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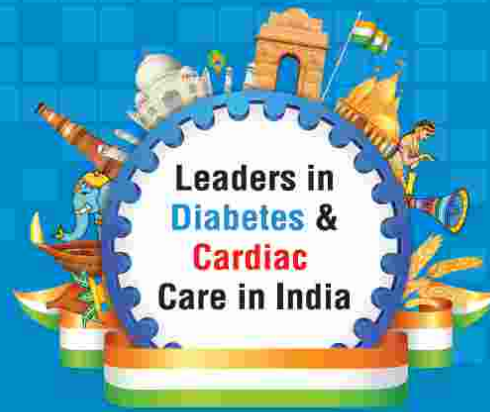
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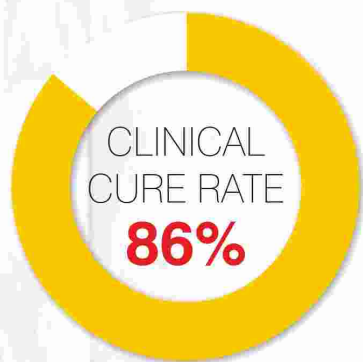
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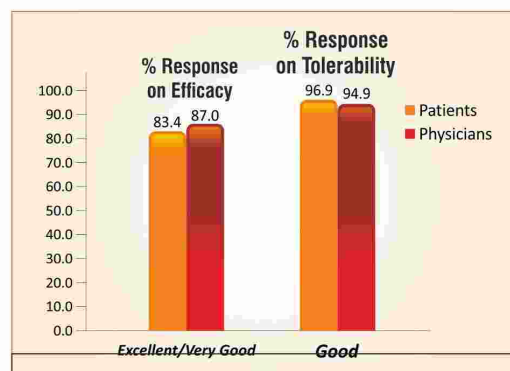
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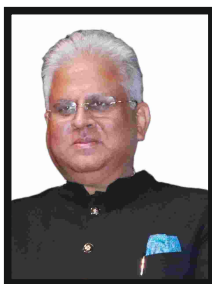


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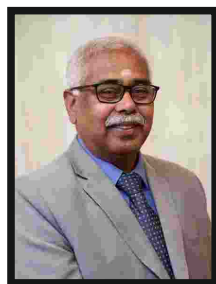
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## Editorial

### The Contagion

The world is witnessing one of the worst disasters ravaging the human race in recent times. The COVID 19 pandemic caused by Severe Acute Respiratory Syndrome corona virus 2 (SARS-CoV-2) which has claimed more than 110,000 lives in 210 countries (as of 12 April 2020).



**Prof. (Dr.) Jyotirmoy Pal**  
MD, FRCP, FICP, FACP  
WHO Fellow, Honorary Editor, JIMA

#### The Scenario

The word pandemic is derived from the Greek word "pan" meaning all and "demos" meaning people. A pandemic is defined as "an epidemic occurring worldwide, or over a very wide area, crossing international boundaries, continents and usually affecting a large number of people". The classical definition includes nothing about population immunity, virology or disease severity.

A true pandemic occurs when almost simultaneous transmission takes place worldwide irrespective of seasons or hemispheric distribution. In the case of pandemic influenza A(H1N1), widespread transmission was documented in both hemispheres between April and September 2009.

The two distinctive characteristics of a pandemic are transmissibility and severity both of which are proving to be considerable in the present scenario.

#### The Reason

The curse of civilization that is, densely populated metropolitan cities, more extensive trade routes, increased communication between different countries, people, ecosystems and urbanization in the developing world, all have led to rapid transmission of infectious diseases.

The notable pandemic of the past namely the bubonic Plague in the 14th century, (The Black Death), the Great Plague of London (1665, which killed 20% of London's population), the Spanish flu (1918), the "Asian Flu" in East Asia in 1957, (H2N2 strain), and the most recent flu pandemic in the US, the "Swine Flu," in 2009 (novel influenza virus, H1N1), have all taught us important lessons on preparedness, readiness and response strategies to combat them but we humans seem to be caught unaware every time.

#### The Response

Many countries are using a combination of containment and mitigation activities to delay major surges of patients and level the demand for hospital beds. Most national response strategies include varying levels of contact tracing and quarantine; promotion of public health measures, including handwashing, respiratory hygiene, and social distancing; preparation of health systems for an onslaught of severely ill patients who require isolation, oxygen, and mechanical ventilation; strengthening health facility, infection prevention and control, and postponement or cancellation of large-scale public gatherings. Finally, research gaps about COVID-19 are being addressed and registries are being created for evaluating hydroxychloroquine prophylaxis.

#### The Consequence

The pandemic has led to severe global socioeconomic disruption, the postponement or cancellation of sporting, religious, political and cultural events, and widespread shortages of supplies exacerbated by panic buying. Schools, universities and colleges have closed in 193 countries, affecting approximately 99.4 percent of the world's student population. Misinformation about the virus is rampant online, and there have been incidents of xenophobia and discrimination.

Two pandemics are engulfing the world at present, the viral and the economic. A pandemic of anxiety over the economic consequences is also at large. Business closures, rising unemployment, and loss of income lead to financial anxiety, which may, in turn, prevent people, desperate for work, from taking adequate precautions against the spread of the disease. Observing successive diminution in stock prices is also creating panic and a vicious cycle.

However every cloud has a silver lining. Due to reduced travel and closures of heavy industry, there has been a decrease in air pollution and carbon emissions, the birds have reappeared on the city treetops. So the human race may yet rise above this mountain of despair and learn from its mistakes.



## Review Article

## A REVIEW ON CARDIORENAL SYNDROME

\* Prof. Dr S Arulrhaj \*\*Dr Princy John P

**Abstract**

Cardio-renal syndrome is a blanket term which is used to denote clinical conditions where there is coexistence of cardiac & renal deteriorations. Considering the multitude of articles written about this topic, still the underlying pathophysiological mechanisms continue to be puzzled and implications for management continue to be debated. A classification for CRS has been proposed in 2008 which is being used in clinical practice. There is also need for cardio-renal interdisciplinary team for early identification of decompensated cardio-renal syndrome and their appropriate management. Here we review the epidemiology, classification of CRS, the pathological mechanisms proposed & then focus on management strategies. In this review article, we try to summarize the results from MEDLINE, PubMed, Cochrane Library, Google and Google Scholar search (last article updated till 2019) on the current understanding Cardio-renal syndrome.

**Keywords:** Decompensated Heart Failure, Nephropathy, Frusemide, Cystatin C

**INTRODUCTION**

The refined relationship between the kidney and the heart was first described in 1836 by Robert Bright<sup>1</sup>. From then onwards, numerous researches & trials were made to explain the cardio-renal link in terms of the phenotypes, pathophysiological mechanisms, treatment and prognosis.

**Definition**

The very first attempt of defining CRS has been put-forward by the National Heart, Lung, and Blood Institute in 2004, where CRS has been described as an interaction between the kidneys and other circulatory compartments that increase circulating volume, which in-turn exacerbates the symptoms of cardiac failure and progression of the syndrome<sup>2</sup>.

The first official definition of CRS was formed at a consensus conference of the Acute Dialysis Quality Initiative in 2008<sup>3</sup>. It defined Cardio-renal syndrome as disorders of the heart and kidneys whereby acute or chronic dysfunction in one organ may induce acute or chronic dysfunction of the other. We can broadly divide it into 2 major groups, Cardio-renal and Reno-cardiac syndrome<sup>4,5</sup>. On the basis of sequential organ involvement this was further grouped into 5 subtypes. The main goal for defining this syndrome was to categorize the clinical presentation, to develop new diagnostic markers and apt management of CRS.

**EPIDEMIOLOGY**

The Acute Decompensated Heart failure National Registry showed that 30% of patients admitted with acute decompensated HF had chronic renal disorder (CKD).<sup>3</sup> It is difficult to get accurate epidemiological data, but it's estimated that 25% to 63% of patients with cardiac failure have some sort of Cardio-renal syndrome.<sup>4</sup>

\* MD, FRCP(G),FRCP(L), MBA, National President API :  
Chief Physician & Intensivist, Head of Acute Medicine,  
Sundaram Arulrhaj Hospitals, Tuticorin  
\*\* DNB General Medicine Resident,  
Sundaram Arulrhaj Hospital, Tuticorin

**Editor's Comment**

- \* Cardiorenal syndrome is a common, but often missed clinical entity.
- \* Vascular inflammation, Oxidative stress and accelerated fibrosis are potent factors in the pathophysiology of this condition
- \* Both cardiac and renal biomarkers are to be used for diagnosis of the condition
- \* Diuretics remain the mainstay of therapy but braking phenomenon can limit its utility
- \* Further trials are needed for deciding on the use of valsartan/sacubitril or nesiritde in cardiorenal syndrome

As per the study by Forman et al, irrespective of cardiac failure, with or without preserved ejection fraction, an increased serum creatinine on admission and worsening renal dysfunction during admission in the hospital, both were associated with long duration of inpatient stay and an increase in mortality.<sup>5</sup>

**CLASSIFICATION****Acute Cardio-renal syndrome (type 1)**

Type 1 Cardio-renal syndrome is characterized by acute worsening of cardiac function resulting in an acute kidney injury (AKI). There are 4 subtypes for Acute Heart failure: Hypertensive pulmonary edema with preserved left ventricular systolic function, acutely decompensated chronic HF, shock, & predominant right ventricular failure.

**Chronic Cardio-renal syndrome (type 2)**

Type 2 Cardio-renal syndrome is characterized by chronic cardiac dysfunction resulting in renal dysfunction. It is the most common and has been reported in 63% of patients admitted with congestive HF.<sup>6</sup> The mechanism is probably because of chronic renal hypo-perfusion.

**Acute Reno-cardiac syndrome (type 3)**

Type 3 Cardio-renal syndrome is characterized by acute cardiac dysfunction due to acute renal dysfunction. The exact incidence and prevalence of type 3 CRS is unknown but from multiple case studies it shows that, in acute kidney

injury, there is cardiac dysfunction. The rise of newer biomarkers and the researches for prevention and management strategies in Acute kidney following radiocontrast or cardiac surgery can also give an insight regarding our knowledge of how Acute kidney injury can induce changes in cardiac function.

**Chronic Reno-cardiac syndrome (type 4)**

Type 4 Cardio-renal syndrome describes Chronic kidney disease leading to cardiac dysfunction (left ventricular failure or diastolic Heart failure). In one of the recent meta-analysis, it described an exponential relation between the severity of renal dysfunction and the risk for all-cause, comparing with a 'normal' glomerular filtration.<sup>7</sup>

**Secondary Cardio-renal syndromes (type 5)**

Type 5 Cardio-renal syndrome is characterized by simultaneous cardiac and renal dysfunction due to a systemic condition whether it will be acute or chronic. The importance is to permit future investigations to know the frequency of combined acute kidney and heart dysfunction in patients with these secondary causes.

**PATHOPHYSIOLOGICAL MECHANISMS REVISITED**

**Neuro-humeral mechanisms**

For many years the reason for kidney dysfunction in

cardiac failure patients was mainly thought to be due to renal hypoperfusion which was secondary to decrease cardiac output.<sup>8</sup> From the ESCAPE Trial (Evaluation Study of Congestive Heart failure and Pulmonary Artery Catheterization Effectiveness) (9), it could not find a correlation between renal and cardiac functional index, and improvement of cardiac function didn't improve renal function. Results from other similar studies also found that there was no role in improving renal function, when there was an improved cardiac functional index or reduced pulmonary wedge pressure.<sup>10,11</sup> In addition, even in patients with normal ejection fraction, worsening of renal function was also found to occur.<sup>12</sup> From all these evidences, mechanisms other than simple renal hypoperfusion should be considered in cardio-renal syndrome.

**The Renin-Angiotensin-Aldosterone System & Vascular inflammation**

RAAS activation is a mechanism to prevent reduced perfusion. But as concluded by Pueyo et al, Angiotensin II also has adverse effects on the circulatory system especially in heart failure patients, which can increase myocardial oxygen needs. But one among the foremost advances recently discovered is the role of vascular inflammation<sup>13</sup>. The Nicotinamide adenine dinucleotide

**Renal Biomarkers in CRS**

Markers of Glomerular Filtration and Integrity

Biomarkers	Source	Diagnostic Value	Prognostic Value
Serum Creatinine	Skeletal muscle	AKI, CRS	HF, CRS
Cystatin C	All nucleated cells	CRS	CRS
Albuminuria	Marker of glomerular integrity	CRS	CRS

**Markers of Renal Tubular Injury**

Biomarkers	Source	Diagnostic Value	Prognostic Value
Serum NGAL	Neutrophils, myocardium, renal tubules, activated immune cells	AKI	CRS
Urine NGAL	Loop of Henle, collecting ducts	AKI, CRS	CRS
NAG	Proximal convoluted tubule	CRS, AKI	CRS
KIM-1	Type 1 cell membrane glycoprotein expressed in regenerating PCT epithelium	AKI	CRS
IL-18	Cytokine mediating inflammation and AKI through the nuclear factor-κB pathway	AKI	CRS
H-FABP	Cardiomyocytes , distal tubule	HF, CRS	--
Urine angiotensinogen	--	AKI, CRS	CRS

AKI, acute kidney injury; CKD, chronic kidney disease; CRS, cardiorenal syndrome; cTn, cardiac troponin; CysC, cystatin C; ellipses (...), data not available or reported.; HF, heart failure; H-FABP, heart-type fatty acidbinding protein; IL, interleukin; KIM-1, kidney injury molecule-1; NAG, N-acetyl-κ-d-glucosaminidase; NGAL, neutrophil gelatinase-associated lipocalin; PCT, proximal convoluted tubules. (22-26,50)

Biomarkers	Origin	Diagnostic Value	Prognostic Value
BNP, NT Pro BNP	Marker of myocardial stretch	HF, CRS	HF, CRS
sST2	IL-1 family of receptors	(--)	HF, CRS
Galectin-3	$\beta$ - Galactoside binding lectin	(--)	HF, CRS

*BNP, B-type natriuretic peptide; ST2, soluble suppressor of tumorigenicity; HF Heart failure; ellipses (--), data not available or reported(27-29,50)*

phosphate oxidase (NADPH) enzyme is activated by Angiotensin II, which result in reactive oxygen species formation. Research evidences suggests that these reactive oxygen species radicles are liable for inflammatory processes and can result in early organ dysfunction (14). Oxidative stress also increase the production of pro-inflammatory mediators such as IL-1, 6 & TNF alpha (interleukin-1, interleukin-6, and tumor necrosis factor alpha)<sup>15</sup>. Among these Interleukin-6 can stimulates fibroblasts can result in both cardiac & renal fibrosis.

#### The role of Sympathetic Nervous System in CRS.

The activation of SNS is also a protective mechanism in CCF patients, akin to RAAS activation. SNS over activity results in reduced adrenoceptor sensitivity in both renal and cardiac failure<sup>16</sup>. It can also result in increased apoptosis of myocytes & release of neuro-hormone, mainly Neuropeptide Y. This may act as a vascular growth promoter resulting in neo-intimal atherosclerosis formation<sup>17,18</sup> & can cause vasoconstriction.

#### The Emergence of Cardio-renal Anemia Syndrome (CRAS)

Silverberg et al. first described Cardio-renal anemia syndrome<sup>19</sup>. They suggested anemia as a condition caused by dysfunction of either heart or kidney dysfunction but which can also exacerbate dysfunction of either of these organs.<sup>20</sup> Evidence from CHARM study (Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality) suggested that anemia was an independent adverse prognostic indicator in CCF patients<sup>24</sup>. However, we discover that, for CRAS, there's a scarcity of consensus over the exact definition followed by management of these patients & there's a vital need for large-scale RCTs.

#### Newer update-Role of Fibrosis in Cardio-renal Syndrome

Travers et al concluded after a cardiac insult, myocardial remodeling occurs when myo-fibroblasts secrete extracellular matrix proteins, but this can result in cardiac fibrosis & subsequent heart failure. In the kidney, the tubule interstitial cells differentiates & can synthesis extra cellular matrix & result in fibrosis<sup>21</sup>. Thus fibrosis can be considered as a newer pathophysiological mechanism for Cardio-renal Syndrome, which should be focused intimately through future trials.

#### AHA Scientific statement- A New dimension in the diagnostic algorithm of CRS

Early diagnosis of CRS, allows early intervention strategies which might hopefully prevent further clinical deterioration. Therefore, the novel biomarkers for Cardio-renal

syndrome, as included in AHA statement 2019, becomes promising.

#### A REVIEW ON CURRENT MANAGEMENT OF CARDIORENAL SYNDROME

Medical management of patients with Cardio-renal syndrome remains challenging at times as evidence for treatment in heart failure from most of trials have excluded patients with renal impairment, apart from this 5 different subtypes of CRS, by itself throws unique challenges in management.

#### The New definition for Renal failure in Cardiorenal syndrome

Besides the typical threshold changes in serum creatinine or eGFR, the new definition require a deterioration in heart failure status not leading to hospitalization (chronic heart failure) or deterioration in heart failure status in which it fails to improve or there is a need for inotropes, ultrafiltration, or renal replacement therapy (acute heart failure). This new definition enable better detection of true worsening renal function.<sup>30</sup>

#### Diuretics

Diuretics always remains the mainstay of management in fluid overload in cardio-renal syndrome. But there's limited data from large trials proving mortality benefit for diuretics in CRS. According to data from the ADHERE registry 81% of decompensated heart failure patients were using long-term diuretics<sup>31</sup>. Studies have shown that, Furosemide may decrease GFR & can also stimulate fibrosis.<sup>30,32</sup> There's unfortunately a scarcity of high-quality trial to support or refute the utilization of diuretics in patients with cardio-renal syndrome. So until there is a definitive report that diuretics is harmful in patients with heart failure, diuretics can be given in fluid overload in CRS patients. This also supported by a Cochrane review<sup>34</sup> in which continuous IV Furosemide decreased mortality rate & reduced the admission days.

#### Diuretic use & Braking Phenomenon in CRS

A recent update in diuretic usage is that it induce, the braking phenomenon within the short term of diuretic therapy and distal tubular hypertrophy within the future. This phenomenon signify decreased diuretic efficacy with serial doses. It is assumed that Sodium loss, during diuretic therapy plays a role in the braking phenomenon<sup>35</sup>.

#### Angiotensin-Converting Enzyme (ACE) Inhibitors

RAAS inhibitors have convincing evidence of benefit on prolonging survival and reducing morbidity in patients with Heart failure, as recommended by both US and European guidelines providing a Class I, LOE (A). The CONSENSUS

(Cooperative North Scandinavian Enalapril Survival), study revealed considerable increase in creatinine levels when started on ACE inhibitors.<sup>36</sup> But in this trial the treatment outcome was better, even when the creatinine was increased. To be on safer side, when used along with diuretics as in case of CRS, an accompanying reduction of diuretic dosage is advisable.

### **Aldosterone Antagonists**

In patients with CRS, similar to ACE inhibitors, aldosterone antagonists also benefits. The RALES and EPHEBUS trials demonstrated that, in patients already receiving standard medications for cardiac failure, adding low-dose spironolactone or eplerenone dramatically improved the result<sup>37,38</sup>. During a study of Norwegian HF outpatients with renal dysfunction, in patients treated with spironolactone there was a 2-year improvement in survival compared to the propensity-matched patients not treated with spironolactone. From one of the recent study from the Swedish Heart Failure Registry which reported an interaction between usage of spironolactone and renal function concerning all-cause of mortality, pointing out a relatively more favorable effect of spironolactone in patients with decreased GFR.<sup>39</sup>

As recent advances in Cardio-renal syndrome pathophysiology confirms, Aldosterone can trigger a cascade of mechanisms that typically causes fibrosis within the heart, vessels, and kidneys which will reciprocally evolve into a cardio-renal syndrome, thus proving the utilization of mineralocorticoid receptor antagonists capable of providing organ protective effects in CRS.

From our experience in the management of CRS, we observed a benefit of using high dose spironolactone, but serum potassium levels were monitored. But our observations were from a small group of patients, it needs a standard control group & further research. Nevertheless, we believe that our findings and those from other trials indicate it's time to conduct a RCT regarding the long-term effects of high dose spironolactone in patients with CRS.

### **Inotropic Support in CRS**

Patients with CRS are mostly hypotensive, if it is associated with heart failure frequently, will end in frank cardiogenic shock or severe hypotensive episodes, but low-dose dopamine is understood to extend renal blood flow. Many trials shown improvement of heart function with dobutamine and milrinone in proportion to renal blood flow, however, there was not much mortality benefit. The OPTIME-HF( Outcomes of a Prospective Trial of Intravenous Milrinone for Exacerbations of a Chronic Heart Failure) trial rejected the hypothesis that milrinone would improve overall renal function and survival.<sup>40</sup> The complexity of pathophysiology in CRS, with both heart failure and renal failure, raise the challenge for adequate RCTs to study the role of inotropes. Current ESC guidelines for heart failure state the evidence for using dobutamine as class II a level B, dopamine as class II a level C, milrinone as class II b level B, and levosimendan class II a level B.<sup>41</sup>

### **Nesiritide**

Nesiritide is a brain natriuretic peptide(BNP) analogue, it

can induce vasodilation & also increase cardiac output. The primary large randomized trial of nesiritide there was no mortality benefit. In a meta-analysis of seven large RCTs of nesiritide, also there was no mortality benefit during follow up<sup>42</sup>. In one of the pooled analysis of three random trials there was even increase in early mortality when treated with nesiritide<sup>43</sup>. Further the results of ASCEND (Acute Study of Clinical Effectiveness of Nesiritide in Decompensated Heart Failure ) trial<sup>44</sup> may also help to know the future of this drug in the management of CRS patients.

