungal infection in form aspergillosis/candidiasis
2. Hematological malignancy or any other solid organ malignancy
3. Organ transplant recipients
4. Patients on radio/chemotherapy
5. On iron or zinc supplement

The study was approved from Institutional Ethics Committee and written informed consent was obtained from all study participants before including them in the study.

Patients’ demographic data, clinical manifestations, comorbid status, laboratory and radiological investigations, medical treatment, and surgical interventions were recorded. A detailed history, comprehensive ophthalmologic evaluation, otorhinolaryngological, and neurological examinations performed were noted to determine the disease’s extent and severity. Flexible nasal endoscopy and computerized tomography (CT)/Magnetic resonance imaging (MRI) of the paranasal sinuses, orbits and brain were done in all patients to assess the extent of the disease. All the findings and reports were obtained from patient records.
Table 2: Laboratory parameters of patients with mucormycosis

<table>
<thead>
<tr>
<th>Variable</th>
<th>Covid 19 coinfection (n=12)</th>
<th>Post covid (n=86)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutrophil lymphocyte ratio</td>
<td>13±3.2</td>
<td>4±1.8</td>
<td>0.001</td>
</tr>
<tr>
<td>HsCRP</td>
<td>156±38</td>
<td>57±24</td>
<td>0.03</td>
</tr>
<tr>
<td>Ferritin</td>
<td>970±122</td>
<td>234±107</td>
<td>0.01</td>
</tr>
<tr>
<td>HbA1c</td>
<td>10.5±1.5</td>
<td>12±2.4</td>
<td>0.07</td>
</tr>
<tr>
<td>Lactic</td>
<td>447±128</td>
<td>221±48</td>
<td>0.02</td>
</tr>
<tr>
<td>Dehydrogenase</td>
<td>Interleukin-6</td>
<td>22±7</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Data is expressed as mean ± standard deviation, n(%) 

lactic dehydrogenase in patients who had mucormycosis along with covid 19 as compared to post covid patients as shown in Table 2.

All the patients were positive for fungal aseptate hyphae in routine microscopy for KOH mount. Fungal culture was available in 12 patients which showed Rhizopus spp.

Patients were treated with liposomal Amphotericin B at a dose of 5-10 mg/kg/day, and oral formulations of Posaconazole and Isavuconazole. Hypokalemia was the commonest adverse effect which was treated with potassium supplements. All the patients were treated with endoscopic surgical debridement of the paranasal sinuses. Intra orbital liposomal Amphotericin B were injected by ophthalmologists in 22 patients. Orbital exenteration was performed in 8 patients.

Table 3 is showing the clinical characteristics and laboratory parameters of COVID 19 associated mucor mycosis and COVID 19 without mucor mycosis which served as control group. The patients without mucormycosis had acute COVID 19 illness, more dyspnea and markers of inflammation. Anemia was significantly higher in mucormycosis patients while serumiron levels were significantly below normal. Zinc levels were reported to be normal and not different in two groups.

In the present study, 16/98(17%) patients were expired. On multivariate logistic regression analysis, age, site of involvement (rhino-orbital-cerebral), presence of DKA and sepsis were associated with increased mortality as shown in Table 4.

**Discussion**

Covid 19 has presented us with a major challenge to find effective ways to mitigate this pandemic. The pathogenesis of COVID-19 is not fully understood, but is probably multifactorial, resulting in a systemic hyperinflammatory response and associated thromboembolic complications in severe cases. It resulted in higher morbidity and mortality in patients with diabetes and hypertension.

Covid 19 is associated with immune dysregulation caused by SARS-CoV-2 virus itself. It leads to over expression of inflammatory cytokines and impaired cell-mediated immunity with decreased cluster of differentiation (CD4+ T and CD8+ T) cell counts that cause more susceptibility to fungal co-infections. White et al and Song et al have reported increased incidence of invasive fungal disease in patients with covid 19.

Mucormycosis is a rare, rapidly progressive disease associated with high morbidity and mortality. Diagnosis is often delayed and management needs multidisciplinary involvement.

In India, particularly we saw a new epidemic of mucormycosis embedded in covid pandemic as coinfection in patients of Covid 19 or when they were in convalescent phase.

In our study, we observed that all our patients had uncontrolled diabetes. Patients with diabetes are prone to have opportunistic infections and mucormycosis. This is contributed by use of corticosteroids which were intensively used as lifesaving drugs. According to existing literature India contributed to 81% of the cases of the global burden of this ‘rare mould’ infection. Patel et al conducted an important study involving 16 centers across the country on prevalence of fungal infections in patients with covid 19 noted a 2.1-fold rise in mucormycosis, uncontrolled diabetes was the most common comorbidity. Presence of COVID-19-related hypoxemia and improper glucocorticoid use independently were associated with CAM. Sen et al have also conducted a multicentric study involving 2826 patients of rhino-orbital- cerebral mucormycosis from states of Gujarat and Maharashtra and reported diabetes and steroid use as most common risk factors. They highlighted the importance of surgical interventions to reduce mortality in these patients.

Mucor is a saprophytic fungus; ubiquitous in nature, especially in soil, air, decaying vegetation and organic matter. It may be present in nasal mucosa as commensal. When there is any breach or immunocompromised state, it can invade paranasal sinuses, orbit and brain. Mucormycosis describes infections caused by fungi of the order Mucorales. The most frequently reported pathogensinmucormycosis are Rhizopus spp, Mucor spp, and

Table 3: Clinical and laboratory parameters of CAM(COVID 19 associated mucor mycosis) and control (COVID 19 without mucor mycosis) group

<table>
<thead>
<tr>
<th>Parameter</th>
<th>CAM (n=98)</th>
<th>Control (n=100)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age years</td>
<td>52±14</td>
<td>53±15</td>
<td>0.5</td>
</tr>
<tr>
<td>Male Gender%</td>
<td>56(57)</td>
<td>55(55)</td>
<td>0.81</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>98(100)</td>
<td>32(32)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43</td>
<td>44(44)</td>
<td>0.72</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5(6)</td>
<td>4(4)</td>
<td>0.5</td>
</tr>
<tr>
<td>Dyspnea at admission</td>
<td>22(23)</td>
<td>85(85)</td>
<td>0.001</td>
</tr>
<tr>
<td>Hemoglobin(g/L) (normal range 125.0-16.0)</td>
<td>8 ±1.5</td>
<td>12± 2.5</td>
<td>0.02</td>
</tr>
<tr>
<td>Neutrophil count (× 10^6 cells/L) (normal range 1.8-6.3)</td>
<td>3.5±0.6</td>
<td>5.5±1.1</td>
<td>0.03</td>
</tr>
<tr>
<td>Lymphocyte count (× 10^6 cells/L) (normal range 1.1-3.2)</td>
<td>1.8±0.2</td>
<td>1.2±0.3</td>
<td>0.3</td>
</tr>
<tr>
<td>HSCRP(mg/L) (normal range 0.0-3.0)</td>
<td>38 ±11</td>
<td>76±17</td>
<td>0.01</td>
</tr>
<tr>
<td>Ferritin (ng/mL) (normal range 10-125)</td>
<td>124 ±23</td>
<td>612±117</td>
<td>0.012</td>
</tr>
<tr>
<td>Iron µg/dl(60-180)</td>
<td>12±7</td>
<td>55±18</td>
<td>0.001</td>
</tr>
<tr>
<td>Zinc mg/dl (80-120)</td>
<td>97±11</td>
<td>105±22</td>
<td>0.56</td>
</tr>
<tr>
<td>D Dimer(µg/mL) (normal range 0.0-0.5)</td>
<td>0.65±0.2</td>
<td>2.2±0.8</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Data is expressed as mean ± standard deviation, n(%), Bold text indicates statistical significance

Table 4: Multivariate analysis of factors associated with mortality

<table>
<thead>
<tr>
<th>Variable</th>
<th>Survivors (48)</th>
<th>Non survivors (n=10)</th>
<th>Odds Ratio, 95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>45±14</td>
<td>62±17</td>
<td>2.3(1.3-4.2)</td>
<td>0.02</td>
</tr>
<tr>
<td>Rhino cerebral involvement</td>
<td>2(4)</td>
<td>10(100)</td>
<td>5.7(2.7-13.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>Presence of DKA</td>
<td>2(4)</td>
<td>6(60)</td>
<td>2.9(1.7-5.3)</td>
<td>0.01</td>
</tr>
<tr>
<td>Presence of sepsis</td>
<td>6(13)</td>
<td>8(80)</td>
<td>2.1(1.2-4.7)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data is expressed as mean ± standard deviation, n(%), Bold text indicates statistical significance

Mucormycosis is a rare, rapidly progressive infection.
Lichtheimia spp. In present study Rhizopus spp. were grown in all the culture specimens.

Hyperglycemia leads to increased expression of the endothelial receptor GRP78, resulting in polymorphonuclear dysfunction, impaired chemotaxis and defective phagocytosis. Hyperglycemia and ketoacidosis favor germination and growth of fungal spores which are present in the environment. Corticosteroids used in COVID-19 by causing impaired neutrophil function and hyperglycemia make diabetic patient more vulnerable for development of mucormycosis.

Acidic pH, a hallmark of DKAl leads to more availability of free iron which is taken up by the mucorales through siderophores or iron permeases. Rhizoferrin produced by fungal hyphae forms iron-rhizoferrin complexes after binding to serum iron.[15] Iron is an essential element for fungal cell growth and development and iron acquisition is adds virulence to fungi. It was noted in all the patients that serum iron levels were uniformly low and most of the patients had severe anemia. Mucorales, have extremely restricted growth in normal serum unless exogenous iron is added. High-affinity iron permease (FTR1) has a role in iron uptake and transport in mucorales especially during the lack of iron in the environment.

Experimental data have shown that compounds interfering with zinc homeostasis process would inhibit fungal growth. Zinc deficiency induces stress in fungal cells and inhibits fungal growth by restricting the activity of zinc-binding proteins, which are mainly transcription factors involved in many biological processes. Further, some zinc chelators have shown promising results against Aspergillus fumigatus strains. Another objective of present study was to estimate the zinc levels in our patients to determine any association with mucormycosis. It was observed that none of the patients in study cohort had zinc deficiency or zinc excess.

We had few notable findings in the present study, firstly not all patients had suffered from severe covid 19 requiring hospitalization and supplemental oxygen therapy, and secondly, significant proportion of the patients did not receive corticosteroids. However, some of them received in large doses for prolonged duration. Therefore, we conclude that covid 19 infection, steroid use and uncontrolled diabetes, were the important factors which were present in our patients similar to the results reported by other studies. Sharma et al have reported increased prevalence of mucormycosis in patients with covid 19.

Large proportion of the patients in the present study were diagnosed to have mucormycosis at the early stage, probably because of the increased awareness of this life threatening condition and that was reason behind relatively low mortality rate recorded in present series. High mortality rates (50-80%) have been reported from intra-orbital and intracranial complications of mucormycosis which is observed in present study also. Is there any mucospecific immunity disturbed during COVID-19 induced immune dysregulation or any other host or environmental risk factor responsible for surge is the question which should be answered. Clinicians and laboratory researchers should pay critical attention to the increased incidence of fungal infections in covid-19 affected or recovered patients.

Conclusion
CAM has posed as a continuum of challenges faced during the pandemic of covid 19. This rare and life threatening complication requires high index of suspicion for early diagnosis. Multidisciplinary involvement and timely interventions including antifungalpharmacotherapy, stringent glycemic control and surgical debridement can reduce the mortality. Mucormycosis is uniformly associated with low iron levels but role of zinc needs to be further studied.

References
Spectrum of Bacterial Pathogens in Critical COVID-19 Patients Admitted in Intensive Care Units of a Tertiary Care Hospital During the First and Second Wave of the Pandemic

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Abstract

Objective: This study intends to compare the clinical characteristics and the prevalence and spectrum of bacterial pathogens in COVID-19 patients admitted to ICU during the first and second waves at a tertiary care, teaching and referral hospital of eastern India.

Method: This is a hospital-based retrospective study which analysed demographic details, clinical profile and bacterial culture results of severe and critically ill COVID-19 patients admitted in intensive care units (ICU) during April-Oct 2020 (1st wave) and April–July 2021 (2nd wave).

Result: The patients admitted during the 2nd wave were comparatively older and had multiple comorbidities compared to the 1st wave. (23.8%) (45/189) and 50% (173/346) of the COVID-19 patients admitted to ICU developed bacterial infection during the 1st and 2nd wave respectively. Overall, there was predominance of multidrug resistant Gram negative bacilli in both the waves. There was increased isolation of intrinsic colistin resistant microorganisms.

Conclusion: Multidrug resistant Gram negative bacterial infections, remain a dreaded complication in severe and critically ill hospitalised COVID-19 patients requiring ICU care and high usage of colistin spirals the emergence and spread of pathogens intrinsically resistant to colistin.

Introduction

India has witnessed two successive waves of Coronavirus Disease-2019 (COVID-19) with regional variations in timeframes among the states in the country in reaching the peak and dipping to a steady level. Although the prevalence of co-infection with bacterial pathogens has been variable across the globe, it has been shown to have a negative impact on the clinical course and outcome of COVID-19.1 Immune response evoked by virulence factors of SARS-CoV-2 compromises innate immunity and predisposes patients to bacterial infections by promoting bacterial attachment and further dissemination.2 Severe and critically ill COVID-19 patients requiring intensive care unit (ICU) admission are more vulnerable to develop bacterial infections due to the presence of multiple additional factors like presence of invasive devices and procedures, associated comorbidities, iatrogenic immunosuppression due to steroid therapy etc.3 As the pandemic continues to evolve over time, several clinical attributes of COVID-19 patients between the first and second waves are being compared,4 however we did not come across any Indian published literature comparing the prevalence and spectrum of bacterial pathogens in severe and critically ill COVID-19 patients admitted to ICU between the two successive waves of the pandemic. This study intends to compare the clinical characteristics and the prevalence and spectrum of bacterial pathogens in COVID-19 patients admitted to ICU during the first and second waves at a tertiary care, teaching and referral hospital of eastern India.

Methodology

Study design and settings

Demographic details, clinical profile and bacterial culture results of severe and critically ill COVID-19 patients admitted in ICUs during April-Oct 2020 (1st wave) and April–July 2021 (2nd wave) were retrieved from the case records and analysed retrospectively. During the 1st wave, our institute (a 960 bedded teaching hospital located in an eastern state of India) had a single dedicated COVID ICU facility (20 bedded ICU) and an additional 21 beds was operationalized (total 41 ICU beds) during the 2nd wave of the pandemic to meet the increasing demand. All the suspected patients presenting with severe acute respiratory illness were initially managed in the Emergency units till the confirmatory diagnosis of COVID-19 after rapid antigen testing (RAT) or real time reverse transcriptase PCR (r RT-PCR) (5) and then transferred to COVID-ICU. The patients who tested positive by RAT were not tested again by r RT-PCR.

Microbiological Methods

Samples from COVID-19 patients admitted to ICUs for suspected bacterial infections were collected based on the

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clinical assessment of the treating physician/intensivist. Endotracheal aspirate (ETA)/ tracheostomy secretions were collected from mechanically ventilated patients in sterile tubes based on the standard clinical procedure. Paired blood cultures and urine specimens were collected on clinical suspicion of bacteraemia and urinary tract infections respectively. Blood culture bottles were incubated for five days in the automated blood culture system (BD BACTEC™ Plus Aerobic medium, Becton, Dickinson and Company, Sparks, MD 21152 USA). Endotracheal aspirate/ tracheostomy secretions were inoculated on 5% sheep blood agar and MacConkey agar and urine samples were plated onto Cysteine Lactose Electrolyte Deficient (CLED) agar. Bacterial identification and antimicrobial susceptibility were performed by the Vitek 2 compact system. Colistin susceptibility was determined by the colistin broth disc elution test.

### Data collection and analysis

The demographic and clinical details of COVID-19 patients admitted to ICUs such as comorbidities, main medications, total length of hospital stay and outcome were entered in Microsoft Excel for analysis along with bacterial culture information. The continuous variables were expressed as mean ± SD. The categorical variables were denoted as n (%) and compared by using the Chi-square test. P values of ≤ 0.05 was used to ascertain statistical significance.

### Result

During the first wave, a total of 189 patients were admitted in the 41 bedded ICU facility and during the second wave a total of 346 patients were admitted in the 125 bedded ICU facility. The demographic and clinical details of patients admitted during the 1st and 2nd wave are tabulated in Table 1. The patients admitted during the 2nd wave were comparatively older and the number of patients having comorbidities like diabetes mellitus (DM), hypertension (HTN), ischaemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD) in the 2nd wave was significantly higher than that of the 1st wave (Table 1).

During the 1st wave, of the 189 patients, (45/189, 23.8%) had at least one culture- positive for clinically significant pathogens during hospital stay, whereas during the 2nd wave, this figure was (173/346, 50%). (P value 0.0001).

A total of 251 and 1361 various clinical specimens were received for bacterial culture during the 1st and 2nd wave respectively. The sample wise distribution and positivity rate of various samples is depicted in Table 2. There was no statistically significant difference in the microorganism profile, except in the cases of isolation of Pseudomonas aeruginosa, which was isolated from 37.5% of positive blood cultures in the 1st wave vs 3% in the second wave (P-value 0.0001) (Figure 1).

The distribution of predominant pathogens from various clinical specimens during the first and second waves is depicted in Figure 1. Overall, there was predominance of Gram negative bacilli in both the waves. There was no statistically significant difference in the microorganism profile, except in the cases of isolation of Pseudomonas aeruginosa, which was isolated from 37.5% of positive blood cultures in the 1st wave vs 3% in the second wave (P-value 0.0001) (Figure 1).
observed in 100% of Staphylococcus aureus isolates (6/6) in the first wave and 93.5% (29/31) in the second wave.

**Discussion**

This retrospective chart review of severe and critical COVID-19 patients admitted in ICUs of a tertiary care hospital of Odisha during the first and second wave of the pandemic, revealed that 50% (173/346) of the ICU admitted patients developed bacterial infection during the 2nd wave compared to 23.8% (45/189) in the 1st wave. The percentage positivity of patients developing secondary bacterial infections during the 2nd wave match with the findings of d’Humières et al, in which 44.7% of 197 COVID-19 patients hospitalised in ICU experienced at least one bacterial infection during the first wave of the epidemic in France.7 Similar findings were also described by Zhang et al from China, where 57.89% of severe and critically ill COVID 19 patients developed secondary infections. The number of patients having comorbidities like DM, HTN, IHD and COPD as well as the use of devices and steroid in the 2nd wave was significantly higher than that of the 1st wave and this could have attributed to this finding.

Gram negative bacterial infections were common during both the waves. The predominance of Gram negative bacterial infections in severe and critically ill COVID-19 patients is in accordance with previously described studies. In the study by Zhang et al, 50% of the infections were caused by various GNB, whereas in the study by Shafran et al, 75% of the secondary infections were caused by various GNB. Infections due to various GNB outnumber GPC in Indian ICU settings and COVID-19 patients are also vulnerable to the same nosocomial pathogens. In our study, Acinetobacter baumannii complex and Klebsiella pneumoniae (among Enterobacterales) were the most common isolates being isolated from respiratory tract specimens followed by blood. The isolation of Acinetobacter baumannii complex and Klebsiella pneumoniae from both respiratory tract and blood stream indicates respiratory tract to be the seeding site for bacteraemia. In a recently published Indian study which described the profile of secondary infections in hospitalised COVID-19 patients, Klebsiella pneumoniae and Acinetobacter baumannii complex were the predominant pathogens from the respiratory tract as well as blood cultures. The higher rate of isolation of Pseudomonas aeruginosa in the 1st wave compared to the 2nd wave could not be explained. The high degree of carbapenem resistance (62.4%-87.1%) in Enterobacterales and Acinetobacter baumannii complex also matches other previous Indian studies and necessitates high rates of usage of colistin.

A notable finding of our study was the increased isolation of pathogens intrinsically resistant to colistin including Burkholderia cepacia complex, Elizabethkingia meningoseptica, Chryseobacterium indologenes, Achromobacter spp. For these rarer pathogens, clinical microbiology laboratories face dual challenges of timely identification, susceptibility testing and distinction between contaminants versus true infection. Availability of automated identification systems such as Vitek 2 is crucial for timely identification of these rare pathogens. Both E. meningoseptica and C. indologenes are resistant to the traditional antimicrobials effective against GNB and respond to antimicrobials like vancomycin, rifampicin, colistin in COVID ICU remains very high. Weaver et al. in a previous study commented that selective pressure exerted by colistin use leads to environmental colonisation of moist surfaces of these non-fermenters in ICU settings. This, in turn, leads to a cycle of cross-contamination and infection in susceptible patients.

Although studies characterising the secondary bacterial infections in severe and critically ill COVID-19 patients are published, our study attempted to compare the prevalence and infecting bacterial pathogens between two successive COVID waves in India and also tried to correlate secondary bacterial infections with disease severity and outcome.

The main limitation of the study is its retrospective nature and from a single centre. Though a single centre study, the profile of pathogens including their drug resistance matches other Indian studies. Our results show that multi drug resistant Gram negative bacterial infections, remain a dreaded complication in severe and critically ill hospitalised COVID-19 patients requiring ICU care and high usage of colistin spirals the emergence and spread of pathogens intrinsically resistant to colistin and thus highlights the importance of implementation of rigorous infection control measures.

**Acknowledgement**

We acknowledge the untiring efforts of all faculty of Department of Anesthesia and Critical Care and General Medicine, residents and nursing officers who worked in the COVID ICU and the residents, technical staffs of the Department of Microbiology for enabling this work to completion.
Spontaneous Pneumothorax in Patients of COVID 19 Pneumonia

Yash Kedia1*, NT Awad2, Jairaj Nair3, Dipak Patil1, Pranavi Amin1, Sruthi Vijayan1, Swapnil Thorve4, Siddharth Waghmare4

Abstract

COVID 19 pandemic has put a massive strain on healthcare all over the world. Every day new data is getting released and various complications are being reported in patients of COVID 19 Pneumonia. One such complication is pneumothorax and pneumomediastinum. Both these conditions can lead to an increase in mortality and morbidity in patients with COVID 19 pneumonia. We studied 476 patients of COVID 19 pneumonia at our hospital, out of which 18 (3.78%) had developed pneumothorax and/or pneumomediastinum. While most of these patients were on some form of positive pressure ventilation (invasive/non-invasive), some of them had a HRCT Chest suggestive of either air trapping and/or cyst formation. Three patients had developed bilateral pneumothorax while on non-invasive ventilator. Nine of the 18 patients expired and nine were discharged.

Through this article, we would like to emphasize that an acute deterioration in hypoxemia in a COVID-19 patient could indicate a pneumothorax. Pneumothorax as well as pulmonary thromboembolism are reported complications in COVID-19 and clinician vigilance is required during assessment of patients, as both share the common symptom of breathlessness and therefore can mimic each other.

Introduction

Spontaneous pneumothorax secondary to underlying lung disease can result in worsening of clinical condition of a patient. Even a small pneumothorax in patients with a diseased lung can severely compromise pulmonary functions and cause hemodynamic instability. Prompt recognition and treatment of pneumothorax is necessary to minimize morbidity and mortality.

Pneumothorax is a potentially life-threatening complication in patients with ARDS, especially those on mechanical ventilation. In a study of 84 patients with severe ARDS from 48 intensive care units (ICUs), 48.8% had an evidence of a pneumothorax.1 Many factors may precipitate the occurrence of pneumothorax in ARDS, such as the mechanical ventilation settings, the clinical severity of ARDS.1,2

Besides, pneumothorax is a known complication in patients with cystic lung diseases and emphysema. CT chest in patients with COVID 19 has revealed a variety of pattern like ground glass opacities, air trapping and in later stages cyst formation and fibrosis. Also, the high pressures on ventilators could lead to barotrauma and subsequent pneumothorax and pneumomediastinum.

Here, we studied 476 patients of COVID 19 pneumonia, out of which 17 developed pneumothorax and one developed pneumomediastinum without pneumothorax during the course of their illness. Four patients had both pneumothorax and pneumomediastinum. One patient presented with pneumothorax and was diagnosed as COVID 19 pneumonia later, rest all the patients developed pneumothorax while in the ward.

Our aim is to provide an insight into how this complication can change the clinical outcome of the patients and can affect the mortality and morbidity.

Method

We studied patients who were more than 12 years of age and diagnosed as COVID 19 by RT-PCR (Reverse transcriptase-polymerase chain reaction) or CBNAAT (Cartridge based nucleic acid amplification test) or Rapid antigen test. 476 such cases

References


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Out of the 476 patients studied, 17 COVID 19 pneumonia patients (3.57%) had developed pneumothorax and one patient had pneumomediastinum without pneumothorax. Three patients had bilateral pneumothorax. Four out of 17 (23.52%) had both pneumothorax and pneumomediastinum. All of them had pneumonia on Chest X-ray which can be attributed to COVID 19. Statistical data of these 18 patients is mentioned below.

