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***In this issue***



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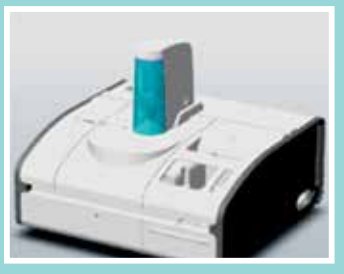

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Indian Journal of Clinical Practice, Vol. 32, No. 3, August 2021

**Dr KK Aggarwal**
5th September 1958 - 17th May 2021

# Minutes of an International Weekly Meeting on COVID-19 in Association with Experts from CMAAO Nations

## OXYGEN CRISIS AND PREPARATION FOR FUTURE

**24th July, 2021 (Saturday, 9.30 am-10.30 am)**

### Key Points from the Discussion

**A presentation on "Oxygen therapy – crisis and preparations for future"** was made by **Dr Rahul Pandit,** *Director-Intensive Care, Fortis Hospital, Mumbai; Member-National Task Force; Member-Maharashtra Task Force; Visiting Consultant-Wagga Base and Bathurst Base Hospital; NSW, Australia*

- In pediatric and neonatology, it's an established fact that too much of oxygen is bad. Oxygen is given only when it's necessary.
- Research has looked at optimum level of oxygen to be delivered. There is a very thin line differentiating what will be useful and what will be probably harmful.
- Oxygen saturation was the indicator relied upon to decide on oxygen therapy as arterial blood gas monitoring not available in many developing countries.
- The oxygen cascade is the transfer of oxygen from atmospheric air to mitochondria. The oxygen partial pressure drops at each step of the cascade.
- Hyperoxia is maintaining a partial pressure of oxygen ($PaO_2$) of more than 100 mmHg for a prolonged time; though the duration is unknown, it is probably in hours and not minutes.
- Fraction of inspired oxygen ($FiO_2$) of 100%, there are good and bad effects. Good effects – vascular $PO_2$, pericapillary diffusion and oxygen delivery improve, inflammation starts to settle down. But vascular perfusion may also start decreasing, reactive oxygen species (ROS) increase leading to lipo-oxidative stress at the tissue level.
- $FiO_2$ >60% causes lung atelectasis. There is Lorrain-Smith effect, where pulmonary oxygen toxicity may present as severe pulmonary inflammation, leading to pulmonary edema and is referred to formation of excess ROS and reactive nitrogen species (RNS).
- Vascular effects include decrease in cardiac output, heart rate.
- Paul-Bert effect can give rise to profound vasoconstriction and generalized tonic-clonic seizures. But these are very rare side effects.
- Several trials have been published on the effect of hyperoxia in intensive care and emergency medicine in conditions like acute coronary syndrome (ACS), myocardial infarction (MI), stroke, cardiac arrest, including in the last 2 years of the pandemic.
- A 50% increase in mortality has been observed in patients who spent 40% time in optimal oxygen

saturation range versus patients who spent 80% time in optimal time.

- Trials in the past 24-36 months have also looked at restrictive oxygen strategy.
- The American Heart Association (AHA) does not recommend oxygen therapy in patients of MI until the oxygen saturation is really low. Too much of oxygen may worsen the outcomes. Until recently, MI patients were routinely treated with oxygen. The rationale being that the increased oxygen delivery to the ischemic myocardium reduces infarct size and subsequent complication.
- The Stroke oxygen trial showed no benefit of oxygen in stroke patients. No difference in mortality was observed.
- For critically ill patients with an intensive care unit (ICU) length of stay of >72 hours, a conservative protocol for oxygen therapy compared with conventional oxygen therapy resulted in lower ICU mortality.
- The reality however was the liberal oxygen strategy was followed. It was found that unnecessary oxygen to patients was not good and giving oxygen to patients to achieve oxygen saturation of 97-100% was not helping the patients.
- The rapid increase in the numbers in the second wave did not help.
- The oxygen requirement of the country increased by 9- or 10-folds as the pandemic worsened; hence, the failure to meet this high oxygen demand precipitating the oxygen crisis. But very soon, rational use of oxygen came in and allocation improved.
- It is first important to calculate the oxygen demand. A survey of 30 hospitals has shown that for around 100 beds, 1.5 metric tonne of oxygen is needed per day during the pandemic.
- The problem was a dynamic change in the need was not available. There was very little information about dynamic change in terms of oxygen requirement. This was dependent on the devices used ventilator, high-flow nasal oxygen (HFNO), noninvasive ventilation (NIV), etc.
- Supply was limited to four ways: Liquid medical oxygen (LMO), oxygen cylinders, portable oxygen concentrators or PSA (pressure swing adsorption) plants. There were not many PSA plants in the country at that time.
- The country had to turn to the industrial grade oxygen available. Lot of oxygen was sourced from steel plants. Industrial grade oxygen seemed to be as good as LMO, though the purity was around 92-93%. However, the problems were that these plants were in different parts of the country as well as the shifting pandemic, which moved from one part of the country to the other. The cryogenic tankers took longer to reach their destination (speed limit for safety) and so the crisis very quickly turned into an acute shortage.
- There were limited refilling plants for oxygen cylinders; they are associated with ease of hoarding, questionable hygiene practices.
- Oxygen concentrators helped but there is a problem of limitation of flow; many of them only give 5-10 L of oxygen. Hoarding is possible and also the oxygen purity declines after using it for sometime at the maximal capacity.
- PSA plants are sustainable solutions, but the zeolite used has to be imported. They cannot be operationalized overnight. They are not the primary source of oxygen; they are best used as backup. The oxygen produced has 94-95% purity.
- Solutions needed at that point of time were dynamic need calculation, allocation formula, distribution techniques, substores for ease of transport.
- Every bed has to be mapped to calculate dynamic need. Real time data from hospitals was initially a problem, but it became available within 1-2 weeks.
- The decentralization model for allocation worked best with an oversight from the centre for equal allocation.
- Empty tanks were airlifted via military aircrafts to filling stations and then put on RORO (roll-on, roll-off) express trains to their destinations. This helped ease the crisis quickly.
- The Mumbai model of oxygen management has won much praise. It was a decentralized process. The city is divided into 24 wards. The real time data was available as every bed in the city was mapped. Six substores were created across the city. And smaller tankers, which could move easily in the city, were used to transport oxygen from hospital to hospital.
- Oxygen stewardship program was introduced. One liter of oxygen saved is one liter produced. Keep oxygen restrictive strategy – keep oxygen saturation between 90 to 94% in patients who were monitored. Leaks, old pipes were repaired. Oxygen

stewards were appointed in each hospital. Each hospital had an oxygen committee.

- Mumbai had long-term sustainable solutions: increased capacity building and keep emergency oxygen stores for 2 weeks requirements.
- Many PSA plants have now been established by the government in rural and urban India.
- The country is now better prepared for the third wave in terms of oxygen requirement.
- Mucormycosis in India was found to be linked to poor glucose control, excessive use of steroids and use of immunosuppressive therapy (tocilizumab) and not oxygen supply in a series of 5,000 patients. Low immunity allowed the opportunistic fungus to grow. Now there are no mucormycosis cases in India.
- More than two-thirds of global cases of mucormycosis are in India. Reasons are not known.
- Mucor is found in soil.
- *Burkholderia pseudomallei,* which causes melioidosis, is found in soil in Singapore.
- High-flow nasal cannula is very recent in India and only few hospitals have this facility. Although they were not the cause of oxygen shortage, they could have contributed to it, so electively shifted to continuous positive airway pressure (CPAP) or bilevel ventilation with noninvasive ventilator use. HFNO has better patient compliance.
- Saving oxygen may be a strategy now.
- In a pandemic situation, in ICUs, oxygen saturation can be maintained at as low as 88% or up to 92% in a monitored environment and ≥93% in an unmonitored environment. We should be targeting lesser oxygen saturation than what was being done before. As soon as the target is reached, oxygen can be reduced by a liter every time and see how the patient maintains at this level.
- Wastage needs to be taken care of hence oxygen stewardship programs are going to be necessary in the future.

**Country updates**

- **Bangladesh update:** The country is in a strict lockdown except for emergency services. The number of cases and deaths are increasing. Vaccines are now available. Vaccination of frontline workers has reduced deaths in this group.
- **India update:** India is still in the second wave and it is slowly plateauing. Situation, state-wise, is very different. Except for five states in the South and the North East part of India, the rest of India is mostly out of the second wave. Maharashtra and Kerala are two states, which show a different pattern. They are early starters. Floods have disrupted COVID care in Maharashtra. The Indian Council of Medical Research (ICMR) study has shown that antibody seropositivity is almost 67%, whereas seropositivity rate in southern states is 43%. The target is to vaccinate all those above 18 years by December end. If the vaccination is in order then it seems unlikely that the third wave will be explosive. It may be a mitigated third wave in unexposed geography, in unexposed people and is expected between September and January. Overall India is stable and cautiously optimistic. Lack of adherence to COVID-appropriate behavior is a major concern now.
- **Pakistan update:** Cases are rising; people are not adhering to standard operating procedures (SOPs). Serious restrictions will be implemented. Delta variant is present in the country. So far, only 5% of the population has been vaccinated.
- **Japan update:** There are around 5,000 daily positive cases and half of these are delta variant cases. Eighty-five percent of people aged ≥65 have been vaccinated at least once. One case of pediatric death has been reported.
- **South Africa update:** About 1.1 million have received the second dose and 4 million have received the first dose (Pfizer). About 1.1.6 people have taken the J&J vaccine. The country is slowly moving out of the third wave. ICU admissions are high. There have been massive superspreading events in Johannesburg and Durban areas and the effects will be seen in the coming week.
- **Hong Kong update:** Very few imported cases and almost no community cases. Two children from a consulate broke quarantine and travelled in a tourist bus tested positive. There were mandatory checks in many districts they had travelled to and so far, no community cases. Five million doses have been administered, more than half are Pfizer-BioNTech and the rest were Coronavac. More than 3 million (40%) have got the first dose and more than 2 million (30%) have got the second dose. The target is to achieve 70% vaccination with the first dose by September end. Teenagers (12-15 years) are also being vaccinated, though the response is not so good.

- **Australia update:** One hundred sixty-three cases in NSW; the state of Victoria has 12 cases. Half of the country's population is in lockdown. There are cases of Delta variant in the country, especially in NSW, which has only partial lockdown. Pfizer vaccine is in short supply, but there is excess of AstraZeneca.
- **Singapore update:** Seventy-five percent vaccinated with one dose, 51% vaccinated with two doses; 70,000 vaccinations per day; 130 cases in a day, lot of Delta cases are coming from Indonesia. Those who had received both doses, 0% needed oxygen; single dose 3.4% needed oxygen, and the vaccinated 5.4% needed oxygen. Delta virus seems to be coming down in terms of severity.

**Participants - Member NMAs:** Dr Yeh Woei Chong, Singapore, Chair-CMAAO; Dr Ravi Naidu, Malaysia, Immediate Past President-CMAAO; Prof Ashraf Nizami, Pakistan, First Vice President-CMAAO; Dr Alvin Yee-Shing Chan, Hong Kong Medical Association, Treasurer-CMAAO; Dr Marthanda Pillai, India Member-World Medical Council; Dr Angelique Coetzee, South Africa; Dr Akhtar Hussain, South Africa; Dr Qaiser Sajjad, Pakistan; Dr Marie Uzawa Urabe, Japan; Dr Salma Kundi, Pakistan; Dr Md Jamaluddin Chowdhury, Bangladesh

**Invitees:** Dr Russell D'Souza, Australia UNESCO Chair in Bioethics; Dr Shashank Joshi, Mumbai, India; Dr Rahul Pandit; Dr Monica Vasudev, USA; Dr Mulazim Hussain Bukhari, Pakistan; Dr Li Ling Lim; Dr Yau Onn Voo; Dr Vanessa Phua; Dr Benny Tan; Dr Catherine Ng; Dr Cheng Jew Ping; Dr S Sharma, Editor-IJCP Group

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# Common Coronary Anomalies on MDCT

RAMA MURTHY SK*, MAHESH C*, AMARESH RAO M†, SUJATA PATNAIK*


## ABSTRACT

Coronary artery anomalies are rare, and the incidence is around 1 to 2% in the general population. Majority of the patients are asymptomatic and detected while investigating another clinical issue. A few anomalies may be life-threatening due to the malignant course with potential for ischemia and even sudden death. Multidetector computed tomography (MDCT) has high accuracy in detecting these anomalies because of volume rendering (VR) and multiplanar reconstruction (MPR). 'High take-off', origin of the coronary artery from the opposite or noncoronary cusp with anomalous course and coronary artery fistula are three most frequent anomalies. MDCT can be a useful screening tool in the study of coronary anomalies.


**Keywords:**

Coronary artery anomalies are rare, and the incidence is around 1 to 2% in the general population. Multidetector computed tomography (MDCT) has high accuracy in detecting these anomalies because of volume rendering (VR) and multiplanar reconstructions (MPRs). Majority of the patients are asymptomatic and detected while investigating another clinical issue. A few anomalies may be life-threatening due to the malignant course with potential for ischemia and even sudden death. Moreover, failure to cannulate these vessels during conventional angiography can be minimized if the existence of these anomalies is known to the operator. This article presents an unpublished retrospective case series and review of literature of common coronary anomalies detected on MDCT.

At Nizam's Institute of Medical Sciences (NIMS), Hyderabad, 770 patients underwent CT-conventional coronary angiography (CAG), on 128-slice single source MDCT (SOMATOM Definition AS ± SEIMENS) during the last 3 years (unpublished data). On analysis, coronary artery anomalies were found in 23 patients (3%). Their ages ranged from 25 to 82 years. Majority of the cases were in 51 to 60 years age group. Among them, 17 were males. The most common anomaly seen was high take-off of coronary arteries, seen in 10 cases. Of them, 2 were having high origin of right coronary artery (RCA) (Fig. 1), 7 were having high origin of left main coronary artery (LMCA) and one was having high origin of both coronary arteries with acute kink at the origin of RCA. Anomalous origin of coronary artery from opposite sinus was seen in 8 cases (Figs. 2-5). RCA from left coronary sinus with interarterial course between aorta and right ventricular outflow tract was seen in 5 cases. Anomalous origin of left coronary artery (LCA) from right coronary sinus with interarterial course between aorta and right ventricular outflow tract was seen in 2 cases. Anomalous origin of left circumflex artery (LCx) from right coronary sinus with retroaortic course was seen in 1 case (Fig. 6). Separate ostia for left anterior descending artery (LAD) and LCx was noted in 3 patients (Figs. 7 and 8). Shepherd crook deformity of proximal segment of RCA was seen in 1 patient. Super-dominant RCA with absent LCx was seen in 1 patient (Fig. 9).