### **Beta-blockers**

Beta-blockers are utilized in the management of chronic HF. During a systematic review by Badve et al.,<sup>45</sup> of patients with HF and CKD, it was found that the utilization of beta-blockers decreased the risk of all causes and cardiovascular mortality. However, it has been related to an increase in incidences of bradycardia and hypotension. So we should be cautious in using them in acute decompensated HF as they'll further reduce forward flow and exacerbate renal dysfunction.

### **Sacubitril/valsartan**

It is a first-in-class drug in ARNI. The benefits of this drug has been revealed by The Prospective Comparison of ARNI with ACE inhibitors to Determine Impact on Global Mortality and Morbidity in Heart Failure (PARADIGM-HF) trial randomized 8442 participants with HFrEF to treatment with sacubitril/valsartan or enalapril and was terminated earlier than planned as it showed overwhelming evidence of benefit at a median follow-up duration of 27 months. Similar to this, in PARAGON-HF trial had 4822 participants with HFpEF to compare sacubitril/valsartan with valsartan. Apart from its known benefits in HFrEF and strong potential for benefit in HFpEF, they also have better effects on the kidney. Sacubitril/valsartan also demonstrated to slow the deterioration of kidney function in the PARADIGM-HF and PARAMOUNT trials. Still more trials are needed to know the efficacy of this drug especially in the setting of Cardio-renal syndrome.

### **Cardiac resynchronization in CRS**

In a systematic review by Garg et al<sup>46</sup>, Cardiac resynchronization therapy improves the LV function, thus improving the GFR in CKD patients. More studies are needed in the setting of CRS, so that, if accurately used based on CRS subtypes, whether it can help in the reversal of this syndrome.

### **Role of Implantable Hemodynamic Monitoring Devices in CRS**

The CHAMPION trial revealed a lower hospitalization rate and a lower mortality in HFrEF(HF with reduced ejection fraction) monitored with PA pressure guided HF management versus.<sup>47</sup> Intra-thoracic impedance was measured directly by implantable device (Optivol, Medtronic) in Heart failure patients.<sup>48,50</sup> But specific data for outcome and prognosis in CRS is still lacking.

### **Ultrafiltration (UF)**

Those patients who are immune to diuretic therapy may enjoy ultrafiltration (UF). This will help in removal of huge

fluid volumes faster than diuretics, without inducing profound hypotension. The UNLOAD trial revealed that, Ultrafiltration was better than IV diuretic therapy to prevent fluid re-accumulation. However, there are trials which failed to demonstrate an improvement in renal hemodynamics with ultrafiltration.<sup>49</sup> Further trials within the setting of CRS is awaited.

## CONCLUSION

The advances till date in this newly emerged branch of Cardio-renal medicine is appreciable & pronounced. However, based on all the major trials & meta-analysis, there is a critical need for new guidelines from the cardio-nephrology societies. A cardio-nephrology multidisciplinary approach is found to be vital in the management of patients with CRS with an emphasis based on Physician priorities. Furthermore, the reversibility of CRS & role of biomarkers for early detection of the syndrome deserves dedicated studies which will resolve today & tomorrow for the patients.

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## CARDIO RENAL SYNDROME CRS TAKE HOME POINTS

*DR M CHENNIAPPAN*

1. Involvement of Kidney in Heart Failure (HF) (Type I and II)
2. Involvement of Heart in Kidney Disease (Type III and IV)
3. Single condition (like DM) producing both heart and kidney diseases (Type V)
4. Worsening renal function ( $>0.3\text{mg}$ ) is a very important bad prognostic marker in HF
5. Creatinine will raise only after 3-5 days of hospitalisation for HF
6. Always estimate creatinine and eGFR on the day of discharge
7. Renal congestion rather than reduced perfusion is the most important cause of CRS
8. Earliest markers of kidney involvement are cystatin and N-GAL
9. Always look for non-traditional risk factors such as abnormal Ca/ PO<sub>4</sub> ratio and homocysteine in CRS
10. Treating congestion with diuretic therapy will improve renal and cardiac function.
11. Avoid combination of ACE, ARB and aldosterone inhibitors in CRS
12. Use Hydralazine and nitrates in ACE, ARB intolerant patients.
13. In stabilised patients, reducing diuretics and increasing Carvedilol will help
14. Look for reversible causes like NSAID use, UTI or urinary tract obstruction
15. Keep looking for kidney disease in HF and HF in kidney disease

*Adjunct Professor, Tamilnadu Dr MGR Medical University, Tamil Nadu; Senior consultant cardiologist, Ramakrishna Medical Centre, Apollo Speciality Hospital, Trichy*



## Review Article

**Management of SARS- CoV-2 (COVID-19) infection with special focus on Use of Hydroxychloroquine and Lopinavir/ritonavir**Murtuza Shujath<sup>1</sup>, Prapthi Bathini<sup>2</sup>, Muruganathan A<sup>4</sup> and Dilip Mathai<sup>3</sup>**Editor's comment -**

- A. The covid-19 pandemic is the greatest challenge for the current generation of physicians, scientists and health administrators
- B. Strict use of PPE, face masks, isolation and quarantine are the most effective methods of prevention of this infection
- C. The immunomodulator hydroxychloroquine is approved for prophylactic use in asymptomatic health care workers and household contacts. It is also approved as compassionate use for treatment of active covid-19 cases in the USA
- D. Lopinavir/ritonavir and remdesivir are used in some countries, but efficacy is doubtful
- E. Treatment with convalescent plasma may be considered in emergency situations.

**Keywords:** Coronavirus; Covid-19; Hydroxychloroquine; Isolation

The SARS- CoV-2 has spread to more than 160 countries in less than 100 days and infected more than a million humans worldwide, once human transmission started in the wet meat markets of Wuhan, China. On 11 March 2020, the WHO declared this global outbreak a pandemic. With no signs of its growing trajectory stabilising and an accompanying threat of a second wave of infection, by secondary transmission from asymptomatics and presymptomatics to the uninfected and unexposed, it is estimated that a third of the seven billion people in the world are at-risk of developing SARS-CoV-2 infection.

The SARS-CoV-2 as the novel COVID-19 is formally known, belongs to the family of coronavirus closely resembling SARS- CoV-1, which was responsible for the Severe Acute Respiratory Syndrome (SARS) outbreak in 2002-03 starting in Guangdong province of China, infecting around 8000 people and claiming around 700 lives globally.

COVID- 19, is a non segmented positive sense ssRNA virus. Originally zoonotic, it has skipped the species barrier following an animal-to-human transmission and subsequent human- to- human transmission<sup>1</sup>. The viral genome encodes four major proteins: spike, envelope, nucleocapsid and membrane proteins<sup>2</sup>. The spike proteins are responsible for facilitating the entry of virus into the target cells, via the specific ACE2 receptor found at various sites in the body. The ones involved in COVID-19 are present on the type 2 alveolar cells and the intestinal epithelial cells (villous cells)<sup>3</sup>. The envelope proteins are responsible for the positive serology.

**Transmission**

COVID-19 is transmitted by large droplets (aerosols) and contact routes (fomites)<sup>4</sup>. In order to manage the COVID-19 pandemic, the transmission of the virus has to be contained. Aerosol or droplet transmission can be prevented by following the WHO guidelines for droplet precautions. Different surfaces harbour the virus particles for varying durations extending from few hours to days. Regular disinfection of surfaces with 70% alcohol or 0.5% sodium hypochlorite, regular washing of hands with soap and water for 20 seconds and avoidance or reduced touching of face, eyes, nose is recommended for limiting the spread of the virus<sup>5</sup>. More importantly, self isolation or physical (social) distancing of individuals needs to be practiced by the general population to limit the spread and contain the infection.

Another important factor contributing to the pandemic nature of COVID-19 is its Replication of virus R0 (naught); current estimates place the value around 2.5-2.9 which is higher than that of seasonal influenza<sup>6</sup>. A value greater than 1 signifies that the infection will increase exponentially in the population. However, the R0 is a modifiable factor and is the reflection of the virus and human behaviour. R0 onboard the Diamond Princess cruise ship was 15, emphasising the importance of social distancing, improved hygiene and isolation in containing the spread of this pandemic<sup>7</sup>. Incubation period is around 4 days (2-7) and may even extend up to 14 day<sup>4</sup>.

**Prevention**

Role of facial masks at all times in community : It is essential that all persons minimize the inoculum through aerosol acquisition through a simple mouth and nostril cover with a home- made triple layer cloth face mask, which can be anything from a handkerchief, dupatta, turban or a bandana that can be easily disinfected ( washed in soap water and dried in sunlight both of which are effective virucidal agents) and worn daily when they foray into open areas away from homes (when isolation ) or national lockdown is lifted. Wearing the mask properly or even two such masks (for

- 1 Clinical Research Associate,
- 2 Associate Professor, Pharmacology;
- 3 Professor, Medicine; Apollo Institute of Medical Sciences and Research, Jubilee Hills, Hyderabad, Telangana-500096
- 4 Governor, American College of Physicians - India chapter, Journal of Indian Medical Association April 2020.

Corresponding Author: Dr.Dilip Mathai MBBS MD PhD FCAMS FRCP (Lond) FICP FIDSA Hon. FFTM RCPS (Glasg)  
Dean and Professor of Medicine and Adult Infectious Diseases;  
Apollo Institute of Medical Sciences and Research

better filtration of virus - free air) at the same time may impact ease of breathing and lessen compliance of its usage due to a closer fit around the face.

In hospitals, as a HCW, thoroughly effective personal protective equipment (PPE) is required as they need to care for patients for longer hours with large viral loads. Currently in triage areas, they would require N95 masks and bio protective items such as goggles or face protection, head cover, gowns, shoe covers and nitrile gloves. Among the individuals who are tested positive for COVID-19 requiring quarantine or isolation, require a triple layered face mask to be worn at all times during their hospital stay. However, N-95 masks are to be reserved for performing aerosol inducing procedures like intubation and tracheal aspiration. HCWs involved in house-keeping functions should wear rubber boots, longer gloves and should be trained to follow certain protective behaviour which is essential to maintain their own good health as well as the well being of the society. These include regular decontamination of surfaces regularly contacted such as mobile phones, keys, pens, etc. Avoid physical examination unless it is definitely indicated. Advise patients regarding limitation to visit clinics during these times. Thorough sanitation at home, of clothes to limit the spread to the family. It is best that we are prepared to have such PPE at all times and testing as many people as possible. Donning protective gears whenever available and complete adherence to social distancing protocols is mandated.

Infection with COVID-19, typically produces no symptoms (asymptomatic) to mild symptoms like mild fever, cough and occasionally diarrhoea. The disease however may progress to potentially fatal Acute respiratory distress syndrome (ARDS) and Severe Acute Respiratory Infection (SARI). The development of ARDS follows destruction of the alveolar cells and hyaline membranes. This is secondary to the cytopathic effects of the virus and the immune response of the body. Fatality of the disease

occurs due to hyperinflammation, a response by the adaptive immunity that progresses to immunopathological dysregulated cytokine storm, macrophage blockade representing a virus induced Haemophagocytic lymphohistiocytosis and effect on coagulation cascade in the pulmonary vessels impacting oxygenation<sup>8</sup>. Besides a virus induced effect on the haemoglobin chain moiety affects the oxygen delivery to tissues and inducing other organ failure.

**Diagnosis:**

Performance of Detection Methods Over Time (Sensitivity Scores, Days Post-Symptom Onset)

Current update of Covid-19 (April 21,2020)  
**Total cases globally: 2314621**  
**Total death globally: 157847**  
**India total cases: 18601**  
**India total deaths: 590**

Table 1: gives the information regarding the various serological tests that can be performed and their sensitivity scores over the timeline of COVID-19 infection<sup>10</sup>.

SARS-CoV-2 Test	Days after Symptom Onset		
	1–7	8–14	15–39
RNA by RT-PCR	67%	54%	45%
Total Antibody	38%	90%	100%
IgM	29%	73%	94%
IgG	19%	54%	80%

The diagnosing criteria includes clinical as well as laboratory and radiological findings. Any patient following clinical suspicion must be isolated and thoroughly investigated.

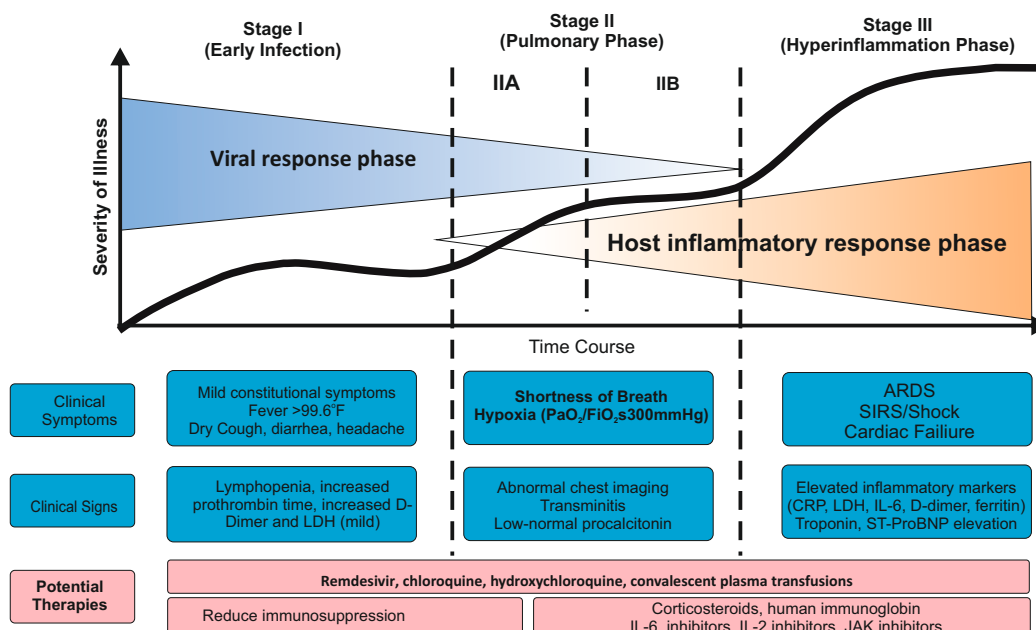


Figure 1: Covid-19: Stages, severity of illness, clinical signs, symptoms and potential therapies



**Table-2 : WHO Guidelines of specimens to be collected and investigations to be done for suspected individuals and contacts 11**

	Test	Type of Sample	Timing
Patient	NAAT	Lower respiratory tract <ul style="list-style-type: none"> <li>• Sputum</li> <li>• Aspirate</li> <li>• Lavage</li> </ul> Upper respiratory tract <ul style="list-style-type: none"> <li>• Nasopharyngeal</li> <li>• Oropharyngeal</li> </ul> Wash/nasopharyngeal aspirate Consider stools, whole blood, urine, and if deceased, material from autopsy	Collect on presentation. Possibly repeated sampling to monitor clearance. Further research needed to determine effectiveness and reliability of repeated sampling
Patient	Serology	Serum for serological testing once validated and available	Paired samples are necessary for confirmation with the initial sample collected in the first week of illness and the second ideally collected 2-4 weeks later (optional timing for convalescent sample needs to be established).
Contact in healthcare centre associated outbreaks or other settings where contacts have symptoms, or where asymptomatic contacts have had high intensity contact with a COVID 19 case	NAAT	Nasopharyngeal and oropharyngeal swabs	Within incubation period of last documented contact
	Serology	Serum for serological testing once validated and available	Baselines serum taken as early as possible within incubation period of contact and convalescent serum taken 2-4 weeks after last contact (optional timing for convalescent sample needs to be established).

If possible send for Influenza virus antigens and RSV test as they have specific effective pharmacological treatment such as Oseltamivir & Ribavirin respectively. Following a diagnosis, the investigations to be done are <sup>12</sup>

- CBP with a differential count(lymphopenia suggests severe infection)
- Creatinine phosphokinase (detecting myocarditis- a significant complication)
- Baseline ECG (QTc monitoring for underlying heart diseases and management)
- Chest X-ray PA view or a CT (for various lung changes varying limited air space consolidation and diffuse interstitial pattern; and extent of lung parenchyma involvement)

**Management**

The management of COVID19 depends on clinical judgement. Adherence to the following principles reduces the risk of transmission and optimises outcome.

**Not recommended <sup>12</sup>**

- Nebulisations are to be avoided as they can result in aerosolization of the virus and increase the risk of transmission.
- Steroids both systemic and inhalational to be avoided as they can reduce immunity; however, use may be

considered for management of patients with refractory shock or acute respiratory distress syndrome. Risks and benefits must be carefully weighed.

- If the patient is on of ACE inhibitors or ARB's, these drugs should not be discontinued unless contraindicated.
- Ribavirin, a purine nucleoside analogue which prevents replication in large number of RNA and DNA viruses, earlier used in the SARS-coV epidemic is not recommended
- Avoid the use of NSAID's as there are reports of clinical deterioration in some patients following their use. For fever management Acetaminophen can be used.

**Drugs used in management**

Many drugs with antiviral and in-vitro activity against the virus are being tried in the treatment. No drug has been approved specifically for treatment.

**Hydroxychloroquine and Chloroquine:**

These are aminoquinoline compounds, used as anti-malarials, in Systemic lupus erythematosus and Rheumatoid arthritis. Currently used as off label drugs in the treatment of COVID-19 due to potential

Epidemiological- Category 1	Vital signs – category 2	Lab findings -Category 3
<ul style="list-style-type: none"> <li>• Age &gt; 55 years</li> <li>• Pre existing pulmonary disease and smoking</li> <li>• CKD</li> <li>• CAD</li> <li>• HTN</li> <li>• DM with HbA1c &gt;7.6</li> <li>• Use of biologics</li> <li>• H/o transplants</li> <li>• All HIV patients</li> </ul>	<ul style="list-style-type: none"> <li>• Respiratory rate &gt;24/min</li> <li>• Heart rate &gt;125/min</li> <li>• SPO2 &lt; 90% on room air</li> </ul>	<ul style="list-style-type: none"> <li>• Absolute lymphocyte count &lt;800 lymphocytes/microlitre</li> <li>• CRP &gt;100</li> <li>• Creatinine &gt;2 times the upper limit of normal</li> <li>• LDH &gt;245 U/l</li> <li>• Elevated troponin</li> <li>• Ferritin &gt; 300 micrograms/ l</li> <li>• D-dimer &gt;1000 ng/ml</li> </ul>

immunomodulatory and direct antiviral effects and perhaps an effect in minimizing the cleavage of the iron from the porphyrin. The world experts are divided on its use as there are no large scale RCT studies to support its use.

Hydroxychloroquine has similar pharmacokinetics as chloroquine with the drugs being well absorbed orally, large volume of distribution, and renal excretion. Hydroxychloroquine is as effective as chloroquine but is less toxic.

At cellular levels, these drugs accumulate in intercellular vesicles such as endosomes and lysosomes where they are protonated. This results in alkalisation of endosomal pH which prevents virus entry and fusion. Inhibition of the terminal glycosylation of ACE2 receptor decreases the viral binding and entry<sup>13</sup>. It also exerts immunomodulatory effect and decreases release of cytokines like interleukin-1 and tumour necrosis factor attenuating the viral cytokine storm<sup>14</sup>

In-vitro data suggests good activity of these drugs against SARS-CoV-2 with some studies suggesting higher potency and less toxicity of hydroxychloroquine compared to chloroquine<sup>15,16</sup>.

Drug concentrations based on pharmacological modelling and in-vitro drug activity suggest that hydroxychloroquine could be used as a prophylactic in prevention of SARS-CoV2 infection<sup>15</sup>. A single dose of HCQ 800 mg may provide a lung tissue concentration that is 20 times higher than the EC50 required for inhibiting Covid-19 in the lung on day 117.

Common side effects are GI upset (nausea, vomiting, and diarrhoea). This can be minimized by dividing the drug dosage or taking it with meals. Cardiac side effects are arrhythmias (QT prolongation), cardiomyopathy and sudden death. Therefore a QTc monitoring protocol has to be followed, where a QTc of > 450ms should be thoroughly evaluated<sup>18</sup>. Hematological side effects, liver toxicity and immunological side effects are also seen. Risk of retinal damage, myopathy, neuropathy, and rarely neuropsychiatric events are reported. It can cause hypoglycaemia (common in diabetics and could be severe) therefore caution is required.

Caution is required in patients with G6PD deficiency, hepatic and renal disease. It also has several drug

interactions. Caution is required when used with drugs like azithromycin (to treat atypical respiratory pathogens causing community- acquired pneumonia which prolong QT interval.

A open label randomized control study with a small sample size (n=26, with 6 lost to follow up) conducted in France, showed that with hydroxychloroquine treatment for 10 days, there was significant viral clearance in upper respiratory tract specimens in Covid-19 patients. On day 6, 70% of hydroxychloroquine-treated patients were virologically cured compared to 12.5% in the untreated control group. The effect of which was further enhanced by azithromycin<sup>19</sup>.

A multi centric study in China reports the beneficial effects of chloroquine in treating more than 100 patients with Covid-19 associated pneumonia compared to control group<sup>20</sup>. Details of the study are not elaborated so it is difficult to evaluate the efficacy.

**Recommendations:**

There is lack of robust data suggesting the use of drug for prophylaxis or treatment. However there is evidence of effectiveness from preclinical and other small studies suggesting the use of drug from China. Based on these data some of the guidelines for the use of the drug in covid-19 patients include:

The Indian ICMR guidelines recommend the usage of hydroxychloroquine as a prophylactic for usage in asymptomatic HCW involved in the care of suspected or confirmed Covid-19 patients. It is also recommended as a prophylactic for asymptomatic household contacts of Covid-19 patients.