Demographics: Five (27.77%) of the 18 patients were males. Four (22.22%) patients were less than 30 years of age while a total of 12 (66.66%) patients were less than 50 years of age.

Clinical presentation and diagnosis: Of these 18 patients, 17 had pneumothorax and one had pneumomediastinum without pneumothorax. Four out of 17 (23.52%) had both pneumothorax and pneumomediastinum. Only one patient presented with pneumothorax and was diagnosed as COVID 19 later, while one patient developed pneumothorax after discharge from ICU. Rest all the patients developed pneumothorax during the course of their treatment in the ward. Three patients had bilateral pneumothorax, with two of the three developing both the pneumothoraces within a week of each other and one patient had an interval of 2 weeks between the development of opposite side pneumothorax. Almost all the patients also had clinically diagnosed subcutaneous emphysema. All of these pneumothoraces were diagnosed on chest radiograph. The pneumomediastinum was diagnosed on HRCT Chest. Eight (38.09%) patients developed pneumothorax early in the disease (within 7 days of admission), rest 10 (47.61%) patients developed between day 8 and day 28 of admission.

Positive pressure ventilation: Most of these patients were on some form of positive pressure ventilation either non invasive or invasive. Nine (50.00%) and four (22.22%) were on non-invasive and invasive form of ventilation respectively. Five patients did not require non invasive or mechanical ventilation but had pneumonia on their chest X-rays. All the three patients who developed bilateral pneumothorax were on non-invasive ventilation.

Intervention done: Of the 17 patients with pneumothorax, 15 patients were treated with an intercostal drainage tube. The other two patients had an evidence of pneumothorax on their chest x-ray and had developed rapid hemodynamic instability. Considering tension pneumothorax, needle was inserted in the pleura, but both the patients expired before a chest tube could be inserted. Pneumomediastinum was managed conservatively.

Clinical course and outcome: All except two patients deteriorated initially after the development of pneumothorax (deterioration in the form of increase...
in oxygen requirement). Nine of the 18 patients expired, i.e., 50%. Of the remaining nine who were discharged, five were treated with non-invasive ventilation. Mortality was higher in the more than 50 years age group (Five out of nine). None of the patients who were intubated and were on mechanical ventilator survived. (100% mortality for those on mechanical ventilation with COVID-19 ARDS and pneumothorax).

Discussion

It is a well-known fact now that COVID-19 is a multisystem disorder which most adversely affects the lungs and its most severe form can lead to acute respiratory distress syndrome (ARDS). Many studies have suggested that apart from the viral damage, uncontrolled inflammation also causes damage to the lungs in COVID-19 ARDS. Supporting this hypothesis, elevated levels of C Reactive Protein, ferritin, d-dimer and inflammatory cytokines and chemokines are observed in patients with severe COVID-19.

Secondary spontaneous pneumothorax is the most common type of pneumothorax which occurs in an already diseased lung. Most common causes include COPD, pulmonary tuberculosis, malignancy, sarcoidosis, pneumocystis jirovecii pneumonia, interstitial lung diseases etc. According to a study published in 2015 from GMERS Medical College in Gujarat, the rate of spontaneous pneumothorax in India is around 99.9 per 1,00,000 hospital admissions. Most of them were secondary to COPD and pulmonary tuberculosis. According to another study from Western India from 2014, off the 57 patients of hydropneumothorax, Tuberculosis (TB) was etiology in 80.7% patients, acute bacterial infection in 14%, malignancy in 3.5%, and obstructive airway disease in 1.8%.

Patients with COVID-19 may be at increased risk of developing pneumothorax. Various factors which can contribute to this include lung fibrosis, use of positive pressure ventilation, patients with already diseased lungs like COPD, tuberculosis etc. CT chest findings in a patient with COVID-19 include ground glass opacities evolving into consolidation, air trapping, cystic changes, and in later stages septal thickening and fibrosis. Lung fibrosis causes a decrease in the compliance of the lungs and can cause injury with even slight increase in airway pressures. Similarly, cystic changes are also noted in a COVID lung which can lead to alveolar tear. There are also reports suggestive of development of air trapping and later bulla formation in patients with COVID-19 with subsequently lead to a pneumothorax. According to a multicentre retrospective case series from 2020 based from UK out of 6574 COVID-19 patients, 60 (0.91%) had pneumothorax and 11
had isolated pneumomediastinum as compared to 3.78% COVID 19 patients who developed pneumothorax in our study. In their series, 44% of the patients who had developed pneumothorax were on positive pressure ventilation as compared to 72.22% in our series. However, their case series concluded that the overall 28 days survival was not significantly different in patients with and without pneumothorax. They also observed that survival was lower in patients on invasive ventilation but the difference was not statistically significant.9

Management of pneumothorax with a chest tube proved beneficial in some of our patients as has been described in some studies. Patients who developed tension pneumothorax along with ARDS had a worse outcome.

It has also been described previously that development of a pneumothorax is a grave prognostic sign10 and same can be reflected in our series where 52.94% patients expired despite a chest tube insertion. However, was their death directly related to development of pneumothorax cannot be established due to multiple factors in patients of ARDS. But our study does show that pneumothorax can result in increased mortality and morbidity in patients with already diseased lungs. Especially in patients with COVID 19 ARDS and fibrosed lungs who are on positive pressure ventilation can have persistent air leak for a long duration. Two patients who died acutely before the tube could be inserted had signs suggestive of a tension pneumothorax in the form of sudden drop in blood pressure, saturation and increase in peak inspiratory pressure on the ventilator and aspiration of air by a needle failed to save them.

Conclusion

Through this study we would like to emphasize that development of a pneumothorax in a COVID 19 patient can be a fatal sign and early diagnosis and treatment with a chest tube may be beneficial for such a patient. In patients of COVID 19 pneumonia with acute deterioration of breathlessness and hypoxemia, apart from pulmonary thromboembolism, a differential diagnosis of pneumothorax should always be kept in mind and prompt intervention with an intercostal drainage tube can improve the prognosis in such patients.

References

In Management of Asthma and COPD Patients

Consider

Esiflo
Salmeterol and Fluticasone Propionate

The Synonym of Trust

COPD - Chronic Obstructive Pulmonary Disease

Abridged prescribing information: Dosage form: Esiflo inhaler is available in 125 & 250 Transhaler (Metered Dose Inhaler) and 100, 250 & 500 Transcap (Dry Powder Inhaler). Indications and usage: Esiflo inhaler is indicated for the regular treatment of asthma, where use of combination (long-acting beta-2 agonist and inhaled corticosteroid) has been found to be appropriate and in patients with severe COPD. Dosage and administration: Dosage is individualised according to disease severity. Asthma: Adult and adolescents (12 years and older) - Esiflo 125/500 transhaler 2 inhalations twice daily or Esiflo 250/500 transcap 1 inhalation twice daily, Children (4 yrs and above) - Esiflo 50 Inhaler 2 inhalations twice daily or Esiflo 100 transcap 1 inhalation twice daily (not recommended for children below 4 years of age), COPD: Esiflo 125/500 transhaler 2 inhalations twice daily or Esiflo 250/500 transcap 1 inhalation twice daily. Contraindications: Patients with a history of hypersensitivity to any component of the drug product. Warnings and precautions: Not to be used to treat acute asthma symptoms. Esiflo inhaler should be administered with caution in patients with pulmonary tuberculosis, severe cardiovascular diseases, diabetes mellitus, uncontrolled hypertension or thyrotoxicosis. Pregnancy: Should only be considered if the expected benefit to the expectant mother is greater than any possible risk to the foetus. Lactation: Should only be considered if the expected benefit to the nursing mother is greater than any possible risk to the infant. Adverse effects: Tachycardia, nasal congestion/foamage, dryness of mouth, weight gain. Full prescribing information is available on request.
The Epidemiology of Intensive Care Unit Readmissions and Proposed Discharge Protocol for a Tertiary Care Hospital

Vijoy Kumar Jha1, Anand Shankar K2, Bhaskar Das3, Rajiv Nair4, MS Sridhar5, Sudarshan Naik6, Gursharan Gill6

Abstract

Background: Intensive Care Unit (ICU) readmissions during the same hospitalization are associated with increased hospital stays, morbidity and mortality. Whereas mortality rates in patients admitted to the ICU for the first time may range from 10 to 20% depending on various factors, readmission mortality rates can be up to 50 to 70%. Factors leading to readmission in ICU in Indian Armed Forces Hospitals have not been well studied till date.

Methods: This was a record based cross sectional descriptive study conducted at the ICU of a tertiary care Armed Forces hospital. Demographic and clinical data of ICU patients were analysed. ICU admission and discharge data for the duration of last three years were acquired from admission and discharge registers and Hospital Informatics system (HIS) software. The primary outcome was readmission rates to ICU during the same hospitalization. Secondary outcomes included diagnosis at time of index admission (first time admission) to ICU and at readmission, multiple readmissions to ICU and mortality rates in readmitted patients.

Results: There were 3021 admissions to the ICU during the study period. 422 patients succumbed to illness during initial admission resulting in a mortality rate of 14%. 198 patients were readmitted to the ICU. The readmission rate to the ICU was 7.8%. The mortality rate in readmitted patients was 31% as compared to the ICU mortality rate of 14%. The triggering factors for readmission were usually respiratory or cardiac decompensations.

Conclusion: Readmission to ICU occurred in about 7.8% of all ICU patients in our study. ICU readmissions increase the risk of adverse outcomes. Objective measures in the form of a discharge protocol incorporating the stability and work index for transfer (SWIFT Score) may help minimizing readmission to ICU. Such protocols must be in place while shifting any patients from ICU so as to improve outcomes in patients of tertiary care hospitals.

Introduction

Readmissions to the ICU are a major concern in the health care industry as they not only increase the cost of medical care but also increase the morbidity and mortality of affected patients. Readmissions to ICU have been defined with diverse time frames in different studies1,2 and simplistically can be defined as “admission to the ICU after discharge from the ICU during the same period of hospitalization”. Though a myriad of factors can result in ICU readmissions, it must be understood that to a certain extent readmissions to the ICU actually reflect on the quality of health care delivered.3 It has indeed been used as a quality indicator in certain settings.

The study of ICU readmissions has generated sufficient interest in the health care industry to prompt studies of factors that lead to increased readmissions. There are numerous studies and meta-analyses that have delved deep into the subject and come out with constructive methods of decreasing ICU readmissions in order to improve standards of health care.

Very few studies have been conducted highlighting this aspect of intensive care in India and this facet has not been addressed adequately in any study from the Armed Forces. This however is a very important issue that is routinely encountered by ICU’s in tertiary care hospitals of the Armed Forces. ICU readmission rates could be useful for policy makers and investigations into causes and consequences of readmissions help improving the prevailing understanding on the subject.3

We chose to study readmissions to the ICU in our tertiary care hospital to understand the various factors that may contribute to it. We also have attempted to make a discharge protocol specifically for ICU discharge/transfer to acute wards in our ICU setting, which may nonetheless be helpful in the other Armed Forces tertiary care hospitals also.

Material and Methods

A record based cross sectional descriptive study was conducted at the ICU of a tertiary care Armed Forces hospital from data of ICU admissions between the period of May 2016 to April 2019.

Inclusion criterion was to include all patients above the age of 18 years admitted to the ICU. Patient details related to index admission and readmission were collected and it included demographics, clinical, laboratory and imaging studies. Data was retrieved from the hospital informatics system (HIS) software and

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admission and discharge register of the ICU. Primary outcome of the study was to calculate the ICU readmission rate. Secondary outcomes included studying multiple ICU admissions, mortality rate of ICU admissions and readmissions and diagnosis at index admission and at readmission to ICU.

Data was analyzed using MS Excel 2003. Descriptive statistics was used to describe the relationship between variables.

Results

A total of 3030 patients were admitted to the ICU between May 2016 and Apr 2019. Nine patients were excluded from the study as they were less than 18 years of age. After exclusion a total of 3021 ICU admissions were analyzed for further study (Figure 1).

The bed occupancy of the ICU was 87.62% and the average length of stay in the ICU was 4.28 days. Demographic analysis of the studied population showed that 76.20% of patients were either serving personnel or their families and 23.80% of patients were ex-servicemen and their families (Table 1).

Of the total of 3021 admissions, 422 patients succumbed to illness during initial admission resulting in a mortality rate of 14% (Figure 2). The patients discharged from the ICU numbered 2538, amounting to approximately 84% of the admitted population. Sixty one patients (2%) were discharged home directly from ICU. These discharged patients to home were also excluded from the study. Those patients advised and planned for palliative care after initial admission were included for calculating readmission and mortality. However, as per hospital protocol patients needing palliative care were not readmitted in ICU (Figure 1).

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>No. of patients (n)</th>
<th>% of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18-30</td>
<td>211</td>
<td>6.98</td>
</tr>
<tr>
<td>40-59</td>
<td>818</td>
<td>27.07</td>
</tr>
<tr>
<td>60-69</td>
<td>932</td>
<td>30.85</td>
</tr>
<tr>
<td>&gt;70</td>
<td>1060</td>
<td>35.08</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1780</td>
<td>58.92</td>
</tr>
<tr>
<td>Female</td>
<td>1241</td>
<td>41.07</td>
</tr>
<tr>
<td>Occupation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serving personnel and families</td>
<td>2302</td>
<td>76.20</td>
</tr>
<tr>
<td>Ex servicemen and families</td>
<td>719</td>
<td>23.80</td>
</tr>
<tr>
<td>Source of ICU admission</td>
<td></td>
<td></td>
</tr>
<tr>
<td>A&amp;E</td>
<td>1803</td>
<td>59.68</td>
</tr>
<tr>
<td>Wards</td>
<td>248</td>
<td>8.20</td>
</tr>
<tr>
<td>Operation theatre</td>
<td>758</td>
<td>25.09</td>
</tr>
<tr>
<td>Other hospitals</td>
<td>212</td>
<td>7.01</td>
</tr>
</tbody>
</table>

A&E : Accident and Emergency
There were a total of 198 readmissions during a period of three years. The total readmission rate was 7.8% (198/2538 admissions). There were 108 readmissions within 48h of discharge from the ICU at a rate of 4.25% (108/2538 admissions). Forty-eight readmissions or 1.89% (48/2538 admissions) of readmission occurred between 48h and 120h. Forty-two readmissions occurred after 120h at a rate of 1.65% (42/2538 admissions) (Figure 3). Day wise ICU readmission data analysis depicted maximum readmissions on day 1 after discharge from ICU (Figure 4).

The diagnosis at index admission and readmission tended to be same in most readmissions. The causes for readmission however could be attributed to mainly cardiovascular or respiratory deterioration (Table 2). Worsening of sepsis or deteriorating neurological status also contributed to readmissions.

Mortality rate of readmitted patients was 31% (61/198 readmitted patients) (Figure 2). Readmitted patients discharged to ward/home amounted to about 69% (137/198 readmitted patients). A uniform discharge protocol was not available in most cases and hence the circumstances under which patients were discharged from ICU and their clinical condition at time of discharge could not be analyzed. A nursing handover checklist was however filled with each discharge from the ICU and available. In general patients were discharged from ICU on ascertaining clinical stability; however data to supporting the same was not available for all of the 3021 cases and hence has not been provided.

There were 12 multiple admissions at the rate of 0.47% (12/2538 of all admissions) and 6.06% (of all readmissions). Ten of the 12 patients were above the age of 60y and had multiple co-morbidities (Table 3). Eight patients expired, two were discharged to ward and two were lost to follow up after being discharged from the hospital directly from the ICU. Mortality rate of multiple readmission patients was 66% (8/12 of multiple admissions) (Figure 2).

Discussion

The need for critical care beds continues to rise and the availability of improved quality of critical care raises the expectations of patients and relatives, thus creating increased stress on the critical care team and the available resources. In view of the escalating cost of medical care in the ICU setting and the increasing mortality and morbidity with each readmission to the ICU, this subject must be dealt with utmost seriousness.4,5

Readmission to ICU has been defined as an admission to the ICU after discharge from the ICU during the same period of hospitalization.1,3,4 Each readmission to the ICU increases the mortality more than two times as seen in our study. Whereas the mortality of index admissions were around 14%, the same reached to 31% in readmitted patients and 66% in patients with multiple admissions. In this study we also touch upon the entity of multiple admissions which is defined as more than two admissions to the ICU during the same period of hospitalization. The aspect of multiple ICU admissions has not been adequately addressed in most studies done so far.

The time to readmission to the ICU has been defined differently in various studies. While there are studies that have defined a time of less than 48h,6 there are others that describe the same in terms of less than 120h.7 The Indian society of critical care medicine (ISCCM) in its guidelines for ICUs in India defines readmission to the ICU as any admission to ICU after discharge from ICU within 24h.8

In our setting we observed that out of the 198 readmitted patients maximum readmissions occurred on the first two days after discharge from ICU. We had 17 readmissions on the same day as discharge, 56 on day one and 35 on day two. This amounted to about 54% of all readmitted patients. The study by Brown et al1 showed that 20% of all readmitted patients got readmitted within 24 hours of ICU discharge. Amongst the readmitted patients in our study 90% were admitted by day 10 and the last patient was admitted on day 42.

In various studies, readmissions have been used to analyze quality of ICU care.9 ICU readmissions may be categorized as early (<48h) and late readmissions (>120h). Early readmissions accounts for more than 50% of all readmissions and may reflect on the quality of ICU care. It is presumed that early readmissions may possibly be related to the events that may have happened during the ICU stay of the patients and also on prevalent ICU practices.1 On the other hand late readmissions may not be related to ICU practices and may be due to the occurrence of a new or unrelated event.

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**Table 2: Medical Diagnosis at index admission and readmission of study population**

<table>
<thead>
<tr>
<th>Medical Diagnosis (Related to system)</th>
<th>Index admission % (of all admissions - n= 3021)</th>
<th>Readmission % (of all readmissions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular system</td>
<td>6</td>
<td>30</td>
</tr>
<tr>
<td>Respiratory system</td>
<td>24</td>
<td>39</td>
</tr>
<tr>
<td>Neurology</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Nephrology</td>
<td>8</td>
<td>6</td>
</tr>
<tr>
<td>Gastroenterology</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Sepsis</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Haematology</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

**Table 3: Diagnosis of patients with multiple admissions to ICU**

<table>
<thead>
<tr>
<th>Age in years</th>
<th>Gender</th>
<th>Diagnosis</th>
<th>Number of ICU Outcome readmissions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Expired</td>
</tr>
<tr>
<td>59</td>
<td>M</td>
<td>Bronchopleural fistula</td>
<td>4</td>
</tr>
<tr>
<td>76</td>
<td>M</td>
<td>Type 2 DM; HTN; CKD; IHD</td>
<td>3</td>
</tr>
<tr>
<td>72</td>
<td>M</td>
<td>Acute limb ischemia in right lower limb</td>
<td>3</td>
</tr>
<tr>
<td>81</td>
<td>M</td>
<td>Type 2 DM, CAD, HTN, SDH, Sepsis</td>
<td>3</td>
</tr>
<tr>
<td>57</td>
<td>M</td>
<td>Type 2 DM; CKD, HTN</td>
<td>3</td>
</tr>
<tr>
<td>69</td>
<td>F</td>
<td>CVA</td>
<td>3</td>
</tr>
<tr>
<td>71</td>
<td>F</td>
<td>Acute Pancreatitis</td>
<td>3</td>
</tr>
<tr>
<td>70</td>
<td>F</td>
<td>CVA</td>
<td>3</td>
</tr>
<tr>
<td>65</td>
<td>M</td>
<td>Necrotising fascitis right lower limb</td>
<td>3</td>
</tr>
<tr>
<td>28</td>
<td>F</td>
<td>Multicentric catelman’s disease with respiratory failure</td>
<td>3</td>
</tr>
<tr>
<td>60</td>
<td>F</td>
<td>RTA with traumatic paraplegia</td>
<td>3</td>
</tr>
<tr>
<td>70</td>
<td>F</td>
<td>Type 2 DM, CKD</td>
<td>3</td>
</tr>
</tbody>
</table>

DM: Diabetes Mellitus; HTN: Hypertension; CKD: Chronic Kidney Disease; CAD: Coronary Artery Disease; SDH: Subdural Haemorrhage; CVA: Cerebrovascular Accident; RTA: Road Traffic Accident
problem in the readmitted patient. Early discharges due to ICU capacity constrains could lead to various adverse events including increased mortality.

The wide variation in readmission rate suggests that there is a need for standardization and improvement in the process of ICU discharge. ICU practices that may contribute to ICU readmissions have been described by a study conducted by Sluisveld et al. The salient features that affect readmissions include ICU discharge policy, step down ward facilities, handing over protocols including written and verbal handovers, medication reconciliation, monitoring facilities and availability of consulting critical care nurses.

Handover protocols have a great impact on quality of critical care patient management. Improved communication between the involved teams, presence of a liaison nurse for communication and coordination of care plays an important role. An appropriate form to facilitate accurate handover of information has also been considered an effective intervention which results in better patient care with improved continuity of care. All above factors were seen to reduce adverse events. However their effect on mortality was not statistically significant.

Risk factors for ICU readmission include afternoon and evening discharges, variations if any in staffing patterns, discharge protocols, quality of handovers, unscheduled discharges from ICU due to bed scarcity and improper or subjective assessment of patients prior to discharge. Increased readmissions could suggest the occurrence of preventable adverse events, but it may be necessary to discharge certain patients early from the ICU and more needy patients may even benefit from it.

ICU readmission rates have been stratified as high (7% to 8% or more), medium or acceptable (4 to 7%) and low (less than 2% to 5%) rates. A high readmission rate indicates that the reasons for readmission are possibly preventable in nature and that discharge from the ICU may have been hasty, or that the wards receiving such patients do not have the requisite and appropriate infrastructure, manpower and training to handle such a patient. In our study we noted that early readmissions accounted for 4.25 % of all patients discharged and 54.5% of all readmissions. A total overall readmission rate of 7.8% was observed.

Rarely circumstances may arise where in step down in the level of care in peripheral wards prompts relatives to insist on transferring back of the patient to the ICU and thus results in readmission to the ICU. This may especially occur in a set up where the patients do not need to pay for ICU care, such as in service hospitals.

A low ICU readmission rate may indicate a conservative approach by the ICU team, who may hold on to patients in the ICU for longer than actually mandated by the patients' general condition. This exposes patients to unnecessary risk of infections and other ICU related adverse events. This also results in denial of ICU care to other needy patients and escalates cost of medical care. It should also be kept in mind that low readmission rate could be attributable to higher than expected mortality or early hospital discharge and therefore any use of ICU readmission as a quality metrics should be accompanied by mortality and hospital length duration. The average length of stay in the ICU was 4.28 days in our study.

Patients who get readmitted to ICU have varying diagnoses and the diagnosis at readmission may be different from the diagnosis at initial admission (index admission). In the study by Brown et al 60% patient retained the index diagnosis while 40% came in with fresh diagnosis.

In our setting usually the index diagnosis was seen to be retained throughout period of admission to the hospital and invariably remained unaltered at time of readmission. It is due to the continuation of the same diagnosis till discharge of the particular patient in Hospital information system (HIS).

The causes of readmission to ICU were however varied and different at the time of readmission. It was seen that the causes for readmissions due to medical reasons tended to be more in number as compared to surgical causes. This means to say that even surgical cases got readmitted with predominantly medical causes. While 30% of all readmitted patients came due to cardiovascular decompensation, 39% patients got readmitted due to desaturation and respiratory compromise in our study.

Multiple readmissions to ICU resulted in the highest mortality of 66% as observed in our studies. Most of these patients were of the elderly age group and suffered from multisystemic diseases. All patients in this subset of patients invariably were readmitted due to deterioration of their primary illness. Despite the fact that they were discharged from ICU the families of these patients had been counseled and prognosticated. In another study, when a recurrent event analysis was used adjusting patient factors it was seen that multiple admissions per se was not associated with increased mortality. However patient factors like age, illness and its severity, limitations to medical treatment were significantly associated with mortality.

The question that arises is what possibly can be done to minimize readmissions and multiple admissions so as to improve medical care given to our critically ill patients. Our study endeavors to discuss this important point. To minimize preventable readmissions to the ICU, robust protocols for discharge from ICU must be in place. Predicting readmission to ICU has always been evasive and no scoring system has been able to determine successfully and with certainty which patient is likely to get readmitted to ICU.