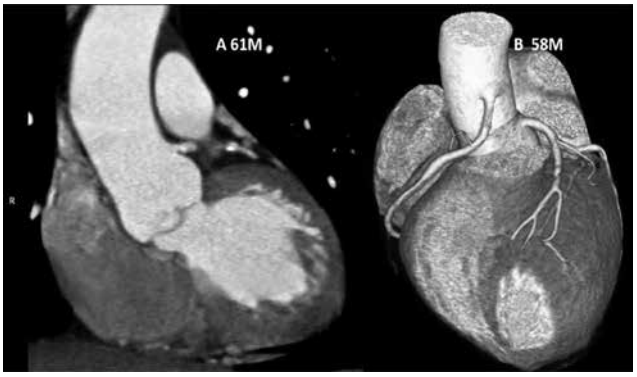


**Figure 1.** Two different patients of 'high take-off' of LCA in patient aged 61/M and RCA in patient aged 58/M.

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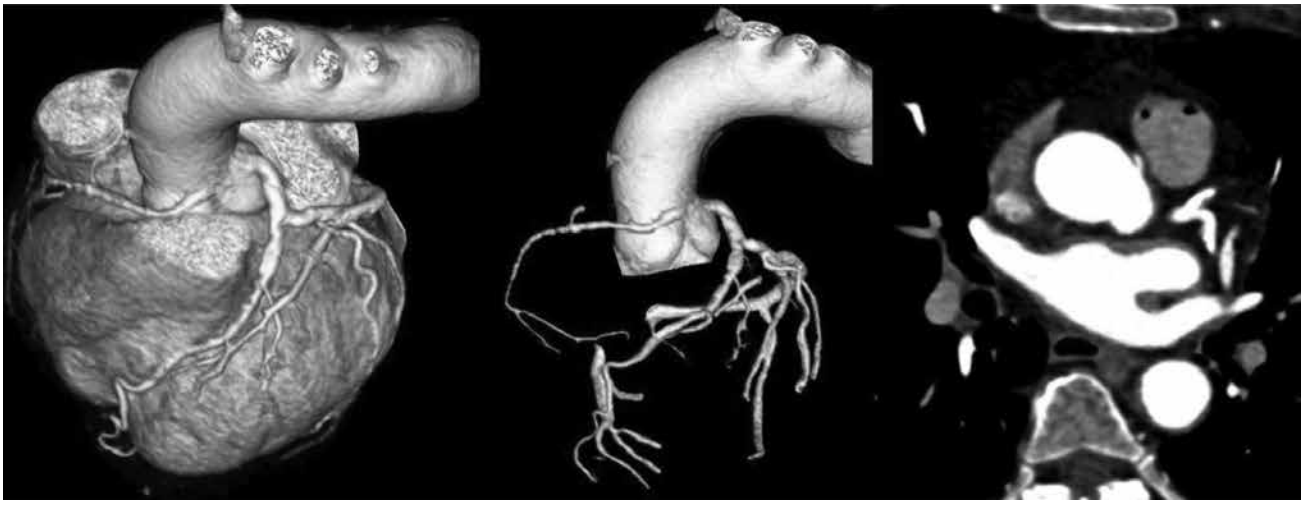

**Figure 2.** VRT and axial images of a patient (55/F) showing RCA originating from left coronary sinus of Valsalva. Course of RCA is interarterial.

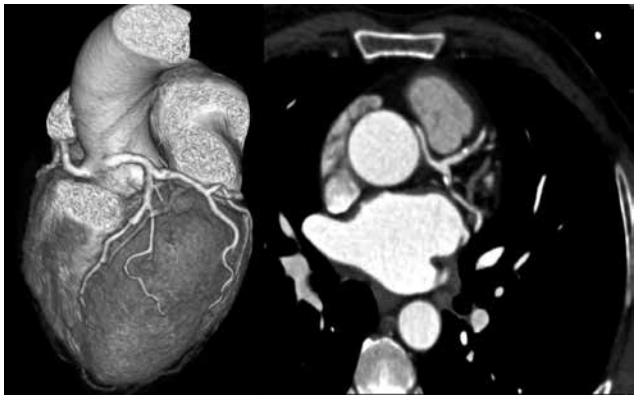

**Figure 3.** VRT and axial images of a patient aged 59/M depicting the origin of LCA from RCA having interarterial course.

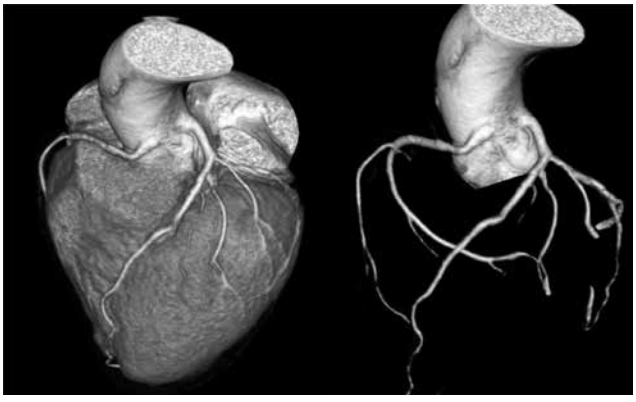

**Figure 4.** Origin of RCA and LCA from left coronary sinus in a patient aged 35/M.

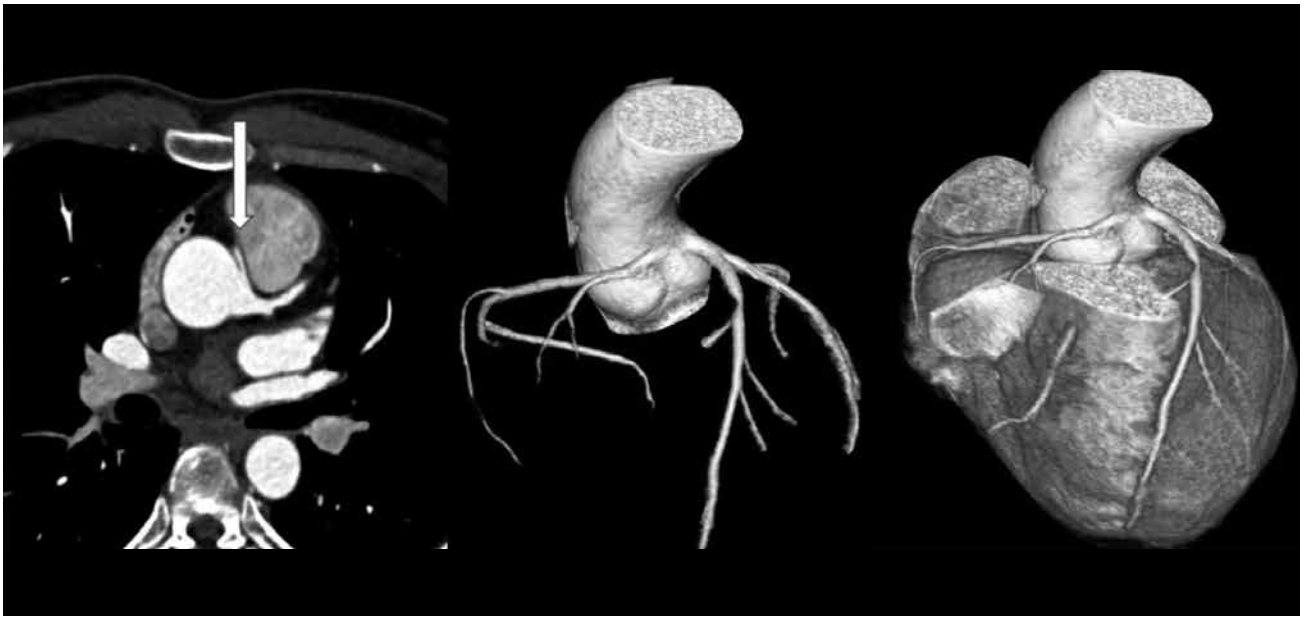

**Figure 5.** Origin of RCA and LCA from left sinus of Valsalva with interarterial course of RCA in a patient aged 25/M.

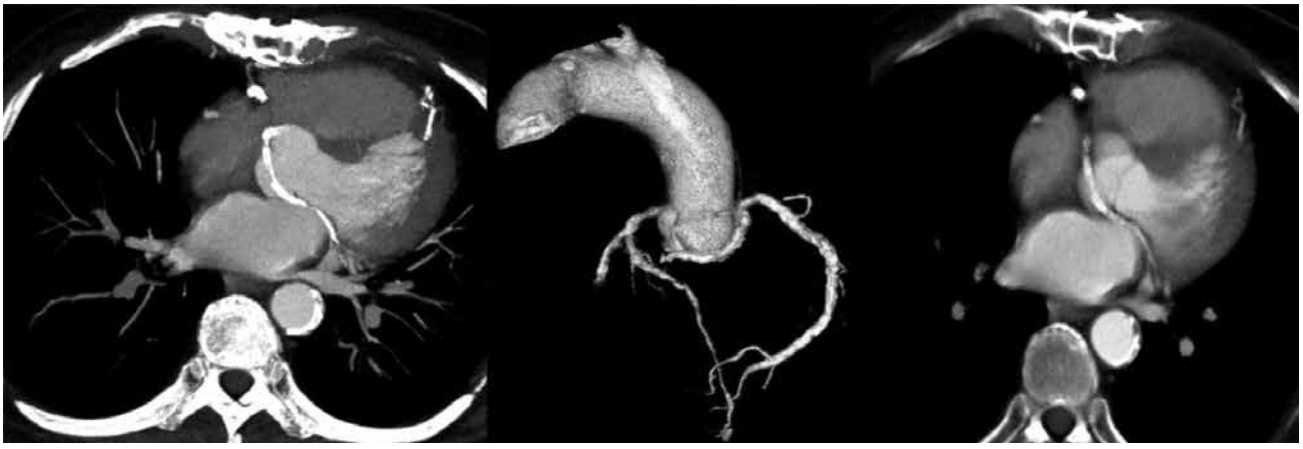

**Figure 6.** LCx is originating from right coronary sinus with retroaortic course in axial and VRT images of patient aged 82/M.

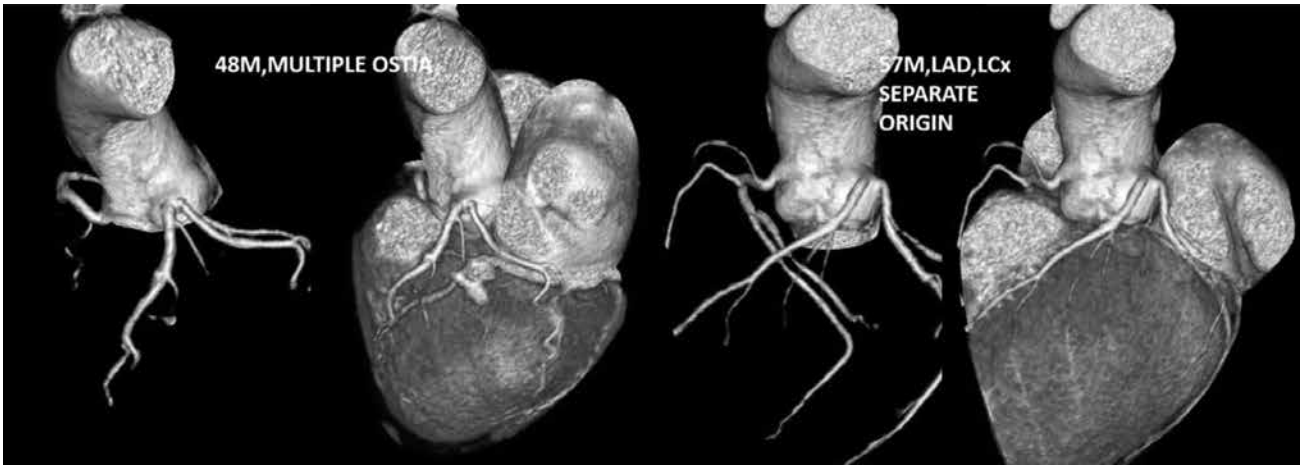


**Figure 7.** Two patients aged 48/M and 57/M, CT-CAG VRT images showing separate origin of LAD, LCx and there is no LMCA.

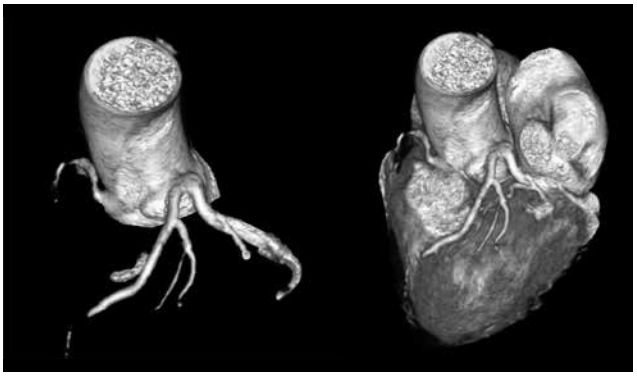

**Figure 8.** Separate origin of LAD and LCx in a patient aged 71/M.

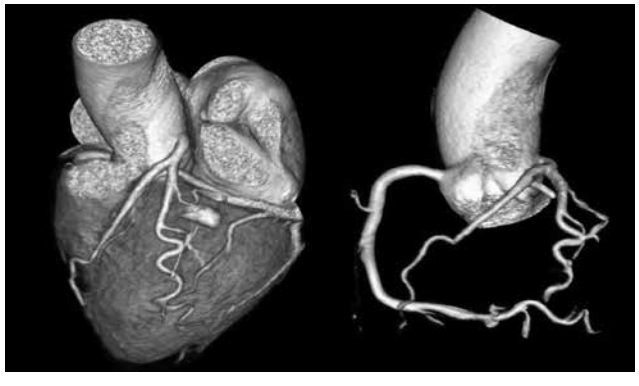

**Figure 9.** A patient aged 52/F having super-dominant RCA. LCx is absent.

The prevalence of coronary anomalies is reported to be approximately 0.3 to 1% in various studies.[1] Due to lack of uniformity of diagnostic criteria, the true incidence is not known. Any coronary pattern with deviation in the number of ostia, variation in the sinus of origin, the course that is not common in the general population, can be counted as an anomaly. It is important to categorize them as major or minor depending on their potential for clinical consequence. With advances in noninvasive imaging, more anomalies are getting diagnosed compared to autopsies or invasive cine-angiograms. Recent advances in MDCT

technology with 100% sensitivity in detecting these anomalies, have made it a more acceptable diagnostic tool. Although majority of the anomalies are benign with conceptual and educational interest, a few have potential for ischemic symptoms, and even sudden cardiac death especially during exercise or during competitive sports. The anomalies associated with structurally abnormal hearts have to be a special group due to their importance during the surgical correction. It is most convenient to consider the isolated coronary anomalies as − 1) Anomalies of the origin and course (High origin, ostia in unexpected sinus, single coronary artery, separate LAD and LCx, etc.); 2) Anomalies of the intrinsic anatomy (Coronary ectasia, hypoplasia, total absence, etc.) and 3) Anomalies of termination (Coronary-cameral fistulae, etc.).

The authors observed coronary anomalies in 3% that is 23 out of 770 cases using 124 slice MDCT. In a study, 6,014 consecutive patients that underwent 64 slice MDCT were analyzed by Yang et al and coronary anomalies were found in 66 (1.09%) patients. All had one or more symptoms like chest pain, dyspnea, palpitations, arrhythmias and myocardial infarction. They found high take-off, origin of the coronary artery from the opposite or noncoronary cusp with anomalous course, and coronary artery fistula as three most frequent anomalies. They opined that due to VR technique in CT angiograms they identified a few lesions, which were not clear in conventional cineangiograms.[2]

Most common anomalies are high origin of coronaries from aorta with a normal course. There are cases when RCA arises few millimeters above sinotubular junction, but distance of 2 cm also been recorded.[3] In our experience, there were 10 (1.3%) out of 770 cases with high take-offs. High take-off usually has no clinical problems but may cause difficult cannulation. Incidence is 0.60% as per a study by Fujimoto et al in their series of 5,869 cases.[4]

Multiple ostia of right and left coronaries can be considered as important anomalies. RCA and conus branch may arise separately. Similarly, LAD and circumflex arise separately with no LCA, which accounts for small percentage with normal course. Incidence of separate ostia for LAD and LCx from left coronary sinus was 0.26% in a series.[4] In our series, we had 3 cases of separate origin of LAD and LCx accounting for 0.39%.

Origin of coronary artery or branch from the opposite or noncoronary sinus is another anomaly that is commonly observed. These anomalies are classified into 4 types. One is interarterial course between aorta and pulmonary artery. Second one is retroaortic course. Third is prepulmonic and septal or subpulmonic course. The interarterial course is clinically important as it is associated with sudden death.[5] Fujimoto et al, in their series of 5,869 cases, noted that 29 cases had opposite coronary sinus and in 27 of these cases RCA arose from left coronary sinus.[4] All these cases had interarterial course. It is reported that 30% of these have sudden cardiac death. Anomalous origin of coronary artery from opposite sinus was seen in 8 cases accounting for 1.04%. RCA from left sinus were 5 and LCA from right coronary sinus were 2 with interarterial course. In 1 case, LCx was arising from right coronary sinus with retroaortic course.