The dosage recommendations for healthcare workers is 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals. For asymptomatic contacts the dosage is 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals.<sup>21</sup>

The Ministry of Health and Family Welfare, India recommends the use of Hydroxychloroquine in patients with severe disease and requiring ICU management, in combination with Azithromycin under close medical supervision, with monitoring for side effects including QTc interval. The dosage recommendation is 400mg twice daily

on Day 1 followed by 200mg twice daily for 4 days.

USFDA guidelines states the Emergency Use Authorization (EUA) to permit the emergency offlabel, compassionate use of hydroxychloroquine sulfate to treat adults and adolescents who weigh 50 kg or more, who are hospitalized with Covid-19 and for whom a clinical trial is not available or participation is not feasible. The dosage recommendation is 1000 mg of hydroxychloroquine sulfate on the Day 1 followed by 500 mg daily for four to seven days of total treatment based on clinical evaluation.<sup>22</sup>

In an era where it may take 12-18 months for an effective vaccine to develop; HCQ offers a practical, cheap, safe and effective agent for prevention of potentially lethal COVID19 infection.

### **LOPINAVIR/RITONAVIR**

Lopinavir and ritonavir are protease inhibitors approved for the treatment of HIV. Ritonavir boosted lopinavir is used to reduce the dose of lopinavir and increase the plasma levels through CYP3A isoenzyme inhibition. This regimen is used as a second line drug in the treatment of HIV and also in post exposure prophylaxis<sup>23</sup>.

Lopinavir is a potent inhibitor of protease Mpro, blocking the cleavage of nascent viral proteins and thus inhibiting coronavirus replication and activity. Among the HIV protease inhibitors, lopinavir has shown highest activity against CoV22,<sup>23</sup>. In vitro studies and preclinical studies on animals has shown good activity of these drugs for coronaviruses (SARS-CoV and MERS-CoV)<sup>26,27</sup>

A similar study, patients with SARS were treated with a combination of lopinavir/ritonavir and ribavirin showed better clinical outcomes and decreased viral load when compared to historical matched controls treated with ribavirin only.<sup>28</sup>

A recently conducted randomized control trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19 (n=199) in China showed that treatment with lopinavir-ritonavir for 14 days was not associated with any significant benefit in comparison to the standard care in time to clinical improvement, mortality or viral RNA titres.<sup>29</sup>

A retrospective cohort study of hospitalized Covid-19 patients in China reviewed the clinical course and risk factors for mortality, included 29 patients who received lopinavir-ritonavir. They found no difference in viral shedding after treatment with lopinavir-ritonavir<sup>30</sup>

### **Dosage**

Lopinavir/ritonavir is given in a dosage of 200 mg/50 mg - two tablets twice daily for 14 days or for seven days after the patient becomes asymptomatic, whichever is earlier, or as 400/100 mg twice daily for 10 days.

### **Side effects**

The side effects with these drugs are gastrointestinal side effects like nausea, vomiting, diarrhea, dysgeusia and abdominal pain. Hypercholesterolemia, increased serum triglycerides, redistribution of fat and hyperglycaemia are seen. Rashes, fatigue, weakness, and hypersensitivity reactions are reported. Rare but severe side effects are

pancreatitis, QT prolongation, increased risk of myocardial infarction and, hepatotoxicity. The drug has significant drug -interactions and care should be taken when combining it with other drugs like azithromycin and chloroquine.

### **Recommendations:**

In view of the efficacy data from in-vitro studies, clinical trials and studies, the Indian Council of Medical Research (ICMR)/CDSCO has suggested off-label emergency use of lopinavir/ritonavir for restricted use in symptomatic Covid-19 patients in India and a trial evaluating its safety and efficacy is underway<sup>31</sup>. Outcomes from this trial will further help in planning of guidelines for our country. FDA has not approved this drug combination for use in Covid-19 patients. This drug combination is evaluated as a part of WHO SOLIDARITY trial.

### **Remdesivir (RDV)**

This is a broad spectrum antiviral agent; a nucleotide analogue with in-vitro activity against corona virus<sup>32</sup>. It is not available commercially. It was first tried on quarantined patients of Diamond Princess Cruise ship at the University of Nebraska medical centre and positive results were seen. Remdesivir has been administered to patients with confirmed, severe SARS-CoV-2 infections in the United States, Europe, and Japan through Expanded Access or Compassionate Use programs. The current dose RDV 200 mg IV loading followed by 100 mg IV daily for 10 days<sup>12</sup>

### **Tocilizumab**

Interleukin-6 (IL-6) Receptor-Inhibiting Monoclonal Antibody Tocilizumab, may ameliorate severe damage to the lung tissue caused by the cytokine release and is given to patients with evidence of cytokine release syndrome. A retrospective review analyzed the effect of tocilizumab, added to standard therapy in COVID-19 patients and preliminary data suggests clinical benefit of tocilizumab as adjunctive therapy<sup>33</sup>.

### **Convalescent plasma**

Plasma from persons who have recovered from COVID-19 infection may contain antibodies to SARS-CoV-2. The possible mechanisms suggesting efficacy of convalescent plasma studies in various respiratory infections is that the antibodies from convalescent plasma might suppress viraemia<sup>34</sup>. ICMR has suggested the use of convalescent plasma to treat patients with severe or life-threatening COVID-19 infections.

### **Other drugs include;**

#### **Azithromycin:**

This is a macrolide antibacterial which has immunomodulatory properties in pulmonary inflammatory conditions. In a small open label study of HCQ in France; azithromycin was given to prevent potential bacterial superinfection. Lower viral loads were seen in the patients but the results did not vary much with those receiving Hydroxychloroquine alone<sup>19</sup>.

#### **Ivermectin**

Studies conducted at Monash University have found the efficacy of Ivermectin, an anti-helminth having broad

spectrum anti viral properties in vitro, in inhibiting the replication of covid19 in -vitro within 48 hours; however these studies have been performed in vitro and determination of its action and appropriate dosage in humans is yet to be determined<sup>35</sup>.

Many others drugs with antiviral activity are being tried in few studies like Ascorbic acid , Inhalational Nitric oxide, Zinc etc. These compounds do not have much clinical evidence and care should be taken in prescribing them to patients.

### Conclusion

COVID-19 has caused a pandemic and has become a pressing issue for physicians around the globe; attention to it is happening at the cost of other ailments which require regular intervention such as dialysis for CKD patients, ART for HIV patients and chemotherapy for cancer patients. Any negligence on this front might result in co- morbidities and fatalities occurring during and after the COVID-19 pandemic. There are several treatment options underway and with the resilience of governments and medical staff around the globe, this pandemic will run its course soon. However, the chances of it prevailing as an endemic disease and resulting in occasional outbreaks is a real long-term threat.

A concept of behavioural distancing where man distances himself from encroaching and exploiting the habitats of the wild offers hope to prevent similar zoonotic pandemics. Another matter of concern is how this pandemic and its consequences have taken a toll on the mental well being of the general population and health care workers alike. Stigmatisation and discrimination are further add-ons to this stress. Identification and minimisation of such is a matter of concern not only for the physicians but also the governments.

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## VOICE OF THE EXPERT

Dr Babasaheb V. Tandale is one of the most well-known and respected epidemiologists of India. Currently he is working as scientist F at the National Institute of Virology, Pune. He has got numerous international publications on public health over the last fifteen years. As the coronavirus pandemic swept the globe, the urgent need for a rational scientific voice was felt by all physicians. In that scenario, we could think of no better name in India to be a source of authentic and up-to-date information than Dr Tandale. This is an interview of Dr Tandale, which is exclusively available for the readers of JIMA. The interview was conducted online by Prof Jyotirmoy Pal and Dr Rudrajit Paul in the last week of March, 2020.



Dr Tandale, on behalf of JIMA, we welcome you to this interview. We would be asking a few questions on the Covid-19 epidemic.

### 1. What is the molecular nature of the coronavirus?

The coronaviruses are a large family of viruses. The emergence of 2019 novel coronavirus (2019-nCoV) since 31 December 2019 in Wuhan City in Hubei Province of China has been detected in unusual cases of pneumonia (Novel Coronavirus Pneumonia, NCP). The virus has been officially named as the SARS-CoV-2 by the International Committee on Taxonomy of Viruses (ICTV). The novel coronavirus disease has been named as the Coronavirus Disease (COVID-19) by the WHO. SARS-CoV-2 is the third beta-coronavirus after earlier SARS in 2003 and MERS in 2012.

The SARS-CoV-2 virus is spherical and hence looks like a crown, therefore the name 'coronavirus' (corona means crown). It is enveloped, positive-stranded RAN virus with nucleocapsid. The genomic structure is organized as +ssRNA of approximately 30kb in length, thereby making it the largest know RNA virus. The size of virus spike protein is 180 kDa with two subunits. It helps in virus receptor binding with the ACE2 receptor. The SARS-CoV-2 has > 95% homology with bat coronaviruses and > 70% similarity with the SARS-CoV-1.

### 2. Is this new coronavirus a zoonotic disease?

#### Editorial note:

1. There are some rumours doing the rounds in social media regarding certain types of food. We would like to stress that coronavirus is not transmitted via food. All types of food, if properly prepared, are safe.
2. This is the reason for social distancing.
3. The hospital wards where coronavirus infected patients are housed needs to be cleaned properly. Bedside furniture may be a temporary reservoir of the virus.

### if so, please explain

The new coronavirus is zoonotic disease at the first emergence. The beta-coronaviruses are originated mostly from bats. The transmission to humans is usually through the intermediate hosts like palm civet cats in the Guangdong province of China for SARS in 2003 and camels in case of MERS in 2012.

However, it is not yet clear which the intermediate host of the SARS-COV-2 is. Pangolins have been postulated to be intermediate hosts due to close match of genomic sequences. The environmental samples from Huanan sea food market provided link to emergence. The first few cases had history of exposure history with the market.

### 3. How did this virus enter human species?

It is not yet clear which the intermediate host of the SARS-COV-2 is. Pangolins have been postulated to be intermediate hosts. However, absence of exposure to the market in a few earlier cases indicated the likely human-to-human transmission. The environmental samples from Huanan sea food market provided link to emergence. The first few cases had history of exposure history with the sea food market. The recent transmission is solely contributed by human-to-human.

### 4. What is the infectivity of this virus?

The SARS-CoV-2 virus has moderate to high infectivity in relation to the earlier known beta-coronaviruses like SARS and MERS. The transmission is very efficient and higher than earlier viruses. This virus is easily transmitted, infects during asymptomatic and pre-symptomatic periods and has maximum infection rate among close contacts. The basic reproduction number for SARS-CoV-2 is ranging between 1.5 3.5. It means that an infected individual leads to transmission of infection in 2-4 people in close contacts. Therefore, the transmission is much efficient and sustained in close contacts leading to rapid spread.

### 5. How long can this virus survive in the environment?

The SARS-CoV-2 is stable in environment and is similar to earlier SARS. Although the most of transmission events are associated with close contacts due to droplet transmission, aerosols (<5 um) could be important in a limited settings with lower temperatures and higher humidity levels due to air conditioning. The aerosols may have viability for over 3 hours. The viability of virus on different surfaces is also significantly higher than earlier SARS. It remains viable on cardboard for 24 hours, on copper for 72 hours, on steel and plastics could be longer, almost for 5-7 days. The fomites are also reported to be important for transmission of SARS-CoV-2 virus.

**6. Is the molecular nature of this virus conducive to vaccine preparation? what is the frequency of mutation?**

The virus spike protein is the most important structure of the virus that helps virus to adhere to the receptor ACE2. It is therefore very important glycoprotein for pathogenesis and immunity. Thus, it is possible to develop vaccines targeting spike protein. However, the mutations in the spike protein may lead to short-term immunity and the possibility of reinfections.

**7. Are there any molecular barriers to anti-viral drug development?**

The antiviral development usually targets three aspects. These include direct antiviral effects, inhibition of virus entry and replication, and enhancement of host immune response. Generally, nucleoside analogues like Ribavirin and alpha-n1, alpha-n3 and beta-1a interferons have been reported to inhibit coronaviruses in vitro. Additionally, lopinavir and ritonavir have also been reported with minimal beneficial effect against SARS-CoV-2. Remdesivir has also been seen promising with inhibition in vitro, however clinical trials evidence of its effect is pending. Chloroquine has also been shown to inhibit virus in vitro.

**8. Is there multi-systemic involvement in this infection?**

Most of COVID-19 patients present with pneumonia. However, there is wide variation in clinical presentations, with spectrum wider than earlier coronaviruses. In addition to respiratory involvement primarily, including very mild to severe features like ARDS, multiple systems may get involved. Gastrointestinal, musculoskeletal, neurological, hematologic, cardiac, hepatic, renal and other major organ systems involvement is reported. Multi-organ failure has been reported in terminal phases of illness leading to complications and mortality.

**9. Why does ARDS develop so fast in this infection?**

The pathogenic mechanisms are complex. It is reported that excessive immune reaction in host could be the likely mechanism. This is broadly labelled as 'cytokine storm'. It leads to extensive tissue damage due to pro-inflammatory cytokine, interleukin-6, produced by activated leucocytes. This could lead to multiorgan dysfunction associated with cytokine release syndrome commonly labelled

as acute systemic inflammatory syndrome. The pathogenic mechanism is postulated to be the dysfunction of surfactant producing cells in alveoli leading to distress.

**10. Is there a cytokine storm in coronavirus infection? If so, what is the effect?**

Yes. Most of the cases are reported with 'cytokine storm' is septic phase. The excessive immune reaction in the host that leads to extensive tissue damage, sloughing of parenchyma, accumulation of debris in alveoli and dysfunction of surfactant producing cells hampering maintenance of critical respiratory function.

**11. Is there lasting immunity to this infection? Can anyone be affected a 2nd time?**

The immunity following natural infections is usually short-term. The immune response in asymptomatic and non-severe stages, specific adaptive immune response is required to eliminate virus and prevent disease progression. The immune response is influenced by various factors including the general host health and response mechanisms. The second response induces innate inflammation in lungs mediated by macrophages and granulocytes. Therefore, general good health may not work for severe lung disease manifestations. Some patients return virus positive and some may even relapse. There are a few reports of reinfections following earlier recovery.

**12. Is this virus temperature sensitive? Will it diminish in summer?**

The SARS-CoV-2 virus is enveloped virus and is reported to be sensitive to sunlight, high temperature and humidity. However, being a novel virus, it is difficult to predict the effect. It seems to be difficult to have the decrease in transmission with higher summer temperatures in India due to high rates of survival on most surfaces with 8-10 days on dry surfaces, use of humidifiers and air conditioning, transmission associated mostly among close contacts, and the completely susceptible population with no immunity against the SARS-CoV-2 virus. Considering the transmission reported in warmer summer climates during the current ongoing pandemic, it seems to indicate that summer may not play a role in decreased transmission. As is seen earlier, the pandemics don't follow seasonal patterns observed in common outbreaks.

*Dr Tandale, we thank you immensely for your time. We are sure our readers will be delighted to hear from you. We hope to talk with you again in future.*

*Dr. Babasaheb V. Tandale, MD  
Scientist F and Group Leader, Epidemiology Group, ICMR-NIV Pune*

## A clinical study on presenting features and prescription pattern for Migraine in a Tertiary care hospital of Eastern India.

Dr. Kaushik Mukhopadhyay<sup>1</sup>, Ms Neenu Elizabeth Joseph<sup>2</sup> Dr. Bikramjit Barkondaj<sup>3</sup>, Dr. Sonali Mukherjee<sup>4</sup>, Dr. Chandan Chatterjee<sup>5</sup>, Dr. Samir Chakraborty<sup>6</sup>

### Abstract

Migraine is the leading cause of headache-related disability in the world. There are different pharmacological options to treat acute attack and prophylaxis of Migraine. We conducted a cross-sectional study to observe prescription pattern of migraines in eastern India and find its association with severity of the disease. We collected data from 75 Migraine patients who attended General medicine outpatient department. It was found that Paracetamol and NSAIDs are mainly used to terminate acute attack and Amitriptyline for prophylaxis of Migraine. Multidrug therapy with combinations of antidepressant, anticonvulsant and Flunarizine is used in patients with relatively high Migraine Disability Assessment Score (MIDAS). The prescription pattern we found in our study was found appropriate as per current treatment guidelines.

**Keywords:** Migraine, MIDAS, NSAIDs, Amitriptyline

### 1. Introduction

Headache is a common ailment in the general population. Globally, it has been estimated that about 50% of adults suffer from headache at least once within previous year.<sup>1</sup> The types of headaches commonly encountered are Tension headache, Migraine, Trigeminal autonomic or other miscellaneous type.<sup>2</sup> Among them, Migraine is the leading cause of headache-related disability in the world. It is characterized by unilateral episodic cephalalgia in presence or absence of various neurologic dysfunction. Association of nausea, photophobia or phonophobia is common. It is prevalent more in young age group and mostly in women. A recent study in eastern India found Migraine prevalence was 14.12% and showed similar female predominant trend in demography also.<sup>3</sup>

The pharmacological options for termination of acute attack are Paracetamol, Nonsteroidal Anti-Inflammatory Drugs (NSAIDs), 5-HT 1B/1D receptor agonists and Dopamine receptor antagonists. For prophylaxis of Migraine Beta Blockers, Antidepressants, Anticonvulsants and Flunarizine are used.<sup>4</sup> There are differences in prescription pattern of Migraine in different countries. A study in Finland showed NSAIDs were prescribed more than Triptans in acute attack.<sup>5</sup> Similar observations were found in a large database-based study in Germany analyzing 56823 prescriptions.<sup>6</sup>

A study in India showed NSAIDs are most commonly used

### Editor's comment

1. Migraine is a common ailment.(14.12% prevalence)
2. Prescription pattern in acute and recurring attacks include cost effective drugs like NSAIDS and Amitriptyline in Eastern India
3. Use of Betablockers and anticonvulsants are less in this study than other countries.

drug for acute attack and beta blockers for prophylactic therapy.<sup>7</sup> We could not any study in eastern India to address the prescription pattern of Migraine of different severity. Therefore, this study is planned with an objective of exploring demographic details and pattern of prescriptions among Migraine patients and to compare it with available guidelines.

Primary objective of this study was to find prescription pattern to manage acute attack of Migraine and prevent frequent attacks of Migraine and observe the association of prescription pattern with severity of Migraine.

### 2. Materials and Methods

The cross-sectional observational study was conducted over three months period (August 2019 to October 2019) in the General Medicine Outpatient Department of ESI-PGIMS and ESIC Medical College, Joka. The study protocol followed the principles expressed in the Helsinki Declaration of 1983 and received prior approval from Institutional Ethics Committee. Informed consents were obtained from all participants. The study population included patients of either sex and age more than 12 years attended General Medicine Outpatient Department with a diagnosis of '**Migraine**' according to International Headache Society Classification characterized by 2 of the following criteria at least Unilateral pain, Throbbing pain, Aggravation by movement, Moderate or severe intensity. It should be accompanied by either Nausea/Vomiting or Photophobia/ Phonophobia.<sup>2</sup> We excluded patients with recent history of CNS infection or any major medical illness such as malignancy, autoimmune disorder and co-existent neurological disorder or a case where attending physician believes any other non-Migraine diagnosis more likely.

We used Non-probability convenient sampling method for

- 1 MD, Assistant Professor, Department of Pharmacology ESI-PGIMS and ESIC MC, Joka
- 2 2nd Yr MBBS student, ESI-PGIMS & ESIC MC, Joka
- 3 MD, Tutor, Department of Pharmacology ESI-PGIMS and ESIC MC, Joka
- 4 MD, Professor, Department of Pharmacology ESI-PGIMS and ESIC MC, Joka
- 5 MD, Associate Professor, Depart. of Pharmacology ESI-PGIMS and ESIC MC, Joka
- 6 MD, Assistant Professor, Department of General Medicine ESIC Medical College, Joka; and Corresponding Author

this study. All the patients matching the inclusion criteria during the study period were included. We could recruit 75 patients during the study period.

Detailed history related to Migraine and other co-morbidities were collected and routine physical examinations were performed for any abnormality. Severity of current episode of headache was assessed using a Visual Analogue Scale of pain by the patient himself. We used **Migraine Disability Assessment Score (MIDAS)** for assessing present disease activity in migraine patients. MIDAS is a questionnaire designed to measure headache-related disability, and to identify patients with high treatment needs.<sup>8</sup> It is a 7-item questionnaire (with 5 scored items) where respondent needs to provide the number of days he suffered from debilitating headache in last 3 months.

The study specific data was collected and entered in a case report form (CRF) specifically designed for this purpose. The data from the CRF were transcribed onto an excel database and analyzed by R version 3.5.1 and R Studio version 1.0.136 (R foundation) statistical software (Language). Data were summarized by routine descriptive statistics and comparison between groups was done using Student's Unpaired t-test for variables showing parametric distribution by Shapiro-Wilk test. For non-parametric data, we used Wilcoxon rank sum test for between group comparison. P value < 0.05 was considered as statistically significant.

**3. Results**

The study population included 75 patients with diagnosis of Migraine recruited from General Medicine Outpatient Department of ESI-PGIMSR and ESIC Medical College, Joka, West Bengal, India. Most of the patients were female (n = 71, 94.7%) around 40 years of age. Baseline parameters in **Table 1** shows mean duration of present episode were 4.13 days and mean duration of disease was 7.87 years.