The modified early warning score (MEWS) score which was based on systemic assessment of cardiovascular, respiratory, renal, neurological systems and body temperature could not reliably predict ICU readmissions. The sequential organ failure assessment (SOFA) score, stability and workload index for transfer score (SWIFT score) and the therapeutic intervention scoring system (TISS-28) were compared and showed similar predictive accuracy in predicting ICU readmissions.

The SWIFT score was developed by Gajic O et al to predict unplanned readmission to ICU. The components of the score include the source of ICU admission i.e. from where the patient was admitted, the total length of stay in the ICU, the last measured PaO2/FiO2 ratio (partial pressure of arterial oxygen/ fraction of inspired oxygen ratio), Glasgow coma score at time of ICU discharge and the PaCO2 (partial
pressure of carbon dioxide in arterial blood) levels at time of ICU discharge (Table 4). Each of these components has a numerical value adding up to the total score of 64. This score has been validated by various researchers and a score of more than 15 was associated with significantly higher readmission rates to the ICU.18-20

As the present study is record based cross sectional study, no scoring system was practised before discharge. As objective as they may seem, no scoring system has provided a universal solution. While scoring systems bring about objectivity, they are far from being accurate. Thus to solve the problems of unplanned readmissions, just relying on scoring systems is inadequate. Discharge from the ICU should be a mix of scoring systems and clinical evaluation.

We suggest a discharge protocol which may be useful in service hospitals.

a. Ensure that the patient has recovered from primary illness or is on an improving trend.

b. Calculate the SWIFT Score and aim for a score below 15/64.

c. Make sure the patient is haemodynamic stable with a mean arterial blood pressure of more than 65mmHg without inotropes or vasopressors for at least 24h.

d. Ventilatory requirements:
   - The patient should be at least 24h post extubation
   - PaO2/FiO2 > 300 (Part of SWIFT score and SOFA score)

e. Decrease in SOFA scores by 2 points

f. There should be no obvious signs of infection
   - Procalcitonin< 2ng/ml (preferably <0.5ng/ml)
   - Stabilizing Total Leukocyte Count trend
   - Absence of fever

Focus on a good handover practice between ICU and the ward nurses and maintain good communication and documentation.

Problems in ICU setting of our hospital are unique. Shortage of manpower, shift system of staff duties in different wards, inadequate facilities in step down wards or absence of a step down ward and lack of appropriate laid down criteria for ICU admissions may be some of them. Wide ranges of clientele and shifting of sick patients from peripheral hospitals also pose the risk of acute shortage of ICU beds. There should also be facility for triage before admissions to the ICU and there is a requirement of extended stay recovery room or intermediate care areas for chronically ill acute patients.

Limitations of the study have resulted from data availability. Data extracted from the HIS was of a basic nature. Case records of all patients were not readily available. Only documents of fatal cases were available where as documents of patients discharged from hospital were not available. Ethical committee clearance was waived as of the study was of a retrospective and observational nature.

Conclusion

Readmission to ICU is a very serious matter and is associated with increased morbidity and mortality. Measures to decrease rates of admissions such as discharge protocols incorporating the SWIFT and SOFA scores must be in place to ensure good quality medical care. It however must be understood that despite all such measures, readmissions to the ICU may occurs and they are associated with higher mortality rates.

References


The Long and Short of Summative Assessment in Competency Based Medical Education: Time to Raise the Bar?

Sarabmeet Singh Lehl¹, Monica Gupta²*, Shyamala Handattu Hande², Manjunatha Handattu Hande³

Abstract

Background: The Competency-based medical education (CBME) has been introduced for MBBS programme in India from 2019. Reorganization of the assessment system is required to meet the challenges imposed by this new framework.

Objectives: An evaluation of the university summative assessments held prior to the introduction of CBME-based curriculum was carried out to analyze the pattern, relevance and distribution of questions.

Methods: Five sets of annual and supplementary summative examination papers from three universities, State (SU), Private (PU) and Medical (MU) were evaluated. The analysis included format i.e. Structured and Modified Essay questions, Short notes, other formats; marks distribution; terminology-based level of cognitive domain; subject-based relevance and topic-based distribution of questions.

Results: A total of 352 questions were analyzed. The maximum number of questions were from the state university (140, 39.7%). The contribution of short notes in the theory papers was 65.8% (PU), 87.1% (SU) and 88.9% (MU). Only the PU had Modified-Essay Questions (10.5%) and Modified short notes (4.7%). Terminology addressing higher cognitive domains was low as the questions assessed mainly the knowledge level (80-96.8%), comprehension 3.1%-6.4%. Only the PU had problem solving questions comprising 11.7% of total questions. Majority of questions had moderate or high relevance and only 2.1%-8.2% were of low-relevance. Inter-university differences in the topics were observed for dermatology, psychiatry, and infections.

Conclusions: The present evaluation of high-stakes assessment in three universities indicates minor differences in the format of questions. Questions were predominantly in the form of short notes, structured essays and modified essays were a rarity; few questions targeted higher cognitive levels although majority had high-moderate relevance.

Introduction

The implementation of the competency based medical education programme brings in a major change for the medical curriculum in India. It revolves around the concept of an Indian Medical Graduate (IMG), a globally aware physician of first contact. The desired subject based competencies have been elaborated in the National Medical Commission (NMC) documents and include horizontal alignment, vertical integration, a foundation course, an Attitudes, Ethics and Communication module, as well as introduction to concepts of early clinical exposure, learner-doctor training, electives and self-directed learning.¹,² This transformation will be achieved only if rapid innovations in teaching and assessment methods are undertaken, in the now popular terminology, at “warp” speed.

Capturing the essential attributes of a concept like medical competence is difficult, as it consists of multiple components. It requires the assembly and deployment of multiple assessment instruments, marshaling inputs from cognitive, psychomotor and affective channels and combining it in some manner to help the assessor and the university issue a marks-based judgment on students’ competence.³

The summative high-stakes university assessment is the stepping stone towards graduation and traditionally has a combination of a written and practical or clinical examination in each subject. The written or “theory” assessment is a mixture of essay-type and short answer questions. While there is a growing undercurrent of teachers and assessors who consider this format to be archaic and advocate for newer methods of assessment of subject domain-specific knowledge, it remains an easy tool fiercely protected and implemented by the majority. The evidence, however, indicates that the validity and ability to test higher cognitive functioning during summative assessment is not superior for constructed response or open ended essay type questions, as compared to the multiple-choice selected response or closed ended questions.⁴

The present educational research was conducted with the aim of evaluating the theory questions of MBBS university examinations in the subject of General Medicine in its present form by a review of papers from three settings:

1. State University (SU): A university having diverse courses and programmes in arts, sciences and includes on-site or affiliated medical colleges and is under the State or Central Government.

2. Private University (PU): privately

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owned and self-financed university having diverse programmes including medical professional courses.

3. Medical University (MU): A university that only includes medical and allied disciplines.

**Objectives**

The objectives of the evaluation of the theory papers were to identify:

1. The pattern of questions being set i.e. Essay type, or its many variations, Short Answer or other forms of questions.
2. The utilization of taxonomy enumerated in the NMC guidelines (including terms in Bloom’s taxonomy).³
3. The cognitive level (based on Bloom’s Taxonomy) addressed by the questions and their relevance (explained vide infra).
4. The topic or disease based distribution of questions.

The information derived from this exercise would answer the fundamental question on the current state of undergraduate medical assessment and help design future assessment to achieve the desired NMC goals for an IMG.

**Material and Methods**

The study was cleared by the Institutional Ethics Committee. There were no ethical concerns, and the authors were advised to maintain anonymity of the universities. In this descriptive study, the final examination question papers from the period 2009-2017 in the subject of General Medicine (MBBS course) from three universities (as highlighted above) were accessed by SH from the library and website of the universities. SH randomly selected 5 sets of question papers (Annual i.e. the final end of course university examination and the supplementary examination) for each university. These questions were tabulated in an Excel worksheet by the data entry operator not associated with the study, re-checked for correctness by SH and one set each was provided to SSL, MG and MH for independent analysis. The instructions for them were to analyze:

**Pattern of the question:**

Unstructured or open ended Essay type, (OE-EQ) where a student has a free response within the subject based topic e.g. Discuss Heart Failure; Structured Essay question (SEQ) in which the framing of the question includes specific sub-heads for the answer to be written e.g. Describe the etiology, pathophysiology and management of heart failure; Modified essay type (MEQ) where a short history or case vignette is provided and questions are framed to identify the problem-solving or analyzing skills of the student e.g. A 65 year old diabetic presents with breathlessness and orthopnea of 2 weeks duration, Enumerate three common clinical disorders producing this presentation at this age, Shortlist 5 investigations to differentiate the possibilities considered by you, Write the treatment for one of the diagnostic possibilities considered by you; or Short note (SN) e.g. Write a note on Enteric fever.

The use of action verbs as per Bloom’s taxonomy: Specifically those listed in the NMC document i.e. Competency Based Undergraduate Curriculum for the Indian Medical Graduate under knowledge component: enumerate, list, describe, discuss, differentiate, define, classify, choose, elicit etc.¹

The questions were then classified by SSL and MG independently for the following:

**Modified Bloom’s Hierarchy of Cognitive domain:** This was done in a manner similar to that used in a previous study.² The Levels were graded as Level I: Knowledge and Recall; Level II: Comprehension, Application, Analysis; and Level III: Synthesis and Evaluation.

**Relevance of the question:** The relevance was rated as High, Moderate and Low subjectively by using the following criteria:

Is the topic common and important from the community point of view?

Is it a key topic or is a typical disorder in a system e.g. “Rheumatic heart disease” is clinically important but “Tumors of the heart” is not.

Is the topic a part of the national programmes?

The discordance in rating between MG and SSL for Level of Cognition was identified. The data was moderated by MH and finally agreed upon by a consensus among the three faculty members (SSL, MG, and MH). The topic or disease based distribution of the questions within the subject of General Medicine (including allied subjects of Dermatology and Psychiatry which are included in General Medicine at undergraduate level) was analyzed by MG and reviewed by SSL and MH. The data was then analyzed by SH for identifying inconsistencies and seeking clarifications from MG, SSL and MH. Finally all authors reached a consensus for presentation of the final results.

**Results**

Five sets of MBBS question papers (Annual and Supplementary) in General Medicine from three different universities: State (SU), Private (PU), and Medical (MU) were analyzed.

**The number and structure of questions (Table 1)**

A total of 352 questions were analyzed with the maximum items (questions) being from the SU followed by the MU and PU, respectively. The majority of questions were short notes with a higher percentage from the MU and SU as compared to the PU. Structured Essay questions ranged from 10.2% to 17.6% across the universities. Only the PU had Modified Essay Questions and Modified short notes

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**Table 1: The number and structure of questions in three Universities over 5 years**

<table>
<thead>
<tr>
<th>University</th>
<th>State (SU)</th>
<th>Private (PU)</th>
<th>Medical (MU)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total questions</td>
<td>140 (39.7)</td>
<td>85 (24.1)</td>
<td>127 (36.07)</td>
<td>352</td>
</tr>
<tr>
<td>Structure of questions</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Essay</td>
<td>-</td>
<td>1 (1.1)</td>
<td>1 (0.78)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>SEQ</td>
<td>18 (12.9)</td>
<td>15 (17.6)</td>
<td>13 (10.2)</td>
<td>46 (13.1)</td>
</tr>
<tr>
<td>MEQ</td>
<td>-</td>
<td>9 (10.5)</td>
<td>-</td>
<td>9 (2.6)</td>
</tr>
<tr>
<td>Short Note</td>
<td>122 (87.1)</td>
<td>56 (65.8)</td>
<td>113 (88.9)</td>
<td>291 (82.7)</td>
</tr>
<tr>
<td>Modified Short Note</td>
<td>-</td>
<td>4 (4.7)</td>
<td>-</td>
<td>4 (1.1)</td>
</tr>
</tbody>
</table>

**Table 2: The distribution of marks among essay type questions and short notes**

<table>
<thead>
<tr>
<th>University</th>
<th>State</th>
<th>Private</th>
<th>Medical</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total marks</td>
<td>597</td>
<td>526</td>
<td>600</td>
<td></td>
</tr>
<tr>
<td>Essay Questions</td>
<td>182 (30.4)</td>
<td>266 (50.6)</td>
<td>140 (23.3)</td>
<td></td>
</tr>
<tr>
<td>Short Note</td>
<td>415 (69.5)</td>
<td>260 (49.4)</td>
<td>460 (76.7)</td>
<td></td>
</tr>
<tr>
<td>Percentages in parentheses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The distribution of marks among Essay Questions and Short notes (Table 2)

The distribution of marks in the PU was evenly distributed between the Essay type and Short notes while in the SU and MU, the proportion of marks was higher for short notes.

Action verbs and terms used in framing the questions as per Bloom's Taxonomy and the NMC document

The most frequently term used in all the three sets was write (n=246), and this word in general usage without further qualification does not indicate more than just performing the act of answering the question. Similarly, the word answer was used 15 times also does not specify any more directions for the examinee. The other terms in descending order of frequency included discuss (n=45), describe (n=28), mention (n=9), name, enumerate or list (n=7), define (n=6), differentiate (n=5), explain (n=2), reason (n=2), confirm, outline, classify (n=1 each).

Analysis of Level of Cognitive Domain addressed by the questions and relevance (Table 3)

The level of the cognitive domain addressed was mainly knowledge in 80-96.8% across the universities. The relevance of the questions was of high or moderately high level in all the universities. There were only few questions which were considered to be of low relevance.

The topic or disease based distribution of questions (Figure 2)

The SU and PU had the maximum proportion of questions from Infectious diseases (20% and 17.6%), while the Medical University had a high percentage of questions from Dermatology (12.5%) and Psychiatry (14.1%). Other than this, the chart shows that the trend of questions in descending order were from neurology, cardiology, gastroenterology, pulmonary medicine, rheumatology, hematology, nephrology, emergency medicine, metabolic disorders, hepatology and other topics. There were very few or no questions from oncology, nutrition, genetics, geriatrics and environmental diseases.

Discussion

The universal appeal, ease of creation and acceptance among examiners of open-ended, structured essay type questions (OE-EQ, SEQ) and short answer questions (SAQ) or short notes (SN) makes them the mainstay of the exit-level summative university examination. The alternative solution is the multiple choice question (MCQ), which when appropriately constructed, has broader coverage, reliability and automated computerized marking but suffers from technical flaws in writing and therefore, is difficult to frame. However, the cautious introduction of this MCQ format to the extent of up to 20% in the NMC guidelines still provides a wide sphere for OE-EQ, SEQ and SAQ / SN in university
In a competency-based system, the end-of-course assessment with reliable and valid written tests intending to capture clinical problem-solving abilities supports the use of Modified Essay Questions over other formats. An analysis of 139 stages of MEQ and 50 MCQ administered to undergraduate medical students from 3 examinations over 2 years indicated that while over 50% MCQ’s focused on recall of knowledge, a major proportion of MEQ also focused on lower level cognitive skill and did little more than measure recall and listing of facts. The authors of the present study reported a low representation of this form of questions (10.5% MEQ, 4.7% Modified Short Notes) and that too only from a Private University. Similarly, all three universities had 80-96% questions at the cognitive level of knowledge and recall.

Exploration of the cognitive skills and abstract thinking of undergraduate medical students through an evaluation of 50 MCQ and 50 MEQ at final and mid-term levels in Medicine indicated that 60% MCQ’s and 40.4% MEQ attained problem solving as well as use of knowledge and understanding in new circumstances while 39.4% MEQ’s and 28% MCQ’s assessed only knowledge and recall of information. Formatting errors were observed in 12% MCQ’s and 16% MEQ’s. The authors also concluded that well constructed MCQ’s were superior to MEQ in testing higher cognitive skills in a problem based learning set-up. The trends in topic based questions (MCQ and MEQ) were highest for Cardiology followed by Surgery, Gastroenterology, Hematology, and Infectious diseases, Nephrology, Rheumatology, Pulmonary medicine, Infectious diseases, Nephrology, Gastroenterology, Hematology, and Endocrinology.

Using Bloom’s taxonomy, to identify the cognitive level of essay questions in an undergraduate medical programme, it was observed that the predominant questions targeted lower order thinking skills in most disciplines, with an increase in middle order thinking skills and a decline in questions requiring higher order thinking skills as the analysis progressed from the pre-clinical to clinical part of the course. The present study in General Medicine, also indicated paucity of terms related to higher order of cognition in the question papers.

A significant variability in marking of essay type questions, as well as reliability of assessment of students’ answers to these questions was borne out in an analysis of three consecutive final undergraduate examinations in surgery wherein coinciding marks were observed in 46.3% occasions with a kappa index of agreement between markers of 0.385 and overall reliability by Cronbach’s alpha 0.672. The assessment system needs minimal variability in assessment between markers to increase reliability. While assessors favor the essay type question format as it has provided a comfort zone for years, medical students seem to prefer the MCQ type of examination at pre-clinical and clinical stages and in-course modes for assessment included written tests, projects, portfolios and take-home examinations.

The assessment of clinical competence requires problem solving ability, an entity that is difficult to measure, quantify and the use of patient management problems format appears to be a tool towards meeting this goal. Comparison of MEQ with MCQ at an institute with wide experience in their use at the final examination and correlation of scores with National Board Examiners rating of clinical performance in third year clerkships and four global areas of postgraduate competence indicated that MCQ grades in internal medicine had the highest correlation with NBME scores and postgraduates rating of medical knowledge while performance on MEQ in family medicine had lowest correlations. However, the Family Medicine scores had highest and consistent correlations with overall third year clinical performance and post graduate performance in diverse areas like data-gathering skills, clinical judgement and professional attitudes resurrecting the place of the MEQ in evaluation of medical trainees.

A critical evaluation of the written exit examination at the University of Adelaide using multiple components like OSCE, MCQ and MEQ identified that the overall examination had good fidelity and validity, the results of MEQ and MCQ were strongly and positively correlated and they had a weak negative correlation with OSCE. The MEQ had higher proportion of questions focused on recall of knowledge and also suffered from structural flaws, and failure to assess higher cognitive skills.

A large multicentre study comparing very-short answer questions with single best answers(SBA) for assessment of applied medical knowledge using a robust marking process with multiple markers and independent checking concluded that SBA questions may give a false sense of student competence and VSA appeared to have higher authenticity, provided useful information on students cognitive errors and helped improve learning and assessment with the advantage of electronic delivery and marking.

The MCI-CBME Module on Assessment has outlined that the university examination will include questions in different formats like structured essays (long answer questions), short answer questions and also objective type questions (MCQ’s) with the latter not exceeding a total of 20% marks. Therefore, there is a need to train faculty in preparing valid and reliable MEQ’s which not only serve as assessment tools but also stimulate students preparing for these examinations to use them for learning. As the Essay and MEQ are to be the main assessment method, the minimum requirement will be content and context validity with multiple markers. The construction of higher order MEQ’s is an arduous task when designed to assess higher cognitive levels and often a well-constructed MCQ may serve as a reasonable replacement. The MCQ and its varied formats including extended-matching questions or true-false questions saves on academic time and allow for easy and uniform scores. A sufficient number of valid MCQ’s and true-false questions infuse reliability into the assessment. Paper-setters will have an arduous task ahead unless sensitization of all faculties on the principles of preparing “good” assessment questions is taken up earnestly and expeditiously.

Conclusion

When curricula are designed to promote clinical ability or competence, the assessment needs to be raised to a level that captures its essence. The formats of summative questions reviewed in the present paper suggest that there is a long way to go. The limitations of the study are that the
Early Initiation of Low-Dose Hydrocortisone Therapy for Septic Shock in Geriatric Patients: A Randomized Control Trial

Mayank Agarwal1*, Minakshi Dhar2, Disha Agarwal3, Aishwarya Murlidharan4

Abstract

Background: The management of septic shock has undergone significant modifications in the past decade. Various studies have concluded that while corticosteroids reduce the duration of shock, they do not have any proven mortality benefit. Moreover, the time of initiation of corticosteroids has been debatable. Since, little literature is available on geriatric patients, we have designed a randomized trial to assess the importance of early initiation of low dose hydrocortisone comparing with the standard therapy.

Objectives: To determine the efficacy of early initiation of low dose hydrocortisone in reducing mortality in septic shock in geriatric patients.

Methods: We conducted a single blinded, randomized controlled trial at a tertiary care hospital in India. Geriatric patients (age>60 years) fulfilling the criteria for septic shock were included in the study. All the participants were randomly assigned to two arms - intervention and standard therapy group. The outcomes were studied in terms of 28-day mortality, duration of ICU stay, duration of vasopressor requirement and need for mechanical ventilation

Results: Total 120 patients were randomized to either Intervention arm (N=61) or the Standard therapy arm (N=59). The number of patients with reversal of shock was higher in the intervention arm (53.4%) but not statistically significant association (p = 0.575) was found. There was no significant difference between the two groups in terms of 28-day mortality, length of ICU stay, need for mechanical ventilation and duration of vasopressor support.

Conclusion: This single centre trial demonstrated that there was no survival benefit associated with the early initiation of low dose hydrocortisone treatment in patients with vasopressor-dependent septic shock. It raised the concern that whether steroids are safe in elderly patients with septic shock.

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Introduction

Sepsis has been recognized by the World Health Organization (WHO) as a global health priority contributing up to 50% in-hospital deaths. Globally, the incidence of hospital-treated sepsis in adults is estimated as 270 per 100 000, with overall mortality estimated at 26%.\(^1\) A study done at a tertiary care hospital in India reported that approximately 6.2% of ICU admissions were due to severe sepsis with ICU mortality, hospital mortality and 28-day mortality being 56%, 63.6%, and 62.8%, respectively.\(^2\) Overall the reported incidence of sepsis is increasing mainly due to aging populations with more comorbidities indicating that sepsis is a leading cause of mortality and critical illness worldwide.\(^3\)

Geriatric patients are at risk for an increased incidence and severity of infections due to impaired host immune system. Multiple factors may be responsible for altered cell-mediated immunity in the elderly, including thymic involution, reduced levels of thymic hormones, and an increase in the number of immature T lymphocytes.\(^4\) In 2010 a prospective observational study to determine the outcome of septic shock in ICU depicted that only age of the patient was an independent predictor for ICU mortality.\(^5\)

Septic shock, a severe complication of sepsis, is a state of circulatory failure with an increased risk of death. The management of septic shock has undergone significant modifications in the past decade. Initiation of corticosteroids in septic shock is based on the concept of supplementation of low dose cortisol to substitute the lack of endogenous steroid activity instead of maximally suppressing the immune response with high-dose steroids. Several trials have been published to evaluate the efficacy of low-dose corticosteroid administration in patients with septic shock, many with conflicting results.

Early trials showed that high-dose steroid therapy is detrimental and should not be a component of severe sepsis therapy.\(^6\) However the interest in steroids was revived by the landmark multicenter, randomized trial by Annane et al who demonstrated that 90-day all-cause mortality was lower in patients who received corticosteroids vs those who received placebo (43% vs 49.1%).\(^7\) However, recent systematic reviews have suggested that the effect of corticosteroid therapy on survival of patients with septic shock is debatable,\(^8\)\(^-\)\(^10\) and recently larger studies have not shown significant effects.\(^11\) Charles L. Sprung et al through a multicentre CORTICUS trial demonstrated that there was no mortality benefit with low dose hydrocortisone when compared to placebo.\(^11\)

The association between the use of corticosteroid therapy and mortality among septic shock patients remains controversial with clinicians attributing this to the timing between onset of septic shock and initiation of low dose hydrocortisone. A retrospective study\(^12\) demonstrated a significant association between early initiation (given within 6 hours of development of septic shock) of low-dose corticosteroid therapy and reduced mortality rate in patients with septic shock. Both Surviving Sepsis Campaign\(^13\) and the American College of Critical Care Medicine (ACCCM)\(^14\) have recommended the administration of hydrocortisone in patients with septic shock who are fluids and vasopressor non-responsive. However, these recommendations have low quality of evidence at present. About one-fifth of the clinicians do not routinely give corticosteroids to septic shock patients owing to lack of substantial survival benefit.\(^15\)

Hence from various studies that have been conducted over time, we can conclude that while administration of corticosteroids does have a benefit in reducing the duration of shock, but they do not have any proven mortality benefit. Moreover, the time of initiation of corticosteroids is crucial in determining the outcome. Since, little or no literature is available on the effects of early initiation of corticosteroid therapy versus standard therapy in reducing mortality in geriatric patients in Indian setting, we have designed a randomized clinical trial to assess the importance of early initiation of low dose hydrocortisone for the outcome in such cases while comparing them with the standard therapy.