Finocchiaro et al in their study of 5,100 cases found anomalous coronary arteries in 0.6%. Anomalous left coronary artery (ALCA) arising from right sinus of Valsalva with interarterial course (11) and RCA originating from left sinus of Valsalva (RACA) with interarterial course (11) were most commonly found. ALCA arising from pulmonary artery was present in 7 cases and in 1 case, the LCA arose from noncoronary sinus.[6] In a similar study by Nguyen, the incidence of anomalies was 47 out of 9,572 cases (0.49%). LCx from RCA/right sinus of Valsalva was seen in 31.9%. High take-off of RCA was seen in 23.4%, RCA from left coronary sinus was noted in 17% and LCA from right coronary sinus was seen in 10.6%.[7] Approximately 1.04% of our cases had anomalous origin of coronary artery (5 RCA and 2 LCA, and in 1 LCx was originating from right coronary sinus with retroaortic course).

Super-dominant RCA with absent LCx artery is an exceedingly rare congenital anomaly that can be confused with atherosclerotic total occlusion. There are a few such case reports in the literature.[8] We observed one such case of super-dominant RCA with absent LCx. Single coronary artery is extremely rare with prevalence of 0.09% (5 out of 5,869 cases) in a study by Fujimoto et al.[4] Its clinical implication is complex when the patient develops atherosclerosis in the proximal segment and it can be a challenging situation for either angioplasty or coronary artery bypass grafting (CABG).

## CONCLUSION

Due to the noninvasive nature of the modality and the advantage of VR and MPR techniques, MDCT can be a useful and preferred screening tool in the study of coronary anomalies.

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# Extended-spectrum β-lactamase and AmpC β-lactamase Production among Gram-negative Bacilli Isolates Obtained from Urinary Tract Infections and Wound Infections

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## ABSTRACT

Extended-spectrum β-lactamases (ESBLs) and AmpC β-lactamases continue to be a major problem in healthcare settings. Due to the scarcity of information regarding the antibiotic susceptibility patterns particularly from urinary tract infection (UTI) and wound infections, the current study was carried out to assist the clinicians to prescribe appropriate antibiotics against Gram-negative clinical isolates. In the current study, urine (n = 620) and pus (n = 228) samples were collected from different sites (at various clinical departments) and subjected to direct microscopic examination, culture and antibiotic susceptibility testing (AST). In the AST testings, the isolates that exhibited reduced zone of inhibition to one or more of the antibiotics such as cefotaxime (≤27 mm), ceftriaxone (≤25 mm), ceftazidime (≤22 mm), cefpodoxime (≤17 mm) and aztreonam (≤27 mm) were considered as potential ESBL producers and the ESBL production was confirmed using phenotypic screening test (double-disk synergy test) and phenotypic confirmatory test (combined-disk test). However, isolates showing resistance or decreased sensitivity to cefoxitin, cefotaxime, ceftriaxone, ceftazidime, cefpodoxime or aztreonam and sensitive to cefepime were considered as a screen positive AmpC producer and subjected to AmpC disk tests. The current study concluded that 72.41% and 21.76% of ESBL and AmpC producers were detected, respectively in our hospital. It was also observed that the double-disk synergy and combined-disk tests were equally effective for ESBL detection. Further, AmpC disk test is simple, easy to perform and interpret, requiring less expertise for the rapid detection of AmpC isolates.

**Keywords:** Extended-spectrum β-lactamases, AmpC β-lactamases, Gram-negative isolates, antibiotic susceptibility testing

A novel class of enzymes imparting resistance to β-lactam antibiotics has emerged over the last few decades, mostly owing to the antibiotic selection pressure and most alarming are the extended-spectrum β-lactamases (ESBLs) produced by *Enterobacteriaceae* that have spread worldwide since the first report in 1983.[1] ESBLs are the enzymes produced by Gram-negative bacilli that have the potential to hydrolyze β-lactam antibiotics containing an oxyimino group (third-generation cephalosporins and aztreonam) and are inhibited by β-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam. Cephamycins (e.g., cefoxitin) or carbapenems (e.g., imipenem, meropenem and ertapenem) are not affected by these enzymes.[2] ESBL production has been reported in a variety of organisms including the members of *Enterobacteriaceae* and other nonenteric bacilli as well.[3,4] Currently, a majority of the clinical laboratories test for production of ESBLs; however, the testing of clinical isolates for the production of plasmid-mediated AmpC β-lactamases is usually ignored. Like ESBLs, AmpC β-lactamases have a broad-substrate profile including penicillins, cephalosporins (apart from zwitterionic cephalosporins) and monobactams. In addition, it hydrolyzes cephamycins and is not inhibited by commercially available β-lactamase inhibitors. Generally, AmpC

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β-lactamases are associated with multiple antimicrobial resistance, limiting the therapeutic regimens.[5,6]AmpC β-lactamase production has been reported in *Escherichia coli*, *Klebsiella pneumoniae*, Salmonella spp., *Citrobacter freundii*, *Enterobacter aerogenes* and *Proteus mirabilis*.[7]

Recently, the incidence of ESBL and AmpC β-lactamase-producing strains among Gram-negative bacilli isolates has considerably increased resulting in the limitation of therapeutic alternatives.[8,9] Further, various outbreaks of infections associated with ESBL and AmpC β-lactamases have been reported across the globe in the last decades.[10,11] Furthermore, geographical distribution of ESBL producers may vary from countries to countries and even between institutions to institutions.[12-15] Various investigators reported the prevalence of ESBL and AmpC β-lactamase production in India with considerable variation between different hospitals and even between various sites of infections such as urinary tract infections (UTIs) and wound infections.[11,16-19] Due to the scarcity of information regarding the antibiotic susceptibility patterns particularly from UTI and wound infections, the clinicians may likely prescribe inappropriate antibiotics for empirical treatments. Considering these issues, the present study was designed to assess the current levels of resistance to antibiotics that are commonly used in our hospital and also to review the prevalence of ESBL and AmpC β-lactamase production among Gram-negative bacterial isolates obtained from wound infections and UTI.

## MATERIAL AND METHODS

### Study Design

The study was conducted among all the patients (suspected to be having UTI and wound infections) who were examined by all the clinical departments of MM Institute of Medical Sciences and Research, Ambala, India (a 750 bedded tertiary healthcare teaching hospital). During the study period, (between March, 2012 and February, 2013), urine (n = 620) and pus (n = 228) samples were collected from different sites (at various clinical departments) and were immediately transported to the Dept. of Microbiology. Immediately after receipt, specimens were subjected to direct microscopic examination (wet mount examination for uncentrifuged urine and Gram-staining for pus specimens), culture and antibiotic susceptibility testing.

### Bacterial Strains and Antibiotic Susceptibility Testing

All the pus samples were cultured on blood agar and MacConkey agar. However, the urine specimens were inoculated on Cysteine Lactose Electrolytes Deficient (CLED) agar and incubated at 37°C for 18-24 hours. After incubation, the bacterial isolates were identified by standard laboratory protocols.[20]

The antibiotic susceptibility testing of Gram-negative bacilli was performed on Mueller-Hinton agar by modified Kirby-Bauer disk diffusion method as recommended by the Clinical Laboratory Standards Institute (CLSI) using ampicillin (10 μg), amoxicillin-clavulanic acid (20 + 10 μg), piperacillin-tazobactam (100 + 10 μg), piperacillin (100 μg), cinoxacin (100 μg), carbenicillin (100 μg), ceftriaxone (30 μg), cefepime (30 μg), ceftazidime (30 μg), cefoxitin (10 μg), cefpodoxime (30 μg), cefotaxime (30 μg), ceftizoxime (30 μg), aztreonam (30 μg), imipenem (10 μg), gentamicin (10 μg), amikacin (30 μg), tobramycin (10 μg), tetracycline (30 μg), cotrimoxazole (1.25/23.75 μg), ciprofloxacin (5 μg), lomefloxacin (10 μg), nitrofurantoin (300 μg), gatifloxacin (5 μg), norfloxacin (10 μg). The inoculated AST plates were incubated at 37°C for 16-18 hours and the results were interpreted as per CLSI guidelines.[21]

### Screening Test for ESBL and AmpC β-lactamases

Isolates that exhibited reduced zone of inhibition to one or more of the antibiotics such as cefotaxime (≤27 mm), ceftriaxone (≤25 mm), ceftazidime (≤22 mm), cefpodoxime (≤17 mm) and aztreonam (≤27 mm) were considered as potential ESBL producers.[22] However, isolates showing resistance or decreased sensitivity to cefoxitin, cefotaxime, ceftriaxone, ceftazidime, cefpodoxime or aztreonam and were sensitive to cefepime were considered as a screen positive AmpC producer and subjected to AmpC disk test.[23]

### Phenotypic Screening Test

This test for ESBL producers (double-disk synergy test) was performed as suggested by Jarlier et al, wherein an enhancement in the zone of inhibition between a β-lactam disk and one containing the β-lactamase inhibitor was indicative of the presence of ESBL.[24]

### Phenotypic Confirmatory Test (Combined-disk Test)

This test was carried as per CLSI recommendations, briefly; ceftazidime (30 μg) versus ceftazidime/clavulanic acid (30 μg/10 μg), (HiMedia, Mumbai, India), used as a phenotypic confirmatory test wherein a >5 mm increase in the zone diameter for the antimicrobial agent tested in combination with β-lactamase inhibitor versus its zone when tested alone indicates ESBL production.[21] AmpC disk test was carried out as recommended by Black et al, briefly; a sterile disk (6 mm) moistened

with sterile saline (20 μL) and inoculated with several colonies of test organism was placed beside a cefoxitin disk (almost touching) on the Mueller-Hinton agar (MHA) plate lawned with a culture of *E. coli* ATCC 25922 and incubated overnight at 35°C. A positive test appeared as a flattening or indentation of the cefoxitin inhibition zone in the vicinity of the test disk and a negative test had an undistorted zone.[23]

### Quality Control

Every new batch of culture media was incubated at 37°C overnight to ensure the sterility. *E. coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as quality control strains for antimicrobial susceptibility testing. However, a non-ESBL-producing organism *E. coli* ATCC 25922 and an ESBL-producing organism *K. pneumoniae* ATCC 700603 were used while testing ESBL screening and phenotypic confirmatory tests.

### Statistical Analysis

Significance between the resistance level of various drugs in ESBL and non-ESBL, AmpC and non-AmpC isolates was performed using the Fisher's exact test (Graphpad Prism online version).

## RESULTS

Table 1 demonstrates the distribution of all Gram-negative bacilli isolates obtained from wound infections and UTIs. Of the 848 nonrepetitive specimens processed (urine [n = 620] and pus [n = 228]), a total of 269 bacterial isolates were obtained. Out of the 269 (31.72%) nonrepetitive isolates (urine [n = 182] and pus (n = 87]), 30 isolates were *Staphylococcus aureus*, *Staphylococcus epidermidis* (n = 5) and *Staphylococcus epidermidis* (n = 7), respectively. After exclusion of these Gram-positive organisms, a total of 227 Gram-negative isolates were subjected to further analysis. Of the 227 Gram-negative bacilli isolates, 96 (40.85%) showed resistance or decreased sensitivity to any one of the 3GCs (third-generation cephalosporins??) such as cefotaxime (≤27 mm), ceftriaxone (≤25 mm), ceftazidime (≤22 mm), cefpodoxime (≤17 mm), aztreonam (≤27 mm) and isolates were further screened for ESBL production using double-disk synergy test (DDST) and confirmed using combined-disk synergy test (CDST) (Phenotypic confirmatory test). Of these 96 isolates, 80 (80/96) isolates were confirmed for ESBL production using CDST. Interestingly, it was observed that both DDST and CDST independently detected all the ESBL producers. Of these, 24 isolates were *E. coli*, *K. pneumoniae* (n = 16), *P. aeruginosa* (n = 10), *P. mirabilis* (n = 7), *Morganella morganii* (n = 6) and *C. freundii*, respectivley. Table 2 summarizes the detection of ESBL and AmpC β-lactamases among Gram-negative isolates as indicated by various detection methods.

Interestingly, we have also noticed the co-existence phenotype of both ESBLs and AmpC in 11.68% isolates of which 7 (7/227) and 6 (6/227) isolates were *E. coli* and Klebsiella spp., respectively. Table 3 illustrates the

**Table 1.** Distribution of All Gram-negative Bacilli Isolates Obtained from Wound Infections and UTIs

| Gram-negative isolates obtained | Specimens | |
|---|---|---|
| | Pus (%) | Urine (%) |
| *E. coli* (77) | 16 (20.7) | 61 (79.22) |
| *P. aeruginosa* (38) | 22 (57.8) | 16 (42.11) |
| *K. pneumoniae* (34) | 3 (8.82) | 31 (91.18) |
| *P. mirabilis* (19) | 3 (15.78) | 16 (84.21) |
| *K. oxytoca* (19) | 4 (21.05) | 15 (78.95) |
| *C. freundii* (11) | 4 (36.36) | 7 (63.64) |
| *E. aerogenes* (7) | 3 (42.86) | 4 (57.14) |
| *M. morganii* (14) | 2 (14.29) | 12 (85.71) |
| *A. lwoffii* (8) | 8 (100) | - |
| **Total (227)** | **65 (28.63)** | **162 (27.31)** |

distribution of antibiotic resistance among ESBL and non-ESBL producers. Further, it is evident from Table 3 that a significant number of ESBL-producing strains were found to be resistant to antimicrobial agents. However, in non-ESBL-producing isolates resistance was found to be relatively low. It is also evident from Table 3 that ceftazidime is the most effective indicator of ESBL production among the 3GCs.

Table 4 demonstrates the distribution of antibiotic resistance among Amp C (n = 26) and non-Amp C (n = 201) β-lactamase producers. Of the 227, Gram-negative isolates, 49 isolates showed resistance or decreased sensitivity to cefoxitin, cefotaxime, ceftriaxone, ceftazidime, cefpodoxime, aztreonam and were sensitive for cefepime. Of theses, 26 (26/49) isolates were confirmed for AmpC β-lactamase production using AmpC disk test method. Out of the 26 AmpC β-lactamase confirmed cases, 7 and 17 isolates were *E. coli* and Klebsiella spp., respectively.

ESBL-producing isolates were resistant to more antimicrobial agents than non-ESBL-producing isolates. Multidrug resistance was seen in 56 (73.75%) ESBL-positive isolates and 35 (23.81%) non-ESBL isolates. This difference was highly significant ($p < 0.01$). On the other hand, AmpC β-lactamase-producing isolates were resistant to more antimicrobial agents than non-AmpC-producing isolates. Multidrug resistance was seen in 18/26 (69.23%) AmpC-positive isolates and 39/201 (19.4%) non-AmpC isolates. This difference was highly significant ($p < 0.01$).