Parameters	Mean (Standard Deviation) N=75
Age in years	38.6 (12.0)
Current headache episode duration in days	4.13 (2.02)
Total disease duration in years	7.87 (4.92)
Pulse rate (per minute)	76.8 (8.95)
Systolic Blood Pressure	117 (5.79)
Diastolic Blood Pressure	76.9 (3.98)

**Table 1: Baseline parameters of study participants**

Mean severity of headache by a self-scored visual analogue scale was 6.79 with a standard deviation of 2.29 indicating most of the patients suffered from severe headache. **Table 2** shows the characteristics of migraine in study participants. It was commonly associated with nausea (59%), photophobia (82.7%) or phonophobia (77.3%). Majority of the subjects reported 'throbbing' type of unilateral headache which sometimes aggravated by movement.

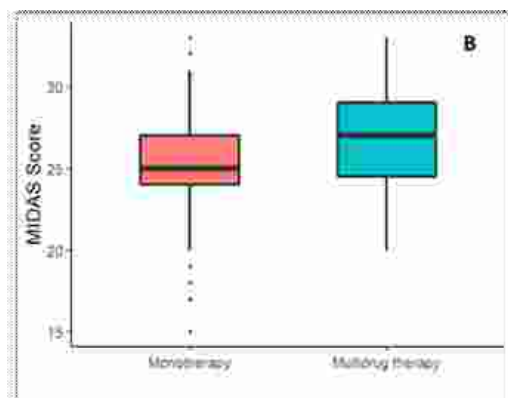
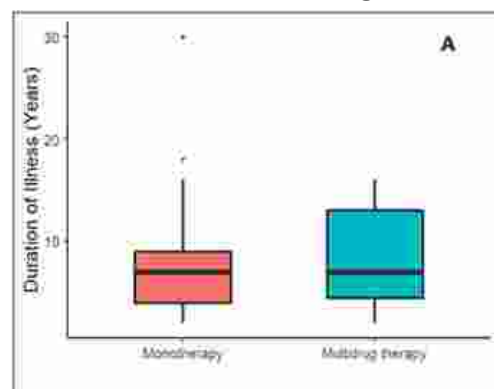
**Table 3** shows the prescription pattern of migraine therapy. Drugs to control acute attack were required for 21.3% cases. Amitriptyline was the mainstay of migraine prophylaxis

Presenting Symptoms	Number (Percent) N=75
Unilateral headache:	45 (60.0%)
Throbbing:	63 (84.0%)
Aggravated by movement:	47 (62.7%)
Nausea:	59 (78.7%)
Vomiting:	44 (58.7%)
Photophobia:	62 (82.7%)
Phonophobia:	58 (77.3%)
Scalp tenderness:	19 (25.3%)
Light headedness:	3 (4.00%)
Visual disturbance:	2 (2.67%)
Convulsion:	0 (0%)
Vertigo:	73 (97.3%)
Aura:	51 (68.0%)
Family history:	22 (29.3%)

**Table 2: Characteristics of headache of study participants**

Pharmacotherapy	Number (Percent) N=75
Drugs to control acute attack (Paracetamol/NSAIDs):	16 (21.3%)
Beta Blocker (Propranolol):	9 (12.0%)
Amitriptyline:	68 (90.7%)
Anticonvulsant (Sodium Valproate):	12 (16.0%)
Flunarizine:	8 (10.7%)
Any other drug	0 (0%)

**Table 3: Prescription pattern of drugs for treatment of Migraine**





Questionnaire component of MIDAS Score	Overall N=75 Mean (SD)	Monotherapy N=52 Mean (SD)	Multi-drug therapy N=23 Mean (SD)	p-value (Student's t-test)
1. On how many days in the last 3 months did you miss work or school because your headaches?	6.49 (2.31)	6.23 (2.01)	7.09 (2.84)	0.200
2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches?	4.47 (1.73)	4.44 (1.59)	4.52 (2.04)	0.869
3. On how many days in the last 3 months did you not do household work because of your headaches?	4.91 (1.76)	4.87 (1.68)	5.00 (1.98)	0.778
4. How many days in the last 3 months was your productivity in household work reduced by half or more because of your headaches?	5.05 (1.98)	4.87 (1.93)	5.48 (2.06)	0.234
5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?	4.64 (1.78)	4.56 (1.59)	4.83 (2.17)	0.597
<b>MIDAS Score</b>	<b>25.6 (3.88)</b>	<b>25.0 (3.86)</b>	<b>26.9 (3.64)</b>	<b>0.041</b>

**Table 4: MIDAS score in study participants. Mean values of Individual item and total MIDAS score are higher in multidrug therapy group than monotherapy group.**

prescribed to about 90% of study participants. Beta blocker Propranolol was used for 12% of cases and anticonvulsant like Sodium Valproate for 16% of cases. Flunarizine was used in 10.7% of cases. 23 patients (30.66%) required more than one drug as prophylaxis and Amitriptyline was commonly combined with Valproate.

As shown in **Figure 1A**, total duration of illness was similar in patients receiving multidrug therapy (Median = 7 years, IQR = 5 year) and monotherapy (Median = 7 years, IQR = 8.5 years) and as expected, difference was not statistically significant (p-value = 0.526, Wilcoxon rank sum test).

But there was a significant difference in total MIDAS score between monotherapy and multidrug therapy group (p-value = 0.041, Student's Independent t-test). (**Figure 1B**) Difference between individual components of MIDAS has been shown in **Table 4**. All the items have higher mean value in multidrug therapy group, but the difference was not statistically significant.

**Figure1: Box and Whisker's plot showing relation of Duration of illness (1A) and MIDAS Score (1B) with drug therapy. The box and whisker plots denote median, interquartile range and range. The dots indicate outlier values**

#### 4. Discussion

Migraine is a common public health problem affecting all parts of society including all vulnerable sections of the population. In a developing country like India, new high cost therapy is inaccessible to those who require them the most. Prevalence and impact of migraine has been studied in Government based health studies in USA has shown women predominance particularly burdensome on female of child-bearing age. A study was carried out in medical students in our country where 42% fulfilled the IHS criteria of migraine.<sup>9,10</sup>

The demographics in this study is similar to other studies of Migraine patients conducted in India. Females of reproductive age group were more commonly affected by the condition.<sup>7,11</sup> We found unilateral headache associated with nausea, photophobia and phonophobia and duration of headache episodes more than 72 hours in most of the patients. All these findings were consistent with several migraine studies.<sup>3,4,11,13</sup> However, we found very high prevalence of migraine with aura (68%) in our study where most resources report this below 30%. A pan-India cross-sectional study reported mean MIDAS score of 27.28 which indicates most of the patients suffered from

moderate to severe migraine (Grade 3 and 4).<sup>8,13</sup> We found overall MIDAS score of 25.6 (SD = 3.88) which was close to their observation.

In our study, Paracetamol and NSAIDs were most common drug used to terminate acute attack and Amitriptyline (90.7%) for prophylaxis of Migraine followed by Valproate, Propranolol and Flunarizine. This trend is evidently different from other studies in India where beta-blockers are mainstay of therapy for prevention of acute episode rather than antidepressants.<sup>7,13</sup> Use of beta-blocker is more common in other developed countries like Germany, USA and Australia.<sup>6,12,14</sup> However, cost-effective studies showed Amitriptyline is most cost-effective drug for migraine prophylaxis.<sup>15,16</sup> This might be a reason for such high prescription rate of this drug here in eastern zone of India.

In a cross-sectional study, Jena et al. Reported 44.7% of migraine patients received (n = 882) more than one anti-migraine drugs for prevention of recurrent attacks. (7) We could not find any study comparing the severity of Migraine with polypharmacy. In our study, 30.66% patients were on multi-drug therapy who had significantly more MIDAS score than those on monotherapy (p value = 0.041). However, total duration of disease was not significantly different between two groups. It can be assumed that progression of disease requiring multi-drug therapy does not depend upon the duration of disease, but extent of disability caused by it.

### 5. Limitations

Association of comorbid conditions and adverse effect profile of the drugs could not be analyzed due to small sample size for time and resource constraints.

### 6. Conclusions

In eastern India, medications used to treat acute attack and prophylaxis of Migraine were found appropriate as per current treatment guidelines. Mostly cost-effective drugs like Paracetamol and Amitriptyline were prescribed and multi-drug therapy were given to patients with higher disability measured by MIDAS score.

**Conflict of interest none.**

**Funding none.**

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### Legends

Table 1. Baseline parameters of study participants

Table 2. Characteristics of headache of study participants

Table 3. Prescription pattern of drugs for treatment of Migraine

Table 4. MIDAS score in study participants. Mean values of Individual item and total MIDAS score are higher in multidrug therapy group than monotherapy group

Figure 1. Box and Whisker's plot showing relation of Duration of illness (1A) and MIDAS Score (1B) with drug therapy. The box and whisker plots denote median, interquartile range and range. The dots indicate outlier values

## LEARNING POINTS ON MIGRAINE

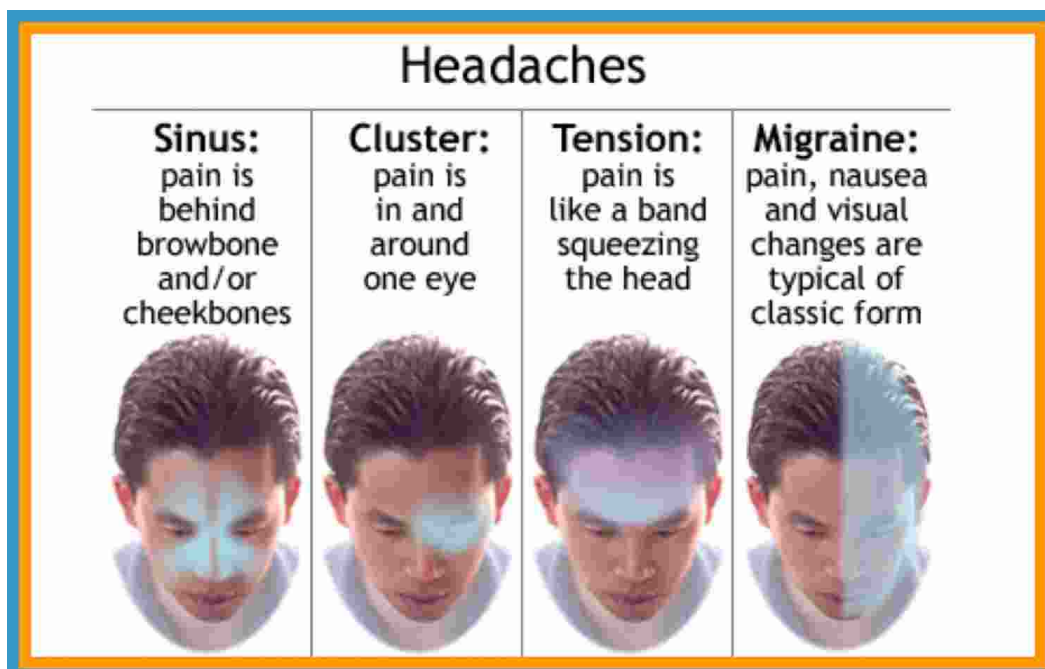
**Dr K. Mugundhan\*, Dr P. R. Sowmini\*\*, Dr K Sakthi Velayutham\*\*\***

- The term migraine is derived from the Greek word “hemikranios” which means 'half head'.
- The migraine attack can consist of up to four phases: the premonitory phase, aura, headache phase, and postdrome.
- The lifetime prevalence of migraine is about 33% in women and 13% in men.
- 2% of the general population has “chronic migraine,” meaning that they have headaches on at least 15 days per month including at least 8 days per month on which they have symptoms of fullblown migraine attacks
- The most commonly identified migraine attack triggers include emotional stress, fluctuating female hormones, missed meals, weather factors, sleep disturbance, odours, certain visual stimuli, alcohol, muscle tension, physical exercise, and being overheated.
- The most frequent prodromal symptoms include fatigue, mild cognitive dysfunction, irritability, neck pain, light and noise sensitivity, blurred vision, excessive yawning and excessive thirst.
- Visual aura, sensory aura, language aura, motor aura and brainstem aura can occur in decreasing order of frequency
- Headache phase - Severe unilateral throbbing pain that is exacerbated by routine physical activities associated with hypersensitivity to visual, auditory, olfactory and somatosensory stimuli, nausea, vomiting, neck pain and dizziness
- Untreated, the migraine headache phase usually lasts from 4 to 72 hours, with the majority subsiding within a day or after a night's sleep.
- When the migraine attack lasts for longer than 72 hours, “status migrainosus” is diagnosed.
- Migraine postdrome - fatigue, mild cognitive dysfunction, atypical mood, generalized weakness, feeling dizzy, neck stiffness, light and sound hypersensitivity, and excessive thirst
- Attention should be paid to examination of the temporal arteries, fundoscopy, cervical and cranial muscles, blood pressure and temporomandibular joint in any patient with headache to rule out secondary causes
- Pathophysiology of migraine Vascular vs Neuronal vs CGRP ( calcitonin gene related peptide ) theory
- NSAIDS and triptans for acute attack.
- Prophylactics antidepressants, beta blockers, calcium channel blockers and anticonvulsants.
- Important associations of migraine : vertigo, seizures and stroke.
- Menstrual migraine : Hormonal pills and Magnesium may be useful in addition to the usual medications.
- Migraine and pregnancy - Paracetamol for mild to moderate attacks; Severe attacks IV magnesium sulphate/ IV methylprednisolone/IV opioids/IV neuroleptics may be tried.

\*MD, DM(Neuro), FRCP(gLASG), Associate Professor, Dept, of Neurology, Govt. Stanley Medical College, Chennai. Tamilnadu

\*\*MD, DM(Neuro), Senior Asst. Professor of Neurology, Govt. Stanley Medical College, Chennai. Tamilnadu

\*\*\* Senior Asst. Professor of Neurology, Govt. Stanley Medical College, Chennai



## Original Research Article

**Occurrence of blood group pattern in Nepalese population of mixed origin in Tarai Region .**

Dr Asim Kumar Basak\*

**Abstract**

Role of different blood groups is very important in the management of transfusion of blood to the needy patient. This is why since the discovery of ABO blood group by Landsteiner in 1900, several attempts were made by different researchers to study on the frequency distribution of ABO blood groups, but similar data among Nepali population specially in one of the main topographical region of Nepal i.e Tarai Region is still lacking. So the aim of this study is to observe the distribution of normal ABO group and Rh factors among the Nepalese population of Tarai region.

A total of 1082 Nepali domiciles from Tarai regions are randomly selected from the Nepali Medical and Dental students, staffs and local domiciled population. Aseptically collected venous blood was used to determine ABO and Rhesus factor by Tile or Slide testing as reported by Egesie et al. 2008. It is observed in our study that prevalence of blood group in Tarai region of Nepal is in the following order : O>A>B>AB. However the occurrence of Rhesus positive individual is comparatively higher in Nepal than other countries. This study reveals that unlike other Asian countries A blood group is 2nd largest blood group in studied population of Nepal. This can be explained as racial variation.

**Keywords:** Blood group, Nepal, Racial, Rh grouping

**Introduction:**

Since Landsteiner<sup>1</sup> published his report regarding the distribution of the ABO blood group in 1900 and Landsteiner and Wiener<sup>2</sup> collectively published their report on the discovery of the Rh factors in 1940, it has been observed that the occurrence of ABO and Rh factors vary worldwide as well as among different races. A study by Chan et al<sup>3</sup> in 1962 from Singapur the O blood group has the highest frequency among Malays, Indians, Eurosiens and also Chinese people in Singapur whereas B group is the 2nd highest and AB is least. On the contrary the blood group A is most common in Russian Federation<sup>4</sup>. In the USA<sup>5</sup> it is 46% of O group, 41% of A, 9% of B and 4% of AB group. The commonest group among Australians are group O and A whereas in African B group is much common<sup>6</sup>. In Pakistan,<sup>7</sup> the occurrence of blood group B was maximum followed by A blood group.

It has also been reported that the occurrence of ABO group is different in different geographical, ethnic and socioeconomic groups<sup>8</sup>. For example in India, the incidence of ABO group is variable- the frequency for B ranges from 6% in Negritos of Andamans to 48% in Birijas of Bihar, while group A has a percentage of 20-30% in Western and Eastern Himalayas<sup>9</sup>. Frequency of blood group in North India is B >O>A>AB<sup>10,11,12,13</sup>, whereas in south India the blood group O was maximum followed by B<sup>14</sup>. This indicates that the occurrence of ABO blood group is not similar in all provinces of a country and depends on different geographical or ethnic groups. In Nepal such type of study is limited only in

**Editor's comments**

1. The distribution of blood groups varies according to geographical and ethnic groups.
2. The high prevalence of B group is similar to the West in contrast to the Asian population.
3. This knowledge may help in research of anthropology and disease associations.

restricted population i.e. either people from hilly region or from medical students community with small sample number<sup>15,16</sup>. Therefore the present study related to the occurrence of ABO blood group and Rh factor is essential in different geographical and ethnic groups (Natives staying in Tarai region of Nepal) so that this data can be used for:

1. The management of blood bank related services in this area.
2. Establishing possible associations of various diseases like cardiovascular disorders, cancers, peptic ulcers etc. to blood group in the said population living there<sup>17,18,19</sup>.
3. In anthropological study of racial classification of said population and also in solution of problems of identity, percentage and etc.

**Material and Method:**

Total of 1082 Nepali domiciles from Tarai regions (Flat river plain of Nepal that extends along the southern border with India, which is one of the major three topographical regions of Nepal) are randomly identified from the Nepalese MBBS and BDS students, staffs of the Medical colleges and local domiciled population. The ethnic group chosen for this study are the largely populated locally domiciled ethnic groups from this belt (Tarai region) who are of heterogeneous origin from Nepalese and Indians as the other studies were dealt in either multi ethnic<sup>20,21</sup> or population from purely Nepali

\* Msc, PhD

Prof & Head, Dept. of Physiology, Sudha Rustagi  
College of Dental Sciences and Research, Sector 89,  
Faridabad, Haryana-121002

Blood Group	Male (N=648)		Female(N=434)		Total (N=1082)	
	Absolute value	% age	Absolute value	% age	Absolute value	% age
O	286	44	176	41	462	43
A	194	30	143	33	337	31
B	136	21	82	19	218	20
AB	32	5	33	8	65	6
Rh+	602	93	391	90	993	92
Rh-	46	7	43	10	89	8

Table-II: Comparative table of ABO blood group & Rh factor in percentage

Country	A	B	O	AB	Rh+	Rh-
Great Britain	42	9	47	3	83	17
USA & Western Europe	41	9	46	4	85	15
Central & Eastern Europe	45	11	40	4	89	11
Australia	44	9	46	4	85	15
India (Mixed)	18	33	39	10	95	5
Pakistan	28	32	30	10	90	10
Nepal (Mixed) <sup>9,10</sup>	28	27	35	10	98.5-99	1-1.5
Nepal (Tribes of Jirels) <sup>11</sup>	34	14	25	9	99	<1

tribes<sup>22</sup>. The above mentioned ethnic group was selected through a questionnaire containing questions regarding their paternal, maternal and ancestral origin. Any doubtful case of ancestral relationship and individuals from purely Nepali origin are excluded from this study. The work was approved by the Institutional review board.

The venous blood was collected aseptically by puncturing the antecubital vein. The ABO and Rh factor are determined immediately after blood collection using the Tile or Slide testing method<sup>7, 23</sup> using antisera-A, antisera-B and antisera-D (Span Diagnostics Ltd. Surat, India). The blood groups were determined on the basis of agglutination (under light microscope as and when required). As per the standard protocol the result was expressed as percentage which is considered as occurrence of each ABO blood group and Rh factor. The significance of difference between the observed frequency and the expected (Reference frequency) is done by Chi Square test<sup>24</sup>.

**Observations:**

The sex wise distribution of ABO and Rh system in the above mentioned population is displayed in Table-I. It is found that amongst the studied group the O group is most prevalent followed by A group, then group B and then group AB. There is also no sex wise significant variations of blood group distribution. Statistical analysis by Chi Square test reflects that the observed frequency distribution does fit to the expected i.e. reference frequency distribution of Nepali (Mixed) population or in otherwise there is no significant difference between the observed frequency distribution and reference frequency distribution. But the observed frequency distribution significantly (P< 0.001) differs with the expected frequency distribution of Indian population. It is also found that the frequency distribution of Rh positive individuals is comparatively more in both genders among the population than the Rh negative individuals and the Rh negative population is significantly lower than that of other countries but matches with the reference distribution of other Asian countries. It is also observed that the percentage of Rh negative population in

Tarai region is not too lower as reported by other workers.

**Discussion:**

The occurrence of four ABO group varies in different population throughout the world though the type O is the most common. The frequency of A blood group is 2nd largest among Americans<sup>25</sup>, Western Europeans<sup>26</sup>, Central and South Americans, Australians and Central and Eastern Europeans<sup>27</sup>, whereas the frequency of B type of blood group is 2nd largest in Asian countries like China<sup>3</sup>, India<sup>9,10,11,12</sup>, Pakistan<sup>7</sup>, Singapore<sup>3</sup> etc. This study reveals that unlike other Asian countries like India A blood group is 2nd largest blood group in studied population of Nepal which defies the findings of some study in Nepal<sup>20,21,28</sup> but similar to some other findings<sup>22</sup>. This can be explained as racial variation as Nepalese are the conglomerate of diverse ethnic communities and mostly a mixture of Indo-Aryan, Tibeto-Burman and other ethnic groups though the people of Tarai region are mostly Indian in origin from northern Gangetic plain<sup>12,13</sup>. Similar difference is even seen in some provinces of India and Pakistan. For example in district Swat NWFP Pakistan<sup>7</sup> it was observed that the group B is most prevalent followed by O, A and AB, whereas in Baluchistan and Sindh provinces of Pakistan the O group is most prevalent<sup>29,30</sup>. Similarly in South India<sup>14</sup> O group was reported as the most common followed by B and A whereas in Northern part of India like Himachal Pradesh & Delhi<sup>9-12</sup> the blood group B group is 2nd most common.