Material and Methods

Study Design

We conducted a single blinded, randomized controlled trial to determine the efficacy of early initiation of low dose hydrocortisone in reducing mortality in septic shock in geriatric patients admitted at a tertiary care hospital in India.

This trial was approved by the Institutional Ethics Committee (IEC) at All India Institute of Medical Sciences, Rishikesh (Ref no.- AIIMS/IEC/20/11). Trial enrollment began in May 2020 and ended in February 2021, while follow-up was completed by March 2021. Participants

Inclusion criteria

1. Geriatric patients (age > 60 years) admitted in the intensive care unit (ICU) with septic shock, or
2. Geriatric patients (age > 60 years) who developed septic shock during their hospital stay.

Inclusion criteria

1. All geriatric patients not fulfilling the criteria of septic shock.
2. Those patients who have received systemic corticosteroid therapy in the past 3 months before the onset of septic shock
3. Refusal of consent for participation

Study Setting

The study was carried out in the the intensive care unit at our hospital. All eligible patients with septic shock fulfilling the inclusion criteria were randomly assigned into either of the two study groups. After taking the informed consent from the relatives, the following information was collected and analyzed for every enrolled patient: demographics, comorbidities, baseline hematological and biochemical parameters including renal and liver function tests, prothrombin time, serum lactate and procalcitonin levels. Amount of fluid administered before initiation of vasopressor, timing of initiation of hydrocortisone in the standard group and initial Sequential Organ Failure Assessment (SOFA) score was calculated. Blood and infection site specific cultures were obtained. Adverse events were recorded in both the arms.

Intervention

All patients fulfilling the inclusion criteria were randomly assigned to either of the two groups- intervention group and standard therapy group. Sequence generation was done by
simple random allocation using an open access computer-based software.

Patients in the Standard Therapy group were managed according to the International Guidelines for Management of Sepsis and Septic Shock: (Surviving Sepsis Campaign), i.e., they were administered low dose Hydrocortisone once fluids and vasopressors fail to maintain blood pressure. In the Intervention group once vasopressor was initiated, low dose Hydrocortisone was administered simultaneously to the patients.

In both the arms Low dose Hydrocortisone was administered as 200 mg/day intravenously in four divided doses. Once all vasopressors were stopped, the taper protocol was initiated (100 mg/day for three days, then 50 mg/day for 3 days and then stopped).

**Operational Definitions**

**Septic shock**: defined as a sepsis (denoted by a Sequential Organ Failure Assessment ≥2 points) plus serum lactate ≥2 mmol/L and persistent hypotension despite adequate volume resuscitation, requiring vasopressors to maintain a mean arterial blood pressure ≥65 mm Hg.

**Reversal of shock**: defined as the maintenance of a systolic blood pressure of at least 90 mmHg without vasopressor support for at least 24 hours.

**Study Assessments**

Follow up and assessment of participants was done daily for 28 days from the initiation of hydrocortisone. The primary outcome was measured in terms of 28-day mortality in septic shock patients receiving early initiation of low dose hydrocortisone therapy versus those receiving standard corticosteroid therapy. Secondary outcomes included duration of ICU stay, duration of vasopressor requirement, need for mechanical ventilation and the incidence of adverse events in both the arms.

**Statistical analysis**

Categorical variables were represented as proportions and continuous or discrete variables as means ± standard deviation (SD). The unpaired Student t-test or Mann-Whitney U-test for continuous variables and the chi-square test or the Fisher exact test for categorical variables were used for comparisons between the groups. IBM Statistical Package for Social Sciences (SPSS) version 26.0 (Chicago, USA) was used for statistical analysis and statistical significance was set at p-value < 0.05 for the final analysis.

**Results**

**Participants**

We enrolled 120 patients who were randomized to either Intervention arm (N=61) or the Standard therapy arm (N=59). The data was analysed for 120 study participants at the end of 28 days (Figure 1).

---

**Table 1: Baseline characteristics of patients enrolled in the study**

<table>
<thead>
<tr>
<th>Variables</th>
<th>Categories</th>
<th>Intervention group (N=61) [n (%) / Mean, SD]</th>
<th>Standard therapy group (N=59) [n (%) / Mean, SD]</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male</td>
<td>40 (54.8) / 68.3±6.3</td>
<td>33 (45.2) / 66.7±4.6</td>
<td>0.350</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>21 (44.7) / 56 (51.4)</td>
<td>26 (55.3) / 56 (51.4)</td>
<td>0.132</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>68.3±6.3 / 56 (51.4)</td>
<td>66.7±4.6 / 56 (51.4)</td>
<td>0.563</td>
</tr>
<tr>
<td>Comorbidities, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td>18 (47.3) / 20 (52.6)</td>
<td>19 (50.0) / 20 (52.6)</td>
<td>0.696</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td>19 (50.0) / 6 (60.0)</td>
<td>18 (54.5) / 9 (69.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>CKD</td>
<td></td>
<td>4 (10.0) / 9 (69.2)</td>
<td>5 (31.2) / 9 (69.2)</td>
<td>0.526</td>
</tr>
<tr>
<td>CLD</td>
<td></td>
<td>4 (10.0) / 9 (69.2)</td>
<td>5 (31.2) / 9 (69.2)</td>
<td>0.526</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td>4 (10.0) / 9 (69.2)</td>
<td>5 (31.2) / 9 (69.2)</td>
<td>0.526</td>
</tr>
<tr>
<td>CAD</td>
<td></td>
<td>11 (68.7) / 5 (31.2)</td>
<td>11 (68.7) / 5 (31.2)</td>
<td>0.179</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td>9 (47.3) / 10 (52.6)</td>
<td>11 (68.7) / 10 (52.6)</td>
<td>0.806</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>4 (66.6) / 2 (33.3)</td>
<td>4 (66.6) / 2 (33.3)</td>
<td>0.680</td>
</tr>
<tr>
<td>Source of sepsis</td>
<td>Lungs</td>
<td>32 (45.0) / 39 (54.9)</td>
<td>39 (54.9) / 39 (54.9)</td>
<td>0.457</td>
</tr>
<tr>
<td></td>
<td>Abdomen</td>
<td>8 (44.4) / 10 (55.5)</td>
<td>10 (55.5) / 10 (55.5)</td>
<td>0.386</td>
</tr>
<tr>
<td></td>
<td>Blood</td>
<td>3 (75.0) / 1 (25.0)</td>
<td>4 (75.0) / 1 (25.0)</td>
<td>0.724</td>
</tr>
<tr>
<td></td>
<td>CNS</td>
<td>2 (66.6) / 1 (33.3)</td>
<td>4 (66.6) / 1 (33.3)</td>
<td>0.276</td>
</tr>
<tr>
<td></td>
<td>Urinary Tract</td>
<td>8 (66.6) / 4 (33.3)</td>
<td>8 (66.6) / 4 (33.3)</td>
<td>0.876</td>
</tr>
<tr>
<td></td>
<td>SSI</td>
<td>8 (66.6) / 4 (33.3)</td>
<td>8 (66.6) / 4 (33.3)</td>
<td>0.618</td>
</tr>
<tr>
<td>Culture Organism, n (%)</td>
<td>Acinetobacter</td>
<td>10 (50.0) / 1 (14.3)</td>
<td>10 (50.0) / 1 (14.3)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Pseudomonas</td>
<td>5 (45.4) / 6 (54.5)</td>
<td>5 (45.4) / 6 (54.5)</td>
<td>0.758</td>
</tr>
<tr>
<td></td>
<td>E. Coli</td>
<td>12 (57.1) / 9 (42.8)</td>
<td>12 (57.1) / 9 (42.8)</td>
<td>0.845</td>
</tr>
<tr>
<td></td>
<td>Klebsiella</td>
<td>3 (42.8) / 4 (57.1)</td>
<td>3 (42.8) / 4 (57.1)</td>
<td>0.476</td>
</tr>
<tr>
<td></td>
<td>MRSA</td>
<td>6 (60.0) / 4 (40.0)</td>
<td>6 (60.0) / 4 (40.0)</td>
<td>0.859</td>
</tr>
<tr>
<td></td>
<td>Enterococcus</td>
<td>0 / 1 (100.0)</td>
<td>0 / 1 (100.0)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Proteus</td>
<td>1 (50.0) / 1 (50.0)</td>
<td>1 (50.0) / 1 (50.0)</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>Aspergillus</td>
<td>0 / 1 (100.0)</td>
<td>0 / 1 (100.0)</td>
<td>1.0</td>
</tr>
</tbody>
</table>
Table 2: Baseline clinical and laboratory characteristics of patients enrolled in the study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (N=61) [Mean, SD]</th>
<th>Standard therapy group (N=59) [Mean, SD]</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukocytes (1000/mm3)</td>
<td>17.6±8.2</td>
<td>17.8±10.8</td>
<td>0.902</td>
</tr>
<tr>
<td>Haemoglobin (gm/dL)</td>
<td>9.5±1.9</td>
<td>9.9±2.6</td>
<td>0.244</td>
</tr>
<tr>
<td>Platelets (1000/mm3)</td>
<td>156.4±78.9</td>
<td>145.8±105.2</td>
<td>0.536</td>
</tr>
<tr>
<td>Creatinine (mg/dL)</td>
<td>1.9±1.5</td>
<td>1.9±1.7</td>
<td>0.901</td>
</tr>
<tr>
<td>Prothrombin time (seconds)</td>
<td>13.2 (9.7, 46.9)</td>
<td>13.6 (9.4, 43.8)</td>
<td>0.881</td>
</tr>
<tr>
<td>Albumin (gm/dL)</td>
<td>2.3±0.7</td>
<td>2.3±0.6</td>
<td>0.642</td>
</tr>
<tr>
<td>Total Bilirubin (mg/dL)</td>
<td>0.8 (0.72, 24.5)</td>
<td>1.4 (0.2, 15.7)</td>
<td>0.131</td>
</tr>
<tr>
<td>Initial SOFA Score</td>
<td>9.6±2.6</td>
<td>10.4±2.4</td>
<td>0.094</td>
</tr>
<tr>
<td>Initial Lactate (mmol/L)</td>
<td>4.4±1.3</td>
<td>4.5±1.4</td>
<td>0.446</td>
</tr>
<tr>
<td>Procalcitonin (ng/ml)</td>
<td>6.8 (0.8, 73.8)</td>
<td>7.4 (1.3, 81.2)</td>
<td>0.678</td>
</tr>
<tr>
<td>Amount of Fluid administered (litres)</td>
<td>1.9±0.7</td>
<td>1.8±0.7</td>
<td>0.118</td>
</tr>
</tbody>
</table>

Table 3: Clinical outcomes of patients enrolled in the study

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention group (N=61)</th>
<th>Standard therapy group (N=59)</th>
<th>p- value</th>
</tr>
</thead>
<tbody>
<tr>
<td>28-day mortality</td>
<td>22 (46.8%)</td>
<td>25 (53.2%)</td>
<td>0.575</td>
</tr>
<tr>
<td>Duration of vasopressor support</td>
<td>6.2±3.8</td>
<td>7.3±3.4</td>
<td>0.847</td>
</tr>
<tr>
<td>(days)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>34 (48.6%)</td>
<td>36 (51.4%)</td>
<td>0.583</td>
</tr>
<tr>
<td>Length of ICU stay (days)</td>
<td>10.4±4.1</td>
<td>10.1±4.2</td>
<td>0.654</td>
</tr>
<tr>
<td>Reversal of shock</td>
<td>39 (53.4%)</td>
<td>34 (46.6%)</td>
<td>0.575</td>
</tr>
<tr>
<td>Adverse events</td>
<td>51 (49.5%)</td>
<td>52 (50.5%)</td>
<td>0.477</td>
</tr>
</tbody>
</table>

Fig. 2: Adverse events in patients

A total of 73 males and 47 females were included in our study (Table 1). The mean age of the patients was 67.5±5.6 years and majority of them were males 60.8% (73 of 120). Overall, 109 (90.8%) patients had a comorbidity of which most of them had Diabetes Mellitus or Hypertension. The primary source of sepsis in patients was predominantly lung infection [59.2% (71 of 120)] followed by abdomen [15% (18 of 120)]. Only 73 patients had culture results where majority of them had E. coli in the intervention arm and Acinetobacter in the standard therapy arm. Timing of initiation of low dose hydrocortisone in the intervention arm was zero hour, i.e., at the onset of septic shock, whereas in the standard therapy arm the mean time was after 18.58±10.76 hours from the onset of shock. All the participants in the standard therapy arm received low dose hydrocortisone once fluids and vasopressors failed to maintain blood pressure. In both the arms Low dose Hydrocortisone was administered as 200 mg/day intravenously in four divided doses. The total dose of hydrocortisone received was different in both arms as steroids were tapered once all vasopressors were stopped.

Rest of the baseline clinical characteristics of the two groups are shown in Table 2. Both the groups had similar characteristics and did not significantly differ in any of the variables considered. The mean of the initial SOFA score was higher in the standard therapy arm, however the difference was statistically insignificant.

Outcomes

The number of patients with reversal of shock was higher in the intervention arm (53.4%) in comparison to the standard therapy arm (46.6%), but no statistically significant association (p= 0.575) was found. There was no significant difference between the two groups in terms of 28- day mortality, length of ICU stay, need for mechanical ventilation and duration of inotropic support. (Table 3)

Adverse events

A total of 103 patients reported one or more adverse events after receiving hydrocortisone. The proportion of patients developing hyperglycaemia was more in the intervention arm whereas as a higher proportion of superinfection was seen in the standard therapy arm (Figure 2). Overall majority of the patients had Hyperglycemia (51) followed by hypernatremia (48) and superinfection (45). Other adverse events noted were bleeding, stroke, and myocardial infarction. There was no statistically significant association (p= 0.506) between the two groups.

Discussion

Early initiation of steroids did not show any survival benefit in elderly patients with septic shock as compared to those who were started on steroids after initial resuscitation with fluids and inotropic agents. There was no statistically significant difference in terms of length of ICU stay, need for mechanical ventilation and duration of inotropic support among the two groups.

Our results depicted that majority of the patients had pneumonia as the primary source of sepsis followed by abdominal infection and UTI. These findings were in line with most of the trials including those by Robert et al where 57% participants had lungs as the primary source. But in contrast these findings were different from those observed by Yaseen et al and Qing-quan Lv et al where an intrabdominal source was attributed as the cause of sepsis. Other sites included skin, bacteremia, etc. which were less commonly seen in our setting. Of note out of the total participants, only 73 had positive culture results. Majority of them had gram negative bacteria in their culture which included E. coli, Acinetobacter and Pseudomonas species. Many
previous studies have concluded similar findings including a pilot study by Huh JW et al. where they noticed the majority patients had a Gram negative organism in their culture.19

The primary-end point of our study was all cause 28-day mortality. We did not find any difference on mortality by starting steroids very early to treatment schedule. The landmark multicenter, randomized trial by Annane et al demonstrated that 90- day all-cause mortality was lower in patients who received the corticosteroids vs those who received placebo (43% vs 49.1%).20 Albeit several factors may have been answerable for the differences in the results of the multicenter studies, the difference in the time window of initiation of steroid should be considered as a potential influence. In the study by Annane et al. steroids were given within three hours of the onset of shock which was later increased up to eight hours and there was a significant mortality benefit, while on the other hand, in the CORTICUS study, this window was increased to 72 hours and there was no benefit of the steroid therapy. Therefore, it can be presumed that the benefit of low-dose corticosteroid therapy may decline with a delay in initiating the treatment. Our findings can partially be correlated with these results because all patients with septic shock in our study received low-dose corticosteroid therapy. But in our study, we could not establish any benefit as far as timing of steroid initiation was concerned. In the present study the mean time of initiation of hydrocortisone from the onset of septic shock was approximately 18 hours and the early administration of low dose hydrocortisone (i.e., at the onset of shock) was not associated with any mortality benefit. However, in a study by Hye Yun et al they concluded that low-dose corticosteroid therapy within 6 hours from the onset of septic shock reduced the relative risk of 28-day mortality by 37% compared with late therapy after 6 hours.21 The limitation of their study was that it was retrospective in nature.

Of note, according to our findings, even though statistically insignificant, early administration of hydrocortisone in septic shock was able to titrate patients off vasopressor therapy earlier with faster reversal of shock. This more rapid shock reversal with steroid therapy is consistent with previous studies. Gordon et al. demonstrated in a study that hydrocortisone group required a shorter time course and lower total dose of vasopressin compared to the placebo group. Their results also did not show any difference in mortality rates between the two groups though.21 Similar results were obtained through a literature review by Wang et al. They found that although low-dose hydrocortisone therapy did not reduce 28-day mortality, it improved the time to shock reversal at 7 days (p= 0.0001) and 28 days (p = 0.006).22 The plausible explanation for such an outcome could be related to increased sensitization of the vasculature to vasopressors caused by hydrocortisone along with its mineralocorticoid action.

As observed in our study, early administration of hydrocortisone did not have significant impact in reducing the duration of ICU stay. Patients in both the arms had similar length of ICU stay. Moreover, the requirement of mechanical ventilation was same in both study groups. In a study by Lv et al they found that there was no significant differences in length of ICU/hospital stay or shock reversal (p= 0.602) and they concluded that addition of steroids did not reduce the duration of ICU stay in septic shock patients.23

Lack of overall benefit of low-dose hydrocortisone therapy is likely because of the adverse events it carries with it, such as hyperglycemia, secondary infection due to immunosuppression, dys electrolytemia, etc. In our study, we found that the occurrence of adverse events following steroid therapy was high in both the groups. Majority reported Hyperglycemia and new onset hypernatremia as the unwanted outcomes. Since both groups received steroids the rate of superinfection was comparable. These findings are in accords with most of the trials which reported more adverse events than any mortality benefit from hydrocortisone. In a study by Nazer et al. they concluded that a higher incidence of superinfection was shown is those receiving corticosteroids compared to the control group (44.8% vs 27.4%; p = 0.028).24 Similarly, when Arabi et al. studied the effect of corticosteroid replacement in septic shock patients with liver cirrhosis they found that the group which received hydrocortisone had an increase in shock relapse (p=0.03) and gastrointestinal bleeding (p = 0.02).25 Hence, we deduced that early initiation of hydrocortisone in geriatric patients had limited role in the outcome of the patients. Infact there was a higher incidence of adverse events which could be explained by the fact that steroids affecting the already immunosuppressed and frail physiology of elderly patients.

The findings in our study point to limited therapeutic benefit for the use of corticosteroids in septic shock. We did not find any advantage of giving early hydrocortisone over the standard recommendations supported by the current Surviving Sepsis Campaign guidelines. Nearly 23 trials and 2 reviews till date have provided conflicting evidence regarding the effectiveness corticosteroid therapy for septic shock. Overall, most of them have demonstrated minimal improvement in outcomes.24

Therefore, based on our study we do not advocate for the early administration of hydrocortisone for septic shock in the geriatric population for it had more adverse outcomes than any benefit. Nonetheless more research is needed to expand upon our results to ascertain benefit of steroids in elderly and find out the optimal dose, timing, duration and specific categories of elderly populations such as those with adrenal suppression, to get a better yield of improved outcomes. Additionally, the possible advantages of adding adjunct therapies like fludrocortisone, vitamin C in addition to corticosteroid treatment have shown promising results. However, their effect in elderly patients is yet to be elucidated and thus calls for larger studies in future.

The chief strength of our study was: first trial to compare the role of early initiation (simultaneously with vasopressors) of low dose hydrocortisone with the standard therapy in septic shock. Therefore, we were able to eliminate the possible influence of time lag in the initiation of steroids on survival benefit. Our study had a few limitations as well: we assessed the 28-day mortality and therefore any long-term association between the two groups could not be assessed; the sample size was relatively small, hence larger, multicentric trials are needed to affirm our findings; measurement of baseline serum cortisol levels for assessment of adrenal
function was not done.

**Conclusion**

Currently the role of corticosteroids in septic shock has thrown open wide conflicting results with many studies showing potentially harmful adverse effects rather than any positive outcome. Our study did not permit us to rush to the conclusion whether there is a survival benefit associated with the early initiation of low dose hydrocortisone treatment in patients with vasopressor-dependent septic shock. It raised the concern that whether steroids are safe in elderly patients with septic shock. Results from multiple controlled clinical trials clearly demonstrate that even though low-dose corticosteroid replacement therapy in septic shock might be associated with improved hemodynamic parameters but mortality benefit is extremely limited. To find a definitive answer we need larger multicentric randomized clinical trials to determine the optimum dose and duration of steroid therapy in septic shock. In the absence of concrete results, we suggest that the clinicians use their clinical judgement combined with expert opinion to determine the role of corticosteroid treatment in fluid resuscitated patients with vasopressor-dependent septic shock.

**References**


5. Nasa P, Juneda D, Singh D, Ding R, Aroa V. Severe Sepsis and Its Impact on Outcome in Elderly and Very Elderly Patients Admitted in Intensive Care Unit. 2015;


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1 Grossmann & Tangpricha et al. Evaluation of vehicle substances on vitamin D bioavailability: A systematic review. Mol Nutr Food Res, 2010 August; 54(8): 1055-1061,
Hypokalemic Paralysis Due to Primary Sjögren’s Syndrome: Case Series

Naisar Nahar¹, Prachi Nahar²

Abstract

Background: Sjögren’s syndrome (SS) is an autoimmune disorder characterized by exocrine glandular involvement and extra-glandular manifestations. Associations between hypokalemic paralysis and SS have not been emphasized enough. Present study evaluates hypokalemic paralysis as presenting feature in PSS.

Methods: A retrospective cross-sectional study from 2015 to 2020 was conducted to evaluate the clinical phenotype of primary Sjögren’s syndrome (PSS) who presented to us with hypokalemic paralysis.

Results: Data of 13 patients were evaluated. All were female patients and mean age was 38 years. 61.5% (n= 8) had more than one episode of hypokalemic paralysis; 61.5% (n= 8) patients had oral dryness and 69% (n= 9) had dryness of eyes. 23% (n= 3) patients had inflammatory arthritis and 1 patient had Raynaud’s phenomenon, myopathy respectively. 1 patient had chronic constipation and hypothyroidism was present in 61.5% (n= 8) patients. Other co-morbidity included hypertension, renal calculi and situs inversus present in 15%, 15% and 7% respectively. The mean ESR at presentation was 64 mm/hr; average serum potassium level was 2.04meq/dl and distal renal tubular acidosis was present in all patients. Paralysis was completely recovered in all patients after supplementation with potassium.

Conclusion: The renal involvement in PSS can uncommonly present as hypokalemic paralysis in the absence of significant sicca symptoms or may precede sicca symptoms. A high index of suspicion for PSS should be kept in all patients with hypokalemic paralysis. This phenotype may represent a distinct subset. Serum electrolytes should be regularly monitored in all patients with SS.

Introduction

Sjögren’s syndrome (SS) is a chronic autoimmune disorder which is characterized by lymphocytic infiltration of exocrine glands, mainly lacrimal and salivary gland. SS has been associated with numerous extra-glandular features including neurologic, renal, hepatic, respiratory, cutaneous and vascular etc. SS is classified as primary Sjögren’s syndrome (PSS) when the clinical manifestations occur alone, or as secondary when associated with another autoimmune disease, usually a connective tissue disease (e.g. Rheumatoid arthritis and Lupus etc.). Renal involvement is well recognized extra glandular manifestation and occurs in 16% to 67% in primary Sjögren’s syndrome. Tubulointestinal nephritis (TIN) is the main renal manifestation associated with PSS and TIN can manifest as distal renal tubular acidosis (dRTA), nephrogenic diabetes insipidus, proximal renal tubular acidosis, nephrocalcinosis and others; of which dRTA is common and reported in 4.3% to 9% of PSS patients. Though dRTA is clinically silent but hypokalemic paralysis is well known but rarely encountered complication of dRTA. First case of hypokalemic paralysis with PSS described by Raski J in 1981 and its associations have not been emphasized enough. We herein present one of the largest case series of PSS which were presented with hypokalemic paralysis as first manifestation.

Material and Methods

Objective: A retrospective cross-sectional study has been conducted to evaluate the clinical phenotype of Primary Sjögren’s syndrome (PSS) who were presented with Hypokalemic paralysis.

Design: Data of 13 subject who presented to us as hypokalemic paralysis as first symptom and later diagnosed as Sjögren’s syndrome. Diagnosis was mainly done through evaluating clinical parameters and standard criteria for Sjögren’s syndrome were applied. Diagnosis of distal renal tubular acidosis (dRTA) was based on normal anion gap metabolic acidosis with hypokalemia with urine pH > 5.5 with positive urine anion gap. A Data was collated and entered in Microsoft excel sheet for demographics and other variables frequency percentage of these parameters were calculated (Table 1).

Site: A single center study at Arham Rheumatology Center, Nashik, India.