**Table 2.** Detection of ESBL and AmpC β-lactamases among Gram-negative Isolates as Indicated by Various Detection Methods

| Microorganism | Screening test (Positive) | | | | Confirmatory test (Positive) | | | | Combined ESBL and AmpC β-lactamase production | |
|---|---|---|---|---|---|---|---|---|---|---|
| | ESBL | | AmpC | | ESBL | | AmpC | | ESBL and AmpC production | |
| | Pus (n = 65) | Urine (n = 162) | Pus (n = 65) | Urine (n = 162) | Pus (n = 65) | Urine (n = 162) | Pus (n = 65) | Urine (n = 162) | Pus (n = 65) | Urine (n = 162) |
| *E. coli* (n = 77) | 5 (7.69%) | 23 (14.19%) | 2 (3.07%) | 22 (13.58) | 4 (6.16%) | 20 (12.35%) | 2 (3.07%) | 13 (8%) | 2 (3.07%) | 5 (3.08%) |
| *P. aeruginosa* (n = 38) | 14 (21.54%) | 5 (3.09%) | 3 (4.62%) | 1 (0.62) | 12 (18.4%) | 4 (2.47%) | 2 (3.07%) | - | - | - |
| *K. pneumoniae* sub. sp. (n = 34) | 1 (1.53%) | 14 (8.64%) | 2 (3.07%) | 14 (8.64) | 1 (1.53%) | 9 (5.55%) | 1 (1.53%) | 6 (3.7%) | 1 (1.53) | 4 (2.47%) |
| *P. mirabilis* (n = 19) | 1 (1.53%) | 6 (3.7%) | - | - | - | 5 (3.08%) | - | - | - | - |
| *K. oxytoca* (n = 19) | 3 (4.62%) | 5 (3.08%) | 2 (3.07%) | 1 (0.62) | 2 (3.07%) | 5 (3.08%) | 1 (1.53%) | - | 1 (1.53%) | - |
| *C. freundii* (n = 11) | 3 (4.62%) | 3 (1.8%) | - | - | 3 (4.62%) | 3 (1.85%) | - | - | - | - |
| *E. aerogenes* (n = 7) | 2 (3.08%) | 4 (2.46%) | - | - | 1 (1.54%) | 4 (2.46%) | - | - | - | - |
| *M. morganii* (n = 14) | 2 (3.08%) | 5 (3.08%) | - | - | 2 (3.07%) | 5 (3.08%) | - | - | - | - |
| *A. lwoffii* (n = 8) | - | - | 2 (3.07%) | - | - | - | 1 (1.53%) | - | - | - |
| **Total = 227** | **31 (47.69%)** | **65 (40.12%)** | **11 (16.9%)** | **38 (23.4%)** | **25 (38.4%)** | **55 (33.9%)** | **7 (10.7%)** | **19 (11%)** | **4 (6.15%)** | **9 (5.5%)** |

**Table 3.** Distribution of Antibiotic Resistance among ESBL (n = 80) and Non-ESBL (n = 147) Producers

| Antibiotics | ESBL producers n = 80 (%) | Non-ESBL producers n = 147 (%) | P value |
|---|---|---|---|
| Ampicillin | 80 (100) | 124 (84.35) | 0.0001 |
| Amoxicillin-clavulanic acid | 42 (52.5) | 36 (24.45) | 0.0001 |
| Piperacillin-tazobactam | 30 (37.5) | 25 (17) | 0.001 |
| Piperacillin | 56 (70) | 31 (21.08) | 0.0001 |
| Cinoxacin* | 78 (97.4) | 89 (60.55) | 0.0001 |
| Carbenicillin* | 79 (98.75) | 72 (48.98) | 0.0001 |
| Ceftriaxone | 78 (97.4) | 39 (26.53) | 0.0001 |
| Cefepime | 78 (97.5) | 34 (23.13) | 0.0001 |
| Ceftazidime | 80 (100) | 36 (24.49) | 0.0001 |
| Cefoxitin | 28 (35) | 45 (30.61) | 0.0001 |
| Cefpodoxime | 79 (98.74) | 32 (21.77) | 0.0001 |
| Cefotaxime | 76 (95) | 38 (25.85) | 0.0001 |
| Ceftizoxime* | 76 (95) | 34 (23.13) | 0.0001 |
| Aztreonam | 77 (96.25) | 34 (23.13) | 0.0001 |
| Imipenem | 0 | 0 | 0 |
| Gentamicin | 41 (51.23) | 38 (25.85) | 0.0002 |
| Amikacin | 18 (22.5) | 24 (16.32) | 0.2846 |
| Tobramycin | 15 (18.75) | 30 (20.41) | 0.0001 |
| Tetracycline | 59 (73.75) | 42 (28.57) | 0.0001 |
| Cotrimoxazole | 62 (77.7) | 40 (27.21) | 0.0001 |
| Ciprofloxacin | 43 (53.75) | 28 (19.04) | 0.0001 |
| Lomefloxacin* | 49 (61.23) | 26 (17.68) | 0.0001 |
| Nitrofurantoin* | 2 (2.4) | 1 (0.68) | 0.2842 |
| Gatifloxacin** | 38 (47.5) | 24 (16.32) | 0.0001 |
| Norfloxacin* | 34 (42.5) | 27 (18.36) | 0.0001 |

*Tested for urinary isolates only; **Tested for both wound infections and urinary tract infections.

## DISCUSSION

ESBL-producing Gram-negative bacteria are emerging worldwide, challenging the clinicians, public health professionals and hospital infection-control teams.[12] ESBLs are the enzymes produced by Gram-negative bacilli that have the potential to hydrolyze β-lactam antibiotics containing an oxyimino group (3GCs and aztreonam) and are inhibited by β-lactamase inhibitors such as clavulanic acid, sulbactam and tazobactam. However, cephamycins (e.g., cefoxitin) or carbapenems (e.g., imipenem, meropenem and ertapenem) are not affected by these enzymes.[2] Like ESBLs, AmpC β-lactamases, a group of β-lactamases, are capable of hydrolyzing penicillins, cephalosporins (apart from zwitterionic cephalosporins) and monobactams. In addition, it hydrolyzes cephamycins and is not inhibited by commercially available β-lactamase inhibitors. Further, AmpC β-lactamases are associated with multiple antimicrobial resistance, limiting the therapeutic regimens.[5,6] Furthermore, the incidence of ESBL and AmpC β-lactamase-producing strains

**Table 4.** Distribution of Antibiotic Resistance among Amp C (n = 26) and Non-Amp C (n = 201) β-lactamase Producers

| Antibiotics | AmpC producers n = 26 (%) | Non AmpC producers n = 201 (%) | P value |
|---|---|---|---|
| Ampicillin | 26 (100) | 183 (91.04) | 0.2368 |
| Amoxicillin-clavulanic acid | 26 (100) | 49 (24.38) | 0.0001 |
| Piperacillin-tazobactam | 26 (100) | 37 (18.41) | 0.0001 |
| Piperacillin | 26 (100) | 43 (21.39) | 0.0001 |
| Cinoxacin* | 24 (92.31) | 122 (60.7) | 0.0009 |
| Carbenicillin* | 25 (96.15) | 102 (50.74) | 0.0001 |
| Ceftriaxone | 24 (92.31) | 61 (30.34) | 0.0001 |
| Cefepime | 79 (26.92) | 59 (29.35) | 0.0001 |
| Ceftazidime | 25 (96.15) | 57 (28.36) | 0.0001 |
| Cefoxitin | 25 (96.15) | 58 (28.86) | 0.0001 |
| Cefpodoxime | 22 (84.62) | 52 (25.87) | 0.0001 |
| Cefotaxime | 24 (92.31) | 61 (30.35) | 0.0001 |
| Ceftizoxime* | 24 (92.31) | 55 (27.36) | 0.0001 |
| Aztreonam | 25 (96.16) | 51 (25.37) | 0.0001 |
| Imipenem | 0 | 0 | 0 |
| Gentamicin | 21 (80.77) | 54 (26.87) | 0.0001 |
| Amikacin | 18 (69.23) | 29 (14.43) | 0.0001 |
| Tobramycin | 16 (61.54) | 42 (20.9) | 0.0001 |
| Tetracycline | 19 (73.08) | 62 (30.85) | 0.0001 |
| Cotrimoxazole | 20 (76.92) | 59 (29.35) | 0.0001 |
| Ciprofloxacin | 13 (50) | 39 (19.4) | 0.0001 |
| Lomefloxacin* | 12 (46.15) | 34 (16.91) | 0.0014 |
| Nitrofurantoin* | 1 (3.85) | 1 (0.5) | 0.2164 |
| Gatifloxacin** | 9 (34.62) | 34 (16.92) | 0.0579 |
| Norfloxacin* | 10 (38.46) | 41 (20.4) | 0.0469 |

*Tested for urinary isolates only; **Tested for both wound infections and urinary tract infections.

among Gram-negative bacilli isolates has considerably increased resulting in the limitation of therapeutic alternatives.[8,9] In India, the prevalence of ESBL and AmpC β-lactamase producers vary among various hospitals and even between various sites of infections such as UTIs and wound infections. However, most of the hospitals in India are lacking accessibility to prevailing antimicrobial susceptibility patterns. This may circuitously result in the inappropriate prescription of antibiotics for empirical treatments.[11,16-19] In view of these issues, the present study was designed to assess the current levels of resistance to antibiotics that are commonly used in our hospital and also to review the prevalence of ESBL and AmpC β-lactamase production among Gram-negative bacterial isolates obtained from wound infections and UTIs. In the current study, the incidence of ESBL-producing organisms was found to be 72.41%. However, this incidence rate is much lower than the previous investigations carried out in other regions of the country.[25-27] This reduced ESBL

production among the Gram-negative isolates could be attributed to the rational use of extended-spectrum cephalosporins and appropriate infection-control measures adopted in our hospital. However, the rate of AmpC β-lactamases (21.76%) production was relatively higher than that of Singhal et al (8%) and Hemalatha et al (9.2%) but was lower than the various documented figures in India.[9,28-31] Interestingly, we have also observed the co-existence of ESBL and AmpC production among 6.15% *E. coli* and 5.53% of Klebsiella spp. These co-existent phenotypes could be due to the transfer of plasmids (encoding both AmpC and ESBL enzyme-producing genes) between members of the family *Enterobacteriaceae*.[5,6]

Various phenotypic and genotypic tests have been proposed to detect ESBL and AmpC production.

However, phenotypic methods are less expensive, easy to perform and to interpret. The phenotypic methods include screening and confirmatory tests.[21] In the current study, among the 3GCs, ceftazidime demonstrated resistance to all the phenotypically confirmed ESBL producers, indicating the potential of ceftazidime to detect ESBL production more effectively than other 3GCs. This data was in consistence with previous reports as well.[32,33] However, among the phenotypic ESBL detection methods, the DDST demonstrated 100% concordance with phenotypic combined confirmatory disk test for ESBL detection and this data was comparable with Tsering et al.[33] But among the AmpC β-lactamase producers, cefoxitin resistance was found to be a good indicator (detected 96.15% cases) as reported by previous investigators.[34,35]

Multidrug-resistant strains of bacteria possess resistance to two or more antimicrobials.[36] Multidrug-resistant strains are expected to be more common among organisms harboring genes for ESBL and AmpC β-lactamases.[5] This study also reveals that the incidence of multidrug-resistant strains is significantly ($p < 0.05$) higher in ESBL and AmpC β-lactamase producers than non-ESBL and non-AmpC producers.

It is evident from Tables 3 and 4 that most of the ESBL-producing strains were resistant to 3GC and 4GC. In addition, it was observed that the resistance to amikacin (22.5% and 69.23%), ciprofloxacin (53.75% and 50%), gatifloxacin (47.5% and 34.62%) and cotrimoxazole (77.7% and 76.92%) among ESBL and AmpC producers, respectively (Tables 3 and 4). This increased incidence of multidrug resistance is attributed to the plasmid-mediated drug resistance, which is often acquired by transfer of genetic information from one organism to another. Such transferable plasmid also codes for resistance to other antimicrobial agents as well.

Therefore, multidrug resistance is expected to be more common in ESBL-producing organisms.[37] However, all the ESBL and AmpC-producing isolates were sensitive to imipenem, indicating the potential of continued efficacy of carbapenems as the first-line agents for treatment of organisms producing ESBL and AmpC β-lactamases.

## CONCLUSION

In conclusion, 72.41% and 21.76% of ESBL and AmpC producers were detected, respectively in our hospital. It was also observed that the DDSTs and CDSTs were equally effective for ESBL detection. Further, AmpC disk test is simple, easy to perform and interpret, requiring less expertise for the rapid detection of AmpC isolates. In addition, imipenem was found to be the most sensitive antibiotic for treatment of ESBL and AmpC β-lactamases- producing Gram-negative isolates.

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■■■■

### Exposure to Nature During COVID-19 Lockdown Benefits Mental Health: Study

According to a new study, exposure to natural spaces during the first COVID-19 lockdown last year was found to be beneficial for the mental health of people in Spain and Portugal.

In Portugal, during the first lockdown, people who maintained or increased exposure to natural public spaces, such as parks or coastal areas or those who could observe these spaces from their homes, had lower levels of stress, psychological distress and psychosomatic symptoms. Additionally, in Spain, people who maintained or increased exposure to private natural spaces, like indoor plants, exhibited lower levels of stress and psychosomatic symptoms.

The study was conducted by the Institute of Environmental Science and Technology of the Universitat Autonoma de Barcelona (ICTA-UAB) and the Instituto de SaudePublica of the University of Porto (ISPUP), and has been published in *Environment International*… (*HT – ANI*)

### Bariatric Surgery Tied to Better Cardiovascular Function in Pregnancy

According to a new study presented at the Royal College of Obstetricians and Gynecologists 2021 Virtual World Congress, pregnant women who have undergone bariatric surgery tend to have better cardiovascular adaptation to pregnancy in comparison with women who have similar early-pregnancy body mass index (BMI) but have not undergone weight loss surgery.

Deesha Patel, Specialist Registrar, Chelsea and Westminster Hospital, London, United Kingdom, stated that pregnant women who have had bariatric surgery exhibit better cardiovascular adaptation via lower blood pressure, heart rate and cardiac output. The study assessed 41 women who had a history of bariatric surgery and 41 women who had no history of such surgery. Blood pressure through the three trimesters was found to be consistently lower in the women who had undergone bariatric surgery compared to those who had not undergone surgery. Heart rate and cardiac output were also lower across the three trimesters in the bariatric surgery group. There appeared to be no difference in stroke volume between the two groups studied… (*Medscape*)

### FDA Issues EUA for Tocilizumab for Treatment of COVID-19

The US FDA has issued an EUA for the use of tocilizumab to treat hospitalized adults and children, aged 2 years and above, who are being given systemic corticosteroids and need supplemental oxygen, noninvasive or invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

The drug is not authorized for use in outpatients. Clinical trials conducted among hospitalized COVID-19 patients revealed that the use of tocilizumab, along with routine care for treatment of COVID-19, including corticosteroid therapy, led to a reduction in the risk of death through 28 days of follow-up. It also reduced the duration of hospital stay.

Tocilizumab is a monoclonal antibody that works by decreasing inflammation as it blocks IL-6 receptor… (*FDA*)

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# ViraNorm
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SCINATURE

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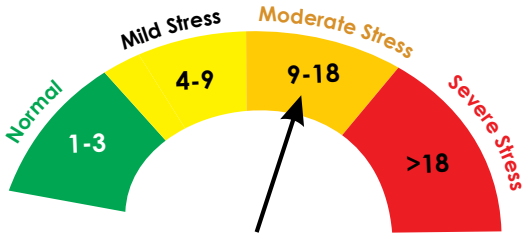
*Viranorm is the first ayurvedic medicine to systematically prove through a large clinical trial, that it reduces NLR and helps in faster & better recovery from COVID.*

*Trial data proves that cell level immunity (Cellular Immunity) improves and inflammation at the cell level is reduced with Viranorm.*

**NLR Stress-o-Meter**




*Increase in cellular immunity and reduction in cellular inflammation can be measured by using a simple formula called Neutrophils – Lymphocytes Ratio (NLR).*

Safe

Clinically Proven

Effective


*Viranorm is AYUSH approved immunomodulator and has antiviral properties*

*Pesticide Free*

*100% Veg*

*Rationally Selected*

*Plant Based Ingredients*

*All Natural*

*Scientifically Tested*

*Gluten Free*

*Heavy Metal Free*

GMP CERTIFIED QUALITY PRODUCT

AYUSH APPROVED PRODUCT
AYUSH

## Ingredients

Cissus Quadrangularis / Hadjod | Allium Sativum / Garlic | Zingiber Officinale / Ginger
Withania Somnifera / Ashwagandha | Tinospora Cordifolia / Giloy

Trials registered with CTRI CLINICAL TRIALS REGISTRY INDIA

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# Role of Herbal Immunomodulator (Viranorm) as Add-on Treatment in Asymptomatic or Mildly Symptomatic COVID-19 Confirmed Cases

PADMANABAN KG*, RADHESHYAM NAIK†


## ABSTRACT

**Background:** Coronavirus disease 2019 (COVID-19) is a highly infectious disease known to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Boosting the immune system seems to be a judicious strategy to combat the coronavirus infection. **Objective:** The primary objective of this study was to compare the efficacy and safety of Viranorm + standard of care with standard care alone in the prevention of disease progression in asymptomatic or mildly symptomatic COVID-19 infection. Secondary objective was to compare the immunological response of Viranorm + standard of care with standard care alone in asymptomatic or mildly symptomatic COVID-19 infection. **Results:** Of the 251 randomized subjects, a total of 123 received Viranorm + standard of care and 128 received standard of care alone. After administration of study treatment, on visit 1, follow-up was done on Days 3, 7, 14 and 21. The patients treated with Viranorm + standard of care showed significantly lesser time to resolution of cough than the patients with standard of care alone. At Day 7 and Day 14, the reverse transcription polymerase chain reaction (RT-PCR) results were available for only few patients. Therefore, no firm conclusions can be drawn on the effect of the drug on the incidence of RT-PCR negative subjects. All subjects from both treatment groups reported recovery and no deaths occurred during the study. At Day 14, neutrophil-to-lymphocyte ratio (NLR) values decreased in both treatment groups. The magnitude of decrease in NLR was substantially higher in the group that received Viranorm as an add-on treatment (8% median decrease) compared to the group that received only standard of care (2.6% median decrease). No adverse events or deaths occurred during the entire study duration. **Conclusion:** The add-on treatment with herbal immunomodulator Viranorm for COVID-19 is safe and effective in reducing the duration of cough and is indicative of a significant decrease in systemic inflammation as shown by NLR.