The present findings also reveals that the percentage of Rh negative population is comparatively less irrespective of sex than that of other countries but is similar with the incidence of other Asian countries like India.

**Conflict of interest none.**

**Funding none.**

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**Karl Landsteiner - Father of Discovery of the Major Blood Groups**

## Blood Grouping for Clinical Practice

Dr. Rajib De\*

Blood group antigens are molecules present on the surface of red blood cells.

There are 30 types of blood groups, each group consisting of several antigens.

ABO group is most immunogenic and most important from transfusion point of view.

ABO blood group consists of A & B Antigen on RBC surface and corresponding opposite naturally occurring antibody (Anti-B, Anti-A respectively) in plasma.

To confirm ABO grouping both forward (for Ag on RBC) and reverse (for corresponding opposite Ab in plasma) grouping as well as detection of H Ag must be done.

For RBC Transfusion, group must be same or compatible and should be properly crossmatched.

Crossmatch involves testing donor RBC with patient's plasma (Major crossmatch: Most important for transfusion) and patient's RBC with donor plasma (Minor crossmatch: not important for transfusion).

Bombay blood group means absence of H antigen with presence of corresponding anti H Ab in the plasma.

Bombay blood group patients can be given only Bombay group RBC as anti H in plasma can destroy all other group RBC including group O.

After A & B Ag, Rh D Ag is most immunogenic and should be matched before transfusion as Rh+(D Ag present), Rh- (D Ag absent).

RBC transfusion should be ABO & Rh(D) compatible.

ABO blood group is not necessary for Random Donor Platelet(RDP) and Cryoprecipitate transfusion.

Rh(D) grouping is not applicable for FFP, RDP, Cryoprecipitate transfusion.

Blood group O are sometimes known as universal donors due to absence of A or B Ags. However, their plasma does contain anti-A and anti-B that, if present in high titre, has the potential to haemolyse the RBCs of non-group O recipients.

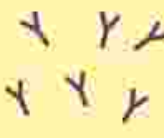


Blood group antigen expression is suboptimal upto 6 month of age, reach adult level at 5-10 years of age and again decline in older age > 65 years.

ABO and Rh(D) grouping is sufficient for occasional transfusion.

For multi-transfused patients extended grouping like Rh(C,c,E,e) and Kell are necessary to prevent alloantibody formation.

Grouping is best done by Tube method, Gel card or automated platforms. Slide method is not recommended for grouping.

Certain diseases like Leukemia, Multiple Myeloma, Autoimmune Haemolytic Anaemia etc can cause group discrepancy (discrepancy in forward & reverse grouping).

<b>ABO Blood Groups</b>				
Antigen (on RBC)	Antigen A	Antigen B	Antigens A + B	Neither A or B
Antibody (in plasma)	Anti-B Antibody 	Anti-A Antibody 	Neither Antibody	Both Antibodies 
Blood Type	<b>Type A</b> Cannot have B or AB blood Can have A or O blood	<b>Type B</b> Cannot have A or AB blood Can have B or O blood	<b>Type AB</b> Can have any type of blood Is the universal recipient	<b>Type O</b> Can only have O blood Is the universal donor

\* MD, DM (Clinical Haematology)  
Haematologist, Haemato-oncologist & Bone Marrow Transplant Physician  
Associate Professor, Department of Haematology, N. R. S. Medical College, Kolkata

## Case Series

### Profile Of Presentation of Panhypopituitarism In The Department of Internal Medicine At A Tertiary Care Center In Eastern India

Prof (Dr) Nirmalya Roy<sup>1</sup>, Dr Suman Sarkar<sup>2</sup>, Dr Ankan Pathak<sup>3</sup>

#### Abstract -

**OBJECTIVE:** Panhypopituitarism is a underdiagnosed entity . The aim of this communication is to highlight its existence and the challenges in diagnosis.

**METHODS:** A retrospective analysis of data of 5 patients of panhypopituitarism from 2017 to 2019 was done. Clinical, investigative, management and follow-up data are analysed.

**CONCLUSIONS:** Serum Cortisol, FSH, LH, TSH, FT4 AND MRI brain enable the diagnosis of panhypopituitarism in background of strong clinical suspicion of patients presenting with Hypotension, Low Capillary Blood Glucose, Hyponatraemia Refractory to Medical Therapy.

**Keywords-**PanhypopituitarismHyponatraemiaLow Capillary Blood Glucose

#### INTRODUCTION:

Panhypopituitarism is a underdiagnosed entity in the society. As the physicians are often not aware of its existence they remain underdiagnosed for significant amount of time. Often times the thyroid function may remain normal in some of these patients which could be attributed to differential affection of various trophic hormones. It could be that they have residual function of trophic hormones and get manifested during conditions of acute stress.

There are scattered reports of panhypopituitarism. This series document the profile of presentation of panhypopituitarism encountered in tertiary practice which is missed out in primary and secondary practice. However a strong clinical suspicion in patients presenting with Hypotension, low CBG, hyponatraemia refractory to medical therapy gives clue to the diagnosis of panhypopituitarism.

#### MATERIALS AND METHODS:

The material for this study is obtained from records of academically interesting patients maintained by the authors in a tertiary care hospital. 5 cases were diagnosed treated and followed up during 2017 to 2019.

The diagnosis of panhypopituitarism were based on clinical presentation, SERUM CORTISOL, LH, FSH, TSH, FT4, MRI BRAIN, management details including administration of low dose steroids and replacement dose of L-Thyroxine are available.

#### SIGNIFICANT SIMILARITIES:

- They all presented at a late stage of their life above the age of 50
- All of them were quite oblivious of their inciting cause that could have led to panhypopituitarism

1. Professor- Dept of Internal Medicine, KPCMCH Dr Suman Sarkar - 1st Year PGT , Dept of Medicine , KPCMCH
2. MSc, PhD, Prof & Head ,Dept. of Physiology, Sudha Rustagi College of Dental Sciences and Research, Faridabad, Haryana
3. Dr Ankan Pathak - 2nd year PGT , Dept of Medicine, KPCMCH



Figure-1: Showing pituitary Pallor



Figure-2 : Showing pituitary Pallor

- All of them had h/o multiple hospital admissions which were treated mainly with iv fluids.
- All of them had pallor which was unaccounted.
- Fatigue, obtundation, hyponatremia are often the most common shared feature.
- The diagnosis was clinched by inappropriately low TSH in the face of low ft4, low cortisol, and low FSH, LH. Doing ACTH and growth hormone are often very difficult in low resource setting.



NAME	AGE	FEATURES AT ADMISSION	SERUM 8AM CORTISOL	LH	FSH	TSH,FT4
Patient -1 / F	52 Years	Obtundation,severe hypotension & persistently low CBG levels, anaemia	0.79ug/ml [5-25]	0.40 mIU/ml [0.5 - 61.2]	2.36mIU/ml [3 - 12]	7.46mcIU/ml, 1.30pg/ml [0.8-2]
Patient -2 / M	51 Years	Obtundation, Hyponatremia	1.88ug/ml [5-25]	1.07mIU/ml [3-57.3]	1.91mIU/ml [3 - 12]	2.35mcIU/ml,1.32pg/ml [0.8-2]
Patient -3 / F	72 Years	Easy fatigability, Hyponatremia	3.16ug/ml [5-25]	3.47IU/ml[14.2-52.3]	6.79IU/ml[19-100.1]	1.81mcIU/ml, 0.28pg/ml[0.8-2]
Patient -4 / F	54 Years	Diarrhoea, Obtundation, hyponatremia, Hypoglycemia	2.5ug/ml [5-25]	0.4mIU/ml [0.6-61.2]	1.8mIU/ml [3-12]	0.02mcIU/ml, 0.4pg/ml[0.8-2]
Patient -5 / F	58 Years	Diarrhoea, vomiting in the face of Hypoglycemia with h/o recurrent hyponatremia and Hypoglycemia	2.27ug/ml [5-25]	0.5mIU/ml [0.8-10.5]	1.74 mIU/ml [3 - 12]	2.6mcIU/ml, 0.67pg/ml [0.8-2]

- In African and low resource countries where PPH remains an important cause of maternal morbidity these simple method of awareness and diagnosis can be of great help to these economically challenged woman.
- This paper further provides a simplistic model to pickup such patients.
- Moreover getting access to ACTH injection in low resource setting is often very difficult. Therefore stimulation test could not be carried out, most of the times. Many studies have reported high interassay variability and low reproducibility of plasma ACTH assays.

**DISCUSSION:**

Panhypopituitarism is a disease characterized by complete or partial deficiency of hormones secreted by the pituitary gland<sup>1,2</sup>. There are a variety of etiologies that range from cranial surgery, Radiotherapy, Tumours, Hereditary, Infiltrative, Infectious and Head Trauma<sup>1</sup>.

The clinical presentation may vary from person to person. It may range from asymptomatic to life threatening features of adrenal insufficiency. Signs and symptoms of the disease may persist for several years without diagnosis. High suspicion of the disease , biochemical evaluation are useful tools in early diagnosis<sup>1,2</sup>. In these patients due to cortisol and thyroid hormone deficiency, qt prolongation and heart rhythm disorders may coexist<sup>3,4</sup>. Moreover accessing all the pituitary hormones particularly with stimulation tests is often very challenging and economically demanding leading to appreciation of diagnosis.

Treatment of panhypopituitarism includes hormone replacement therapy. The main goal of hormone replacement therapy is to achieve normal levels of circulating hormone to maintain natural hormonal milieu and relief of symptoms<sup>1</sup>.

Considering the extent of clinical signs of panhypopituitarism we must keep a high index of suspicion. Though the authors understand that for complete wellbeing growth hormone remains an important entity. But nonetheless it is an expensive proposition in most of the cases. However as this is not life threatening growth hormone supplementation can be safely avoided in low resource setting.

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- Hon Editor

## Pictorial CME

### A 50 year old woman with personality change

N.Reema\*, Dr S.Bhagyabati Devi\*\*

#### Take home messages:-

- Even in the era of HAART, AIDS dementia complex is still a possibility
- HIV positive patients with cognitive dysfunction or motor abnormalities should have an early CNS imaging study
- Clinicians dealing with PLHA should be aware of the long term neurological complications

**Keywords-**AIDS Dementia Complex HIV associated dementia HAART therapy

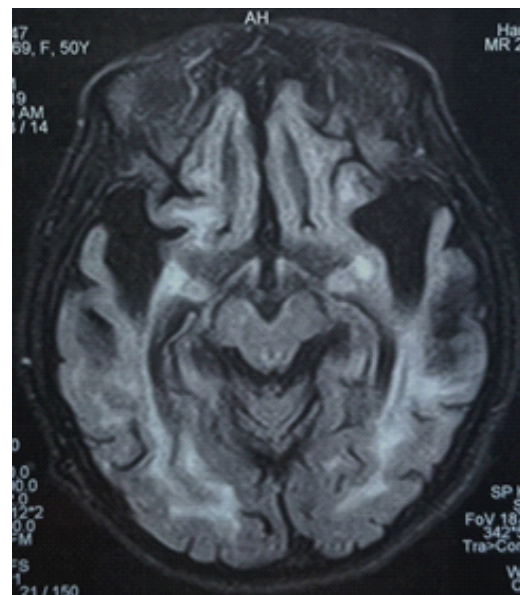
A 50 year old HIV positive female presented with forgetfulness (dementia), inability to recognize her relatives, tremor of the hands, inability to hold objects, an episode of aggressiveness and violent behaviour along with focal seizures and emotional liability. Her laboratory investigations including CSF examination were all within normal limits. Her CD4 count was 488 with a viral load of 175 copies/ml. MRI images of her brain are given here (figures 1 and 2).

1. What is the probable diagnosis?
2. What are the criteria for diagnosis of this condition?
3. What is the treatment?

#### Answers:-

1. HIV associated dementia (HAD)/AIDS dementia complex (a part of the spectrum of HIV associated neurocognitive disorder-HAND)

2. AIDS Dementia Complex (ADC) is a subcortical dementia. HAD incidence is 10.5/1000 patients per year and typically presents with loss of attention, concentration, slowing of motor execution with behavioural change. The American Academy of Neurology (AAN) criteria for HAD are 1) abnormality in at least two cognitive (non-motor) functions causing work, daily activities and 2) either motor function or specified psychiatric or psychosocial functions alterations (e.g., lack of motivation, emotional liability, social behavioural change).
3. Treatment wise, HAART therapy has decreased the occurrence of HAD significantly. Substituting ART drugs which can cross blood brain barrier, eg; Zidovudine, stavudine, abacavir, nevirapine, indinavir and lamivudine to lesser extent, should be included.



\* SR,

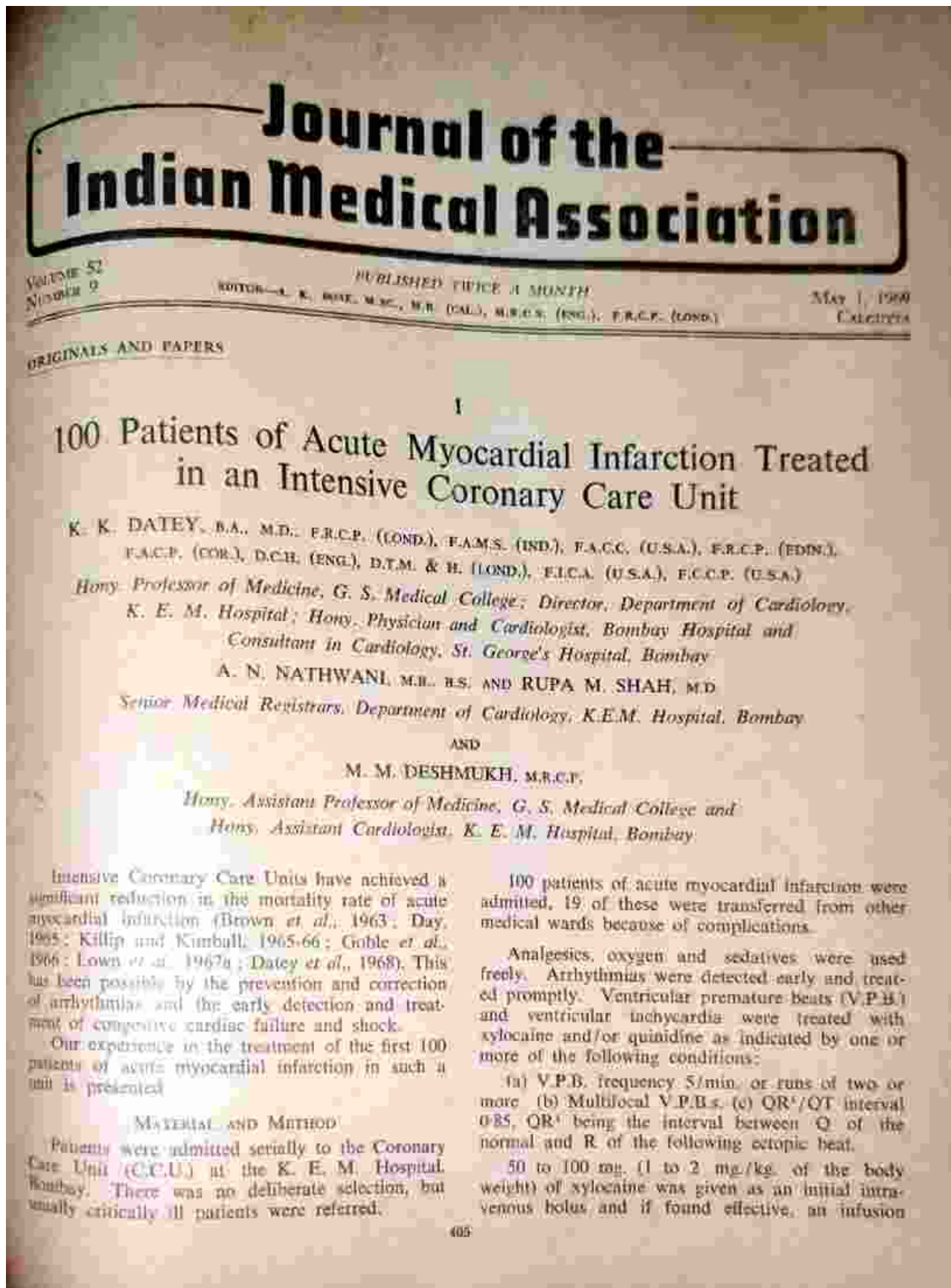
\*\* Professor, Dept. of Medicine, RIMS, Imphal

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of 1-4 mg./min. was maintained. When necessary, quinidine (200 mg. 6 hourly) was used.

Ventricular fibrillation was promptly treated with external cardiac massage, artificial respiration and when necessary by one or more countershocks (50 to 400 J). The resulting metabolic acidosis was treated with 100-400 ml. of 7.5 per cent sodium bicarbonate.

Sinus bradycardia was treated with intramuscular or intravenous atropine so as to maintain the heart rate at about 80/min. First and second degree A-V blocks were treated with corticosteroids (40 mg. or more of prednisolone daily), atropine and oral isoprenaline. High grade A-V blocks were treated with isoprenaline infusions (0.5 mg. per cent) at about 15 drops per minute and when necessary by transvenous catheter pacing.

Ventricular asystole was treated with external cardiac massage and artificial respiration.  $\frac{1}{4}$  to 1 ml. of 1:1000 intracardiac adrenaline was given. 10 ml. of 10 per cent calcium gluconate was given intravenously. Acidosis was treated by 100-400 ml. of 7.5 per cent sodium bicarbonate.

Cardiac failure was treated with diuretics and digitalis. Diuretics were also used in cases where the urine output was diminished even when overt signs of cardiac failure were not present.

Shock was treated by one or more drugs after evaluation of several parameters, viz., blood pressure, urinary output and central venous pressure. The drugs used consisted of one or more of the following, viz., beta stimulators (0.5 mg. per cent isoproterenol infusion), alpha stimulators (nor-adrenaline), alpha blockers (25 mg. chlorpromazine), corticosteroids 1-2 g. daily, digitalis and diuretics.

RESULTS AND DISCUSSION

**Age, sex and period of monitoring**—There were 90 males and 10 females. Their ages ranged from 34 to 80 years with a mean of 54 years. The average period of monitoring was 5½ days.

**Site of infarction**—54 had anterior, 44 posterior and 2 had a double infarction.

**Rapidity of admission**—The interval between the onset of symptoms and admission to hospital is shown in Table 1. 64 per cent of patients were admitted within 12 hours of the onset of symptoms.

TABLE 1—SHOWING THE INTERVAL BETWEEN ONSET OF SYMPTOMS AND ADMISSION

Interval	Percentage of cases
< 6 hours	44
6 to < 12 hours	29
12 to < 24 hours	8
24 to < 48 hours	7
48 hours and more	21

Most of the patients admitted after 48 hours were transferred to the C.C.U. because of complications.

**Severity of infarction**—The mortality in the acute stage depends upon the severity of infarction. The severity should be graded by standard criteria. The severity in different series could be compared with respect to mortality, treatment and prognosis.

Table 2 shows the distribution of patients according to the severity of infarction as evaluated by the coronary prognostic index of Peel *et al.* (1962). More than half the patients had moderate to severe myocardial infarction.

TABLE 2—SHOWING THE DISTRIBUTION AND MORTALITY

	I n f a r c t i o n			
	1-8	9-12	13-18	17 and more
Pre-coronary care era (Peel <i>et al.</i> , 1962)				
Distribution %	22.2	28.0	22.4	17.4
Mortality %	2.5	12.5	23.4	64.1
Coronary care era (Dacey <i>et al.</i> , 1968)				
Distribution %	18.0	28.0	24.0	32.0
Mortality %	—	—	25.0	42.0
Coronary care era (Lown <i>et al.</i> , 1967b)				
Distribution %	22.1	26.2	25.7	26.0
Mortality %	1.0	16.5	14.5	42.1

**Mortality**—The total mortality was 19 per cent. Table 2 shows the mortality in different severity groups. The mortality between the pre-coronary care era (Peel *et al.* loc. cit.) and the post coronary care era at the C.C.U. at Peter Bent Brigham Hospital (Lown *et al.*, 1967b) is compared with our own.