Study period: 2015 to 2020 and data was extracted from database.

Results

Total 13 patients were identified during our study period and all were female (female: male ratio- 13:0). The mean age of onset in our cohort was 38 years. 61.5% (n= 8) of patients had history of more than one episode of hypokalemic paralysis. Hypokalemic paralysis was presenting complaints in all these patients.

On enquiry 61.5% (n= 8) of patients had history of oral dryness and 69% (n= 9) had history of eye dryness which was confirmed by ophthalmologist later. Inflammatory arthritis were present in 23% of patients (n= 3) and 1 patient had history of Raynaud’s phenomenon and one patient had myopathy. One patient had history of chronic constipation.
and hypothyroidism was present in 61.5% of patients (n= 8). Other comorbidity were hypertension, history of renal calculi and situs inversus were present in 15%, 15% and 7% patients respectively. None of the patient reported history of neuromuscular diseases or family history of connective tissue disorder.

Distal renal tubular acidosis (dRTA) was present in all patients. Paralysis was completely recovered in all patients after potassium supplementation. ANA positivity was noted in all patients either by ELISA or IFA. Antibody to SSA antigen was positive in all patients and antibody to SSB was present in 61.5% of patients (n= 8). Other co-association of hypokalemic paralysis with PSS is altogether distinct clinical subset needs to be reviewed in future. First report from India came in 1996 by Thomas et al and later Chandramohan G et al (2018) presented spectrum of hypokalemic paralysis in tertiary care center and they found 36% of patient had dRTA and most common cause was PSS.

Age of onset in our cohort is in 4th decade. Similar observation noted in case series published by Goroshi M et al (2017). Contrary to this finding, a case series published by Nachiket N et al (2018) showed younger age of onset that is in 3rd decade. PSS is primarily seen in female patients as observed in previous studies though few male cases reported (less than 10 cases) in the literature.

Renal involvement in PSS is most common extra-glandular manifestation and is very well described in the literature and is very well described in the literature and is most frequent systemic autoimmune disorder and its prevalence is 0.5 to 1%. There are 2 age peaks seen in PSS, first peak during 20s to 30s and the second in mid 50s. Less than 100 cases reported in the literature who presented as hypokalemic paralysis as first manifestation in PSS. Majority of case reports and case series were from Asian countries mainly India. Whether association of hypokalemic paralysis with PSS is altogether distinct clinical subset needs to be reviewed in future. First report from India came in 1996 by Thomas et al and later Chandramohan G et al (2018) presented spectrum of hypokalemic paralysis in tertiary care center and they found 36% of patient had dRTA and most common cause was PSS.

**Discussion**

Primary Sjögren’s syndrome (PSS) has wide variety of presentation and it is heterogeneous autoimmune disease whose pathophysiology remains incompletely understood. PSS is among the most frequent systemic autoimmune disorder and its prevalence is 0.5 to 1%. There are 2 age peaks seen in PSS, first peak during 20s to 30s and the second in mid 50s. Less than 100 cases reported in the literature as first manifestation in PSS. Majority of case reports and case series were from Asian countries mainly India. Whether association of hypokalemic paralysis with PSS is altogether distinct clinical subset needs to be reviewed in future. First report from India came in 1996 by Thomas et al and later Chandramohan G et al (2018) presented spectrum of hypokalemic paralysis in tertiary care center and they found 36% of patient had dRTA and most common cause was PSS.

**Conclusion**

1. This study highlighted underreported presentation (hypokalemic paralysis) of PSS even before sicca symptoms.

2. Clinical suspicion of PSS should be thought in middle age female patient who presented with hypokalemic paralysis.

3. Hypokalemic paralysis may be first clue in identifying underlying autoimmune disorder and need detailed serological evaluation.

4. Serum electrolytes monitoring should be regularly done in all patients.
Clinical Spectrum of Henoch Schönlein Purpura in Adults: A Hospital Based Study

Ramnath P Nevrekar1, Prachi Bhandare2, Anar Khandeparkar3

Abstract

Background and objectives: Henoch Schönlein purpura (HSP) is a small vessel vasculitic disorder common in children and has been extensively studied. Although it is known to also occur in adults there is relative paucity of data as regards to its clinical spectrum, complications and outcome, particularly in Indian context. Hence the study was undertaken with the objective to evaluate the various skin manifestations, systemic complications of HSP in adults and also compare it with data available in children in various published clinical studies.

Study design, materials, methods: In this retrospective, observational, hospital-based cohort study conducted at Goa Medical College the premier teaching institute from Goa, clinical data of adult patients (>18 years age) fulfilling the diagnostic criteria as per European League Against Rheumatism (EULAR) 2010 criteria for HSP was obtained, over period of 6 years. All the clinical manifestations, complications, investigations, outcomes were recorded. Skin biopsy histopathology and immunofluorescent test findings were also obtained. The data was analysed and results were compared to the data available in pediatric studies to ascertain the similarities and differences.

Table 2: Comparative analysis of published case series

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Current study</th>
<th>Kulkarni N et al.11</th>
<th>Goroshi M et al.11</th>
<th>Paliwal V et al.11</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arthritis</td>
<td>45 (n=11)</td>
<td>60</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Myopathy</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Extra-glandular manifestations</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Arthritis, Raynaud’s phenomenon</td>
<td>93</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Arthralgia, arthritis, neuropathy, ILD, Raynaud’s phenomenon</td>
<td>50</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Arthritis and vasculitis</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>RF Positivity (%)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>SSA Antibody Positivity (%)</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>SSB Antibody Positivity (%)</td>
<td>61.5</td>
<td>50</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Minor Salivary Gland Biopsy</td>
<td>--</td>
<td>--</td>
<td>--</td>
<td>--</td>
</tr>
</tbody>
</table>

References


*Assistant Professor, Dept. of Internal Medicine, 2Assistant Professor, Dept. of Skin and VD, 3Associate Professor, Dept. of Internal Medicine, Goa Medical College, Goa; *Corresponding Author
Received: 31.03.2021; Revised: 17.10.2021; Accepted: 15.11.2021
**Results:** In our study cohort of 30 patients, we found a higher incidence of atypical and more extensive skin lesions particularly bullae (40%), necrotic ulcers (53.3%), urticarial wheals (53%) unlike in children as well as differences in distribution especially sparing of buttocks in adults. The incidence of gastrointestinal involvement was 80% which was higher than that reported by other studies in adults (35% to 70%). A significant 40% of patients had upper GI bleeding with endoscopy revealing small hemorrhages in gastric mucosa. Lower GIT bleed was seen in 8 patients. Renal involvement (microscopic hematuria, overt glomerulonephritis, nephrotic syndrome) was seen in 65% patients which was higher than that reported in children (43%). Skin biopsy immunofluorescence was found to be positive in almost 66% cases confirming IgA deposition which is the hallmark pathological finding.

**Conclusions:** HSP, though less common in adults than children, presents with atypical and more severe cutaneous manifestations like bullae, necrotic ulcers, urticarial wheals. Systemic involvement appears to be more frequent and causing more morbidity and mortality as compared to the data in children mentioned in standard literature and most of the patients required steroid therapy for treatment unlike in children where majority of these cases are self-limiting. Skin involvement does not necessarily mirror gastrointestinal involvement in terms of severity and temporal occurrence.

**Introduction**

Henoch-Schönlein purpura (HSP) is the commonest immune complex mediated vasculitis affecting the small vessels of the skin, joints, gastrointestinal (GI) tract and the kidneys.1 Though the peak incidence is in the 4-6-year-old age group with figures around 70/100000 population, with a very slight male predominance, this vasculitis is seen in adults too.

**Table 1: Sex distribution**

<table>
<thead>
<tr>
<th>Males n (%)</th>
<th>Females n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hsp criteria fulfilled 21 (70)</td>
<td>9 (30)</td>
</tr>
<tr>
<td>n=30</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Presenting cutaneous and systemic features**

<table>
<thead>
<tr>
<th>Manifestations</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Purpura</td>
<td>28</td>
<td>93.3</td>
</tr>
<tr>
<td>Urticarial wheals</td>
<td>16</td>
<td>53.3</td>
</tr>
<tr>
<td>Necrotic ulcers</td>
<td>16</td>
<td>53.3</td>
</tr>
<tr>
<td>Bullae</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>20</td>
<td>66.6</td>
</tr>
<tr>
<td>Vomiting</td>
<td>10</td>
<td>33.3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6</td>
<td>20</td>
</tr>
<tr>
<td>Upper GI bleeding</td>
<td>12</td>
<td>40</td>
</tr>
<tr>
<td>Lower GI bleeding</td>
<td>8</td>
<td>26.6</td>
</tr>
<tr>
<td>Intussusception</td>
<td>8</td>
<td>26.6</td>
</tr>
<tr>
<td>Intestinal pseudo obstruction</td>
<td>10</td>
<td>33.3</td>
</tr>
<tr>
<td>Arthritis</td>
<td>26</td>
<td>86.6</td>
</tr>
<tr>
<td>Renal involvement</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Microscopic hematuria</td>
<td>8</td>
<td>26.6</td>
</tr>
<tr>
<td>Glomerulonephritis</td>
<td>8</td>
<td>26.6</td>
</tr>
<tr>
<td>Nephrotic syndrome</td>
<td>4</td>
<td>13.3</td>
</tr>
</tbody>
</table>

**Table 3: Investigation profile in adults with HSP**

<table>
<thead>
<tr>
<th>Investigations</th>
<th>Mean (± SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hb (gm/dl)</td>
<td>12 (3)</td>
</tr>
<tr>
<td>Tc (×10³/μl)</td>
<td>12,200 (1860)</td>
</tr>
<tr>
<td>Platelet (×10³/μl)</td>
<td>5.5 (1.3)</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>50 (20)</td>
</tr>
<tr>
<td>Stool occult blood</td>
<td></td>
</tr>
<tr>
<td>Positive (%)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Negative (%)</td>
<td>18 (60)</td>
</tr>
<tr>
<td>Urinalysis</td>
<td></td>
</tr>
<tr>
<td>Proteinuria (%)</td>
<td>12 (40)</td>
</tr>
<tr>
<td>Hematuria (%)</td>
<td>8 (26.6)</td>
</tr>
<tr>
<td>Skin biopsy</td>
<td></td>
</tr>
<tr>
<td>Positive IF</td>
<td>20 (66.6)</td>
</tr>
<tr>
<td>CT abdomen</td>
<td></td>
</tr>
<tr>
<td>Bowel wall edema (%)</td>
<td>10 (33.3)</td>
</tr>
<tr>
<td>Intussusception (%)</td>
<td>8 (26.6)</td>
</tr>
</tbody>
</table>

**Endoscopy**

| Upper GIT hemorrhages (%)      | 12 (40) |
| Lower GIT hemorrhages (%)      | 8 (26.6) |

**Fig. 1: Hemorrhag ic bullae at presentation**

**Fig. 2: Response post steroids**

**Aims**

1. To study the various clinical manifestations of cases of Henoch Schönlein Purpura in adult (>18 years) patients
2. To compare the disease spectrum in adults with the data available in children with HSP.

**Materials and Methods**

This was a retrospective, observational, hospital-based cohort study of the clinical profile of adult patients (>18 years), diagnosed as Henoch Schönlein purpura, admitted in Goa Medical College, a tertiary care hospital and teaching institute in Goa, from Jan 2013 to Dec 2019. Institutional Ethics Committee approval was obtained. We reviewed the case papers and reports of 30 adult patients admitted in Dept of skin and medicine wards/OPD follow up in whom HSP was confirmed based on the European League Against Rheumatism (EULAR) 2010 criteria for HSP.
Schonlein purpura.

Palpable purpura (mandatory) in the presence of at least one of the following four features:
- Diffuse abdominal pain
- Arthritis (acute) or arthralgia
- Renal involvement (any hematuria and/or proteinuria)
- Any biopsy showing predominant IgA deposition

We studied various parameters like mean age, sex ratio, duration of illness, presenting features on history and examination, and various types of cutaneous manifestations, gastrointestinal, rheumatological, and nephrological and other systemic complications.

The average duration of hospital stay and disease outcomes were obtained. Various relevant lab investigations were studied including the skin biopsy histology as well as immunofluorescence picture of the lesions.

The data was compared to that mentioned amongst the children, in the review of literature and various published clinical studies.

**Results**

There were total 30 adult patients from 2013-2019, that fulfilled the inclusion criteria for HSP. Out of these 21(70%) were male and 9 (30%) females (Table 1). Male: female ratio was 2:1, suggesting a male preponderance. The mean age at presentation was 28 yrs (SD±5).

The commonest presenting features were mainly cutaneous in the form of purpura in 28 (93.3%), followed by urticarial wheals in 16(53.3%), necrotic ulcers 16(53.3%), bullae 12 (40%) while one patient did not have any skin involvement at onset of presentation but developed petechial rash after 5 days of presenting with abdominal complaints.

The rashes were mostly seen on extremities and trunk rather than on buttocks as commonly seen in children, also we noticed a higher occurrence of extensive skin lesions, hemorrhagic bullae, necrotic ulcers and urticarial wheals. The skin lesions were biopsied during active stage and sent for histology with immunofluorescence which were found to be positive in almost 66 % cases showing IgA deposition in the dermis.

Gastrointestinal involvement was seen in 80 % cases, commonest being diffuse abdominal pain 20(66.6%). Most of these patients described severe diffuse colicky pain, mimicking an acute abdomen and requiring opioids. Abdomen being soft and not showing clinical signs of peritonitis .This was followed by hematemesis in 12 (40%), vomiting 10 (33.3 %), intestinal pseudoobstruction 10 (33.3%), lower GI bleeding 8(26.6%), intussusception 8(26.6 %), and diarrhea in 6(20%).

Endoscopies performed in patients of GI bleeding showed multiple, punctate hemorrhagic erosions and pin point ulcers in stomach and esophagus and even in rectum and colon suggesting focal small vessel involvement in bowel. CT abdomen done in patients with severe abdominal pain and GI bleeding showed thickening and echogenicity of bowel wall suggestive of bowel wall edema in 10 patients and evidence of intussusception in 8 patients.

Arthritis was seen in 26 (86.6%) patients with acute, symmetrical, polyarticular, involvement of large joints and sparing of small joints. Renal involvement was seen in 65 % patients with microscopic hematuria (26.6%) and overt nephritis (26.6%) was the commonest abnormality seen in patients. 4of the patients developed nephrotic syndrome which responded to steroid therapy.

Treatment and outcome analysis: The average duration of hospitalization was 7 days while overall duration of illness was 12 (SD±5) days. Steroids were used as the mainstay of treatment and complete recovery was seen in majority of the patients within 3 weeks. Myoarthritis was seen in one patient who had refused to take steroids and was fatal while another patient succumbed to a massive lower GI bleed.

**Discussion**

Henoch Schonlein purpura (HSP) is a leukocytoclastic vasculitis involving the small blood vessels with deposition of immune IgA complexes. Although HSP primarily affects children (approximately 15 cases/100,000 per year), it is also seen in adults.1 Male preponderance in adults with HSP as seen in this study was also seen in most of the other studies.2,3,10,17

In our study the commonest dermatological manifestations included palpable purpura involving the dependent areas of both the lower limbs. This again was consistent with previous studies in adults.12 Atypical lesions like necrotic ulcers, hemorrhagic bullae, and urticarial wheals were observed in 53.3 % of patients. In a review of literature by Saghia et al13 atypical rashes, bullae, vesicles were frequently seen in adult patients. Rash on buttocks was not seen in any of our patients highlights the difference in distribution of rash in children where buttocks are frequently involved. Similar clinical differences in pattern of rash and distribution in adults were reported by Garcia-Porrua.10 Majority of the patients in our study, skin lesions showed a good response to steroid therapy, with complete resolution of lesions within a maximum time of 3 weeks. In the present study, adult patients with HSP had a more severe course and higher occurrence of atypical cutaneous presentations as compared that mentioned in children. We also found that in adults (as opposed to children), systemic involvement particularly gastrointestinal and renal
involvement is more frequent and severe. This finding was consistent with the results reported by previous studies by Garcia-Porrua et al. and Blanco et al.

In our study, the incidence of gastrointestinal complications was 80% which was much higher than that reported by other studies 35% to 70%. However the incidence of GI involvement in Indian population is lacking. A recent study in North India by Gupta v et al., frequency of GI manifestations was found in 66.7% of adult patients with HSP; however it did not differ in children. The common GI manifestations mentioned in literature include periumbilical colicky abdominal pain (worse with food intake), nausea, vomiting, diarrhea, malena, hematemia, hematochezia and abdominal distension. The abdominal pain in our patients was diffuse and not associated with any inflammatory signs such as rigidity or tenderness. This highlights the importance of considering vasculitis in the differential diagnosis of medical causes of acute abdomen in children as well as adults.

In a retrospective study by Troiller et al., of 23 patients rare GI manifestations were observed including intestinal perforation, ischemic vasculitis, intussusception, esophageal ulcers, pancreatitis, pseudomembranous colitis and extensive GI blood loss. Mucosal lesions develop anywhere within the GI tract. Hyperemic mucosa, scattered hemorrhagic purpura and hemorrhagic erosive duodenitis are characteristic endoscopic findings. All these findings were consistent with the results obtained in our study with 40% patients developing upper GI bleeding due to mucosal lesions (pin point hemorrhages) and 26% patients who had lower GI bleeding.

Usually skin manifestations precede the GI manifestations, but a literature review study by Sohagia et al. showed that in one fourth of the cases the skin lesions may appear later in the course of illness. In the current study we had 4 patients in whom GI symptoms preceded skin lesions and in one patient, skin lesions were mild however he succumbed to a massive bout of bleeding per rectum while two female patients developed acute abdominal pain with CT showing extensive bowel wall edema following resolution of cutaneous lesions. The above observations highlight the fact that skin lesion and GI symptoms may not always correlate with severity as well as in terms of temporal occurrence, in the sense the GI symptoms may precede purpura or can also develop during or after resolution of purpura.

We observed renal involvement in 65% patients which was higher than that reported in children 43%. Commonest abnormalities were microscopic hematuria, with RBC casts suggesting glomerular involvement followed by overt glomerulonephritis, and nephrotic syndrome in 4 patients. They improved with short course of steroids and there were no relapses. Kidney involvement usually determines the prognosis. Although the most frequent histological finding is mesangial proliferation, lesions range from minimal change to severe crescentic glomerulonephritis.

A significant number of patients (up to 36%) in some series may suffer permanent renal damage. The following predictors of a poor renal course in adults have been proposed: high creatinine levels at onset, proteinuria greater than 1 g/day, arterial hypertension, increase of proteinuria during follow-up, extracapillary proliferation in the renal biopsy, interstitial fibrosis and tubular atrophy.

In a North Indian study by Gupta et al., the frequency of renal involvement was found to be 60% in adults and 50% in children (difference being not significant statistically).

Myocarditis was seen in one patient who had refused to take steroids despite skin involvement and arthritis, and this lead to congestive cardiac failure and death. Cardiac involvement in Henoch Schonlein purpura is extremely rare. Myocardial necrosis in association with nephritis and tracheobronchitis was mentioned in a 63 year old Hispanic male.

Overall the occurrence of systemic involvement was seen to be more frequent and causing more morbidity and mortality as compared to the data in children mentioned in standard literature and most of the patients required steroid therapy for treatment unlike in children where majority of these cases are self-limiting.

Conclusions

1. HSP, though less common in adults than children, presents with atypical and sometimes more severe cutaneous manifestations like bullae, necrotic ulcers, urticarial wheals. Rash is usually on extremities and trunk and not on buttocks as seen in children.

2. Systemic involvement in the form of gastrointestinal, arthritis and renal is more common than children and the course of illness is often prolonged and requires steroid therapy unlike in children where majority of cases are self-limiting.

3. Skin involvement does not necessarily mirror gastrointestinal involvement in terms of severity and temporal occurrence of the two, the latter may be more severe even if skin lesions are minor/resolving.

Limitations of the Study

- Less sample size
- Hospital- inpatient based study. Hence underestimates the true incidence of HSP in adults.
- No long term follow up to asses recurrence/ relapse.

References

Assessment of Disease Activity in Rheumatoid Arthritis: A Comparative Study of Clinical and Laboratory Evaluation with Musculoskeletal Ultrasonography Assessment

Anugrah Nair¹, Punit Pruthi², Sasikala L³, Vishal Marwaha⁴, Sandeep Suredran⁵, Arun Tiwari⁶, Anne Rijo Mathew⁷

Abstract
Background: Rheumatoid arthritis (RA) is a chronic inflammatory disease and musculoskeletal ultrasonography (USG) is gaining popularity for assessing the disease activity bedside, objectively and cost effectively. There is paucity of such studies from India which establish the correlation between RA disease activity and musculoskeletal USG.

Objective: The objective of this study was to compare the disease activity scores in RA patients, assessed by ‘clinical and laboratory evaluation’ with ‘musculoskeletal ultrasound scoring of the affected joints’.

Methodology: It was a cross sectional study conducted from December 2015 to May 2017. We enrolled the diagnosed patients of RA, having at least one USG assessable joint with definite clinical synovitis. Disease activity was assessed by swollen joint count, tender joint count, Clinical Disease Activity Index (CDAI), Disease Activity Score (DAS) 28 ESR and DAS 28 CRP. Musculoskeletal USG was performed by experienced radiologist. Grayscale scores (GSUS) and Power Doppler scores (PDUS) were calculated in 22 joints as per SONAR criteria and each joint was examined as per standardized score.

Results: Our study showed that DAS 28 CRP, DAS 28 ESR, CDAI, tender joint count and swollen joints count had positive correlation (p<0.001) with various musculoskeletal USG scores, whereas ESR and CRP failed to show any significant correlation.

Conclusion: GSUS-PDUS can be used for diagnosing joint space narrowing, joint effusion, and synovial thickening. PD may become a cost-effective alternative to gadolinium enhanced MRI. Strong correlation exists between USG and physical examination of joint swelling as well as disease activity scores in RA patients.

Introduction
Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by the development of synovitis which damages cartilage, bone, ligaments, and tendons. Assessment of inflammatory activity is essential in daily clinical practice to evaluate disease outcome and response to treatment.¹ The three main components of disease progression are clinical, radiological, and functional. Currently, clinical scores to judge disease activity include DAS 28 (Disease Activity Score 28-joints count) ESR, DAS 28 CRP, and CDAI (Clinical Disease Activity Index).²,³

In patients with RA an active disease and progressive structural damage are associated with functional disability. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) are the most used inflammatory markers in RA to assess disease activity and progression. Ultrasonography (USG), magnetic resonance imaging (MRI), and computed tomography (CT) have also been used to study radiological damage at a given time point and progression over time. These newer techniques appear to be more sensitive in detecting erosions earlier than conventional radiography and correlate well with subsequent development of erosions on x-rays.⁴

Recently many studies have shown that assessment of disease activity score by power doppler ultrasonography (PDUS) and grayscale ultrasonography (GSUS) has added value and objectivity to the clinical and laboratory scoring. USG has the potential to assess disease activity in RA patients which has advantages over clinical assessment like more objectivity and better reproducibility. Higher frequency USG has greatly improved musculoskeletal (MSK) imaging in rheumatology.⁵–¹⁰

Rheumatologists have started using USG for quantitative and qualitative real-time assessment of MSK pathology. USG is increasingly being used as an extension to physical examination. Its application in rheumatology goes beyond the detection of inflammation in joints. It can differentiate between synovial hypertrophy, tenosynovitis, bursitis, and other soft tissue lesions that can mimic synovitis.¹,⁴,⁵ Apart from diagnosis, USG plays a key role in disease monitoring, assessment of damage, and therapeutics.⁵,⁷,¹¹

Growing evidence has made it clear that early and aggressive therapy of inflammatory arthritis with a treat to target approach alters prognosis significantly. assessment of RA disease
severity and identification of so that early therapeutic decisions can be made. The use of musculoskeletal ultrasonography (MSK-USG) in patients with RA could help identifying individuals who would benefit from early aggressive immunosuppressive therapy. However, there is a paucity of studies correlating clinical and radiological severity in RA patients from India. Our study was aimed to compare disease activity scores in RA patients assessed by ‘clinical and laboratory evaluation’ with ‘musculoskeletal ultrasound scorings’.

### Material and Methods

#### Study Design

This was a cross-sectional observational study conducted at the Internal Medicine and Rheumatology departments of two tertiary care hospitals in India. The study was conducted from December 2015 to May 2017. A sample size of 50 patients was calculated using PS power and sample size calculator Vs 3.1.2 and for a type I error probability error associated with the null hypothesis is 0.05. In accordance with this, 50 RA patients, visiting the internal medicine department were enrolled in the study. Patients of 18-70 years age group, both genders, and satisfying American College of Rheumatology/European Alliance of Associations for Rheumatology (ACR/EULAR) 2010 classification criteria for RA, with at least one USG assessable joint with definite clinical synovitis were included. All other conditions, other than RA causing joint damage (genetic disorders, trauma, previous surgery) were excluded.