**Keywords:** COVID-19, SARS-CoV-2, immunomodulatory, NLR, LMR, inflammation

Coronavirus disease 2019 (COVID-19) is a highly infectious disease known to be caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This highly transmissible virus has caused a global pandemic and continues to surge across several countries worldwide.

The death toll due to this viral disease has crossed the 4 million mark globally, and the daily cases continue to spike in different parts of the world.[1] The total COVID-19 case count, as of July 12, 2021, stood at over 187 million.[2]

The novel coronavirus attacks the human body by attaching its spike (S) protein to the angiotensin-converting enzyme 2 (ACE2) receptors present on the surface of many human cells, including the lungs. This enables the virus to enter the cells.[3] While the virus uses the ACE2 receptor for cell entry, the cellular serine protease TMPRSS2 is required for spike protein priming.[4]

Accumulating evidence points to a considerable increase in inflammatory cytokines in patients with COVID-19. SARS-CoV-2 can induce a cytokine storm in some patients with COVID-19. A cytokine storm is a result of an imbalance between proinflammatory and anti-inflammatory mechanisms and the interaction of numerous cells and cytokines, giving way to immune regulation disorder. It is characterized by increased systemic inflammation.[5]

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Fever and cough are the most common symptoms among adults infected by SARS-CoV-2.[6] The spectrum of COVID-19 ranges from asymptomatic to clinical illness marked by acute respiratory failure requiring mechanical ventilation, septic shock and multiple organ failure. A large number of symptomatic patients present with fever, cough and shortness of breath and sore throat, anosmia, dysgeusia, anorexia, nausea, malaise, myalgias and diarrhea are some of the less common presentations.[7]

A strong immune system is probably the best defense against coronavirus infection. Having an immuno-compromised state or a weakened immune system can increase an individual's odds of getting severely ill from COVID-19.[8] Some of the immunocompromised people have a risk of prolonged viral replication and poor clinical outcomes.[9]

Therefore, boosting the immune system offers a critical strategy to combat the coronavirus infection. Natural products have long been used in traditional medicine to treat a range of diseases, including viral infections. Herbal preparations strengthen the body's immune system, which may help in the fight against invading infectious viruses.

Natural preparations may have immense potential in prevention and therapeutic management of COVID-19.

Viranorm is a novel Ayurvedic immunomodulator and has been approved by AYUSH. It has been specifically formulated with Ayurvedic herbs that strengthen immunity, possess antiviral activities and play an important role in modulating the cytokine levels associated with viral infections.

The rationale behind this randomized controlled trial was to assess the effect of Viranorm, an Ayurvedic proprietary medicine, on development of symptoms in asymptomatic patients or duration of symptoms in mild COVID-19 patients and time of virus shedding as an important tool to reduce the risk of further community transmissions. This data was intended to provide information for practice of larger community-based clinical studies on clinical efficacy of Viranorm in the treatment and post- and pre-exposure prophylaxis of COVID-19 and as a tool for reduction of community transmission.

## OBJECTIVES

**Primary objective:** To compare efficacy and safety of Viranorm in addition to standard of care, with standard care alone, in the prevention of disease progression in asymptomatic or mildly symptomatic COVID-19 infection.

**Secondary objective:** To compare the immunological response of Viranorm and standard of care with standard care alone in asymptomatic or mildly symptomatic COVID-19 infection.

### Study Endpoints

Primary endpoints:

- Difference in disease manifestation in asymptomatic patients
- Difference in time to resolution of clinical signs and symptoms of mild COVID-19 treated with Viranorm and standard of care or standard care alone
- Proportion of patients with negative COVID-19 reverse transcription polymerase chain reaction (RT-PCR) test at Day 14 in per protocol population
- Difference between Viranorm-treated patients on an ordinal outcome scale until Day 21 (death, admission to intensive care, hospitalization, duration of hospitalization, continuing disease, recovered).

Secondary endpoint:

- COVID-19 antibodies and clinical immunological markers.

## METHODS

### Study Design

This was a prospective, interventional, randomized, open label, study designed to compare the efficacy and safety of oral Viranorm and standard of care, with standard care alone, for the prevention of disease progression in asymptomatic or mildly symptomatic COVID-19 infection.

Patients diagnosed with asymptomatic or mildly symptomatic COVID-19 were eligible for inclusion in the study. A total of 250 patients were planned for enrollment in this study at multiple study centers after obtaining voluntary written consent. In all, 251 participants were actually enrolled. Efficacy and safety were analyzed in all the enrolled subjects.

The study treatments were administered as 1 capsule orally every 6 hours for 21 days from visit 1 onwards. After administration of study treatment, on visit 1, follow-up was done on Days 3, 7, 14 and 21. The study observation period ended on 29 days from enrollment. The patient's symptoms were analyzed throughout the study period. The viral load was measured at baseline and at Day 7 and Day 14. A telephonic follow-up was also conducted every day with the patients undergoing home isolation and treatment. The total duration of a patient's participation was approximately 30 days

and the total duration of the study was approximately 6 months.

Of the 251 randomized subjects, a total of 123 received Viranorm + standard of care and 128 received standard of care. All subjects (100%) completed the study and there were no study discontinuations. The disposition of study participants is described in Figure 1. The composition of Viranorm is summarized in Table 1. The herbal immunomodulator includes *Cissus quadrangularis*, *Allium sativum*, *Zingiber officinale*, *Tinospora cordifolia*, *Withania somnifera* and *Andrographis paniculata*.

*C. quadrangularis* possesses antiviral activity and anti-inflammatory potential.[10]

*A. sativum* has anti-inflammatory, antioxidant and antiviral properties.[11]

*Z. officinale* stimulates mucosal cells to secrete interferons that boost immunity. It has antiviral and anti-inflammatory effects.[12]

*T. cordifolia* exhibits antiviral and anti-inflammatory properties.[13]

*W. somnifera* has antiviral effects and immune boosting potential.[14]

*A. paniculata* has potential anti-inflammatory and antiviral action.[15]

## Inclusion Criteria

- Subjects ≥18 years and ≤70 years at the time of signing the informed consent.
- Able to understand and voluntarily sign an informed consent document prior to any study related assessments/procedures.

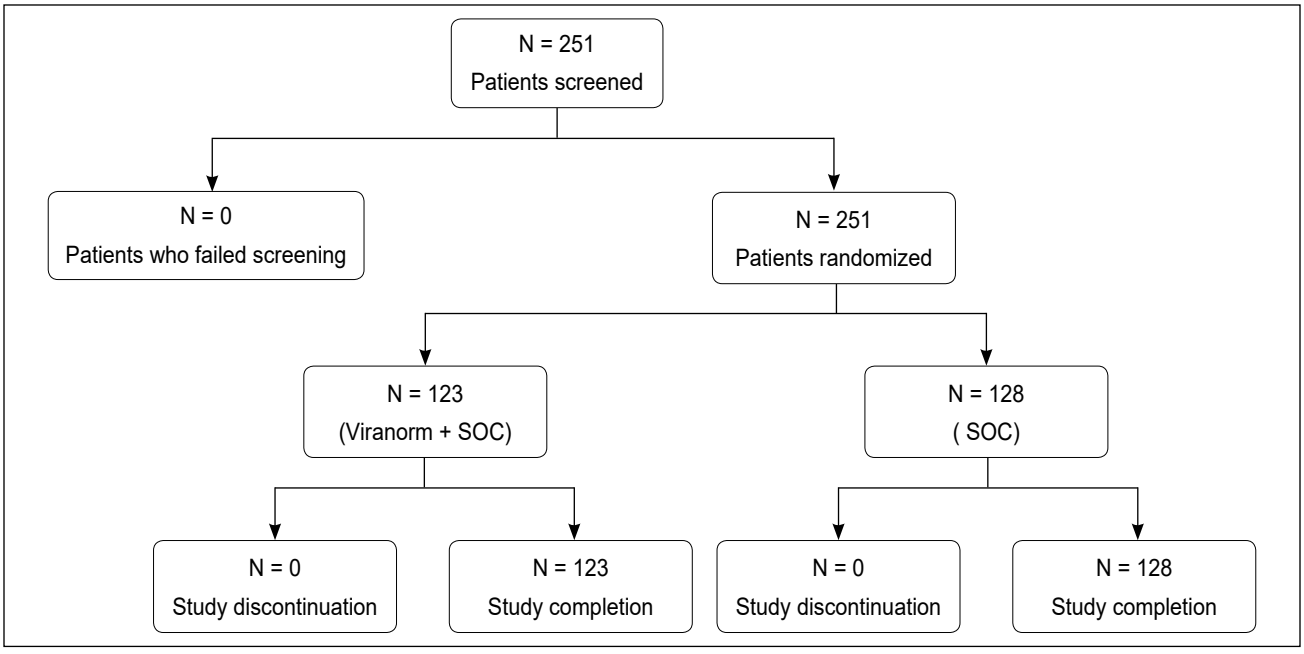


**Figure 1.** Disposition of study participants.

SOC = Standard of care.

**Table 1.** Composition of Study Drug

| Ingredient | Common name |
|---|---|
| *Cissus quadrangularis* | Asthisamharaka, Hadjod, Pirandai |
| *Allium sativum* Linn | Garlic, Lahasu, Lasuna |
| *Zingiber officinale* | Ginder, Adrak |
| *Tinospora cordifolia* | Guduchi, Giloy, Gulvel |
| *Withania somnifera* | Asvagandha, Asgandha, Ashvagandha |
| *Andrographis paniculata* | Chirota, Neemba |

- Able to adhere to the study visit schedule and other protocol requirements.
- Asymptomatic or mildly symptomatic, PCR positive for COVID-19 infection (with or without comorbid conditions) with outpatient/inpatient management as decided by the treating physician.
- With early warning score for COVID-19–infected patients <5.
- Females of childbearing potential were required to utilize two reliable forms of contraception simultaneously or practice complete abstinence from heterosexual contact for at least 21 days before starting study drug, while participating in the study (including dose interruptions), and for at least 21 days after study treatment discontinuation and agreed to perform regular pregnancy testing during this timeframe.
- Members of the same household could participate in the study as long as they met study inclusion and exclusion criteria.

### Exclusion Criteria

- Requirement for oxygen administration.
- Shortness of breath in resting position.
- Creatinine >2.0 mg/dL.
- Concomitant bacterial respiratory infection documented by respiratory culture (Subjects on empirical antibiotic treatment for possible but unproven bacterial pneumonia, but who were positive for SARS-CoV-2, were allowed in the study).
- Women during pregnancy and lactation.
- Participation in other clinical trials or observation period of competing trials.
- Use of adrenocorticosteroids (except topical or inhaled preparations or oral preparations ≤10 mg of oral prednisone) or immunosuppressive or immunomodulatory drugs (e.g., immunosuppressants, anticancer drugs, interleukins, interleukin antagonists or interleukin receptor blockers).
- Serious chronic disease (e.g., human immunodeficiency virus [HIV], cancer requiring chemotherapy within the preceding 6 months and/or moderate or severe hepatic insufficiency).
- Physician decision that involvement in the study is not in the patient's best interest.
- History of alcohol or drug abuse in the previous 2 years.

### Statistical Methods

In general, continuous variables were summarized by using summary statistics (number of observations, mean and standard deviation, median, minimum and maximum). Categorical values were presented using frequencies and percentages. Safety analysis set, modified intention-to-treat analysis set (mITT), per-protocol analysis set (PP) were used for analysis purpose.

Time of onset of change in the patient's clinical condition was estimated by using Kaplan-Meier method. The 95% confidence intervals of the median time for each treatment were presented along with 95% confidence intervals. Log rank test was used to compare the two treatments in terms of time of onset of change in the patient's clinical condition.

Proportion of patients with negative COVID-19 PCR test at Day 14 was presented for each treatment with 95% confidence intervals. Treatment difference for proportion of patients with negative COVID-19 PCR test at Day 14 was also be presented with 95% confidence intervals.

The ordinal outcome scale values were summarized descriptively for both the treatments arms. Proportion of all-cause mortality was presented for each treatment with 95% confidence intervals. Treatment difference for proportion for all-cause mortality was presented with 95% confidence intervals.

The study was conducted according to the protocol and in compliance with the regulatory requirements in India (The New Drugs and Clinical Trials Rules, 2019, Ministry of Health and Family Welfare, Government of India; and ethical guidelines for biomedical research on human participants, Indian Council of Medical Research [ICMR] 2017), and applicable international guidelines (ICH-GCP and the Declaration of Helsinki 2013).

## RESULTS

### Demographic Characteristics

The overall mean age of the subjects was 46.58 years (age range, 18-70 years). The mean age was 48.35 years in Arm A (Viranorm + SOC) and 44.88 years in Arm B (SOC). A total of 84 subjects enrolled in the study were <40 years of age, total of 102 subjects were between the age of 40 and 60 years and total of 65 subjects were >60 years.

The proportion of male subjects (57.8%) was slightly higher than female subjects (42.2%), with a comparable

distribution observed across both the study arms. Majority of subjects (87.6%) had no diabetes or hypertension (87.3%) when enrolled in the study.

Overall, the majority of subjects did not receive any concomitant medication, a small portion of study participants (<4%) received at least 1 concomitant medication during the study, and the frequency was comparable across treatment groups.

## Efficacy

### Time to resolution of clinical signs and symptoms

The mean time for resolution of cough, fever and shortness of breath was about 14 days in both treatment groups. The patients treated with Viranorm + SOC had a lesser time to resolution of cough than the patients with standard of care alone. The p value on log rank test to compare the overall time to cough resolution showed statistical significance ($p < 0.0001$). No significant difference between the treatment groups was observed in time to resolution of other symptoms of fever and shortness of breath ($p = 0.3229$ and 0.1703, respectively).

The time for resolution of clinical signs and symptoms is presented in Table 2.

### Incidence of negative RT-PCR test

All the subjects were RT-PCR positive at the time of enrollment. On Day 7 (3rd visit), 2.4% in Arm A and 3.9% in Arm B had positive RT-PCR. At 4th visit, 0.8% in both the arms had RT-PCR positive results. The RT-PCR results were not available for most of the patients. No definite conclusions can be drawn on the effect of Viranorm add-on treatment on the incidence of RT-PCR negative subjects.

### Ordinal outcome scale until Day 21

All the subjects enrolled in the study were hospitalized during the study duration; none of them was admitted to intensive care unit (ICU). At the end of the study period on Day 21, all the subjects recovered and no deaths occurred during the study duration.