TABLE 3—SHOWING THE RESULTS OF RESUSCITATION

Peel <i>et al.</i> (1962) Index	No. of cases	Unsuccessful	Temporary only	Left hospital alive	Survival rate (%)
1-8	4	—	—	4	100
9-12	—	—	—	—	—
13-18	8	7	1	1	10
17 and above	12	7	5	—	—
Total	22	9	6	7	32

**Resuscitation**—Resuscitative measures were applied to both groups of patients, viz., those deve-

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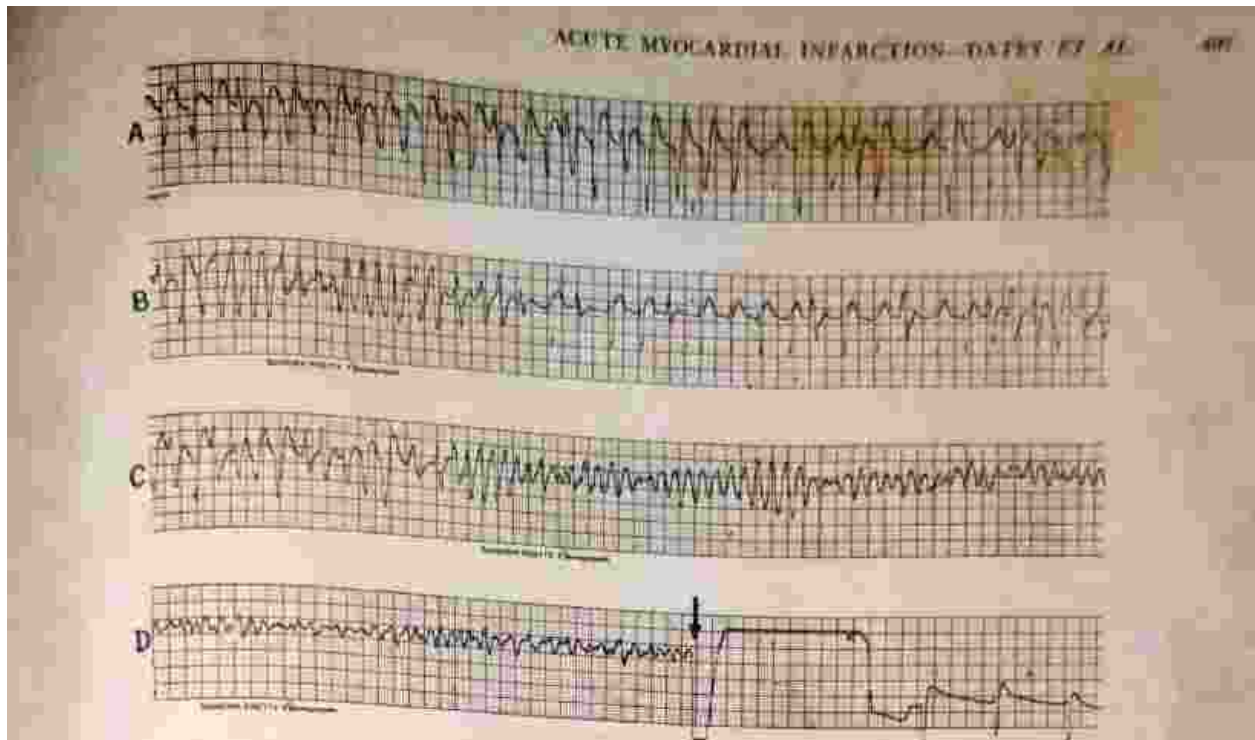


FIG. 1—R. H., M.M.F. 45 YEARS, ACUTE MYOCARDIAL INFARCTION. CONTINUOUS STRIP OF ECG SHOWING: (A) MULTIPLE MULTIFOCAL VENTRICULAR ECTOPIC BEATS; (B) SHORT RUN OF VENTRICULAR TACHYCARDIA; (C) VENTRICULAR TACHYCARDIA LEADING TO FLUTTER AND FIBRILLATION; (D) VENTRICULAR FIBRILLATION BEING TERMINATED BY T.S. J COUNTERSHOCK (ARROW SHOWS DELIVERY OF SHOCK)

veloping "sudden" cardiac arrest or "primary electrical failure" due to serious arrhythmias and those with electrical failure secondary to cardiac decompensation or "pump failure" (congestive cardiac failure, shock and pulmonary oedema). The results in the former group were very gratifying whereas those in the latter, though initially encouraging, were eventually unsuccessful. Resuscitation in this group of patients is usually not compatible with long term survival (Nachlas and Miller, 1965; Goble *et al.*, *loc. cit.*; Durey *et al.*, *loc. cit.*). As shown in Table 3 though resuscitation was successful in 57 per cent of the cases, only 23 per cent survived to leave the hospital. All 5 cases of "primary electrical failure" who survived (left the hospital alive) had ventricular fibrillation. A representative case is shown in Fig. 1. No case of ventricular asystole survived. More or less similar results have been shown by other workers (Nachlas and Miller, *loc. cit.*; Goble *et al.*, *loc. cit.*).

RESUSCITATION

**Arrhythmias**—84 per cent of patients had arrhythmia. Table 4 shows the incidence and mortality in patients who had major arrhythmias. Several patients had more than one arrhythmia.

Xylocaine was found to be safe and effective in 11 patients; however, it failed to control ectopic beats in 2 patients who later responded to quinidine.

TABLE 4—SHOWING THE INCIDENCE OF MAJOR ARRHYTHMIAS

	Primary		Secondary	
	No. of cases	Mortality rate (%)	No. of cases	Mortality rate (%)
Ventricular tachycardia	8	12	4	50
Complete heart block	5	20	3	80
Second degree A-V block	8	—	2	50
Sinus bradycardia	—	10	1	100
Multiple, multifocal V.F.B.s	25	4	3	33

12 patients with sinus bradycardia were treated with atropine, but the heart rate failed to increase in 3 patients. Side effects were not rare, specially difficulty in evacuating the bladder. One patient developed paralytic ileus.

Worsening of A-V block can usually be prevented with drugs (corticosteroids, atropine and isoprenaline). However, should a high grade A-V block ensue, transvenous pacing seems to be the only safe and effective method for increasing the ventricular rate. A representative case is shown in Fig. 2. With the semi-floating pacing catheters which can be introduced percutaneously, there is no need for sophisticated fluoroscopic equipment.

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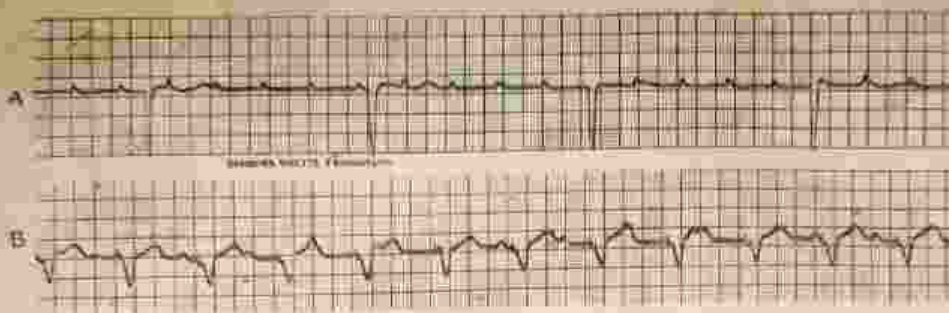


FIG. 2—S. H., FEMALE, 64 YEARS, ANGIOLIC MYOCARDIAL INFARCTION WITH STOKES-ADAMS ATTACKS. ECG FROM 24/1/69. (A) COMPLETE HEART BLOCK WITH ATRIAL RATE 130/MIN. AND VENTRICULAR RATE 27/MIN. (B) TRANSVENOUS PACE AT 75/MIN., EACH QRS IS PRECEDED BY A PACEMAKER STIMULUS

To prevent "competition arrhythmias" the use of a "demand" pacemaker has been advocated.

**Congestive cardiac failure**—49 patients showed evidence of cardiac decompensation. Diuretics and digitalis were used. The mortality was 34 per cent. This high mortality is probably due to the severity of the infarction and to the extensive myocardial damage.

Gallop rhythm without any other evidence of decompensation was present in 8 patients. Only 1 of these died, the mortality being 12.5 per cent. When this is compared to the overall mortality of 19 per cent, we feel that gallop rhythm (unaccompanied by other signs of congestive cardiac failure) need not be considered as an ominous sign.

Diminished urine output was not an unusual finding even in the absence of other signs of cardiac decompensation. We considered this as early evidence of incipient cardiac failure and gave diuretics. In many cases the clinical improvement was perceptible and several episodes of overt cardiac decompensation were probably thus prevented (Fig. 3). In our opinion, the danger from the use of diuretics has been exaggerated. In case of marked diuresis, with replacement of potassium orally, hypokalaemia can be prevented and ventricular arrhythmia is unlikely to be precipitated. In our patients, even with a systolic blood pressure of 100 mm. Hg, the B.P. increased instead of falling after the diuresis. None of these patients developed thromboembolic phenomenon and we feel that the danger of increased blood viscosity and liability to thrombosis is probably only a theoretical consideration.

**Shock**—Shock was considered present with a systolic B.P. of less than 90 mm. Hg accompanied by oliguria and other signs of peripheral vasoconstriction. Table 5 shows the incidence and mortality in cases of shock.

The mortality due to shock is itself alarmingly high and when associated with congestive cardiac failure it becomes higher still.

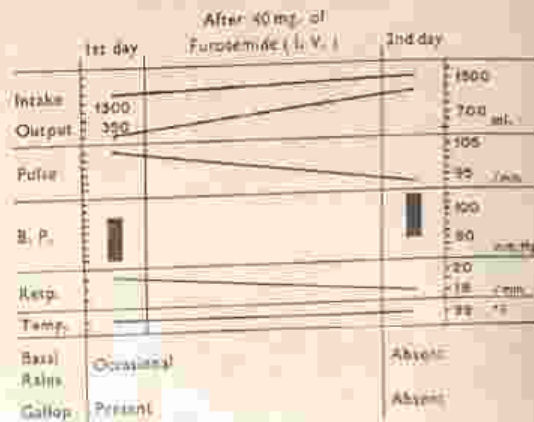


FIG. 3—B. P., MALE, 50 YEARS, ACUTE ANTERIOR MYO CARDIAL INFARCTION, SHOWING IMPROVEMENT FOLLOWING 40 MG. OF I.V. FUROSEMIDE IN SEVERAL PARAMETERS (OUTPUT, PULSE, B.P., RESPIRATOR, BASAL RAINS AND GALLOP)

TABLE 5—SHOWING THE INCIDENCE OF SHOCK AND MORTALITY THEREON

	No. of cases	Mortality rate (%)
Shock	10	90
Combination of congestive cardiac failure and shock	7	90

**Late deaths**—Of the 19 patients, 7 (35 per cent) died (Table 6) after the first 5 days, i.e. after transfer into the General Medical Ward. 2 of these died suddenly, presumably due to primary electrical failure. Some form of monitoring is therefore necessary for the first 2 to 3 weeks.

**Future of coronary care units**—The therapeutic focus has shifted from resuscitation of cardiac arrest to its prevention. With this, electrical failures will cease to take their toll of life. Power failure still remains the major hurdle to be surmounted. The possible avenues of research may be directed

## Comments on Archive

Dr Ruchit Shah, Dr BR Bansode, Dr Nihar Mehta

Dear friends, it gives me immense pleasure to write a commentary on an article published way back in 1969. The importance of this write up is in understanding the milestones that have finely crafted the management of ST elevation myocardial infarction (STEMI).

### **Article summary**

This article was published in JIMA in 1969. It speaks about the management of 100 patients of Acute Myocardial Infarction (AMI) at KEM hospital, Bombay. These patients were admitted in a coronary care unit (CCU) and administered analgesics, oxygen and sedatives. Ventricular arrhythmias were treated with xylocaine, quinidine and cardioversion. Sinus bradycardia was treated with intravenous or intramuscular atropine. First and second degree atrioventricular (AV) blocks were given oral corticosteroids, injectable atropine and isoprenaline. Temporary pacing was done for high grade AV blocks at bedside with semi floating catheter without fluoroscopy. Ventricular asystole was treated with external cardiac massage, artificial respiration, intracardiac adrenaline, intravenous calcium gluconate and intravenous sodium bicarbonate for acidosis. Cardiac failure was monitored clinically with auscultation of gallop rhythm, crepitations and decreased urine output. Digitalis and diuretics were given to treat it. Shock patients underwent blood pressure, urine output and central venous pressure (CVP) monitoring. Shock was treated with isoproterenol infusion, noradrenaline, digitalis, diuretics, oral chlorpromazine and corticosteroids. They predicted that future in management would be in monitoring myocardial contractility by mechanical and biochemical means. Arrhythmia prone patients would be managed by radio telemetry. Research should be focussed on newer drugs, mechanical and surgical procedures to manage power failure.

### **Evolution of AMI (Table 1)**

**Phase 1 (1912-61)** Bed rest and expectant treatment - Initially, patients were offered bed rest for six weeks which was reduced to five days and hospitalisation reduced to one month. Drugs were administered as a supportive measure. Arrhythmias were detected by clinical auscultation. Most of the deaths were due to arrhythmias.

**Phase 2 (1961-75)** Coronary care units (CCU) Patients underwent cardiac monitoring with ECG monitors, with round the clock staff available for cardiac resuscitation. Even ambulances were equipped with pre hospital resuscitation

The article above crisply describes every aspect of

management in CCU. The focus was on mortality reduction due to arrhythmias. A lot of morbidity and mortality was due to pump failure. Hence the next phase focused on salvaging myocardium.

**Phase 3 (1975 till date)** Myocardial reperfusion This phase marks a metamorphosis in the management of STEMI as compared to the previous phase. There are striking differences as compared to the nostalgic article.

- 12 lead ECG, which is a century old modality still remains the gold standard for diagnosing STEMI.
- ECG monitoring with defibrillation when required is the norm since the CCU era.
- Previously Oxygen supplement was given routinely. Now it is advised only if SaO<sub>2</sub><90% or PaO<sub>2</sub><60%. Opioid analgesics or benzodiazepines may be given to alleviate pain and anxiety.
- Pre hospital care In the CCU era, staff was trained in pre hospital resuscitation. Cardiac ambulances are now equipped with ECG and radio telemetry as rightly predicted by the authors in 1969. Today, trained staff can correctly identify STEMI; administer pre hospital thrombolysis and defibrillation if needed.
- Revascularization (Table 2) In the CCU phase, there was no option of revascularization.

With focus on restoring the flow of infarct related artery, primary PCI emerged as the therapy of choice (balloon angioplasty bare metal stents new generation drug eluting stents). It was observed that the earlier the infarct related artery is revascularised, more the mortality benefit. Thus, came the saying "time is muscle". Attempts were made to reduce time delays by reducing symptom onset/ first medical contact (FMC)/ STEMI diagnosis to revascularisation time. In a country like India, with multiple logistic issues and non-uniform availability of the cathlab; we have developed STEMI systems of care. This system involves extensive training of staff, standardised protocols, improvement of emergency services and developing a network of the hub and spoke model. The hub and spoke model of India involves multiple ambulances with trained personnel. These personnel take ECG at first medical contact and transmit it for interpretation via radio telemetry/ smartphones to the hub. If the patient is diagnosed as STEMI, he is transferred to pre designated hospitals for treatment. If primary PCI is feasible in the designated time, he undergoes the procedure; else he is fibrinolyzed and moved from spoke to hub for early PCI. The cost of STEMI treatment is a huge expenditure on the family especially when it is out of pocket. The present government insurance schemes are a big relief to patients.

- Hospital logistics Contrary to the CCU era, early ambulation (≤24 hours) and early discharge (≤72hours) is done in uncomplicated cases.
- Imaging - There was no luxury of imaging in the CCU era. Presently, echocardiography is used to assess resting left/ right ventricle function and mechanical

**Dr Ruchit Shah DNB Med, DNB Cardiology Interventional Cardiologist- Hon at Babasaheb Ambedkar Railway hospital**

**Dr BR Bansode MDHOD, Dept of Medicine, Babasaheb Ambedkar Railway hospital**

**Dr Nihar Mehta MD Med, DNB Cardiology Hon Cardiologist, Jaslok hospital**

complications. A follow up echocardiography can be done at 6-12 weeks after the STEMI. Cardiac MRI, SPECT, PET are also available if further information is desired.

- Cardiac biomarkers Biomarkers to detect cardiac injury have been in use since more than 50-60 years. Aspartate transaminase was the first clinically used biomarker in 1954. Then came creatine kinase, lactate dehydrogenase and CK-MB. They were not specific. Presently, quantitative serial high sensitive troponin testing is used to determine infarct size and prognosis.
- Pharmacotherapy Intensive pharmacotherapy in the form of high dose statins, beta blockers, ACE inhibitors, ARB (in ACE inhibitor intolerant patients) and mineralocorticoid receptor antagonists (MRA) have mortality benefits. These classes of drugs were not available in the CCU era.
- Arrhythmias The management of atrial and ventricular arrhythmias in the CCU era was primitive. Apart from temporary pacing for high grade AV blocks and cardioversion for ventricular arrhythmias, everything has been revolutionised.
  - i) Atrial fibrillation (AF) Intravenous beta blockers, amiodarone and electrical cardioversion is used. Intravenous digitalis is used only if there is associated heart failure and hypotension. In patients with long term AF, CHADS2VaSc score is calculated and oral anticoagulation is considered.
  - ii) Ventricular arrhythmias Repeated electrical cardioversion, complete revascularisation and correction of electrolytes is the most important. Beta blockers, amiodarone and overdrive pacing can also be done. In case of an electrical storm, intubation with deep sedation and radiofrequency ablation can be done. Implantable cardioverter defibrillator is given to patients at a high risk of sudden cardiac arrest.
  - iii) AV blocks Urgent PCI, temporary pacemaker and positive chronotropic agents (atropine, epinephrine, vasopressine) are given.
- Heart failure In the CCU era, heart failure was managed clinically with diuretics and digitalis. Now bedside echocardiography and invasive

hemodynamic monitoring has revolutionised the management heart failure. Loop diuretics and nitrates are used for symptomatic management. ACE inhibitors, ARB (in ACE intolerant), beta blockers and MRA have mortality benefit in patients with LVEF $\leq$ 40% and/or heart failure. Oxygen and mechanical ventilation is done if required.

- Cardiogenic shock - In the CCU era, shock patients underwent clinical and CVP monitoring. They were managed conservatively. Today, doppler echocardiography and invasive hemodynamic monitoring is available. Immediate PCI is done if anatomy is suitable. If mechanical complications are there, heart team discussion followed by emergency CABG/ hybrid procedure is done. Inotropes, intra-aortic balloon pump, short term mechanical circulatory support, ultrafiltration and mechanical ventilation can be lifesaving.
- Cardiac arrest Now, primary PCI gives an added chance of survival. If patient remains unresponsive after resuscitation, targeted temperature management (32-36 degrees C) is strongly recommended.

**Phase 4** (The future) The future lies in prevention of lethal myocardial injury and use of biologicals.

#### **Mortality**

As science progressed and technology evolved, we saw a drop in mortality over the decades. The mortality rate was 30% (1912-61), 15% (1961-75) which reduced to 3-8% in the present day. A Danish cohort studied the mortality risk in acute myocardial infarction patients less than 50 years old between 1980-2009. The 30 day mortality was 12.5%, 8.4% and 3.2 % in 1980-89, 90-99, 2000-09 respectively.

#### **Summary**

We have seen a paradigm shift in the management of AMI since the above article was published. The authors had rightly predicted that arrhythmias could be monitored by radio telemetry and the future research should be focussed on newer drugs and better procedures. Primary PCI, systems of care for STEMI, aggressive CCU management, drugs with trials for mortality benefit, better thrombolytics, heart team approach and mechanical circulatory devices have helped to significantly reduce the mortality associated with AMI.



## History of Medicine

### Scenario of India during the last pandemic: A century ago

The Coronavirus pandemic, starting from January 2020, has affected all walks of life all over the world. International travel has been halted, major events have been cancelled and the financial market has been in free fall. After ravaging China and Europe, the disease has come to India. It is still the early stages of the epidemic in India but experts are apprehensive that the disease has the potential to grow exponentially in the population. At this juncture, it may be prudent to take a look back to a similar scenario a century ago.

1918 was the year when the First World War ended. It was the year Prohibition first came into effect in the USA. It was the year Poland became independent, the Romanov family in Russia was brutally killed. But it was also the year a deadly disease struck humanity: The Spanish flu. The name is a misnomer. It did not start in Spain. But Spanish media were the first to report about the disease extensively and the moniker was coined.



**Copyright free image (Wikimedia commons) of flu ward in Washington D.C. during 1918-19 pandemic (copyright free)**

The Spanish flu affected around 500 million people, approximately one-third of the world population at that time. Mortality was estimated to be between 2050 million. No region of the world was spared and India was affected severely. The disease was notable for affecting young, healthy people.

In all probability, the Spanish flu came to India with a garrison of soldiers coming back from the War in June, 1918. The ship carrying the soldiers docked at Bombay and the epidemic started among the population of that city. Bombay was already overcrowded at that time and a recent famine in the countryside had forced many villagers to the cities in search of work and food. In such a petridish of undernourished population with almost no medical support, the disease spread like wildfire. Recent research has found out that there was probably a second entry of the virus from the Madras port. The virus ravaged South India and also spread to Ceylon.

By July 1918, more than 200 people were dying daily in Bombay from the flu. Almost all the houses of the city had at least one patient; sometimes whole families were down with the malady. An excellent graph was prepared by the office of the Sanitary Commissioner of India showing the weekly death rates in Calcutta, Bombay and Madras. It is seen that the peak death rate, around 260, was reported in Bombay in the first week of October, 1918 while for Madras, the death rate of around 200 was reached in the third week of October. Calcutta recorded much lower death rate, with the highest being around 60. In the Bengal province, the overall death rate was 8.5 per 1000 population. The epidemic peaked in December in Bihar and Bengal. There was one small focus of hotspot in the Hindu pilgrimage site of Puri in Orissa. But generally, other coastal areas were spared. The government instructed the people to avoid crowded places. Newspapers also instructed the people to avoid going to places like fair or circus.

The epidemic in India lingered on. A Times of India archive document shows that in Bombay, in the week ending March 5, 1919, the number of deaths recorded was 1471. Places of the country which received less rain were more affected. It must be remembered that at the same time, epidemics of plague, small pox and Malaria were also devastating the country. So, the death rate was astronomical. The population of India in 1911 was 315 million. In 1921 census, it was 318 million. This was much lower than the natural rate of increase. Influenza epidemic, along with the world war and the notorious crop failure season of 1920 were to blame for this.