**Patient details and clinical outcome measures**

Basic clinical information regarding age, gender, and smoking were obtained using a predesigned proforma. Patients were subjected to a thorough general and systemic examination. The RA disease activity was measured by clinical disease activity scores and ultrasound scores. The clinical disease outcome measures are:

- **Disease Activity Score 28 (DAS28)** includes joints of hands - metacarpophalangeal (MCP) and proximal interphalangeal (PIP) bilaterally, both wrists, both shoulders, both elbows, both knee joints are examined for swelling and tenderness. Logarithmic calculation of disease activity using Swollen 28-Joint Count (SJC-28), Tender 28-Joint Count (TJC-28), Patient Global Disease Activity (PGA), Evaluator’s Global Disease Activity (EGA) along with ESR and CRP values for DAS 28 ESR and DAS 28 CRP respectively. RA disease activity is defined as - high disease activity if the DAS-28 is ≥ 5.1, moderate disease activity 3.2-5.1, low disease activity ≤ 3.2, and remission ≤ 2.6. CDAI interpretation: High activity if CDAI > 22, moderate activity >10 and ≤ 22, low activity ≥2.8 and ≤ 10, and remission ≤ 2.8

- **CDAI** was calculated using the formula: CDAI = SJC (28) + TJC (28) + PGA + EGA. Here we define remission if CDAI ≤ 2.8, low disease activity if CDAI > 2.8 and ≤ 10; moderate disease activity if CDAI > 10 and ≤ 22 and high disease activity if CDAI > 22.

### Ultrasound measurements and outcome measures

We used the Swiss Sonar USG scoring. Here the joints scored are identical to those of DAS28, except for
Table 2: Correlation analysis of clinical and laboratory parameters of RA disease activity assessment with musculoskeletal ultrasonography assessment scores

<table>
<thead>
<tr>
<th>Clinical Disease Outcome Measures</th>
<th>Musculoskeletal ultrasonography assessment scores</th>
<th>GSUS</th>
<th>PDUS</th>
<th>GSUS +PDUS</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>R2 p-value</td>
<td>R2 p-value</td>
<td>R2 p-value</td>
<td>R2 p-value</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>0.629 &lt;0.0001</td>
<td>0.661 &lt;0.0001</td>
<td>0.769 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Tender joint count</td>
<td>0.578 &lt;0.0001</td>
<td>0.584 &lt;0.0001</td>
<td>0.670 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>CDAI</td>
<td>0.738 &lt;0.0001</td>
<td>0.667 &lt;0.0001</td>
<td>0.732 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>DAS 28 CRP</td>
<td>0.712 &lt;0.0001</td>
<td>0.651 &lt;0.0001</td>
<td>0.708 &lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>DAS 28 ESR</td>
<td>0.542 &lt;0.0001</td>
<td>0.526 &lt;0.0001</td>
<td>0.549 &lt;0.0001</td>
<td></td>
</tr>
</tbody>
</table>

GSUS- Grey scale ultrasonography, PDUS- Power doppler ultrasonography, CDAI- Clinical disease activity index, DAS 28- Disease activity score 28 joint count, CRP- C reactive protein, ESR- Erythrocyte sedimentation rate and R2 – Correlation Coefficient

Fig. 1: Correlation analysis of GSUS+PDUS with DAS 28 CRP (A) and DAS 28 ESR (B)

Statistical methods

The data was tabulated on MS excel and then statistical analysis was done by using SPSS software v 20.0. In cases of continuous variables data, results were presented as mean ± standard deviation (SD); while non-continuous variables are shown as proportion. The USG derived score was correlated with clinical and laboratory score values using Pearson’s correlation. A p-value of < 0.05 was considered statistically significant.

Results

A total of 50 RA patients were enrolled in the study after applying the inclusion and exclusion criteria. The mean (SD) age of the cohort was 51.24 (12.09) years. The baseline characteristics of the study participants are mentioned in Table 1.

The ultrasound score of the cohorts was calculated. The mean (SD) of GSUS score, PDUS score, and GSUS+PDUS score was 6.92 (4.36), 2.68 (2.34), and 6.96 (6.96) respectively. Correlation analysis of RA disease activity parameters with various MSK-USG scores was assessed and shown in Table 2.

The DAS 28 CRP, DAS 28 ESR, CDAI, tender joint count, and swollen joints count were found to have a statistically significant positive correlation (p<0.0001) with various MSK-USG scores, whereas CRP and ESR failed to show any significant correlation with the MSK-USG scores. The correlation analysis of DAS 28 CRP, DAS 28 ESR with GSUS+PDUS is depicted in Figure 1.

Discussion

We found out in our study that MSK-USG was as sensitive as physical examination and laboratory variables (disease activity scores) in detecting Rheumatoid joint involvement. In addition, USG findings correlated with DAS 28 CRP, DAS28 ESR, and CDAI better than with ESR and CRP alone. Our findings were in concordance with a done study by Issar et al where USG showed higher sensitivity than conventional radiography (CR) for detecting abnormalities like erosions.16 Similarly, Brown and colleagues showed that RA patients who were judged by a rheumatologist to be in remission had significant evidence of active inflammation on USG.13

Previous studies comparing clinical and USG assessment have also reported a stronger correlation between USG and physical examination of joint swelling than between USG findings and patient’s perception of joint tenderness. In a study conducted by Saigal et al of 90 patients with active RA, USG Disease Activity Score was not only more reliable in assessing disease activity but was also better at anticipating future joint damage.14 In Saigal et al study we found that USG was more sensitive than CR for the detection of erosions. USG including PDUS and greyscale imaging detected cumulative flow signal (an indicator of ongoing inflammation) in clinically quiescent RA. USG reliably predicted disease severity and had a significant correlation with other validated markers of disease activity. Ultrasound, therefore, appears to be a useful adjunct in the management of patients with RA.16,18 Recently, PDUS has demonstrated high sensitivity (88.8%) and specificity (97.9%) for the assessment of inflammatory activity in the MCP joints of patients with RA.

A systematic literature review analysis of ultrasound joint count and scoring systems to assess synovitis in RA patients according to the OMERACT Filter done by Mandal et al also concluded that USG can be regarded as a valuable tool for globally examining the extent of synovitis in the first metacarpophalangeal joints bilaterally and bilateral shoulders. One radiologist experienced in MSK-USG, who was unaware of the clinical findings assessed for synovitis in 22 joints as per SONAR criteria, and each joint was examined as per standardized score proposed by OMERACT score by using LogiqS7 expert USG machine with L8-L18i hockey stick probe (frequency 8-18 Megahertz). We recorded:

- **Grey Scale (GS) Score:** GS synovitis was evaluated using a subjective 0 – 3 scale with the definitions for each category of joint inflammation. Grade 0 = absence of hypoechoic synovial thickening Grade 1 = mild hypoechoic synovial thickening Grade 2 = moderate hypoechoic synovial thickening Grade 3 = marked hypoechoic synovial thickening.

- **Power Doppler (PD) Score:** PD synovitis scoring is evaluated using a 0 to 3 scale with the following - Grade 0 = no flow in the synovium (grey scale area), Grade 1 = up to 3 single spots signals or up to 2 confluent spots or 1 confluent spot + up to 2 single spots, Grade 2 = vessel signals in less than half of the area of the synovium (< 50%), Grade 3 = vessel signals in more than half of the area of the synovium (> 50%).

PDUS and GSUS scores were added together, and a cumulative score was determined.
RA. EULAR recommendations for the use of imaging of the joints in the clinical management of RA, 2014 also recommends that US and MRI are superior to clinical examination in the detection of joint inflammation; these techniques should be considered for more accurate assessment of inflammation. Also, the results of a study done by Jevtic et al confirmed that in joints with inflammatory active pannus detected by MSK-USG, progression of bone destructive changes are expected. Hypervascularization and angiogenesis of the synovial membrane are considered to be primary pathogenic mechanisms responsible for invasive and joint destructive behaviour of rheumatoid pannus. Similarly, a review article on Assessing RA disease activity with USG by Chakr et al concludes that USG is an excellent tool for RA inflammatory assessment as to the joint, scanning the exact joints that truly reflect overall RA disease activity, therefore predicts radiographic progression.

One advantage of USG over MRI is that examination of all peripheral joints can be done as many times as required and prosthesis or implants do not interfere with USG images. Our 22 joint counts for USG effusion, synovitis, and PD signal correlated well with the 28 joint counts. Thus, the reduced joint count could be used in US evaluation in rheumatological practice. The proposed USG evaluation of 22 joints can be performed in 15 minutes in daily practice. Recent studies have reported the validity and reliability of cheaper USG machines for assessing rheumatoid synovial inflammation. However, MSK-USG is highly operator dependent, one must ensure that the operator has been trained adequately and single operator assessment of USG parameters are a limitation of our study. As we have the standardized OMERACT group definitions, we aimed to diminish this factor.

Conclusion

A strong correlation exists between USG and physical examination of joint swelling as well as disease activity scores. Hence, rheumatologists can be trained to perform USG, removing the need for referral to a radiologist and thus saving time and money. The USG has become a useful tool in the detection of early disease, differential diagnosis, the guidance of treatment decisions, and treatment monitoring of RA. USG is inexpensive, non-invasive, and lacks radiation, and the images are acquired in real-time the combination of GSUS and PDUS could be used as a sensitive and reliable non-invasive and widely available method, complementary to standard clinical assessment for evaluating rheumatoid synovial inflammation in the daily management of patients. To Conclude, GSUS-PDUS can be used for diagnosing joint space narrowing, joint effusion, and synovial thickening. PD may become a cost-effective alternative to gadolinium-enhanced MRI. More longitudinal studies that correlate PD findings with long-term clinical changes and radiographic erosive joint damage in patients with RA are highly warranted.

References


Candida Score: a Predictor of Mortality in Patients with Candidemia

Deven Juneja¹, Ravi Jain²*, Omender Singh³, Apurba Kumar Borah⁴

Abstract

Background: Candida score has been developed and used for identifying patients at risk for developing Candida infections. However, its usefulness in predicting outcome of patients with candidemia has not been evaluated. We aimed to determine the risk factors for mortality in patients with candidemia admitted to an Indian medical intensive care unit (ICU).

Methods: We conducted a retrospective cohort analysis of 56 patients with candidemia presented in 18 months duration. Baseline patient characteristics, ICU course and outcome were noted and Candida score was calculated. We conducted analysis based on the primary outcome measure of ICU mortality.

Results: Out of 3,142 ICU admissions, the incidence of candidemia was 17.8/1,000 admissions. The mean interval between ICU admission and candidemia was 12.9 ± 14.4 days. C. tropicalis was the commonest species isolated from 28.6% isolates, followed by Candida albicans (21.4%) and C. glabrata (12.5%). The mean length of ICU stay was 22.9 ± 28 days and hospital stay was 30.1 ± 30.2 days. Crude ICU mortality was 33.93%. There was no statistically significant difference between mortality of patients with albicans and non-albicans candidemia (p=0.732). On multivariate analysis, only two factors, previous antifungal therapy (p=0.004, OR=101.4, 95% CI=4.52-227.7) and Candida score >3 (p=0.028, OR=13.2, 95% CI=1.3-125) were found to be independently predicting mortality.

Conclusion: Candida infection is generally late-onset and is associated with a prolonged ICU and hospital stay, and a high mortality. Candida non-albicans infection was more common but there was no difference in mortality among patients with C. albicans and non-albicans infection. Previous antifungal therapy and Candida score were found to be independently predicting mortality.

Introduction

Candida spp. is the most common cause of opportunistic fungal infections worldwide.¹ Candida are generally a part of normal microbial flora of skin and mucous membrane in immune-competent individuals but may cause severe systemic infections in critically ill patients with underlying disease such as diabetes mellitus, prolonged duration of stay in intensive care unit (ICU), or other factors which may suppress the immunity.² They may cause a wide variety of infections, ranging from mild mucocutaneous to severe invasive infections that can involve virtually any organ.³ Term candidemia describes the presence of Candida spp in blood stream. It is a life threatening fungal infection associated with a mortality rate of 38%. It also prolongs hospital stays by as much as 30 days and increases the cost of medical care.⁴ Candida spp. is one of the most common causes of bloodstream infection among the patients admitted in the ICU.⁵⁻⁶

Although Candida albicans remains the most prevalent species globally, there has been a clear shift towards non-albicans species namely Candida tropicalis, Candida parapsilosis, Candida kruzei particularly found in the neutropenic patients and Candida glabrata found especially in patients with solid tumor.⁷⁻⁹ Prompt and accurate diagnosis of invasive fungal infection is crucial so that appropriate antifungal agents can be started rapidly. Several prediction rules and scores based on clinical, laboratory, and microbiological parameters have been proposed to help clinicians identify patients at high risk of developing invasive fungal infections.⁹⁻¹²

The Candida score, an easy-to-use bedside assessment system proposed by Leon et al.,⁹ integrates four risk factors (total parenteral nutrition, surgery, multifocal Candida colonization, and severe sepsis). Candida score has a high negative predictive value (0.98) to rule out invasive candidiasis.¹³ The Candida score has been developed and used for identifying patients at risk for developing candida infections. However, its usefulness in predicting outcome of patients with candidemia has not been evaluated till now. In this study, we aimed to determine the epidemiology of candidemia and evaluate the risk factors for mortality in patients with candidemia admitted to an Indian medical ICU.

Material and Methods

Medical records of 18 month duration, from May 2012 to October 2013, of all the ICU admissions in a tertiary care hospital in New Delhi were analysed for presence of candidemia. A total of 3142 ICU admissions were screened and 56 patients with candidemia were selected for further analysis and outcome study (Figure 1).

For the purpose of categorization of patients, previous antibiotic use was defined as use of at least two broad

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Available records were recorded for baseline patient characteristics, isolated candida spp, ICU course and outcome in a predesigned pro forma. The Candida score was calculated as previously described by Leon et al. These data was further analysed for primary outcome measure, ICU mortality.

Blood culture and organism identification

For diagnosis of candidemia/bacteraemia, 5–10 ml blood was collected in BacT/ALERT® FA PLUS aerobic blood culture bottles (bioMe’rieux). The bottles were incubated and monitored regularly using the BACT/ALERT® 3D System (bioMe’rieux). All positive samples were processed for microbial identification by standard semi quantitative culture methods for further identification. Identification of these isolates was carried out by both conventional and automated methods. The automated VITEK 2®System ID-Sensicards were used for identification. Antifungal susceptibility to 6 drugs: amphotericin B, fluconazole, flucytosine, voriconazole, caspofungin and micafungin, was also performed with the VITEK 2® system using ID-sensicards. The minimum inhibitory concentration (MIC) breakpoints recommended by clinical and laboratory standards institute (CLSI) and European Committee on Antimicrobial Susceptibility Testing (EUCAST) guidelines were followed.

Statistical analysis

SPSS version 20.0 for Windows (SPSS Inc., Chicago, IL, USA) was used for data management and statistical analysis. Qualitative data were analyzed using Chi square or Fisher Exact tests and quantitative data were analyzed using Student’s t-test. Primary outcome measure was ICU mortality. Secondary outcome measures were organ support, which included requirement of inotropes, renal replacement therapy and mechanical ventilation and length of stay in ICU and hospital. Univariate and multivariate analysis were done to find out the factors associated with ICU mortality. All tests were two-tailed, with p< 0.05 being considered significant.

Results

A total of 3,142 patients were admitted to ICU during the period of study. The incidence of candidemia was 17.8/1,000 admissions. Fifteen patients had co-existing candiduria with the same species. The mean interval between ICU admission and candidemia was 12.9 ± 14.4 days. Majority of patients 49/56 (87.5%) had central venous catheters (CVCs) in place and were using antimicrobials 49/56 (87.5%) before developing candidemia. CVCs were removed in all of them after the diagnosis of candidemia. The baseline patient characteristics are given in Table 1.

Candida albicans was isolated in only 12 (21.4%) of candida-positive blood cultures. Among the non-albicans species C. tropicalis was the commonest species isolated from 16 (28.6%) isolates, followed by C. glabrata that was isolated from 7 (12.5%) patients (Table 2).

Among the patients with candidemia, 30 (53.6%) required vasopressor support, 23 (41.1%) required renal replacement therapy (RRT) and 36 (64.3%) required mechanical ventilation during their ICU stay. The mean length of ICU stay was 22.9 ±28 days and the mean hospital stay was 30.1 ± 30.2 days.

The crude ICU mortality was 33.93%. There was no statistically significant difference between mortality rates of patients with C. albicans and non-albicans candidemia (p = 0.732). Patient parameters such as age, admission APACHE II score, candida score, previous antifungal therapy and underlying co-morbidities, which were statistically significant in differentiating survivors and non-survivors in the univariate analysis, [Table 2] were included in the multi-variate analysis. Only two factors, previous antifungal therapy (p = 0.004, odds ratio, OR = 101.4, 95% confidence interval, CI = 4.52 to 227.7) and candida score >3 (P = 0.028, OR =13.2, 95% CI = 1.3 to 125) were found to be independently predicting mortality.

Discussion

In our retrospective cohort study, the incidence of candidemia was found to be 17.8/1000 ICU admissions and non-albicans species were found to the
predominant isolates (78.6%). A great majority of patients (87.5%) had CVCs and previous exposure to antibiotics. In multivariate analysis, that previous antifungal exposure and candida score of >3 were found to be independent predictors of ICU mortality.

Candida infection is the most common opportunistic infection worldwide with a reported incidence ranging from 6.5/1000 to 110/1000 ICU admissions.1 This wide variation may be attributed to different patient populations being studied, capricious reporting of incidence rates and variable denominators in different studies.15–20 Our reported incidence of 17.8/1000 admissions, was well within this range.

In the present study, non-albicans candida spp accounted for 78.6% of total candidemia with C. tropicalis being the most common candida isolated. A similar trend towards increasing non-albicans candidemia has been reported in various Indian ICUs with studies reporting an incidence up to 84%.15–20 This trend is in stark contrast with the contemporary epidemiological studies of candidemia coming from developed, temperate climate countries.21,22 This difference in distribution of species among the climate zones may probably help explain the disparate crude mortality figures reported from various part of the world in ICU patients with candidemia. It emphasizes the importance of knowing the local epidemiology as the empiric treatment and overall patient prognosis depends on it as inappropriate initial antifungal therapy has been shown to be associated with poorer outcomes.23

Several studies have shown that the presence of CVCs and previous antibiotic use are associated with increased risk of development of candidemia.16–20 In our patient cohort too, we found that 87.5% patients had CVC in place and had a history of previous antibiotic use.

Many scores and prediction models have been proposed for early identification of invasive candidiasis and help in early initiation of antifungal therapy, like candida score, clinical prediction rule, CI, and CCI. Among these the candida score is arguably one of the most studied and validated score among different ICU populations.9–11,24,25 The candida score, an easy-to-use bedside assessment tool, was first proposed by Leon et al for ascertaining need of antifungal treatment in case of candida colonization in neutropenic patients.9 Later it has been validated for non-neutropenic patients also.10 It integrates four risk factors (total parenteral nutrition, surgery, multifocal candida colonization, and severe sepsis) and also has a high negative predictive value (0.98) to rule out invasive candidiasis.10 But this score has never been evaluated as a prognostication model for prediction of mortality.

Contemporary studies have reported that non-albicans candida (tropicalis) infection, old age, co-morbidities, higher APACHE II score, worsening organ dysfunction, septic shock and use of corticosteroids is associated with increased risk of mortality.26–28 Whereas, in our study APACHE II score, status of co-morbidities, use of antibacterial agents, use of CVCs and TPN was not associated with any increase risk of mortality. Furthermore, we found that two factors, previous antifungal use and Candida score >3 were independent predictors of ICU mortality. Association of candida score with ICU mortality, may not be very surprising as the various components of candida score have been separately reported to be associated with poor prognosis in previous studies also.21,23,26–29

A study has found that prior antifungal exposure leads to higher chances of non-albicans candida (most commonly C. tropicalis) infections and increase in mortality.20 Although our study did not find any difference in albicans and non-albicans candida mortality, but other studies report that non-albicans candida infections have high rates of azole resistance and hence may be associated with increased mortality.16–20 One of the reasons why we did not find any difference in mortality among albicans and non-albicans infection could have been that we had initiated anti-fungal therapy with echinocandins in almost all of our patients as they were critically ill and azoles were never used as the treatment of choice.

This study has several strengths. It provides vital data for epidemiology of candidemia in medical ICU population, as other contemporary regional studies have included surgical patients that have significantly higher prevalence of candidemia.15–20 Till date, no candidemia specific prognostication model or mortality predictor tool is available. Hence, critical care physicians have to rely on general prediction models like APACHE II and sequential organ failure assessment (SOFA) score to predict the severity of disease and disease outcome. As described above various researchers have suggested different factors that may affect outcome of these patients but none have evaluated the utility of any specific score for prognostication in patients with candidemia. Although our’s is a retrospective study, it is a pioneering effort in the direction of predicting severity of candida disease and gives a positive correlation between candida score and mortality. These results if evaluated in a larger
study, may provide a strong bedside and quick assessment tool to predict mortality in these patients.

A few limitations of the present study should be noted. First, this study was inherently retrospective in design and thus missing values and potential information bias may have arisen. Second, in-vitro susceptibility results were only available for the preserved isolates, and appropriate or inappropriate therapy could not be defined for all of the study population. As a result, the analysis of mortality did not include the use of specific antifungal agents. Further multicentre prospective studies are needed to evaluate these results as well as investigate the impact of antifungal therapy and catheter removal on the prognosis of patients with candidemia.

Conclusions

Candida infection is generally late-onset in ICU patients and is associated with prolonged ICU and hospital stays, and a high mortality. Candida non-albicans infection was much more common in our cohort of ICU patients but there was no difference in mortality among patients with albicans and non-albicans infection. Patients who develop candidemia, despite being on antifungal therapy, were at a higher risk of dying and a simple bedside candida score (>3) may be useful in predicting mortality of ICU patients with candidemia.

References


Parenteral Iron in Heart Failure: An Indian Perspective

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Abstract
Iron deficiency (ID) is clinically significant comorbidity usually reported with acute and chronic heart failure (HF) and associated with prognostic outcomes, independent of anemia. The exact cause of ID and anemia and their association with HF is not entirely clear. Current evidence highlights neuro-hormonal and pro-inflammatory cytokine activation and renal dysfunction favoring the development of anemia and ID. Intravenous iron therapy (IV Iron) enhances exercise capacity, HF-associated symptoms and health-related quality of life. Oral iron therapy might be less effective compared to IV Iron in HF patients. At the same time, large, well-designed cardiovascular outcome studies are warranted to establish the long-term efficacy and safety of IV Iron in patients with HF with coexisting ID. In India, the high prevalence of anemia increases the burden of ID in patients with HF. HF being a complex multifactorial disease, it is essential to understand the association of ID with HF which can be easily corrected to improve the patient outcomes. At the same time, there is a need to generate more robust clinical evidence on IV Iron therapy for in Indian patients of HF.