### Evaluation of biomarkers

The neutrophil-to-lymphocyte ratio (NLR) was evaluated at screening and at Day 14. At baseline, the mean NLR across treatment arms was 5.36 and 6.00 in Viranorm + SOC and SOC groups, respectively. At Day 14, there was decrease in NLR values in both treatment groups. The magnitude of decrease in NLR was substantially higher in the group that received Viranorm as an add-on treatment (8% median decrease) compared to the group that received only standard of care (2.6% median decrease). The change in NLR assessed by excluding outliers showed a significant decrease in the group with Viranorm add-on treatment compared to the group that received standard of care (Table 3; $p = 0.0488$). Similar trend in NLR decrease was observed when the assessment was carried out stratified by age (<40 years of age, 40-60 years >60 years) and diabetes status.

The platelet-to-lymphocyte ratio (PLR) was evaluated at screening and at Day 14. At baseline, the mean PLR was 165.83 and 211.83 in Viranorm + SOC and SOC groups, respectively. At Day 14, there was decrease in PLR values in both treatment groups, though the difference between the groups was not statistically significant. There were no significant differences in the PLR change between Viranorm add-on group and SOC group across the age groups.

**Table 2.** Time to Resolution of Clinical Signs and Symptoms (mITT Population)

| Characteristics | Viranorm + SOC (n = 123) | SOC (n = 128) |
|---|---|---|
| **Cough** | | |
| N | 103 | 109 |
| Mean | 14.08 | 14.26 |
| SD | 1.41 | 1.33 |
| Median | 14.00 | 14.00 |
| **Fever** | | |
| N | 76 | 77 |
| Mean | 14.12 | 14.00 |
| SD | 1.63 | 0.16 |
| Median | 14.00 | 14.00 |
| **Shortness of breath** | | |
| N | 63 | 57 |
| Mean | 14.27 | 14.47 |
| SD | 1.99 | 1.81 |
| Median | 14.00 | 14.00 |

**Table 3.** Percentage Change in NLR without Outliers

| Parameter | Statistics | Viranorm + SOC | SOC |
|---|---|---|---|
| Change from baseline to Day 14 | N | 99 | 120 |
| | Mean | -12.66 | -3.12 |
| | SD | 62.59 | 68.87 |
| | Median | -23.53 | -5.46 |
| P value | | 0.0488 | |

The lymphocyte-to-monocyte ratio (LMR) was evaluated at screening and at Day 14. There was no statistically significant difference in LMR values in the two study groups at follow-up.

C-reactive protein (CRP) was evaluated at screening, Day 7 and Day 14. At baseline, the mean CRP across treatment groups was comparable with mean values of 37.37 mg/dL and 36.49 mg/dL in Viranorm + SOC and Viranorm groups. At Day 7 and Day 14, there were decreases in CRP in both groups. Between the treatment groups, the differences were not statistically significant ($p = 0.0677$ and 0.1121, at Day 7 and 14, respectively). Similar trends were observed when CRP was assessed stratified by age, diabetes status and hypertension status.

#### COVID-19 antibodies (IgM and IgG)

The proportion of patients developing the antibodies was similar across the treatment groups.

#### Laboratory evaluation

Blood testing was performed for all the subjects enrolled in the study during screening and at visit 4. There was increase in mean absolute lymphocyte count at the follow-up visit for both the arms, as compared to screening test.

### Safety Evaluation

There were no adverse events reported across the treatment groups in the study. There were no deaths during the study. No serious adverse events occurred during the study. Additionally, there were no discontinuations due to adverse events.

Treatment with the herbal immunomodulator as an add-on treatment to standard of care in asymptomatic or mildly symptomatic COVID-19 patients was safe and well-tolerated.

## DISCUSSION AND CONCLUSION

The purpose of this study was to evaluate the role of herbal immunomodulator Viranorm as add-on treatment in asymptomatic or mildly symptomatic COVID-19 confirmed cases.

Patients treated with Viranorm + standard of care showed significantly lesser time to resolution of cough, compared to patients treated with standard of care alone ($p < 0.0001$ based on log rank test). Cough is one of the most commonly reported symptoms in COVID-19. A systematic review and meta-analysis including 148 studies from 9 countries, involving 24,410 adults with confirmed COVID-19, noted that cough was among the most prevalent symptoms in the patients. It was noted in 57% of the cases.[6] A study conducted by researchers at the Leipzig University Hospital also noted cough as the second most frequently reported symptom (67%) in COVID-19 outpatients.[16] Add-on treatment with Viranorm resulted in quicker resolution of cough in COVID-19 patients, thereby decreasing the discomfort in these patients.

Increasing amount of evidence supports the role of inflammation in the progression of viral pneumonia, including in COVID-19. Severe inflammatory responses add to the weakening of adaptive immune response, thus leading to immune response imbalance. Biomarkers known to represent inflammation and immune status have been shown to predict the prognosis of COVID-19 patients. Peripheral white blood cell (WBC) count, NLR, PLR and LMR have potential role in predicting the prognosis of patients with viral pneumonia. Yang and colleagues noted in their study that NLR could be an independent biomarker for indicating poor clinical outcomes in COVID-19 patients. Elevated NLR has been tied to illness severity.[17]

In this study, after 14 days of treatment, patients receiving Viranorm as an add-on treatment had higher reduction in NLR compared to the group that received standard of care alone. Similar results were shown when assessed across age groups, including the vulnerable age group of >60 years. Viranorm add-on treatment also showed greater decreases in NLR in patients with diabetes.

Although statistical significance of Viranorm add-on treatment associated with NLR and LMR could not be shown with the ITT population, the ad-hoc analysis conducted excluding the outliers showed a statistically significant decrease in NLR in Viranorm add-on treatment group ($p = 0.0488$). Further large-scale studies designed to detect and quantify the changes in NLR and LMR with Viranorm add-on treatment are required.

No adverse events or deaths occurred during the entire study duration. And the add-on treatment with Viranorm in asymptomatic or mildly symptomatic COVID-19 patients was safe and well-tolerated.

Overall, the add-on treatment with the herbal immunomodulator Viranorm for COVID-19 was safe and effective in reducing the duration of cough and is indicative of a significant decrease in systemic inflammation as shown by NLR.

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# A Rare Case of SLE Flaring-up as Acute Spinal Subarachnoid Hemorrhage and Acute Transverse Myelitis

N VEDHANAYAGAM*, BALASENTHIL KUMARAN†


## ABSTRACT

Systemic lupus erythematous (SLE) flaring-up as acute spinal subarachnoid hemorrhage (SSH) with acute transverse myelitis at conus medullaris is a rare presentation among various demyelinating syndromes in SLE. Presented here is the case of a 47-year-old female, a known case of SLE, who presented with sudden back pain with abrupt onset of symmetrical weakness of both lower limbs and double incontinence. MRI showed subarachnoid bleed with associated myelitis. The patient was treated with prednisolone, mycophenolate mofetil and hydroxychloroquine and has been without any flares for 18 months.


**Keywords:** Systemic lupus erythematosus, spinal subarachnoid hemorrhage, acute transverse myelitis

Diagnosis of demyelinating syndrome in systemic lupus erythematous (SLE) is made after careful exclusion of primary demyelinating diseases, infectious diseases, neoplastic and paraneoplastic syndromes. As per Chessa et al, various patterns of demyelinating syndrome observed in SLE are: i) neuromyelitis optica (NMO), ii) neuromyelitis optica spectrum disorders (NMOSD), iii) demyelinating syndrome prominently involving the brain (DSB), iv) demyelinating syndrome prominently involving the brainstem (DSBS) and v) clinically isolated syndrome.[1] SLE flaring-up as acute spinal subarachnoid hemorrhage (SSH) with acute transverse myelitis at conus medullaris is a rare presentation among various demyelinating syndromes in SLE.

## CASE REPORT

A 47-year-old female, a known case of SLE, presented with sudden back pain with abrupt onset of symmetrical weakness of both lower limbs and double incontinence. On motor system examination, patient had symmetrical spastic paraparesis (3/5) below L1, brisk deep tendon reflexes (DTR) with bilateral extensor plantar reflex. Sensory examination revealed reduced touch sensation with perianal pain and temperature loss. Autonomic system had bowel and bladder incontinence. Clinically, the deficit was localized to spinal cord at conus medullaris. Magnetic resonance imaging (MRI) whole spine study showed an extra-axial T1 hyperintense and T2 hypointense well-defined subarachnoid bleed noted from D1 with mild compression on dorsal aspect of spinal cord at D8 vertebral level along with subtle long segment signal changes at the conus medullaris, suggestive of associated myelitis (Figs. 1 and 2).

MRI brain screening including optic nerves was normal. MR angiogram (MRA) with

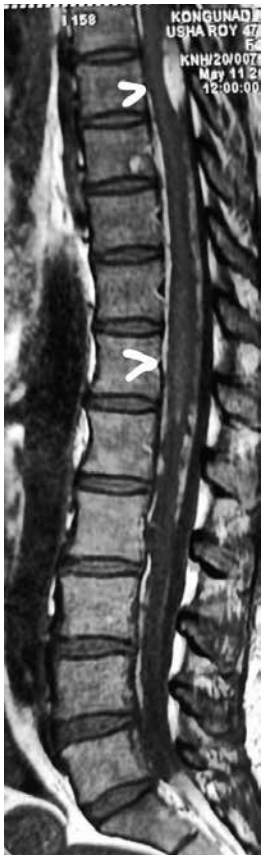


**Figure 1.** T1 Fat suppression image showing subarachnoid bleed with myelitis at D11, D12 level.

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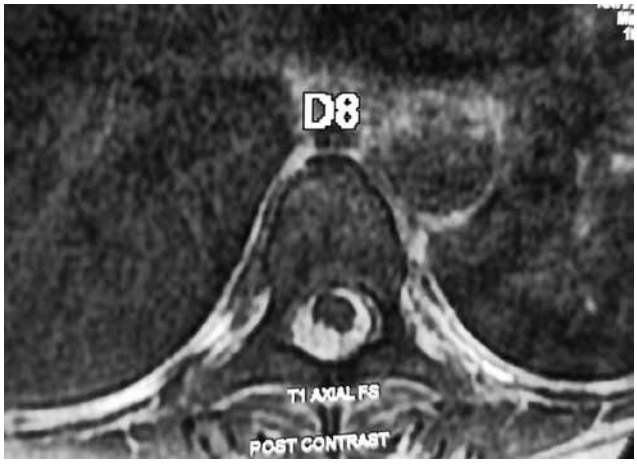


**Figure 2.** Post contrast axial view at D8 level showing cord compression at posterior aspect.

contrast showed normal intracranial and spinal vessels. Complete blood counts, coagualtion profile and serum complement levels were normal. Cerebrospinal fluid (CSF) analysis showed predominant lymphocytic inflammatory picture with xanthochromia (Total cells 100; polymorphs 40/mm$^3$, lymphocytes 60/mm$^3$); CSF biochemistry showed decreased glucose (38 mg/dL), raised protein (113 mg/dL) and no oligoclonal bands. Gram-staining acid-fast bacillus (AFB) staining and CSF bacterial culture were negative. Serum antinuclear antibody (ANA) profile showed positive results for dsDNA, nucleosomes and for histones antibodies. Serum antineutrophil cytoplasmic antibodies (ANCA) profile (pANCA, cANCA, anti-MPO [myeloperoxidase] antibodies), antiphospholipid antibodies, Venereal Diseases Research Laboratory (VDRL), enzyme-linked immunosorbent assay (ELISA) for human immunodeficiency virus (HIV) screening, hepatitis B surface antigen (HBsAg), hepatitis C virus (HCV) and scrub typhus antibody, were negative. Serum angiotensin-converting enzyme (ACE) level and computed tomography thorax was normal. Patient was treated with intravenous methylprednisolone 1 g daily for 5 days. Within a week, she was able to walk without support. However, bowel and bladder dysfunction took 35 days to recover. Follow-up MRI with MRA showed complete resolution of myelitis with mild reduction in spinal subarachnoid bleed and no evidence of vasculitis (Fig. 3)

Patient was on mycophenolate mofetil 500 mg b.i.d., hydroxychloroquine 100 mg b.i.d. and prednisolone 20 mg b.i.d. for 4 weeks. Steroid dose was tapered over 6 months and stopped. Now patient is taking mycophenolate mofetil 500 mg b.i.d. and hydroxychloroquine 100 mg b.i.d. without any flares for 18 months.

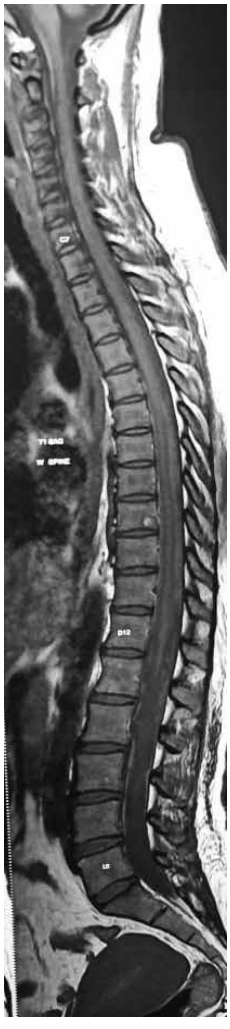

**Figure 3.** Reduction of SSH and myelitis.

## DISCUSSION

Acute severe back pain and headaches followed by symptoms of transverse myelopathy is usually the clinical manifestation of SSH. The causes of SSH include arteriovenous fistula, coarctation of aorta, angioma, telangiectasia, mycotic aneurysm of a spinal artery, syphilis, polyarteritis nodosa, tumors such as ependymoma, schwannoma, neurofibroma, glioblastoma multiforme, meningeal sarcoma) and anticoagulant therapy. Delay in diagnosis of SSH will result in poor outcome.[2]

On review of literature, we were able to find only few reports of SSH in patients with SLE. Most of them were due to vasculitis of spinal vessels which results in SSH, diagnosed either by digital subtraction angiography or autopsy.[3] Probable cause for transverse myelitis in SLE is antiphospholipid antibody associated thrombosis of spinal vessels, which results in spinal cord ischemia or necrosis.[4] However, data to support this theory has been sparse. But in our case, serum vasculitis profile, antiphospholipid antibody and MR spinal angiogram was normal. Spinal DSA was not done as patient was not willing. Hence, the cause for SSH in our case is not known.

Diminished CSF glucose level has been suggested to be associated with SLE-induced transverse myelopathy; however, spinal subarachnoid bleed may also yield this finding.[2] One more finding which supports inflammatory nature of the disease process here is predominant lymphocytes in CSF.

Transverse myelitis is a very rare complication occurring in only 1 to 2% of patients with SLE.[5] Other systemic autoimmune disorders associated with transverse myelitis or NMOSD are Sjögren's syndrome (SS), primary antiphospholipid antibody syndrome, sarcoidosis and various forms of vasculitis.[6] Pittock et al noted NMO-IgG seropositivity in some patients with SLE and in SS having NMO or NMOSD.[7]

However, autoimmune disorders had been seen equally in both NMO seropositive and negative cases.[8] In our case, serum NMO antibody was negative. Spinal cord involvement in SLE is usually cervical and less often in thoracic segments. But, our case had acute transverse myelitis at conus medullaris which is a rare presentation and this type of demyelination, most likely to be clinically isolated syndrome in SLE, has good clinical improvement in more than 90% of cases.[1] There is no available biomarker for predicting neuroflares in SLE; hence, identification of such markers will help in better management.

Treatment of acute SSH with transverse myelitis includes high-dose steroids and plasmapheresis followed by long-term immunosuppression. Our case had good clinical response to intravenous steroids without any further intervention.

## CONCLUSION

Clinicians must be aware of the rare presentation of SLE flare-up as acute SSH and various types of demyelination in SLE. In future, identification of predicting biomarkers for neuroflares in SLE will help in better management.