Various countries of the world tried various techniques to contain the spread of the virus. In St. Louis, USA the mayor closed all schools, pool halls and movie theatres. The epidemic curve was flattened. In San Francisco, it was a law to wear gauze masks and anyone not wearing them was fined.

In October 1918, several cities in Europe banned public gatherings and church sermons were limited to five minutes. Free soap was distributed. Number of passengers in public transport was restricted. Spitting on the street was prohibited.

At first, the global nature of this infection was not known. So, local Indian newspapers referred to the illness as "Bombay fever". According to JA Turner, the then health officer of Bombay, the disease "...came to Bombay like a thief in the night". It must be remembered that Bombay at that time was also home to other infectious diseases like Plague, small pox and Cholera. Plague had just killed about 70 to 80 million people in different parts of India. Thus, the authorities were slow to take notice of this new disease.

By popular accounts, seven policemen posted at Bombay port docks were the first recorded victims of this flu in the city. Next to follow were multiple employees of the Bombay port trust and telegraph office. By the last week of June, 1918, there were thousands of patients with fever, extreme

body ache and chest congestion all over the city. The mortality figures started rising from July. The disease then spread to the great plains of North India and people of all ages started dying in large numbers. In some accounts, the Ganges river was clogged with dead bodies. The total number of the dead will never be known with certainty but historical estimates put the number somewhere between 10 and 25 million. So, a large part of the global mortality was from India only. The urban areas had much more mortality compared to the rural belts.

People hoped that the infection would go away with the monsoon. But it came back with vengeance again in September-October of the same year. This time, the target was the working age population: adults between the ages of 20 and 40. One researcher documented that in one day, 06 October, 1918, there were 768 deaths from influenza in Bombay city alone. This gives some idea of the severity of the epidemic. However, except for some sporadic accounts, records of the epidemic in both photographic and written form are largely missing from contemporary Indian narrative. Some people have argued that in a country already on the brink of destruction with food shortage, rising inflation and death in war, this was not something which the people prioritized at that time. Novels written around the same time are almost devoid of any detail mention of the epidemic. The only exception was "The final Question" written by Saratchandra Chattopadhyay in Bengal. In chapter no. 18 of this great novel, he has given a vivid description of the influenza epidemic in Agra. He writes that people fled their homes, leaving the patients behind. The city of Agra was reduced to a necropolis with all shops and businesses closed. The only people in the streets were the undertakers. The main affected areas were the slums of the poor workers and labourers. 1918 is the worst year in modern Indian economic history. GDP fell by more than 10% and inflation was at an all-time high.

Worldwide, a number of famous people, including Woodrow Wilson, the president of USA, the prime minister of Britain and the king of Spain fell prey to the virus.

Mahatma Gandhi, residing in his Gujarat Ashram at that time, was also struck down with the illness. Many members of his ashram also fell violently ill, as attested by Mahadev Desai, the personal secretary of Gandhi. In a letter, Gandhi wrote, "I am myself confined to bed still. It appears I shall have to keep to it for many days more." Suryakant Tripathy, a Hindi poet, lost many family members in the flu. He writes, "I travelled to the riverbank in Dalmau and waited. The Ganga was swollen with dead bodies. At my in-laws' house, I learned that my wife had passed away." The virus spread from Bombay province to Madras and then to the North and East. One peculiarity of the Indian epidemic was much more death rate of women compared to men. Historians and scientists have tried to explain this phenomenon in various terms. The general consensus is that women at that time in the Indian society were much more malnourished compared to men. In households, the major portion of the food went to the boys. Naturally, these malnourished women fell easy prey to the virus.

The question is, what would happen if a similar epidemic enters India now? On one hand, medical science has improved a lot. The molecular pathogenesis of viral infections is now known. There are many more doctors,

hospitals and health workers in India, compared to 1918. In 1918, not only were there fewer doctors, but also, a large number of them had gone to the War and not yet returned. But there are other people who would like to be cautious.

Recently, an article was published by Dr Lalit Kant, titled "Pandemic Flu, 1918: After hundred years, India is as vulnerable". In it, he argues that if such a pandemic happens again, India would again have the highest number of deaths in the world: around 15 million. And why is that? Dr Kant argues that India is more densely populated now. So the chance of rapid person-to-person spread is higher. Also, India does not have the capacity to manufacture vaccines for 1.3 billion people at a short notice. Finally, most Indians do not have the luxury of working from home like the privileged IT sector. They must go out every day to earn their living. So a complete lockdown of all businesses will be very difficult for India.

We can only hope that Indian society will be able to contain the current epidemic very soon. However, at such a time, it may be worthwhile to take a look back at history so as to avoid repeating the mistakes.-----RP

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**THE INFLUENZA EPIDEMIC.**

**KARACHI, July 18.**

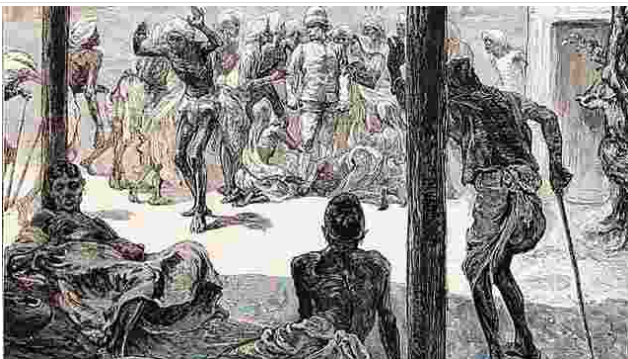
The influenza epidemic in Karachi is apparently less severe in type than in Bombay or Calcutta. So far as can be ascertained no European has been affected and no deaths have been reported. About fifteen per cent. of the office staff of business establishments throughout the city are absent. Telegraph and post office are little affected and service is in no way disturbed. Most of the victims hitherto have arrived by sea or come in contact with them. The Port Trust has suffered little but over hundred coolies working at Keamari are ill.

**MADRAS, July 18.**

The influenza epidemic has reached here. Hundreds of cases are treated at the hospitals, and there is hardly any household which has not caught the infection.

**ALLAHABAD, July 18.**

The new epidemic has arrived at Allahabad, one of the first to fall a victim being an employee of Messrs. G. F. Kellner and Co. A number of the staff of the firm are down.



Nearly every house in Bombay has some of its inmates down with fever and every office is bewailing the absence of clerks and others through the same cause. We know of one workshop in the city which had over three hundred absentees yesterday morning and of one large office from which everybody except one was away ill. Fortunately, there is no need for the belief which seems to have possessed most people that this is some new mysterious disease. The Health Department, in response to our inquiries, inform us that it is a form of influenza, which generally sweeps over the city and the whole countryside about August. The chief symptoms are high temperature and pains in the back and the complaint lasts three days and leaves its victims feeling rather "flat." Like all forms of influenza, it is very infectious and therefore the most susceptible people are those living under conditions of overcrowding and the close intimacies of family life, while the least susceptible are those whose houses are well ventilated and who spend a good deal of time in the open air. The main remedy is to go to bed and not worry. Perhaps the medical men in the Municipal Corporation will bring in a measure for the prevention of epidemics of the kind in future. It would be a great benefit to the city.



## Hydroxychloroquine emergence of a COVID Warrior ?

Prof (Dr) Nandini Chatterjee\*

### Abstract -

Hydroxychloroquine is a safer derivative of chloroquine that is being used in the treatment and prophylaxis of COVID19. Evidence of its efficacy is sparse, two small studies demonstrating clinical, radiological and serological improvement. However, scarcity of available treatment options has projected this drug into prominence. Drug interactions and risk of QT prolongation are to be kept in mind during use.

**Key Words :** treatment, prophylaxis, COVID19, QT prolongation

The Corona Virus Disease 2019 or COVID 19 was declared a pandemic by WHO on 11th March 2020.

Hydroxychloroquine (HCQ) is being advocated as a treatment modality as well as a prophylactic drug in the management of COVID 19. Though not substantiated by any large randomized trial, in the absence of any other definitive therapeutic option, hydroxychloroquine has emerged as a viable option in the present scenario.<sup>1</sup>

Hydroxychloroquine Sulphate was synthesized in the late forties as a hydroxy-derivative of chloroquine. Chloroquine phosphate was first synthesized in India in 1934 by the Bengal Chemical Works founded by Acharya Prafulla Chandra Ray. Hydroxychloroquine is produced by adding a hydroxyl moiety to chloroquine and is found to be about 40% less toxic. Both these drugs are weak bases with large volume of distribution and long half-lives, because of which their actions are persistent for a considerable time after discontinuation. They have been used in autoimmune diseases for a long time. The antiviral activity of this drug has been investigated for more than a decade with variable results.

### Conventional indications

Rheumatoid arthritis

SLE

Anti-Phospholipid Syndrome

Primary Sjogren Syndrome

### Newer indications

Prevention/treatment of Type 2 diabetes retinopathy is a concern

Treatment and prophylaxis of COVID 19 talk of the day.

### Actions

Anti-inflammatory

Immunomodulatory

Anti-viral activity- prevents viral entry, transport in cells

and post entry events.

Anti-thrombotic activity

Anti-hyper glycaemic activity

Antihyperlipidemic activity

### Recommendations for treatment(2)

For severe illness requiring ICU management

Hydroxychloroquine 400mg BD on Day 1, then 200mg BD for 4 days

Along with Azithromycin 500mg OD for 5 days

### Recommendations for prophylaxis of COVID 19-

Asymptomatic healthcare worker caring for suspected or confirmed case of COVID19.

Household contacts of confirmed case of COVID19.

Dose 400mg weekly for 7 weeks with meals for healthcare workers, for 3 weeks in house hold contacts

### Important points to remember

1. The drugs are to be taken only by prescription of a registered medical practitioner.
2. It should not in still a false sense of security- to maintain hand hygiene, respiratory hygiene, PPE where necessary.
3. If anyone becomes symptomatic on prophylaxis to contact health facility for testing and management
4. Pharmacovigilance of adverse drug reactions through self-reporting via app/helpline is advocated

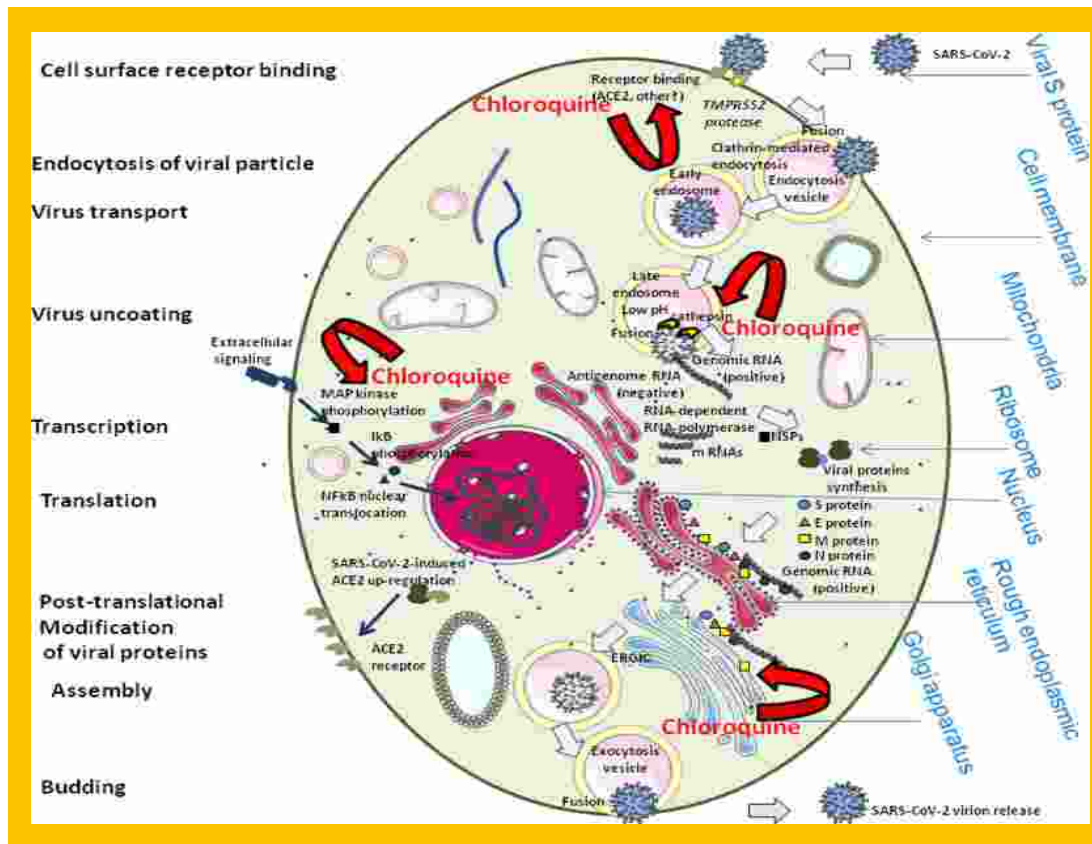
### Mechanism of action

Though not clearly delineated, this weak base causes changes in PH in endosomes and lysosomes that has been postulated as a major factor leading to various alteration of viral functions.

In vitro studies indicate that the drug inhibits infection of cells by SARS CoV-2 by glycosylation of the cellular receptors of the viral cell surface that is it cannot bind to the angiotensin-converting enzyme 2 (ACE2) expressed in lung, heart, kidney and intestine.<sup>3</sup>

The drug also inhibits the quinone reductase-2, which is involved in sialic acid biosynthesis (an acidic monosaccharides of cell transmembrane proteins

MD, FICP.  
Professor,  
Dept. of Medicine,  
IPGMER /SSKM Hospital.



required for ligand recognition) that makes this drug a broad antiviral agent. There is formation of an autophagosome which cleaves SARS-CoV-2 spike protein.<sup>4,5</sup>

Through the inhibition of MAP-kinase it interferes with SARS-CoV-2 molecular crosstalk, besides altering the virion assembly, budding and interfering with the proteolytic processing of M Protein of the virus.<sup>6</sup>

There is inhibition of immune activation by inhibiting Toll like receptor signalling and cytokine production in T cells. This may be helpful in the prevention of cytokine storm found in severe COVID 19.<sup>6</sup>

Though having similar mechanism of action hydroxychloroquine was found to be more effective antiviral activity than chloroquine in vitro (EC50 6.25micro MVS 100 micro M respectively at 24 hours)

A Chinese study involving more than 100 patients of COVID-19, that represents the first human trial, found chloroquine superior to the control group in reducing symptom duration, exacerbation of pneumonia including radiological improvement and promoting virus-negative seroconversion without any severe side effects<sup>7</sup>

The second human study which is currently available was conducted with HCQ. In an open-label, non-randomized trial (n ¼ 36) conducted in Marseille, France, Gautret et al. found that HCQ alone and combination of HCQ plus azithromycin was highly and significantly effective in clearing viral nasopharyngeal carriage<sup>8</sup>

**Side Effects**

- Nausea, vomiting, diarrhoea
- QTc prolongation
- Cardiomyopathy in rheumatologic patients

- Retinopathy
- Hypersensitivity reaction
- Myopathy
- Hypoglycaemia in diabetics on other antivirals(9)
- Caution in G6PD deficiency

**Monitoring**

Complete hemogram, serum electrolytes, blood glucose (because of hypoglycemic potential of HCQ) hepatic as well as renal function tests. Due to potential to prolong QTc, routine electrocardiography is essential prior to starting these drugs.

**Drug Interactions**

Co-administration of other drugs known to prolong the QTc interval (such as anti-arrhythmic, anti-depressants, anti-psychotics, antihistaminic) are to be done with cautious monitoring e.g addition of azithromycin to HCQ as done in French trial by Gautret et al. may increase the risk of QTc prolongation. ECG is to be performed daily if QTc is 450e500 msec.

Hypo glycemia as well as anticipated QTc prolongation must be looked for in patients with diabetes especially with concurrent use of chloroquine/HCQ and lopinavir/ritonavir.<sup>10</sup>

**Contraindications**

Hypersensitivity to this drug, retinopathy, porphyria, epilepsy, pre-existing maculopathy, G6PD deficiency, recent myocardial infarction and QTc >500 msec.

Hydroxychloroquine and Chloroquine are not contraindicated in pregnancy'

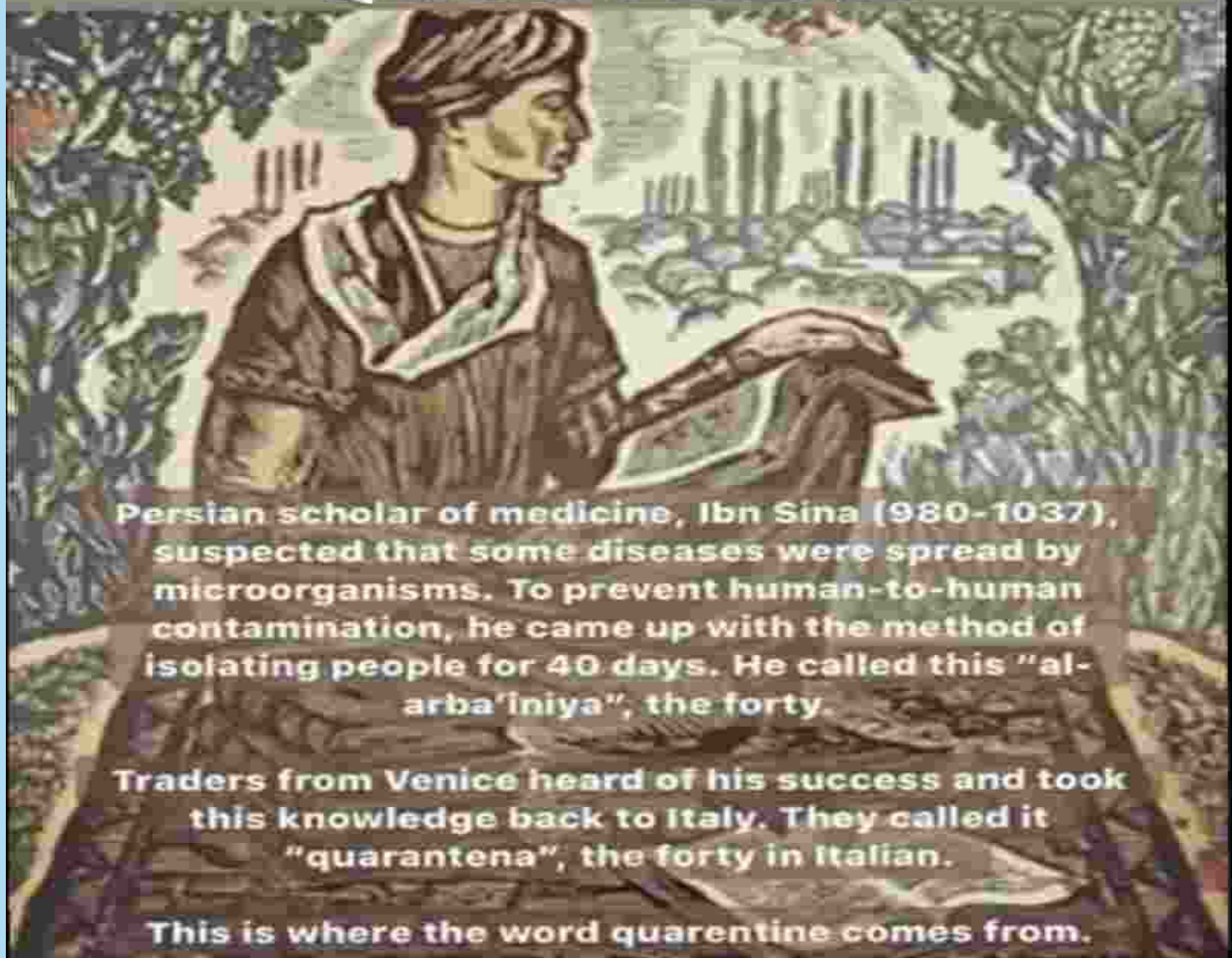
To conclude, although documentation of chloroquine and Hydroxychloroquine efficacy in COVID19 is limited (based

on the experimental data and only two small human trials), the potentially favourable benefit-risk ratio of chloroquine and HCQ in absence of any other valid treatment option has been taken into account. Therefore such treatment has been recommended by various official bodies in the current scenario of pandemic of COVID-19.

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# QUARANTENA



## Mediquiz

Series 3:

### Epidemic



**Dr Rudrajit Paul**  
Quiz Master

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#### Questions

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1. **A new viral disease has been introduced into a village by a few migrant labourers coming back from work. The disease is characterized by fever and rash. After one week, one of the labourer's wife, daughter and one friend of the daughter developed similar illness. What is the stage of the epidemic?**
  - a. Stage one
  - b. Stage two
  - c. Stage three
  - d. Stage four
2. **In the aforementioned report, as the new cases developed, a team of health experts arrived. They isolated the confirmed cases, collected their blood samples and advised no human contact for some time. What step of epidemic control are they trying?**
  - a. Anticipation
  - b. Early detection
  - c. Containment
  - d. Control and mitigation
3. **As news about the disease outbreak spread in the community, there were a lot of rumours. Some people started circulating a social media post about witches. The parents of the labourer were marked as witches and asked to leave the village. Some people also said that the pond beside their house should not be used any more as it contains the disease. What is this phenomenon called?**
  - a. Infodemic
  - b. Social distancing
  - c. Isolation
  - d. Fear psychosis
4. **A patient with confirmed Ebola virus infection is kept in an isolation ward. Which of the following precautions are unnecessary to prevent spread of the infection?**
  - a. Proper disposal of syringe
  - b. Negative air pressure in the room
  - c. Proper disposal of urine and stool
  - d. Level 3 safety measures in the laboratory
5. **Which of the following epidemics have not yet occurred in the 21st century?**
  - a. Bubonic plague
  - b. H1N1
  - c. Zika Virus
  - d. London Flu
6. **In 2011, the WHO adopted the PIP framework to battle epidemics. Which disease was targeted by this framework?**
  - a. Ebola
  - b. Influenza
  - c. Lassa fever
  - d. Polio
7. **In a village of Africa, certain cattle farmers came to the local health officer with complaint of sudden wave of abortion among the sheep and cows. Many of the animals had also died recently. A few of the farmers had also developed fever with body ache. One of them had developed jaundice. What is the likely diagnosis?**
  - a. Lassa fever
  - b. Hantavirus infection
  - c. Rift valley fever
  - d. Ebola infection

*(Answers on Next Page)*

## Mediquiz Answers :

1. **(B): Explanation** - The disease has been introduced in the community and now, there is localized transmission and sporadic infections. So, this is stage two.