Introduction
Heart failure (HF) is a heterogenous disease manifested by exercise intolerance due to impaired ventricular filling or ejection of blood or both. It is a major public health concern with substantial morbidity and mortality.¹ Presently, HF is sub-classified according to the left ventricular ejection fraction (LVEF) into 3 categories: HF with reduced (HFrEF; LVEF <40%), mid-range (HFmrEF; LVEF 40–49%), or preserved (HFpEF; LVEF ≥50%) ejection fraction.²

Globally almost 64.3 million people (8.52 per 1,000 inhabitants) are living with HF out of which almost half are patients with HFrEF. In developed countries, the prevalence of HF is estimated at 1% to 2% of the general adult population (Table 1).³

An epidemiological survey in Singapore from 1991–1998 involving 15,774 elderly patients with HF hospitals highlighted that majority of patients were of Chinese origin (77%), followed by Malay (14%) and Indian (10%).⁴

One Indian study reported HF prevalence of 1.2/1000.⁵ The projected prevalence of HF in India is about 1% of the population which is approximately 8–10 million people. The predictable mortality attributable to HF in India is about 0.1–0.16 million individuals per year.⁵ Trivandrum HF Registry highlighted that Indian patients with HF have different characteristics and profiles as compared to HF patients across the world. The important difference is in terms of the younger age of onset (61.8 years).⁶ The important factors contributing to HF are hypertension (65%), IHD (50%), chronic kidney disease (43%), atrial fibrillation (41%), osteoarthritis (36%), diabetes mellitus (27%), obesity (23%), cancer (23%) and depression (22%).⁷

ID is a commonly noted comorbidity in patients with HFrEF and HFpEF.⁸ ID was observed in almost one-third to half HF patients of Asian origin, also ID had a negative impact on the quality of life and survival in these patients.⁹ Reported evidence highlighted that in Indian patients with chronic HF, absolute ID was noted in 53.8% with more predominance in females (51.3%) than males (46.5%). Functional ID was present in 6.34% of patients with chronic HF with a more female predominance.¹⁰ Almost two-third and one-fourth of Indian patients with HF reported ID with or without anemia respectively.¹¹

Similar results were reported from a north Indian registry suggesting ID prevalence of 58.8% with a higher rate in women than in men (72.2% vs. 42.0%). About one-third of the patients reported anemia. ID was considerably higher in patients with anemia compared with those without anemia (91.4% vs. 40.6%).¹² Interestingly in patients with HF, ID was prevalent more in patients with Indian origin than Malays and Chinese origin (81.6 vs. 62.9 vs. 58.1% in HF, P =0.001).¹³

Over the past few years, a substantial change in the management of HFrEF was noted with the successful use of antagonists of maladaptive biologic pathways, including vasodilators, angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs), beta-blockers & mineralocorticoid receptor

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Iron Deficiency in Heart Failure

Comorbidities associated with Heart Failure

Comorbidities associated with HF often lead to poor prognosis, increased hospitalizations and mortality. Therefore, awareness and prompt attention to these comorbidities are needed. These comorbidities are mainly cardiovascular (CV) and non-CV as mentioned Table 2.14

Iron Deficiency in Heart Failure

ID with or without anemia is usually underreported amongst all comorbidities associated with HF. ID is widespread in chronic HF patients. ID is diagnosed when serum ferritin is <100 µg/L, or when serum ferritin is between 100–300 µg/L with transferrin saturation <20%.15,16 ID has been classified as absolute and functional. In absolute ID body iron stores are depleted, thus impairing hemoglobin synthesis and ultimately leading to anemia. The causes of absolute ID are drug interactions, poor dietary intake of iron, gastro-intestinal malabsorption and gastrointestinal blood loss. In functional ID, iron is trapped inside the reticuloendothelial system, rendering it unavailable for cellular and metabolic processes. Functional ID is coupled with pro-inflammatory cytokines, including hepcidin, which traps iron in the reticuloendothelial system and prohibits dietary iron uptake.17 Reported evidence suggests that independent of anemia, ID is a strong predictor of HF severity, left ventricular function and all-cause mortality, in patients with HF.18 The pathophysiology of ID in HF is complex.19 In patients with HFrEF, over-activity of renin-angiotensin-aldosterone system (RAAS) and sympathetic nervous system noted in addition to inflammation. This leads to inhibition of transferrin receptor protein 1 (TFRI) which is required for iron transfer into cells, thereby leading to ID. In view of this IV iron is useful as it bypasses intestinal absorption. In addition to oxygen transport, iron is essential for crucial enzymes involved in the citric acid cycle and reactive oxygen species scavenging. Therefore ID leads to reduced exercise capacity, fatigue, poor prognosis and increased rate of hospitalizations.19 Activation of neurohormonal and proinflammatory cytokine along with renal dysfunction lead to development of anemia.20 There are many clinical and prognostic consequences of ID in HF21 which are summarized in Table 3.

Recent data suggests that certain new molecules viz: hepcidin, ferroportin, divalent metal transporter are involved in the iron metabolism.22 Oral iron is easily available, cheap and convenient to administer however there is limited evidence and lower efficacy in terms of its clinical and biochemical efficacy in HF patients compared to IV iron.
The Iron Repletion Effects on Oxygen Uptake in Heart Failure (IRONOUT-HF) trial highlighted that oral iron supplementation insignificantly increased iron stores and did not improve exercise capacity in patients with HF, with reduced ejection fraction and ID.\textsuperscript{21} Interestingly, high hepcidin levels were linked to poor repletion effects of oral iron. As chronic HF is always associated with chronic low-grade inflammation which augments pro-inflammatory cytokine and hepcidin levels in whom oral iron therapy might be less desirable compared to IV Iron in HF patients with high hepcidin levels.\textsuperscript{24,25}

**IV Iron Therapy in HF**

The clinical evidence from randomized, placebo-controlled studies involving patients with HF and coexisting ID, reported a satisfactory effect on exercise capacity, functional class improvement, LVEF, renal function and quality of life with the administration of IV Iron. Clinical studies with ferric carboxymaltose (FCM) as parenteral Iron therapy revealed good efficacy in terms of improvements in NYHA class; 6-min walk test; peak oxygen consumption; and quality of life (Table 4). Also, the results from meta-analysis suggest beneficial effects of FCM in terms of decreased hospitalization rates and reduction in cardiovascular mortality in HF patients.\textsuperscript{26}

Two meta-analysis of IV Iron in patients with HF are reported. One analyzed five clinical trials involving 851 patients with HF, of which 509 received iron sucrose or FCM. The analysis demonstrated that the IV Iron in patients with HF reduced the combined endpoint of death or CV hospitalizations due to worsening of HF. Further, there was an improvement in NYHA functional class, an increase in 6 min walk distance and improvement in the quality of life using different assessment tools.\textsuperscript{32} The second meta-analysis evaluated four randomized clinical trials comprising 839 patients of which 504 received IV FCM. Patients who received IV FCM had shown a lower incidence of CV mortality and recurrent CV hospitalizations. Improvement in recurrent HF hospitalizations and all-cause mortality was correspondingly noted.\textsuperscript{33} IV Iron therapy had shown some promising clinical and biochemical improvements in chronic HF patients as well. Large scale trials with long-term follow-up with more clinical endpoints are needed to assess the definitive role of IV Iron in the treatment of ID in chronic HF patients. Unless this data is available, IV iron therapy should at least be considered in patients of HF with coexisting ID for improvement of HF-related symptoms, quality of life and recurrent hospitalisations.\textsuperscript{7}

As discussed earlier, a high prevalence of ID with female predominance is noted among patients with HF. Also, many Indian studies noted patients with ID tend to have advanced NYHA class,\textsuperscript{11,34,35} In India, the female gender, vitamin B-12 deficiency, shortage of iron and folic acid supplementation and vegetarian diet are possible causes for ID. Unfortunately, there is no sufficient data on IV Iron in Indian patients with HF and coexisting ID. Therefore, there is a need for studies of IV Iron in these types of Indian patients of HF with ID evaluating its role in terms of reduction in hospitalizations, mortality and improvement in the quality of life.\textsuperscript{5,6,10,11,34,35}

The current evidence supports the effectiveness and safety of IV Iron therapy in patients of HF with coexisting ID. The choice of the formulation will depend upon the cost, availability and convenience in terms of frequency of visits required for administration IV Iron for correcting ID.

Currently available IV Iron preparations are FCM, Iron Sucrose, Iron dextran, Ferumoxytol, Ferric pyrophosphate citrate and Ferric gluconate. Iron dextran has a higher incidence of anaphylactic reactions while iron sucrose and ferrous gluconate need frequent low doses of administration at multiple settings. FCM is a colloidal iron hydroxide complex that can be administered in a single large dose with reasonable cost. Therefore, FCM is preferred in settings where rapid correction of the ID is indicated.\textsuperscript{36}

A French study analyzed the budgetary impact of FCM in patients with chronic HF and ID. The study highlighted that cumulative cost savings resulted from a reduction in the hospitalization costs associated with worsening HF (€-35.8m) as well as a reduction in the follow-up costs (€-2.9m). These cost savings balanced the costs of FCM treatment (€37.7m).\textsuperscript{37} Cost per patient was lower in all countries, with reductions ranging from EUR 36 to EUR 484. The main driver for decreased costs was fewer hospitalizations.\textsuperscript{38} This signifies FCM is a cost-saving alternative for the treatment of chronic HF patients with ID.\textsuperscript{39}

The convenience and number of administration required for IV Iron are important factors in the selection of iron preparation, besides the cost. These factors are critical in terms of less interruption in patient’s personal life, less time away from home and work and less time spent traveling to health care center for IV Iron administration.\textsuperscript{40}

**Guidelines Recommendation for IV Iron**

Various guidelines recommend evaluation of iron status as a part of the diagnostic workup for all newly diagnosed HF patients (Class I, Level C). These guidelines recommend treatment of ID based on serum ferritin level of <100 µg/L, or 100–299 µg/L when TSAT < 20%. IV Iron therapy with FCM is recommended for the treatment of ID and should be considered in all symptomatic patients with EF < 45% and ID (Class IIa, Level A). Oral iron therapy is not effective to treat ID in a patient with chronic HF.\textsuperscript{41,42} 2021 ESC Guidelines mentioned periodic screening of all patients with HF for anemia and iron deficiency as Class I recommendation. Also mentions IV iron supplementation with FCM in symptomatic HF patients recently hospitalized for HF and with LVEF ≤50% and ID to reduce the risk of HF hospitalization as Class IIa recommendation.\textsuperscript{43}

**Future directions for IV Iron and HF**

There are few ongoing clinical trials viz: FAIR-HF2 (NCT03036462), HEART FID (NCT03037931) and IRONMAN (NCT02642562) to assess the mortality and morbidity benefits from IV Iron therapy in patients with HF.\textsuperscript{43} FAIR-HpEF (NCT03074591) will reveal the effects of IV Iron in HFMpEF with ID.\textsuperscript{46} The newer evidence which will be generated through these studies will help us to find a place in therapy for IV Iron in management of patients of HF with coexisting ID.

**Conclusions**

In developing countries like India, there is a burden of HF with coexisting...
ID. Usually, the ID is underreported in patients of HF and this needs to be addressed by evaluation of ID as a part of the routine diagnostic workup in patients with HF. Prompt correction of ID with IV Iron will improve the clinical outcomes, enhances exercise capacity and better quality of life. Based on current clinical evidence, FCV can be administered as a single dose in patients with HF which is recommended in various guidelines as well. Unfortunately, there is limited clinical evidence of IV Indian patients of HF with coexisting ID. There is an urgent need for generating new clinical evidence of IV Indian patients of HF with coexisting ID.

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A Rare Cause of Breathlessness in a Patient on Hemodialysis

Varun Gulshan Bansal¹, Umesh Balkrishna Khanna¹, Agam Vora², Bhavin Shah², Aakash Shingada¹

Abstract

Patients suffering from end stage renal disease (ESRD) often present to the emergency with breathlessness, mostly due to fluid overload. We report a rare case of recurrent unilateral massive pleural effusion in an ESRD patient on maintenance hemodialysis (MHD). The patient was on MHD thrice weekly for the last 2 years with right internal jugular vein (IJV) tunneled cuffed catheter (TCC). Chylothorax was identified as the cause of recurrent pleural effusion which was due to superior vena cava stenosis (SVCO). It was managed successfully by balloon venoplasty of SVC and anticoagulation. SVCO is a rare but a serious complication in patients on long term indwelling dialysis catheters. Physicians involved in the care of dialysis patients must be aware about complications of long term dialysis catheters like central vein stenosis. A strong suspicion of chylothorax should be reserved for a patient with recurrent unilateral pleural effusion and long term dialysis catheters.

Case Description

A 43 year old gentleman suffering from hypertension and stage 5 chronic kidney disease (chronic tubulo-interstitial disease) was initiated on MHD with right IJV TCC. After 18 months, left brachiocephalic arterio-venous fistula (AVF) was constructed. Once AVF matured after a period of 8 weeks, TCC was removed and AVF was used for MHD. Patient noticed gradually progressive swelling involving left arm over one month and secondary AVF failure. Examination revealed prominent collateral veins on chest wall (CT Image Figure 1). A venogram of the neck veins revealed distal right IJV thrombus (Figure 2) and significantly attenuated calibre of left and right brachiocephalic vein with long segment tight stenosis of SVC (Figure 2). Right innominate vein and SVC balloon venoplasty was done and right external jugular vein (EJV) TCC was inserted. The patient presented with repeated attacks of breathlessness without any constitutional symptoms after 2 months. Investigations revealed recurrent massive right pleural effusion. Repeated thoracentesis revealed sterile exudative effusion which tested negative for tuberculosis (Adenosine Deaminase and TB Genexpert were negative). Pleural fluid cytology was negative for atypical cells. Further examination revealed high concentration of triglycerides in pleural fluid (1770 mg/dl) confirming the diagnosis of chylothorax. Patient required ICD insertion for symptom relief and was started on anticoagulation with apixaban. Patient had significant improvement in his symptoms over next 3 weeks and ICD was removed. There was no recurrence of effusion. Patient continues hemodialysis with right EJV TCC awaiting kidney transplant on last follow up.

Discussion

Nontraumatic chylothorax is a relatively rare condition in which the intestinal lymph (chyle) leaks into the pleural cavity from the thoracic duct or one of its tributaries.¹ When untreated, chylothorax is associated with high morbidity and mortality. The diagnosis, which is often elusive, should be prompt so that therapy can be quickly initiated. Malignancies such as lymphomas, chronic leucocytic leukemia, lung carcinoma are typically the leading causes of nontraumatic chylothorax.² SVC obstruction presenting as chylothorax is very rare.³ Most patients with chylothorax present with dyspnoea induced by the mechanical effects of a pleural effusion. Additional symptoms include a heavy feeling in the chest, fatigue, and weight loss. Fever and chest pain are rare because chyle within the pleural space does not evoke an inflammatory response and rarely becomes infected due to the bacteriostatic effect of immunoglobulins that are contained in chyle.⁴ Chylothorax should be suspected in a patient who presents with a persistent or recurrent pleural effusion of obscure etiology that is milky, turbid, bloody, or serosanguineous as noted through thoracentesis or in chest tube drainage. Because a milky or opalescent appearance of the pleural fluid is noted in only approximately one-half of patients with chylothorax, a high degree of suspicion is needed.
Five Times Reactivation of COVID-19 in a Patient with Thymoma

Manoj Meena, Krishnapriya S Kumar, Govind Singh Rajawat, Sumit Kumar Jain

Abstract
Background: The possibility of recurrence in COVID-19 is very rare and hence mostly underdiagnosed. In the face of pandemic, this can lead to circulation of the virus like a hidden iceberg. Better understanding about this topic can improve our knowledge of the COVID-19 pathogenesis and ways to control the transmission.

Case presentation: A 41 year old male with no known comorbidities was admitted five times during a period of 7 months each time after being detected RTPCR positive for SARS-CoV-2 and more symptomatic than previously. He had no contact with other COVID-19 patients and was asymptomatic in between admissions. Despite this, he did not develop antibodies against SARS-CoV-2. Later on, he was diagnosed with thymoma on biopsy of the anterior mediastinal mass. Patient's condition deteriorated on last hospitalization and he died, despite the treatment. Here we present an interesting report on multiple times recurrent COVID-19 infection, probably a case of reactivation and different plausible explanations on the role of thymoma.

Conclusion: Acknowledging the potential of SARS-CoV-2 to cause recurrence is very important during the pandemic as a part of the long term transmission mitigation. The case report shows that previous infection does not guarantee complete immunity from COVID-19, especially in immuno-compromised patients. Hence, despite the status of prior infection, vulnerable individuals who recovered from COVID-19 should be under surveillance.

Introduction
The rapid spread of coronavirus disease 2019 (COVID-19) was declared as a pandemic by the World Health Organisation on March 2020. As various measures have been taken successfully to combat the epidemic caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), a growing number of fully recovered patients have been discharged from hospitals. However, some of them have relapsed. Recurrent COVID-19 infection is a new entity and is underdiagnosed. Despite the improvement of our
knowledge about this virus, it is still a challenging and controversial matter, whether all patients with SARS-CoV-2 infection will reactivate the illness and which risk factors predict eventual recurrence. A recent cohort study observed 27% incidence of COVID-19 reactivation during a median follow-up of 29 days. Better knowledge on this topic is important to understand the immune responses to the virus and contain disease transmission.

Case Report

A 41 year old male, active smoker and policeman by occupation, from Dausa, Rajasthan was admitted in district hospital on day 7 of symptom onset. He presented with complaints of loss of smell and taste for one week and detected COVID-19 positive for first time by reverse transcription polymerase chain reaction (RT-PCR) assay of oropharyngeal swab. Patient did not report any underlying medical condition or immunosuppression. After improvement on symptomatic treatment, he was discharged with twice negative swab (day 12 and day 15) and remained quarantine for next 14 days.

On day 34, he developed symptoms of dyspnoea, cough and fever and chest x-ray showed bilateral consolidation. He was hospitalized again in COVID Containment Unit (CCU) under SawaiMan Singh (SMS) Medical College and was detected second time positive for SARS-CoV-2 by RT-PCR assay of both oropharyngeal and nasopharyngeal swabs. Patient was treated with favipiravir, hydroxychloroquine and azithromycin. He became asymptomatic and got discharged after negative COVID report on day 54. During the 14 days quarantine period, he remained afebrile.

Computed tomography (CT) chest done in view of persisting mediastinal widening in chest radiographs, showed ill-defined soft tissue density mass lesion measuring approximately 74mm*55mm*78mm in right paramediastinal location with parenchymal changes suggestive of interstitial lung disease (ILD). 2D-Echodcardiography revealed no abnormality. He was planned for biopsy of the mass lesion, but pre-procedural COVID testing came out to be positive on day 78. He was asymptomatic and advised strict quarantine for next 14 days. But, his RT-PCR for COVID19 was persistently positive on days 91 and 100.

Later, patient was referred again to CCU for hospitalization on day 103 with complaints of worsening dyspnoea and fever. He was diagnosed with COVID-19 infection for the third time as his RT-PCR was positive with detection of genes “E” and “RdRp” at Ct values of 17 and 21, respectively. He did not give any history suggestive of contact with COVID-19 cases during quarantine period. His SARS-CoV-2 serology was negative for both IgM and IgG. Based on ICMR guidelines, patient had moderate form of disease (SpO2 <94%) and was treated with oxygen via face-mask upto 40% FiO2, remdesivir, enoxaparin, dexamethasone and symptomatics. He improved on treatment and swab tests came negative for COVID on day 119. He was maintaining oxygen saturation on room air and met the discharge criteria. After discharge, his symptoms gradually improved and disappeared completely during quarantine.

Repeat contrast enhanced CT (CECT) thorax and whole abdomen (Figure 1 a, b) revealed the poorly demarcated anterior mediastinal mass with abutting of superior vena cava and also findings suggestive of ILD (NSIP pattern). CT imaging (Figure 2) which showed glass opacity in bilateral lung parenchyma likely sequelae to COVID pneumonitis.

Fig. 1: (a, b) CECT Thorax showing solid heterogeneously enhancing poorly demarcated anterior mediastinal mass with abutting of superior vena cava and also findings suggestive of ILD (NSIP pattern)

Fig. 2: PET-CT showing negligible FDG avid (metabolically very minimally active) lobulated mass in anterior mediastinum (SUV 2.7) with multinodular enhancement pattern and minimal FDG avid randomly distributed fibrosis and ground glass opacity in bilateral lung parenchyma likely sequelae to COVID pneumonitis
RT-PCR), epidemiological history, real-time polymerase chain reaction detection in nasopharyngeal swab by mainly depends on SARS-CoV-2 RNA 2–14 days. The diagnosis of the disease incubation period is approximately transmission, etc. are also possible. other routes such as direct contact, oral–faecal route, mother-to-child as fever, cough, anosmia, dyspnoea, shock, his condition deteriorated and entered in CCU and managed. His clinical condition improved in few days and got discharged with negative COVID report on day 182. He was again referred for resection of the tumour.

After an asymptomatic quarantine period of 15 days with no close contact with other COVID patients, he was tested COVID RT-PCR positive for fifth time on day 197. He was brought to hospital with central cyanosis, severe respiratory distress and altered sensorium. He was admitted in COVID ICU and intubated. Despite the treatment, patient went into septic shock, his condition deteriorated and he died 3 days later.

**Discussion**

SARS-CoV-2, a highly contagious virus, belonging to the family Coronaviridae, is an enveloped, positive-sense single-stranded RNA virus. WHO designated the disease caused by SARS-CoV-2 infection as COVID-19. In December 2019, in Wuhan, China first case of COVID-19 was reported and the virus then rapidly spread to over 200 countries in a short time period.

The main route of transmission is via aerosolised droplets, while other routes such as direct contact, oral–faecal route, mother-to-child transmission, etc. are also possible. Incubation period is approximately 2–14 days. The diagnosis of the disease mainly depends on SARS-CoV-2 RNA detection in nasopharyngeal swab by real-time polymerase chain reaction (RT-PCR), epidemiological history, clinical manifestations and lung imaging. The most common symptoms are fever, cough, anosmia, dyspnoea, fatigue, diarrhoea and myalgia.

The invasion and pathogenesis of SARS-CoV-2 are associated with the host immune response. The virus invade by binding spike glycoprotein (S protein) on the viral envelop to its receptor, angiotensin-converting enzyme 2 (ACE2), on the surface of human cells (eg. alveolar epithelial cells). Innate immunity is the first line of defence against virus infections. Type-I interferons (IFN) are ubiquitously expressed cytokines that contribute to both innate and cellular immunity against viral infections. SARS-CoV-2 tends to inhibit IFN production through multiple mechanism, thereby enhancing its replication capacity. Weakened innate immunity cause delayed stimulation of adaptive immunity, which play an important role in viral clearance via activated CD8+ cytotoxic T cells and antibody-producing B cells. CD4+ helper T cells stimulate B cells to produce specific antibodies.

Recurrent COVID-19 infection is a rarely diagnosed entity. So far little is known about the causes of recurrence of SARS-CoV-2 infection. Few studies concluded that the possibility of recurrence is very low and the causes of repositivization are false positive test or prolonged shedding of dead virus as the true positive detection rate of RTPCR test ranges from 30-60% and the half-life of respiratory epithelial cells being 1-2months, the non-viable viral RNA fragments can be detected during this period. But in our patient, the possibility of these are low as he was more symptomatic during each hospitalization. Therefore we consider this patient as a case of recurrence.

Recurrent can occur due to reactivation with the same strain or re-infection with a different strain. Reactivation or relapse is caused by activation of the dormant virus persisting in the body. It is a re-detectable positive viral RNA in a recovered patient which occurs within the first 4 weeks of previous infection. Probable explanation is that despite a negative RTPCR test, virus may be present in other organs with abundant ACE2 receptors like kidney, small intestine (ileum), bladder, myocardium, etc. which can reactivate anytime. Reinfecion is subsequent COVID-19 infection after recovery from a previous infection. Few studies supporting reinfecion by a new strain of virus with a different gene sequence has been reported but the underlying pathogenesis is still under study. Our patient was in strict isolation according to quarantine norms and the possibility of reinfection with a new strain is unlikely. The absence of antibody production even after repeated infection is also in favour of reactivation.

According to Lafaie et al. study, a probable COVID-19 recurrence may have symptoms with repeat positive SARS-CoV-2, clinical and radiological worsening, positive cell culture during the second episode and absence of neutralizing antibody. Though many studies have concluded that the repositivization might be attributed to false-positive laboratory results and prolonged viral shedding, rather than recurrence, the failure of protective antibody formation might be the key reason for the possible recurrence of SARS-CoV-2 infection. But in this particular patient, there is yet another plausible explanation, discussed below.

Thymomas are rare tumours arising from thymic epithelial cells. Function of thymus is maturation, differentiation, positive and negative selection of T cells. Negative selection prevent autoimmunity by eliminating T cells that react with self-MHC or self-peptides. Thymoma causes autoimmunity as the thymocytes escape negative selection and becomes auto-reactive. According to the combined cellular and humoral deregulation theory, these CD8+ T cells initiate an autoimmune cascade and activation of CD4+ T cells which in turn activate B cells to produce autoantibodies. Autoantibodies to IFN-α, IFN-λ, IFN-ω and interleukin-12 (IL-12) are seen in thymomas. Anti-cytokine autoantibodies may be important in the pathogenesis of opportunistic infections in patients with thymic malignancy. Bastard P et al. showed in their study that neutralizing IgG autoantibodies against type-I IFNs, including IFN-ω and IFN-α can lead to life-threatening COVID-19. Presence of neutralizing anti-cytokine autoantibodies against type-I IFNs can affect both innate and adaptive immune responses against viral infections like COVID-19 leading to reactivation of the disease.