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Indian Journal of Clinical Practice, Vol. 32, No. 3, August 2021

# Law on Euthanasia in India

Life and death as concepts have invited many thinker, philosopher, writer and physician to define or describe them. **Swami Vivekananda** expects one to understand that life is the lamp that is constantly burning out and further suggests that if one wants to have life, one has to die every moment for it. One may like to compare life with constant restless moment spent in fear of extinction of a valued vapour; and another may sincerely believe that it is beyond any conceivable metaphor. Death is complicated and life is a phenomenon which possibly intends to keep away from negatives that try to attack the virtue and vigour of life from any arena.

In spite of all the statements, references and utterances, be it mystical, philosophical or psychological, the fact remains, at least on the basis of conceptual majority, that people love to live - whether at eighty or eighteen - and do not, in actuality, intend to treat life like an—autumn leaf.

The perception is not always the same at every stage. There comes a phase in life when the spring of life is frozen, the rain of circulation becomes dry, the movement of body becomes motionless, the rainbow of life becomes colorless and the word life' which one calls a dance in space and time becomes still and blurred and the inevitable death comes near to hold it as an octopus gripping firmly with its tentacles, so that the person shall rise up never.

The **ancient Greek Philosopher, Epicurus**, has said, although in a different context:

*Why should I fear death?*

*If I am, then death is not.*

*If death is, then I am not.*

*Why should I fear that which can only exist when I do not?*

But there is a fallacy in the said proposition. It is because mere existence does not amount to presence. And sometimes, there is a feebleness of feeling of presence in semi-reality state when the idea of conceptual identity is lost, quality of life is sunk and the sanctity of life is destroyed and such destruction is denial of real living.

The society at large feel that a patient should be treated till he breathes his last breath.

Every doctor is supposed to take specific oath that he will make every attempt to safe the life of the patient whom he/she is treating and who is under his/her treatment. This oath, thus, puts a moral and professional duty upon a doctor to do everything possible, till the last attempt, to save the life of a patient.

The **Medical Council of India (MCI) Code of Ethics rejects Euthanasia** (deliberately ending a patient's life at his/her own request or at the request of close relatives).

*"6.7* ***Euthanasia: Practicing euthanasia shall constitute unethical conduct****. However, on specific occasion, the question of withdrawing supporting devices to sustain cardio-pulmonary function even after brain death, shall be decided only by a team of doctors and not merely by the treating physician alone. A team of doctors shall declare withdrawal of support system. Such team shall consist of the doctor in-charge of the patient, Chief Medical Officer/Medical Officer in-charge of the hospital and a doctor nominated by the in-charge of the hospital from the hospital staff or in accordance with the provisions of the Transplantation of Human Organ Act, 1994."*

If that is so, would it not be against medical ethics to let a person die by withdrawing medical aid or, even for that matter, life supporting instruments.

Medical scientists have been, relentlessly and continuously, experimenting and researching to find out better tools for not only curing the disease with which human beings suffer from time to time, noble attempt is to ensure that human life is prolonged and in the process of enhancing the expectancy of life, ailments and sufferings therefrom are reduced to the minimal. There is, thus, a fervent attempt to impress the quality of life.

It is this very advancement in the medical science which creates dilemma at that juncture when, in common perception, life of a person has virtually become unlivable but the medical doctors, bound by their **Hippocratic Oath and medical ethics** want to still spare efforts in the hope that there may still be a chance, even if it is very remote, to bring even such a person back to life.

The Hippocratic Oath taken by a doctor and the MCI Code of Ethics may make him feel that there has been a failure on his part and sometimes also make him feel

scared of various laws. There can be allegations against him for negligence or criminal culpability.

There is a **distinction between the administration of lethal injection or certain medicines to cause painless death and non-administration of certain treatment,** which can prolong the life in cases where the process of dying that has commenced is not reversible or withdrawal of the treatment that has been given to the patient because of the absolute absence of possibility of saving the life. To explicate, the first part relates to an overt act whereas the second one would come within the sphere of informed consent and authorized omission. The omission of such a nature will not invite any criminal liability if such action is guided by certain safeguards. The concept is based on nonprolongation of life where there is no cure for the state the patient is in and he, under no circumstances, would have liked to have such a degrading state.

In the landmark judgment **Common Cause versus Union of India, 2018 (5) SCC 1, the Hon'ble Constitution Bench of 4 Judges of Supreme Court** held that **Euthanasia** is basically an intentional premature termination of another person's life either by direct intervention **(active euthanasia)** or by withholding life-prolonging measures and resources **(passive euthanasia)** either at the express or implied request of that person **(voluntary euthanasia)** or in the absence of such approval/consent **(nonvoluntary euthanasia)**.

**Active euthanasia** also includes physician-assisted suicide, where the injection or drugs are supplied by the physician, but the act of administration is undertaken by the patient himself. Active euthanasia is not permissible in most countries.

**Passive euthanasia** occurs when medical practitioners do not provide life-sustaining treatment (i.e., treatment necessary to keep a patient alive) or remove patients from life-sustaining treatment. This could include disconnecting life support machines or feeding tubes or not carrying out life-saving operations or providing life-extending drugs. In such cases, the omission by the medical practitioner is not treated as the cause of death; instead, the patient is understood to have died because of his underlying condition.

Further, In **Gian Kaur versus State of Punjab, (1996) 2 SCC 648**, the Hon'ble Constitution Bench of Apex Court expounded that the **word "life" in Article 21** has been construed as life with human dignity and it takes within its ambit the **"right to die with dignity"** being part of the **"right to live with dignity"**. As part of the right to die with dignity in case of a dying man who is terminally ill or in a persistent vegetative state, only passive euthanasia would come within the ambit of Article 21 and not the one which would fall within the description of active euthanasia in which positive steps are taken either by the treating physician or some other person. That is because the right to die with dignity is an intrinsic facet of Article 21.

In **Aruna Ramachandra Shanbaug versus Union of India, 2011 (15) SCC 480**, Hon'ble Supreme Court has observed that **autonomy means the right to self-determination where the informed patient has a right to choose the manner of his treatment.** To be autonomous the patient should be competent to make decisions and choices. In the event that he is incompetent to make choices, his wishes expressed in advance in the form of a Living Will, or the wishes of surrogates acting on his behalf ('substituted judgment') are to be respected.

Thus, **all adults with the capacity to consent have the common law right to refuse medical treatment and the right of self-determination.** Doctors would be bound by the choice of self-determination made by the patient who is terminally ill and undergoing a prolonged medical treatment or is surviving on life support, subject to being satisfied that the illness of the patient is incurable and there is no hope of his being cured.

In "**Common Cause versus Union of India, 2018 (5) SCC 1,** the Constitution Bench of Hon'ble Supreme Court held that **Advance Medical Directive** would serve as a fruitful means to facilitate the fructification of the sacrosanct right to life with dignity. The said directive will dispel many a doubt at the relevant time of need during the course of treatment of the patient. That apart, it will strengthen the mind of the treating doctors as they will be in a position to ensure, after being satisfied, that they are acting in a lawful manner. However, Advance Medical Directive cannot operate in abstraction. The Hon'ble Court in the said judgment has enumerated various safeguards and procedure of advance medical derivatives and also in cases where there is no advance medical derivatives which will remain enforced till Parliament makes a law on Advance Medical Derivatives.

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Indian Journal of Clinical Practice, Vol. 32, No. 3, August 2021

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## CORONAVIRUS UPDATES

### Delta Variant Spreads by Cell-to-Cell Fusion

Compared to the spike protein on the previous versions of the coronavirus, the spike on the Delta variant has a better capability to break into lung cells and fuse them together, according to a preprint posted on BioRxiv.

Spread by cell-to-cell fusion enables the virus to spread faster in infected individuals and partially hide from the immune system. And by spreading through cell-to-cell fusion, the virus reduces its chances of encountering immune system cells that can attack and inactivate it, said Markus Hoffman of Georg-August-University Göttingen in Germany, co-author of the study. These "skills" might make the Delta variant more transmissible, and the resulting illness more severe. It was also found that although the Delta variant can evade antibodies, it is not completely resistant. (*Source: Medscape*)

### Germany Strongly Recommends Mixing of COVID-19 Vaccines

Germany has become one of the first countries to make a strong recommendation for the mixing of coronavirus disease 2019 (COVID-19) vaccines on the basis of efficacy. The German Standing Committee on Vaccination (STIKO) said that people who receive a first dose of the Oxford-AstraZeneca vaccine *"should get an mRNA vaccine as their second dose, regardless of their age."* STIKO said that current study data suggest that the immune response generated after a mixed dose vaccination is superior. (*Source: CNN*)

### Sickle Cell Disease Patients with History of Pain are at Risk of Severe COVID-19

Patients with sickle cell disease (SCD) having a history of disease-related comorbidities have been reported to have a greater risk for worse COVID-19 outcomes. A new study published in the journal *Blood Advances* has shown that children were more likely to require hospital admission for COVID-19, if they had frequent prior acute care visits for pain (relative risk [RR] 2.15, $p < 0.0001$), and had SCD-related heart and lung comorbidities (RR 1.61, $p = 0.0001$).

- Previous acute care visits for pain were the most common SCD-related comorbidity among children (55.5%) as well as adults (78.5%).
- History of pain was also a risk factor for hospital admission in adults (RR 1.78, $p = 0.002$).
- Children with a history of pain (RR 3.09, $p = 0.009$), SCD-related heart and lung comorbidities (RR 1.76, $p = 0.03$), and SCD-related renal comorbidities (RR 3.67, $p < 0.0001$) had a greater risk of developing serious COVID illness.

The researchers said, "SCD is a chronic inflammatory disease. An infection like COVID-19 that targets the lungs can lead to decreased oxygenation and blood hypoxia, which promotes sickling, vaso-occlusive episodes and pain." Patients at high risk should consider vaccination. (*Source: Medpage Today*)

### Repurposing Hepatitis C Antiviral Drugs as Possible Treatment of COVID-19

An antiviral combination sofosbuvir/ledipasvir, used to treat hepatitis C infection, and an antiprotozoal drug nitazoxanide may eliminate severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), according to preliminary results presented at the International Liver Congress 2021. Sofosbuvir/ledipasvir was particularly efficacious. Molecular docking studies that make use of computation to find ligands that bind to proteins, revealed that both sofosbuvir/ledipasvir and nitazoxanide might block key proteins in SARS-CoV-2.

The study grouped 190 patients with mild and moderate COVID-19 infections into three groups. One group was given sofosbuvir/ledipasvir, another group also received nitazoxanide. All the three groups also received standard care. The effect of sofosbuvir/ledipasvir appeared within 5 days and viral clearance was achieved in most patients within 2 weeks. Nitazoxanide had a weaker effect but still appeared to achieve a benefit. No serious adverse events or mortality was recorded. (*Source: Medscape*)

### US FDA Cautions About Increased Risk of Guillain-Barré Syndrome with J&J COVID-19 Vaccine

The US Food and Drug Administration (FDA) has revised the Janssen COVID-19 vaccine fact sheet for healthcare providers administering vaccine (vaccination providers) and for recipients and caregivers to include a warning about increased risk of Guillain-Barré syndrome following vaccination.

The Fact Sheet for Recipients and Caregivers notes that vaccine recipients should seek medical attention right away if they develop any of the following symptoms after receiving the Janssen COVID-19 Vaccine: weakness or tingling sensations, especially in the legs or arms, that's worsening and spreading to other parts of the body; difficulty walking; difficulty with facial movements, including speaking, chewing or swallowing; double vision or inability to move eyes; or difficulty with bladder control or bowel function... (*Source: US FDA*)

### Beta Variant may also be More Transmissible

The second wave of COVID-19 in South Africa, primarily driven by the Beta variant (B.1.351), recorded a dramatic increase in the number of cases compared to the first wave (240.4 per 1,00,000 people vs. 136 per 1,00,000, respectively), hospital admissions (27.9 per 1,00,000 vs. 16.1 per 1,00,000) and deaths (8.3 per 1,00,000 vs. 3.6 per 1,00,000), as per a study in *The Lancet Global Health*. A multivariable analysis of the second wave showed a 31% increased risk of in-hospital death (adjusted odds ratio [OR] 1.31, 95% confidence interval [CI] 1.28-1.35). Mortality was particularly high when the hospitals were stretched to their capacity. According to the authors, the Beta variant binds more strongly to the angiotensin-converting enzyme 2 (ACE2) receptors thereby increasing the risk of transmission. (*Source: Medpage Today*)

### Do not Ignore Atypical Symptoms in Older Adults with Severe COVID-19

A study reported in the *Journals of Gerontology: Series A* stated that over a third of older adults who were hospitalized with COVID-19 during the early months of the pandemic had an atypical presentation, with a mix of typical and atypical symptoms. Almost a quarter of patients ages 65 and older presented with functional decline, while 11.3% presented with altered mental status and around 9% had gastrointestinal symptom. Among those with an atypical presentation, 49% presented with atypical symptoms only. But, patients with typical symptoms were 1.39 times more likely to be admitted to the ICU than those with atypical symptoms.

Study author, Allison Marziliano, PhD, from the Feinstein Institutes for Medical Research in Manhasset, New York said, *"While we found that atypical presentation in older adults does not necessitate the same need for ICU-level care as typical presentation (often characterized by respiratory distress), it must not be dismissed, as those presenting atypically have just as poor short-term outcomes of hospital length of stay, 30-day readmission and hospital mortality as those older adults presenting typically"... (Source: Medpage Today)*

### Sequential Contralateral Facial Nerve Palsies in the Same Patient After COVID Vaccine

*BMJ Case Reports* has described the case of a 61-year-old man, who developed two discrete contralateral facial palsies after each dose of the Pfizer-BioNTech vaccine. The patient initially developed right-sided facial weakness 5 hours after taking the first dose of the Pfizer-BioNTech vaccine. The second episode occurred 2 days after the second dose and the patient developed more severe left-sided facial nerve palsy. On both occasions, the patient was diagnosed with Bell's palsy.

"The occurrence of the episodes immediately after each vaccine dose strongly suggests that the Bell's palsy was attributed to the Pfizer-BioNTech vaccine, although a causal relationship cannot be established," the researchers wrote ... (*Source: MedPage Today*)

### Some Countries are Adopting the Mix-and-Match COVID Vaccines Strategy

Despite the data being preliminary, certain countries are going ahead with mixing and matching mRNA and adenoviral vector COVID-19. Germany has recommended to mix-and-match, encouraging citizens to follow AstraZeneca vaccine dose with a dose of an mRNA vaccine. Chancellor Angela Merkel followed her initial AstraZeneca dose with a shot of Moderna in June. Canada and Thailand have also started administering vaccines on a heterologous schedule.

The European Medicines Agency (EMA) and the European Centre for Disease Prevention and Control (ECDC) have not issued any specific recommendations, but say in a press release that the approach "may allow populations to be protected more quickly and make better use of available vaccine supplies."Neither the World Health Organization (WHO) nor the CDC endorse the approach. (*Source: Medpage Today*)

### Journal Retracts Study on Masks in Children

*JAMA Pediatrics* has retracted a research letter *"Experimental assessment of carbon dioxide content in inhaled air with or without face masks in healthy children: a randomized clinical trial"* published online June 30, 2021, which suggested that children should not be forced to wear face masks as masks may harm them by exposing them to high carbon dioxide levels. The research letter had reported unacceptably high levels of carbon dioxide

as per German standards in air inside masks worn by children in a laboratory environment. In the retraction notice, the editors cited "numerous scientific issues", also including questions over the applicability of the $CO_2$ measurement device and the validity of the study conclusions.

CDC does not outline any known risk to children from wearing face masks, and has recently recommended that unvaccinated children should wear masks when school reopens in the fall... (*Source: Medpage Today*)

## A Different Approach to Reach the Unvaccinated

Ozarks Healthcare, based in the city of West Plains, Missouri in the United States adopted a unique approach to encourage people to come forward to take the vaccine. They recently issued an impassioned plea for people to get vaccinated, even if it is done in secret. They offered to answer any questions about the vaccine and help with scheduling in a recent statement. The health system said in a statement: "If you are afraid of walking into a public area where you might be seen getting your vaccine, we will work to accommodate even more of a private setting for you to receive your vaccine."