Stage three is widespread epidemic with amplification and threat of spilling over beyond the community. In stage four, there is reduced transmission due to development of immunity.

2. **(C) Explanation** - This is the stage of localized transmission in the community. The measures mentioned in the stem are for containment. This is the most vital step in epidemic control to avoid going into stage 3. The social lockdown in the recent coronavirus pandemic was a containment measure. Once epidemic explodes, we can only try control and mitigation.

3. **(A) Explanation** - This rapid spread of questionable information and rumours during an epidemic is called infodemic. It is a very dangerous phenomenon and can thwart public health efforts. During an outbreak response, it is one of the duties of the response team to monitor the infodemic and mitigate it. Sometimes, legal steps may be necessary to stop false information.

4. **(B) Explanation** - Ebola is not an airborne virus. Hence, negative air pressure in the room is not necessary. The others mentioned here are vital steps for prevention. Ebola is present in body fluids and secretions (including vomit) and any contact with them must be avoided.

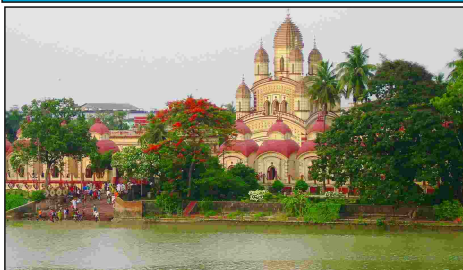
5. **(D) Explanation** - London flu was the influenza pandemic of 1972. The rest of the diseases have caused outbreak within the last decade. Plague appeared as an epidemic in Madagascar in 2017. Zika virus epidemic occurred in 2015.

6. **(B) Explanation** - PIP: pandemic influenza preparedness. This framework is a WHO initiative to bring together member states, industry and other stakeholders.

7. **(C) Explanation** - The symptoms described here are classical of Rift valley fever, a viral zoonosis. It is mainly confined to the African subcontinent although some cases have been reported from the Middle East. Animals are mainly affected. Animal to human transmission has been reported. Most human infections are mild. But some severe forms like meningoencephalitis or haemorrhagic fever are also reported.

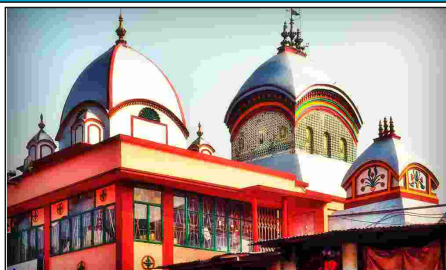
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Howrah Bridge

The Pride of India



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 Tel. No. 033-22257010; imahq.kolkata@gmail.com



## Letters to the Editor

*The Editor is not responsible for the views expressed by the correspondents*

Sir,

I am writing this letter to share my observations and thoughts on some cardiovascular aspects during COVID 19 pandemic.

I have no hard data or references to share with you.

I observed in my practice that during this national lock down, the incidence of myocardial infarction and other acute coronary syndromes have reduced drastically. Eminent cardiologists from all parts of India concurred with me in personal communication.

There may be two reasons for this.

Firstly, it may be due to under reporting. People may not be going to hospital quickly and trying home remedies. Pain may be subsiding eventually. There could be a spate of retrospective diagnosis once the situation normalizes. Then the question would arise about the outcome of such STEMI. Did they have higher mortality compared to primary angioplasty or thrombolysis, or they fared equally? If they fared well, then the question will come if all STEMI require PPCI or there should be some risk stratification, even in normal situation, for urgent invasive management, particularly in resource limited countries like India.

The second possibility of lower STEMI is a real reduction of incidence. In my experience, many of my patients are reporting normalization of their blood pressure during this period. We know home blood pressure monitoring always gives lower values compare to office BP. When people are at home, not only their BP is better controlled, but due to lock down they are doing more physical work at home, eating healthy (as there is no junk or home delivery food), supply of tobacco and alcohol are limited, and stress of professional life is minimal. Also, there is undoubtedly much less environmental pollution. It is well known that all these factors can significantly and positively affect cardiovascular health, but it has never been observed to affect the incidence of acute coronary syndromes in such short period of time. If this is the case, then we should think seriously to try to implement these positive factors as far as practicable even when the situation normalizes.

Just another area for thought I present before ending. What is Corona virus death for epidemiological or statistical stand point? Take four cases, all corona positive, one dies of pneumonia and ARDS, one has STEMI and dies of cardiogenic shock, one dies of a head injury by falling from the staircase and one gets acute depression and hangs himself. What should be the number on registry of corona death, one, two, three or four?

With kind regards,

Yours Sincerely

**Prof Dr Saumitra Ray**

Vivekananda Institute of Medical Sciences, Kolkata

### **Preventive Care in India-86 Years Ago: Resemblance with COVID-19 Prevention**

Dear Sir,

Eighty-six years ago, in February 1934, preventive measures implemented in rural India show an uncanny resemblance with our predicament in preventing morbidity and mortality from COVID-19. In 1976, soon after the death of my father, Dr. Navnidhrai C. Mankad, I decided to preserve his legacy consisting of various notes, newspaper announcements and photographs. His public education announcement for prevention of an epidemic of meningococcal meningitis is relevant in the present context. He learned that cases of meningococcal meningitis had occurred in the city of Ahmedabad and surrounding villages about 30 miles from his town of Viramgam. Given poor transportation and comparatively slow movement of populations in the 30s, the spread of this disease was expected in days to weeks (rather than hours in the modern era). As a general practitioner and an elected member of the municipality, he was in charge of public health for Viramgam and surrounding villages. His Public Education announcement in a local newspaper (in Gujarati language and my English translation) can be accessed through the link<sup>1</sup>.

There were no antibiotics or meningococcal vaccine available in 1934. Alexander Fleming had discovered the antibacterial properties of *Penicillium notatum* in 1928. However, it was not until 1941 that the first patient received penicillin in Oxford, England. The drug was not produced in large quantities until 1945. Even sulfonamides were not yet invented in 1934. Therefore, much like today for COVID-19, the preventive measures had to focus on quarantine, hygiene and sanitation. The key features of the preventive measures included the following.

1. Preemptive rather than reactive implementation of public health education
2. Forbidding spitting on walls and other surfaces
3. Isolation of the patient and the care givers
4. Disinfecting nasopharyngeal secretions and sputum in a spittoon containing phenol
5. Disinfecting clothes and linens in boiling water

Dr. Mankad's preemptive steps must have prevented countless cases of meningitis in Viramgam in 1934. Compare that with successful control of COVID-19 in Taiwan and Korea and contrast that with unacceptable delays and poor preparation in the United States and Italy. Hopefully, aggressive, early steps in India to prevent the spread of COVID-19 will be successful assuming that public health measures after lifting the lockdown such as testing for both viral genetic material and antibodies to inform the decision makers to contain the new cases through isolation. The SARS-Coronavirus-2 spreads by droplets and possibly even through aerosol. Thus, isolation and quarantine

## Letters to the Editor

*The Editor is not responsible for the views expressed by the correspondents*

of the patient or a person carrying the virus is critical. Since a person infected with coronavirus is contagious even before symptoms are noticeable, the current strategy is to maintain a physical distance. Disinfecting any surface with possible contamination of secretions from nose and throat was a strategy in 1934 as it is now.

It is interesting that administration of anti-meningococcal serum in the spine was suggested as an experimental approach by Dr. Mankad and other doctors in 1934. In the absence of anti-microbial therapy or a vaccine, delivery of a specific antibody to the lesion was a logical approach; compare that with the suggested use of convalescent plasma in case of severely ill patients with COVID-19.

Those who ignore history are doomed to repeat it. Key lessons from this historical review are to remember that the first focus of preventive care should be on sanitation, hygiene and public education. The Swatchha Bharat movement is particularly important in prevention of bacterial, viral and parasitic diseases. A healthy India and the world will be a more productive and happy society.

With best regards,

**Dr Vipul Mankad, M.D.**

Former Professor and Chairman of Pediatrics  
University of Kentucky, United States

### **Corona Virus Disease 2019 (COVID-19) due to Severe Acute Respiratory Syndrome Corona virus (SARS-CoV2) infection**

**An update.**

**JIMA, Vol-118, No-3, March 2020**

Sir,

The authors have comprehensively pointed out the burden of recent ongoing highly infectious pandemic of COVID-19 in great details. They have described the implicating virus, updated time line of the disease, varying clinical features, methods of diagnosis, supportive management and follow up of the confirmed cases.

Fever, cough and shortness of breath are the major clinical features-when present with bilateral patchy infiltration on X ray or CT scan and having an epidemiological link almost dictates the diagnosis. ICMR has given the Guidelines when to test. RT-PCR from respiratory samples does confirmation. Screening can be done by Rapid kit test of antibody also.

I beg to differ on the statement "Virus survives only for 3 hours in vitro". It may survive up to 72 hours depending on the surface. Apart from Isolation, Contact tracing, Personal Hygiene, use of designated mask etc. "Cluster Containment" plays a major role in breaking the chain of transmission to control the recent outbreak of COVID-19.

**Dr. Md. Hamid Ali**

MD in General Medicine, Assistant professor  
Murshidabad Medical College, Berhampore

To  
The Editor,  
JIMA,

Dear Sir,

I read with interest the Editorial titled "Tropical Fever - Tropical or Global Challenge?" published in 2020 March Edition of JIMA. I thank the Editor for this timely article which I feel is a very important one in relation to the Syndromic Approach of the global problem. The approach to the problem has been nicely addressed. It highlights the need of the Physician concerned to follow proper protocols that has been depicted in the article as well as generation of awareness in the community. It will go a long way in containing the infection and help in providing proper treatment at the very onset of the disease.

With this, I thank the Editor for writing this timely Article which is an eye opener for controlling the infectious diseases in this Sub-continent and thus to prevent spread to other parts of the world. As, this is an era where disease can be easily transmitted via travel and communication, so awareness of the Physician as well as various organisations associated with Medical Fraternity is very important in this regard. This article needs a round of applause from our side for bringing that up.

With kind regards,

Yours Sincerely

**Professor Dr M.K. Roy**

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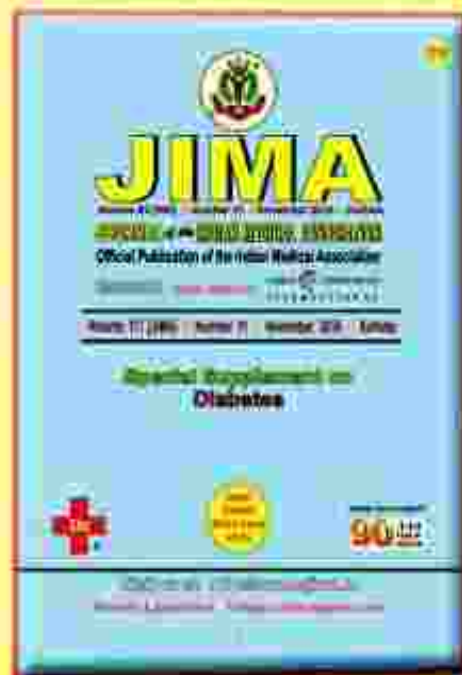
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NOT ALL SOLDIERS CARRY GUNS TO SAVE COUNTRY  
SOME CARRY A STETHOSCOPE

WE DON'T NEED STONES, WE NEED YOUR LOVE AND GOOD WISHES!!

TAKE CARE OF YOUR PARENTS AND GRAND PARENTS

60 PLUS WITH HYPERTENSION, DIABETES ETC. PLEASE BE SAFE YOU ARE IN HIGH RISK CATEGORY

SAVE OUR SAVIOURS  
SAY NO TO VIOLENCE AGAINST DOCTORS

**MOST COMMON SYMPTOMS**

- FEVER
- FATIGUE
- DRY COUGH

**SOME PATIENTS MAY ALSO HAVE**

- ACHES AND PAINS
- RUNNY NOSE
- SORE THROAT
- SHORTNESS OF BREATH
- DIARRHOEA

**IMA Banaras Initiative**

BEST TIME TO QUIT PAN MASALA SMOKING, DRINKING ALCOHOL AND GOOD TIME TO START NEW HOBBY

ONLY SEPARATION CAN STOP EXPLOSION  
STAY HOME, STAY SAFE

EVEN THEY ARE UNDERSTANDING WHEN WILL YOU ?  
STAY HOME, STAY SAFE

THE GAME BEGINS IF YOU GO OUT DON'T PLAY WITH YOUR LIFE  
STAY HOME, STAY SAFE

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STAY HOME, STAY SAFE

छोड़ के सारी दुनियादारी परिवार के साथ निभाओ यारी  
STAY HOME, STAY SAFE

YOU ARE RISKING YOUR LIFE

1. If You are visiting small shops regularly in vicinity
2. If You are visiting barber shop or calling him home
3. If you are calling your maid & washerman daily

STOP THIS IMMEDIATELY

STAY SEPARATED TO STAY TOGETHER  
MAINTAIN SOCIAL DISTANCING, SAVE LIFE

APNA MASK KHUD BANAO CORONA KO MIL KAR BHAGAO

बाहर जाते समय अपने नाक और मुँह दोनों को ढक लीजिए

हौसला और घोंसला मत छोड़ो हिम्मत एवं संयम से कोरोना को तोड़ो  
STAY HOME, STAY SAFE

SALUTING OUR SUPER HEROES

DOCTORS, POLICE, NURSES, SAFAI KARMI, MEDIA FOR THEIR COURAGEOUS EFFORTS

TU CHEEZ BADI HAI MASK MASK

WEAR MASK IF YOU GO OUTSIDE. IT'S MUST

सब्जी वाले से कहें सब्जी साबुन से हाथ धोकर ही दे

क्योंकि स्वच्छता में ही है सुरक्षा

मास्क पहनना व्यर्थ है अगर उसे सही तरीके से नहीं पहना गया है सजग रहे, सुरक्षित रहे.

STAY HOME STAY SAFE

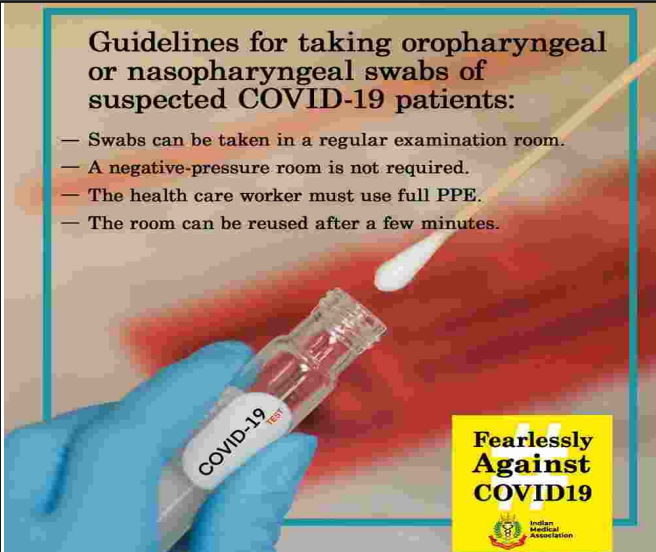
THINGS WILL BE IN CONTROL A BRIGHT TOMORROW AWAITS US

LET'S FOLLOW SOME MORE TIME WITH DISCIPLINE AND GOOD HYGIENE

Courtesy : IMA Banaras Branch

**Guidelines for taking oropharyngeal or nasopharyngeal swabs of suspected COVID-19 patients:**

- Swabs can be taken in a regular examination room.
- A negative-pressure room is not required.
- The health care worker must use full PPE.
- The room can be reused after a few minutes.



**Fearlessly Against COVID19**

Indian Medical Association

**Dr. Rajan Sharma**  
NATIONAL PRESIDENT

**Dr. R V Asokan**  
HONORARY SECRETARY GENERAL

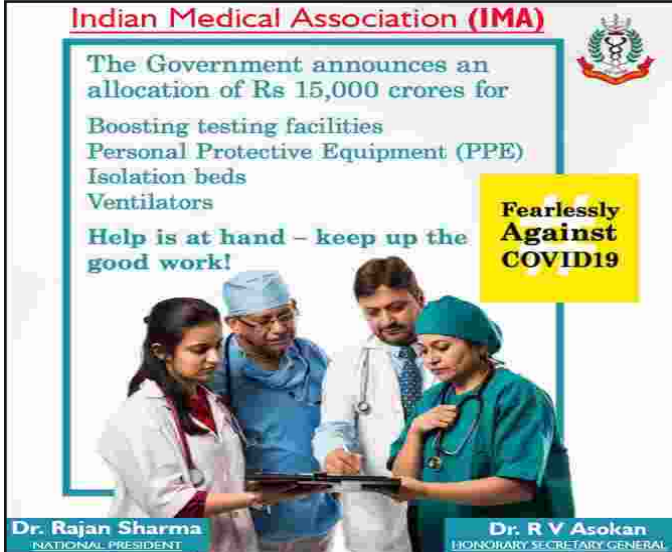
**Indian Medical Association (IMA)**

The Government announces an allocation of Rs 15,000 crores for

- Boosting testing facilities
- Personal Protective Equipment (PPE)
- Isolation beds
- Ventilators

**Help is at hand – keep up the good work!**

**Fearlessly Against COVID19**



**Dr. Rajan Sharma**  
NATIONAL PRESIDENT

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**Indian Medical Association (IMA)**

We understand it's a difficult time, but the country is depending on you.

**Stay calm & energized**



**Fearlessly Against COVID19**

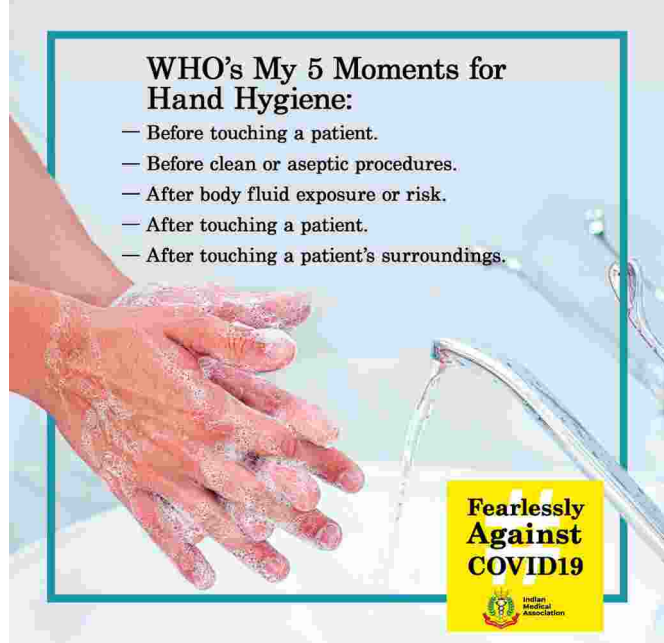
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**WHO's My 5 Moments for Hand Hygiene:**

- Before touching a patient.
- Before clean or aseptic procedures.
- After body fluid exposure or risk.
- After touching a patient.
- After touching a patient's surroundings.




**Fearlessly Against COVID19**

Indian Medical Association

**Indian Medical Association (IMA)**

Let's advise social distancing for a COVIDless life!



**Fearlessly Against COVID19**

Indian Medical Association

**Dr. Rajan Sharma**  
NATIONAL PRESIDENT

**Dr. R V Asokan**  
HONORARY SECRETARY GENERAL

**Indian Medical Association (IMA)**

Let's make our clinics COVID-19 ready!

Wipe surfaces and objects with disinfectants.



**Fearlessly Against COVID19**

Indian Medical Association

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**Acute ( $\leq 7$  Days), diffuse (bilateral, involving multiple areas), inflammatory lung injury**  
**Hypoxia (P/F ratio  $< 300$  with PEEP  $\geq 5$ )**  
**Not explained by cardiac disease or fluid overload**

**Stages: -**

1. **MILD P/F 200-300**
2. **MODERATE P/F 100-200**
3. **SEVERE P/F  $< 100$**

**Pathophysiology:**

**Non-uniform process**  
**Alveolar-capillary damage**  
**Exudation**  
**Proteinosis**  
**Fibrosis**  
**Decreased compliance**

**Causes:**  
Infection (e.g. **coronavirus**)  
Aspiration  
Sepsis  
Toxic fumes  
Poisoning

**Treatment:**

- ✓ Mechanical ventilation [Early]
  - Low tidal volume
  - High PEEP
  - Altered I:E ratio
  - Prone ventilation
  - Recruitment maneuvers
- ✓ Fluid restriction
- ✓ Nutrition
- ✓ **ECMO**

**ARDS: What every clinician must know**  
**Dr Rudrajit Paul & Dr Jyotirmoy Pal**

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