Studies have reported that anti-SARS-CoV-2 IgM antibodies were detectable 1-4 days and IgG antibodies after 14 days from symptom onset in most patients. According to WHO, a negative antibody test against SARS-CoV-2 could mean no prior exposure, immunosuppression or samples collected too early (<14 days from symptom onset). The most plausible
though many studies dispose the concept of re-infection in COVID-19, this case report shows that it is not unlikely and should be kept in mind while treating repeatedly positive COVID-19 patients. Such patients can be contagious and should be thoroughly evaluated and followed up, rather than ignoring it as a dead virus detection. More precautions needed while declaring patients recovered and monitoring of vulnerable patients with regular follow-up should be emphasized in public health policies. Underestimation of reactivation can end in catastrophe.

List of Abbreviations


Declarations

Ethics approval and consent to participate- This study was approved by the ethics committee of SMS Medical College, Jaipur and informed consent were waived.

Consent for publication: Written informed consent was obtained from the nearest kin of the patient.

Availability of data and materials: All data used during the study are available from the corresponding author on reasonable request.

Acknowledgements: Authors would like to thank the patient’s family for their kind cooperation.

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Johann Heller-Father of Clinical Chemistry

Jayan Pai-Dhungat

Still 1970s, teaching hospital wards had a small attached side laboratory equipped with necessary chemical reagents, stains, test tubes, burner, centrifuge and a microscope. Resident physicians had to carry out basic 3-5 lab tests of every admitted patient. Although overtaxing, it also gave us good training in the laboratory medicine.

Johann Florian Heller (1813–1871), was an Austrian chemist, and is considered father of clinical chemistry. He was born in Iglau, Czechoslovakia, and earned his PhD in chemistry at the University of Prague; Heller later studied chemistry under Justus Liebig (1803–1873) and Friedrich Wohler (1800–1882) in Germany. During these years he characterized rhodizonic acid and its potassium salt (1837).

Heller joined Allgemeines Krankenhaus (Vienna’s General Hospital,) in 1842. Here he was influenced by the premier pathologist Karl von Rokitansky (1804–1878) who had personally carried out more than 30,000 autopsies. Rokitansky believed that diseases are due to abnormality of body fluids. Heller’s interest was to determine the chemical background and changes in the body fluids in various diseases, and he established a laboratory of pathological chemistry in the Vienna Hospital (1843). Heller studied chlorides, urea nitrogen, and proteins in the blood and body fluids in diseases like Bright’s disease, cholera, anasarca; he also detected lead in lead poisoning cases. While studying the chemistry of urine, he developed his well-known Heller’s nitric acid ring test for albumin in the urine (1852) which is used till today. He also developed the caustic Potash Test for blood in urine. Bens John’s protein in urine was also observed by Heller but complete test was only worked out by Bens John. Heller also identified a fatty substance that he called urostealith, a constituent of certain bladder stones (1845).

Heller’s appointment as head of the lab was delayed until 1855, because some of the faculty thought that the position should be occupied by a medical doctor.

Florian Heller founded the first journal which exclusively deal with pathological chemistry in 1844 with him as editor. His contributions were well recognized and today the Austrian Association for Clinical Chemistry (ÖGKC) awards a scientific prize named after Johann Florian Heller.

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Pragmatic Parsimony in COVID-19 Management

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Sir,

Coronavirus disease 2019 (COVID-19) has overwhelmed the health care systems and medical resources across the world. Health care professionals struggle to cope with the challenges and demands of exceedingly large numbers of patients. This situation calls for resource husbandry at all levels of policy-making, planning and provision, and budgeting of health care.

The law of Therapeutic Parsimony states that “minimal necessary therapeutic interventions should be used, in place of multiple ones, as long as this can achieve equivalent therapeutic outcomes”2. A related law, the law of Investigative Parsimony proposes that “minimal investigations should be employed for screening, diagnosis, monitoring and follow up of disease, provided this does not adversely affect patient recovery and outcome”3.

These concepts overlap with the philosophy of resource husbandry, which encourages judicious and optimal use of all available resources.1 A few simple suggestions, as detailed below, may offer relief to the overstretched health care system during the COVID-19 pandemic. We use the term ‘pragmatic parsimony’ to describe our approach.

Prevention: Prevention is better than cure. Follow personal and social hygiene to prevent COVID-19 infection. Vaccination against COVID-19 prevents severe disease and death and remains one of the proven approaches to minimize the impact of the deadly pandemic.

Screening: Flu-like symptoms with the loss of smell and taste is specific for COVID-19 infection. When testing is unavailable and there is a clustering of cases in the household, we need to treat them as COVID-19 infection unless proven otherwise. Samples can be pooled for analysis in low prevalence areas. The use of rapid-antigen testing at the point of care is helpful when RT-PCR is not readily available.

Evaluation: Investigations should be ordered if the results will influence clinical decision-making. Serum creatinine/eGFR, basic liver enzymes, complete blood count, C-reactive protein, and D-dimer are mandatory, but serum lactate dehydrogenase, gamma-glutamyl transferase, ferritin, and especially interleukin-6 (IL-6) in mild cases will rarely be necessary as it does not change the therapeutic decisions. Serum IL-6 should be advised only if clinically indicated.

High-resolution computed tomography (HRCT) should be ordered if there are specific symptoms pointing to lower respiratory tract involvement and the results are expected to alter the therapeutic strategy. Situations, where HRCT is mandated include persistence of high fever beyond the eighth day, hacking cough on deep breathing, chest congestion or drop in oxygen levels, especially on exertion or six-minute walk test. A repeat HRCT scan is a waste of resources unless searching for specific causes of non-response to therapy such as secondary bacterial or fungal infections.

Triaging: Optimal triaging should be based upon overall health status and patient, family preferences, and advance directives by the patient. Efforts should be channelized to save salvageable patients who do not have terminal diseases.

Medical management: Therapeutic strategies that have proven benefit should be employed. Drugs such as multiple antibacterial agents with no demonstrated antiviral efficacy increase the cost of therapy and offer a sense of false reassurance. The chance of dispensing error also increases with poly-pharmacy. A large proportion of these patients are elderly and susceptible to adverse effects from multiple medicines. Indiscriminate use of steroids, especially early in the first week, should be strictly avoided. Steroid to date is the only therapy that has mortality benefit but should be judiciously administered in indicated situations, at the right time, in the optimal dose, and for the appropriate duration (with the need for gradual tapering in most cases). We would again like to re-emphasize, probably at the cost of being repetitive, that optimal use of steroid therapy at the right point in the course of infection to the appropriate candidate can prevent disease progression to severe category and prevent hospitalization.

Nursing management: Nursing staff is in closest contact with patients, and hence, at maximum risk of infection.4 Barrier nursing must be ensured. Nursing activities should be based upon the principle of pragmatic parsimony and limited to essential care.

Respiratory management: Oxygen is a life-saver for hypoxic patients with COVID-19 pneumonia and should be used judiciously. Prescribing oxygen only to those who need it and ensuring efficient delivery without wastage conserves this life-saving therapy. Leakage in ports can cause up to 30% wastage. The use of nonpharmacological maneuvers such as awake proning is also recommended to optimize oxygen delivery.2 It is equally important that oxygen should be weaned off during recovery whenever the requirement goes down.

Focusing on the above aspects of COVID-19 management will ensure optimal utilization of health care resources and assist us in tackling this pandemic.

References

Apoplectic Ambulation to an Apocalyptic Abyss: Why we should not do Crazy Experiments on Humanity without Ethical Evaluation?

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Sir,

Two events have cast a serious doubt on the continued existence
Gain of function research was considered too risky and hence most experts had warned of the risks of conducting such experiments without proper safety. While the world was still reeling from the effects of this pandemic on lives and livelihoods came news of a scenario which was to violate the solemn assurance of preventing the weaponisation of artificial intelligence. Asimov had given the famous laws of robotics where the robots would never ever harm a human being. At that moment it seemed a faraway happenstance. But in May 2021, Operation Guardian of the Walls played out in the Middle East between Israeli forces and Hamas in and around the Gaza strip. Israel’s operation against Hamas was the world’s first overt artificial intelligence (AI) war. Intensive strikes were carried out against Hamas and alleged Islamic Jihad key infrastructure and personnel. An advanced AI platform collected signal intelligence (SIGINT), visual intelligence (VISINT), human intelligence (HUMINT), geographical intelligence (GEOINT) data on these groups in the Gaza Strip analysing and extracting information as and when required using algorithms and programs like “Alchemist,” “Gospel” and “Depth of Wisdom.” The Gospel suggested targets in even real time like missile launchers firing at Tel Aviv and Jerusalem. Five minute warnings were issued to civilians to clear out of the buildings before they were leveled to ground by bombing. Hamas’s underground “Metro” tunnel network was mapped using intensive multi signal data gathering and Big Data to fuse all the intelligence. They claimed to have complete picture of the network above and below ground including such vital parameters like depth and thickness of the tunnels. In addition, the “Iron Dome” and “David’s Sling” brought down the missiles directed at the Israeli targets with great accuracy.

Both these developments represent the unleashing of powers which humans would find hard to control and thereby hastening the extinction of the species. In April 2013, the Campaign to Stop Killer Robots was formed and now has membership of over 27 countries. It requested governments and the United Nations to issue policy to outlaw the development of lethal autonomous weapons systems (LAWS). United Nations Secretary-General António Guterres called for a ban on killer robots in 2018 as he felt that, “For me there is a message that is very clear – machines that have the power and the discretion to take human lives are politically unacceptable, are morally repugnant, and should be banned by international law.” Prior to it over 200 technology companies and 3,000 programmers signed a public pledge that they would “not participate nor support the development, manufacture, trade, or use of lethal autonomous weapons.” About a thousand experts in artificial intelligence in 2015 had warned of the threat of an arms race in military artificial intelligence while advocating a ban on autonomous weapons. This famous charter was presented in Buenos Aires at the 24th International Joint Conference on Artificial Intelligence (IJCAI-15). It was signed among others by Stephen Hawking, Elon Musk, Steve Wozniak, Noam Chomsky, Skype co-founder Jaan Tallinn and Google DeepMind co-founder Demis Hassabis.

While the intellectuals across the world have been warning of impending catastrophe some countries like Israel, Russia, South Korea, the United States and the United Kingdom have opposed it. They want the existing international humanitarian law to regulate work in this area. Slaughterbots, a short film by Campaign to Stop Killer Robots looks at a scenario where terrorists could unleash swarms of tiny drones capable of identifying and killing specific people. The dystopian future where rogue HAL lives for its algorithm in the famous “2000: A Space Odyssey” was to impress upon the humans that the big red button should remain in human control.

Both these developments now underline the need to have an international regulatory control over ethical development of these two technologies as self regulation has clearly failed and put entire humanity in danger.
the incidents. A greater role of public oversight mechanisms to check abuse of power vested in the scientists is imperative. Only time can tell if we will rise to the occasion or humanity will rue this missed last warning.

References


Changing from Tenofovir/Emtricitabine to Cabotegravir for Pre-Exposure Prophylaxis for HIV in Men who have Sex with Men: A Cost-Utility Analysis from an Endemic Country

Beuy Joob1, Viroj Wiwanikit2

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Sirs,

HIV is still an important global public health problem. The high incidence is still observed in many areas of the world such as Africa and Southeast Asia. In Indochina, the HIV infection is endemic and there are many local people infected with HIV. The prevention for HIV important is very important and there are many local public health policies for HIV prevention. A new preventive measure is the use of pre-exposure prophylaxis (Prep) program. This program has just been used for a short period and the local standard regimen is Tenofovir/Emtricitabine (TFN/ETB). The recent study form Thailand confirmed for the cost effectiveness of using HIV Prep by TFN/ETB. The prophylaxis is specifically used for HIV prevention in men who have sex with men (MSM), which is the main group of high risk population for HIV infection in this area.

Recently, new evidences show that there is a newer alternative pre-exposure prophylaxis using cabotegravir. Comparing to the classical TFN/ETB regimen, according to the study by HIV Prevention Trials Network 083, the higher effectiveness or the HIV prevention rate, is observed in cabotegravir regimen. Therefore, it should consider for feasibility for changing from the TFN/ETB to cabotegravir for Prep for HIV. The simulation on the mentioned scenario is done the the cost utility values comparing between TFN/ETB regimen cabotegravir regimen are analyzed. For analysis, the standard cost utility analysis technique as used in previous studies is done. Cost is assigned as overall unit cost of the HIV Prep per person per year. For utility, the data on effectiveness or incidence rate of no HIV infection of both regimens in the referencing study by HIV Prevention Trials Network 083 is directly referred to. For simulation, the cost and cost utility of TFN/ETB regimen are based on the previous referencing report and cost of is according to the most updated data on cost of carbotegravir in 2020. Finally, the cost unit value is assigned as cost per utility. Based on this analysis, the cost of carbotegravir is about 4.2 times higher than TFN/ETB (Table 1). At present, based on cost-utility analysis, the classical TFN/ETB is still more appropriate than cabotegravir for this setting.

Table 1: Cost utility analysis of pre-exposure prophylaxis for HIV in men who have sex with men comparing between Tenofovir/Emtricitabine and cabotegravir regimens

<table>
<thead>
<tr>
<th>Regimens</th>
<th>Cost (USD)</th>
<th>Utility (%)</th>
<th>Cost utility value (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tenofovir/Emtricitabine</td>
<td>221.34</td>
<td>98.79</td>
<td>224.05</td>
</tr>
<tr>
<td>Cabotegravir</td>
<td>935.01</td>
<td>91.62</td>
<td>1020.53</td>
</tr>
</tbody>
</table>

References


Emergency Medicine in India - First Step towards Capacity Building

Arva Koushik1, Aiman Perweeen Afsar2, Tarun Kumar Suvarvi3, Lokesh Edara4, Arunachalam Einstein5, Ashima Sharma6

1Emergency Medicine, Nizam’s Institute of Medical Sciences, Hyderabad, Telangana; 2MBBS Student, Maulana Azad Medical College, New Delhi; 3MBBS Student, Dr NTR University of Medical Sciences, Vijayawada, Andhra Pradesh; 4Assistant Professor, Medicine, WMU School of Medicine, MI 49007, United States; 5Professor, Emergency Medicine, Providence Regional Medical Centre Everett, Washington; 6Professor, Emergency Medicine, Nizam’s Institute of Medical Sciences, Hyderabad, Telangana

Sirs,

India is witnessing the momentum to increase the postgraduate seats in the speciality of Emergency Medicine because of the clause of the mandatory department by 2022 in all teaching hospitals. The need was realised way back in 2009 when the Medical Council of India (present National Medical Council) had recognised emergency medicine as a separate academic department. The National Board of Education also acknowledged the same in 2013. However, over the last 12 years, only 144 MD and 139 DNB Emergency Medicine seats have been granted by the Officiating Medical bodies. This should be viewed seriously in context of the standard treatment guidelines for most common emergencies e.g., Time is Muscle as in acute coronary event, Time is Brain for stroke, Golden Hour of Resuscitation for trauma, the first hour sepsis bundle and the rapid triage of a Covid-19 patient.

Sir, we want to bring to your notice the comparative statistics of our postgraduate seats to the other countries. There are 46704 total active physicians in 2020 in emergency medicine in the United States (population of 330 million), with an overall density of emergency physicians per 100,000 population as 14.9. We are
the second-largest populated country in the world (with more than 1.36 billion people) and four times more populated than the US. 467044 casualty cases reach our emergency departments every year with a 3% steadily increasing number of emergencies yearly. Unfortunately, our Emergency trained physician density is very dismal. The USA has one emergency physician for 6757 people. If we want to improve our emergency medical care to the same standard, we should also aim for the same ratio and build a force of 192390 emergency physicians to cater to our population. This can be achieved by at least allotting 11,340 pg seats in emergency medicine every year.

The World Health Organization (WHO) has promulgated a desirable doctor-population ratio as 1:1000. India plans to have MBBS admissions from 83,000 (current number) to 104,000 by 2024 to achieve one physician to 1000 people. However, there is a further roadblock as postgraduate seats are currently only 45000 with a significant disparity of specialities. An unpublished survey of medical interns in India has shown that young doctors are more willing to choose emergency medicine as their postgraduate course.

Using the mathematical equations suggested by James Holliman et al, supply should be equal to number of Emergency Physicians at the beginning of the year plus annual residency graduates minus annual attrition; demand should be 5 full-time equivalent positions/ED X the number of hospital EDs.

The Medical Board should encourage the growth of this much-needed speciality for improving early resuscitation and stabilization of critically ill patients. We strongly recommend a fair share of 20% of the present total postgraduate seats for emergency medicine. It will not be an easy task as it will still take 40 years to realise the dream of appropriate and timely emergency care of patients.

Impact of Health Care Worker Burnout on Patient Outcome in Infectious Pandemic

Prakhar Gupta1, Mehak Singh2
Assistant Professor, Dept. of General Medicine, 1Assistant Professor, Dept. of Dermatology, LN Medical College, Bhopal, Madhya Pradesh

Sir,

Burnout is work-related stress syndrome which can manifest in a variety of professions1 and can have varying implications. Healthcare workers (HCWs) also experience burnout in a variety of settings2 and prior studies have shown its unfavorable impact on patient care.3 Studies have shown similar findings among HCWs in the ongoing COVID-19 pandemic across various countries including India.4

We conducted an observational study to determine the impact of burnout among HCWs in a dedicated COVID-19 facility on patient outcome in terms of mortality percentages with increasing duration of involvement in such facility. The duration of study was from 1 August to 30 December 2020. Burnout was determined using Copenhagen Burnout Inventory. Questionnaire was shared using messaging apps and participant anonymity was ensured. Burnout questionnaire was handed out after 3rd month of consecutive COVID-19 duties (October, 6th month of beginning of pandemic in India). The questionnaire had 3 domains: personal, work-related and pandemic related burnout. Each domain had different set of questions and each question had 5 response categories. The scores ranged between 0 to 100 points and cut-off was >50 points).

Total number of admitted patients was charted for every month and number of deaths per month were then compared. The mortality percentages for the first 4 months were charted against the 5th month (December) as patient admissions were suspended during second half of November due to expiration of COVID-19 care facility contract, assuming a reduction in burnout after a break in hospital workload.1 Patients were age and gender matched for all the months. After collection of data, correlation was determined between increasing duration of duties with mortality percentages for subsequent months.

Results

Total number of participants was 310 (Table 1). Range of age w. Most prevalent burnout domain was pandemic related (50.7%) followed by personal burnout (42.3%) and work-related (30.2%). More than half of the respondents feared contracting COVID-19 infection (53.9%) and carrying the infection home (51.8%). Other significant factors contributing towards burnout were pressure of staying separately from family, fear of death due to the infection, not being appreciated enough by the institute and feeling unwelcome in the society after being involved in high risk zones (COVID ICUs, emergency dept, COVID-19 wards etc.). More than 30%

Table 1: Distribution of healthcare staff, burnout and month-wise mortality rates

<table>
<thead>
<tr>
<th>Profile</th>
<th>Number (Percentage)</th>
<th>Work Zones</th>
<th>Number (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor</td>
<td>90 (29.0)</td>
<td>High Risk</td>
<td>272 (88%)</td>
</tr>
<tr>
<td>Nurses</td>
<td>153 (49.3)</td>
<td>(ICU, ER, Ward)</td>
<td></td>
</tr>
<tr>
<td>Technicians</td>
<td>25 (8.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Support Staff</td>
<td>42 (13.5)</td>
<td>Low Risk</td>
<td>38 (12%)</td>
</tr>
<tr>
<td>Total</td>
<td>310 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Domain Burnout %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pandemic</td>
<td>50.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Work-related</td>
<td>30.2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Personal</td>
<td>42.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aug</td>
<td>1.27</td>
<td>67</td>
<td>9</td>
</tr>
<tr>
<td>Sept</td>
<td>2.23</td>
<td>65</td>
<td>9</td>
</tr>
<tr>
<td>Oct</td>
<td>2.68</td>
<td>65</td>
<td>14</td>
</tr>
<tr>
<td>Nov</td>
<td>2.72</td>
<td>61</td>
<td>7.5</td>
</tr>
<tr>
<td>Dec</td>
<td>1.33</td>
<td>59</td>
<td>11.5</td>
</tr>
<tr>
<td>Total</td>
<td>1.99</td>
<td>63</td>
<td>10.6</td>
</tr>
</tbody>
</table>

References

of the participants admitted colleagues being the most significant source of support during the current scenario.

A total of 3801 patients were admitted over 5 months and 76 deaths took place during that period, mortality percentage was 1.99%. Mean age among the deceased patient was 63± 2.69 years the mean duration of hospital stay between admission and death being 10.6 days (median 10.5, mode 1, SD 6.12 days).

We observed a gradual increase in mortality percentage with each passing month from August up till November (Table 1) and then subsequent fall in mortality percentage in December when the hospital staff received break from duties during second half of November (Figure 1). The average number of days between hospital admission and death was minimum for the 4th month of study (7.5 days) along with highest mortality percentage.

The Pearson correlation coefficient between increasing duration of COVID-19 care facility duties (in months) and mortality percentage was 0.91 for the months before break from hospital duties, it came down to 0.13 after the hospital staff received break.

**Discussion**

More than half of the participants reported pandemic related burnout, almost one-third reported work-related burnout. Our observations suggest that there is a strong correlation between increasing duration of hospital shifts during a pandemic with worsening patient outcome. This is further evident by decreased timeframe of hospital stay between admission and death of the patient after 4 months of consecutive shifts. The mortality percentage reduced significantly after the hospital staff received a break. Various studies have suggested healthcare workers experiencing burnout when burdened with stress and overwork, this happens particularly when healthcare system is overwhelmed during situations like a pandemic, COVID-19 being the most recent one. Measures like psychological support, incentives, peer support are needed to be in place to reduce the burnout among healthcare workers in order to improve patient outcome as well as maintaining efficiency of healthcare facilities not just during a pandemic but also during routine times.

**References**

isolation clothing during work. Hence, the body is in a state of physical and mental fatigue.3

This study showed that nurses working in jumbo COVID centers showed moderate levels of burnout, disengagement and exhaustion. They did not have a good quality of life and showed little job satisfaction. Psychiatric counseling must be done on a regular basis for such healthcare workers to assess their levels of anxiety and depression.

References

COVID-19, DM and Mucormycosis: Prevention is a Mother of Cure

Himmatrao Saluba Bawaskar
Bawaskar Hospital and Clinical Research Centre, Mahad, Dist. Raigad, Maharashtra

Sir,

I read with great interest the most brilliant piece on mucormycosis published in your esteem journal by the team doctors from Pune and Mumbai.1 Admire their complete gold standard review on the role of steroids, pathophysiology of mucormycosis and possible its intervention. Threat of mucormycosis not only seen in COVID-19 but also in uncontrolled hyperglycemias, malnutrition, and bad ENT hygiene. Recently there were many news in news paper regarding life threatening infection by mucormycosis including death and blindness. These cases are reported from tertiary care hospital with ARDS on long duration of excessive steroid and ventilators. Usually these burned out cases are referred to tertiary care hospital from a primary care or peripheral hospital where they received incomplete initial treatment. At primary care hospital patient is treated as a common cold but failed to take detailed history of fever, body ache, dry cough, weakness, transient diarrhoea, loss of taste and smell sensation, exertion dyspnoea, recent onset of hyperglycemias without rise in HbA1C as a result of cytokine storm, lymphopenia, eosinopenia and raised CRP and altered SPO2 saturation after six minutes walk. It is most painful that many victims died in ambulance, waiting for oxygen and ventilator bed. In my experience if the COVID-19 victim properly intervened in early phase, no victim required such advanced facilities. Even excessive oxygen for long time is tissue toxic.

At mahad we managed 1500 COVID-19 cases of which 232 gave history exposure to family member quarantine at home due RT-PCR positive. 1260(84%) cases reported within one week after the initial symptoms, of these 330(22%) had uncontrolled diabetes, while 450(30%) had recent onset of hyperglycemias. Those cases with symptomatic COVID -19 with lymphopenia, eosinopenia and raised CRP were given oral flavipiravir (antiviral), ivermectin a antiviral action of ivermectin can be attributed to its role as an inhibitor of nuclear transport for the translocation of various viral species protein indispensable for their replication; this inhibition appears to affect a large number of RNA viruses including SARS-COV-2 beta virus.2 Aspirin, glyiphage given to all victims (as a peiotropic action), doxycyline a anti-inflammatory drug. Aspirin, glyciphage given to all victims (as a peiotropic action), doxycyline a anti-inflammatory drug. Aspirin, glyciphage given to all victims (as a peiotropic action), doxycyline a anti-inflammatory drug. Aspirin, glyciphage given to all victims (as a peiotropic action), doxycyline a anti-inflammatory drug. Aspirin, glyciphage given to all victims (as a peiotropic action), doxycyline a anti-inflammatory drug. Aspirin, glyciphage given to all victims (as a peiotropic action), doxycyline a anti-inflammatory drug.

References
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