Amid misinformation and vaccination status largely divided by political lines, making a public appeal to offer the COVID vaccine in private seems to be a unique approach... (*Medpage Today*)

*With inputs from Dr Monica Vasudev*

## HCFI Round Table Expert Zoom Meeting on "Delta Plus Variant and Third Wave of COVID"

**3rd July, 2021 (11 am-12 noon)**

### Key points of HCFI Expert Round Table

- India is currently in between waves. In North India, the second wave is almost over. A potential third wave looms large.
- The coronavirus is a medium sized virus, but has the largest mRNA genome. The virus has 4 or 5 structural proteins (S, M, N, E and HE). Each of these structural proteins has a function to perform and is better understood today. The spike protein is crucial for receptor binding.
- The SARS-CoV-2 binds 10-20 times more strongly to ACE2 receptors than the SARS-CoV. The concentration of ACE2 receptors is highest in type 2 alveolar cells followed by the bronchial epithelium, buccal epithelium, upper gastrointestinal (GI) epithelium, myocardial cells, proximal tubule cells of the kidneys and bladder urothelial cells. It is now known that it also binds to the pancreatic β cells.
- Antibody-dependent enhancement, i.e., antibodies can create a backdoor enhancement for viral replication.
- The Delta variant is B.1.617.2, which is predominantly seen as a mutation in the spike protein.
- Large number of cases in the UK and USA are Delta variant.
- The second wave in India had a geometric spike. As per the prediction susceptible-infected-removed (SIR) model, the wave should have continued for much longer, but there is a sudden decline in the number of cases, i.e., a higher peak and a very sharp and precipitous decline. The reasons for this sudden fall in the cases are being explored. The second wave was predominantly driven by the Delta variant.
- New symptoms to watch out for in the second wave are nausea, abdominal pain, hearing impairment, vomiting, diarrhea, GI complications, joint pain, weakness, loss of appetite, skin rash, discoloration of finger and toes.
- The second wave has not yet ended in the country; around 40,000 new daily cases are still being reported. Of these, around 10,000 are from Maharashtra, another 10,000 are from Kerala and the remaining 20,000 are from the North East, West Bengal, Odisha, Telangana, Andhra Pradesh and Tamil Nadu (at the time of the meeting).
- The three strains that emerged from genomic sequencing and which predominantly led the second wave are 617.1 (Kappa variant), 617.2 (Delta variant) and 617.3. The Alpha variant was still present in Delhi, Punjab and Haryana.
- A new variant, Delta plus, has become a cause for concern and has been red flagged. Delta plus or AY.1 has a new K417N mutation, similar to the Beta variant (first found in South Africa). This mutation was mainly seen in UK and Nepal prior to being detected in India.
- The first Delta plus was in the UK, where it was found that it was more transmissible, had a tighter binding to the ACE2 receptor and escaped the monoclonal antibodies; it also caused immune escape.
- Genomic sequencing labs in India documented around 41 cases of Delta plus (at the time of the meeting). Genomic sequencing is still ongoing.

There were two deaths: one was not vaccinated, the second was >80 years with comorbidities.

- These genomic samples were taken at the end of May, so the patients have survived for at least 4 weeks with mild-to-moderate disease; so far this variant does not appear to be sinister in nature.
- No connection has been found between AY.1 strain found in Nepal and AY.1 strain found in Ratnagiri in Maharashtra (Mango belt).
- The features of Delta variant are cluster spreading, faster spreading and faster recovery with low case mortality.
- Delta is a cause for concern as it is rapidly transmissible and cluster spreading. It may be faster recovering but virulence is not known. Delta has immune escape mainly to Covishield.
- Delta is now the predominant strain in the country; in Mumbai, Kappa strain is still present and in Punjab, the Alpha strain is still found.
- Early observation shows that Delta plus is also fast spreading but probably not as fast as the Delta variant.
- Three challenges when unlocking: Keep the test positivity rate by reverse transcription polymerase chain reaction (RT-PCR) <5%, try to saturate 70% of population with vaccination and have zero tolerance for nonadherence to COVID-appropriate behavior and follow COVID-appropriate protocol.
- The second wave is not abating in some parts of the country because of the rapid unlocking.
- Earlier we vaccinate, lesser will be the intensity of the next wave, if and when it comes.
- The factors which may cause an outbreak are immune escape and lack of adherence to COVID-appropriate behavior.
- To prevent this, make sure to double mask whenever in public, follow COVID-appropriate protocols, take both vaccine doses at the earliest, aggressive vaccination and have better ventilated environments. Avoid crowded and poorly ventilated spaces.
- The third wave may come faster and the second wave may merge into the third wave, which is expected somewhere between September and November.
- It appears that the disease is becoming endemic in Maharashtra and Kerala; hence, testing, tracking and treating strategy needs to be ramped up regularly.
- Five states are contributing to 36% of cases in the country, with Kerala contributing the maximum.
- Any modeling will take into consideration factors like how we unlock, how much is our susceptible pool (though serosurveys show 60-70% seroconversion; we do not know how long these antibodies will last for), how much of the population is following COVID-appropriate behavior, how much percentage of population is immunized and the efficacy of the vaccines. How we manage the second wave will be the most important.
- COVID-appropriate behavior and immunization coverage will ultimately decide about the susceptible pool of the population.
- Efforts are ongoing to educate about the management of children. IAP is closely involved in this.
- Probably the third wave will not be as ferocious as the second wave, but we have to closely monitor the genetic variations. Genomic sequencing therefore becomes very important.
- There is a need to be more transparent in sharing data between organizations.
- Some punitive measure for nonadherence to COVID-appropriate behavior is required.
- Issues such as the need for a booster dose and mixing of two vaccines are being discussed at the National Technical Advisory Group meetings.
- Vaccination can prevent development of new variants.
- The gold standard to detect neutralizing antibodies is the plaque reduction neutralization test (PRNT). It is done in special (BSL3) labs. N serology test is an indirect test; it is expensive and cannot be done as a routine. A test for T-cell response is not yet available in routine practice.
- Hybrid immunity is immunity due to natural infection, immunity due to vaccine and a combination of both.
- Vaccines are protective; antibody tests may be misleading; antibody tests may not be sufficient; continue to wear the mask.
- How we unlock and how strictly we follow COVID-appropriate behavior will decide about the next wave.

**Participants:** Dr AK Agarwal, Dr Shashank Joshi, Dr Suneela Garg, Dr Anita Chakravarti, Dr DR Rai, Dr Alex Thomas, Mrs Upasana Arora, Dr Yang Ing Woei, Mr Saurabh Aggarwal, Dr S Sharma

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# 72nd Annual Cardiology Conference

## RIVAROXABAN: SIMPLIFYING THERAPY, SYMBOLIZING COMPLIANCE

**Dr Saket Goyal, Kota**

In clinical trials, non-vitamin K antagonist oral anticoagulants (NOACs) have demonstrated favorable efficacy and safety profiles vs. vitamin K antagonists (VKAs). They are all noninferior to VKAs with regards to ischemic stroke and systemic embolization, but superior with regard to preventing systemic bleeding, especially intracranial bleed. They have the advantage of once- or twice-daily dosing and also do not require INR monitoring of dosing unlike VKA. But, which NOACs should we choose, as they differ slightly from each other in their pharmacological properties.

Rivaroxaban and edoxaban are given once-daily; apixaban and dabigatran are given twice-daily. Rivaroxaban needs to be given with food to facilitate gut absorption. Renal clearance for dabigatran is 80%, adaxoban 50%, rivaroxaban 33% and apixaban 25%. Dose reduction for NOACs is needed in renal dysfunction.

Dabigatran is not recommended with creatinine clearance (CrCl) <30, and apixaban <15 mL. Although rivaroxaban and edoxaban are not recommended below CrCl of 15 mL, caution should be exercised if CrCl <30 mL. Patients with AF have other comorbidities: hypertension (70-80%), heart failure (40%), coronary disease (30%), diabetes (25%); hence, they are already taking many pills. If they want to reduce their pill burden, rivaroxaban and edoxaban, taken once-daily, would be the preferred choices. Dabigatran is a prodrug, highly acidic in nature and tends to get activated in gastrointestinal (GI) wall. It produces more GI irritation and may enhance GI bleed in those patients with tendency to GI bleed. So, it may be given with food to minimize the gastric irritation. Dabigatran may not be right choice in these subset of patients.

In available choices in India, rivaroxaban is a better choice as compared to other NOACs and it has a broader therapeutic window. It's approved in six Food and Drug Administration (FDA) indications, like reduction of risk of stroke and systemic embolism in nonvalvular atrial fibrillation (AF), treatment of deep-vein thrombosis (DVT) and pulmonary embolism (PE), reduction in the risk of recurrence of DVT and PE, and prophylaxis of DVT following hip or knee replacement surgery, and recently, based on results of the COMPASS trial, the US FDA approved a new indication for rivaroxaban, in conjunction with aspirin, for reducing risk of major adverse cardiac event (MACE) (Cardiovascular death [CV] death, myocardial infarction and stroke) in patients with coronary artery disease (CAD) and peripheral artery disease (PAD).

## WHICH IS MY PREFERRED P2Y12 INHIBITOR IN ACS? WHY PREFER TICAGRELOR OVER PRASUGREL

**Dr Arun Gopi, Kozhikode**

Ticagrelor is the only P2Y12 inhibitor to demonstrate a significant reduction in CV death/all-cause mortality, whereas no mortality benefit was seen in TRITON TIMI. Benefits of ticagrelor in PLATO were seen across the entire spectrum of acute coronary syndrome (ACS) unlike prasugrel with no significant difference in major bleeding, fatal bleeding, intracerebral hemorrhage (ICH) or coronary artery bypass grafting (CABG)-related major bleeding compared to clopidogrel.

Benefits of ticagrelor – faster onset and offset of action: Ticagrelor is the only P2Y12 inhibitor approved for use beyond 1 year with aspirin in select patients with high ischemic risk (60 mg).

Limitations of prasugrel – it is recommended only in patients whose coronary anatomy is known. Even in patients undergoing percutaneous coronary intervention (PCI), there was a significant increase in primary safety endpoint (Non-CABG-related TIMI major bleeding), increase in fatal bleeding and CABG-related major bleeding.

## ANTICOAGULANTS IN PATIENTS WITHOUT AF BUT WITH HIGH CHADS SCORE

**Dr Lawrence Jesuraj M, Coimbatore**

The $CHA_2DS_2$-VASc score is a simple and reliable tool for CV risk stratification and select patients who will benefit the most from intensive treatment aiming to curb the progression and evolution of the atherothrombotic disease. Present evidence vis-à-vis the significant increase in bleeding episodes precludes a recommendation for NAO in patients with elevated $CHA_2DS_2$-VASc score and no documented AF. The $CHA_2DS_2$-VASc or $CHADS_2$ scores can be used in patients with chronic CAD and/or PAD to identify

patients at the highest risk of MACE. Therefore, likely to achieve the greatest benefit of dual pathway inhibition with the combination of rivaroxaban and aspirin compared with aspirin alone. In the clinical trial, the effects of combination therapy with rivaroxaban and aspirin on MACE, bleeding and net clinical benefit were consistent across $CHA_2DS_2$-VASc and $CHADS_2$ score categories, with the greatest benefit in those with the highest scores.

## DEMYSTIFYING MITRACLIP

**Dr Sengottuvelu G, Chennai**

MitraClip is a breakthrough innovative catheter-based technology that uses a small clip attached to the mitral valve to treat degenerative mitral regurgitation. It is a minimally invasive treatment option for patients with mitral regurgitation who are not good candidates for surgery. The advantage of this minimally invasive procedure compared to open-heart surgery is that it enables faster recovery leading to a better quality of life. It is approved for use in both structural and functional MR. Our early experience has shown good results in high-risk patients. MitraClip is currently approved in India by DCGI and done in a few experienced centers in the country.

## THROMBOLYSIS IN STEMI: HOW TO DO IT RIGHT?

**Dr HK Chopra, New Delhi**

- Challenges of ST-segment elevation myocardial infarction (STEMI) care in India and the real world are enormous, including lack of awareness, poor transport, lack of EMS protocol, poor ambulance service, Primary PCI feasible only 12-15%, delay in time from the first medical contact (FMC) after chest discomfort to hospital time, door-to-needle time and door-to-balloon time.
- There is a tremendous need to create Smart Heart App all over India to enhance the awareness on S/S of STEMI, emergency heart ambulance services in the vicinity phone no., instantaneous ECG, mobile ambulance, transfer of ECG by telemedicine or WhatsApp to the heart station or the cardiologists concerned and then instantaneous use of thrombolytic therapy (TLT) and/or PCI depending on the time of reaching the PCI capable centers.
- Rapid diagnosis, early reperfusion, irrespective of TLT or primary PCI are pillars of success in STEMI as "Time is Muscle". Pre-hospital thrombolysis with tenecteplase is the best timely reperfusion therapy. The success rate of tenecteplase and reteplase for thrombolysis in STEMI is 96% in first 3 hours.
- Early tenecteplase in STEMI is strongly recommended as protocol strategy in myocardial salvage window of <3 hours, followed by PCI within 24 hours. (As primary PCI is feasible in only few centers and not practical <90 min.) Minimize the time from chest discomfort to ECG to less than 30 minutes, ECG to drug intervention to less than 60 minutes and drug intervention to PCI to less than 90 minutes. Pharmacoinvasive approach is the only solution for India.
- Consensus on STEMI Management in COVID Era in 2020: PI approach preferred effective solution to reduce STEMI inflicted morbidity and mortality. However, primary PCI is promising gold standard. Selective primary PCI may be recommended in large anterior wall myocardial infarction, cardiogenic shock, hemodynamically unstable patient with malignant arrhythmias, contraindications to TLT.

## CHARACTERISTICS AND TREATMENT PRACTICES AMONG PATIENTS WITH JUVENILE RHEUMATIC HEART DISEASE ENROLLED IN A TERTIARY CARE HOSPITAL-BASED REGISTRY

**Dr Kunal Mahajan, Shimla**

**HP-RF/RHD Registry Study** is the one of the largest prospective single-center studies of mortality and morbidity in rheumatic heart disease (RHD) patients from India. Clinical RHD is associated with high mortality and morbidity in **young patients at the primes of their lives. Strategies** to make proven percutaneous and surgical valve interventions more accessible are needed to improve the outcome of patients with RHD living in low- and middle-income countries. Patients with RHD seeking tertiary care present with **advanced disease** and the markers of severity are the greatest determinants of poor outcome.

## ATRIAL FIBRILLATION BURDEN – DOES IT REALLY MATTER?

**Dr Natarajan KU, Kochi**

With improvements in wearable and implantable monitoring, improved detection of subclinical AF is a reality. In patients without overt clinical AF, the threshold of AF burden that warrants anticoagulation is not clear. Prolonged durations in subclinical AF (high AF burden), even with borderline $CHA_2DS_2$-VASc scores, appear to be an independent stroke risk marker. Long-term follow-up of larger population sets will shed

more light and help improve future guidelines. There is emerging data to believe that AF burden in subclinical AF does matter. Arriving at a threshold of subclinical AF burden that merits anticoagulation is a work in progress.

## OPTIMIZATION OF PERCUTANEOUS CORONARY INTERVENTION USING OPTICAL COHERENCE TOMOGRAPHY

**Dr Deebanshu Gupta, Ahmedabad**

Optical coherence tomography (OCT) changes physicians' decisions about PCI strategy as a change in stent length, stent diameter and landing zone. Compared to coronary angiography (CAG), OCT better identifies atherosclerotic lesion morphology and helps select proper stent size, stent length and localize landing zone properly. Angiographic co-registration (ACR) further co-registers angiographic and OCT images together and further increases precision. Thus, post-PCI OCT helps to optimize PCI results.

## OPTIMAL INITIATION OF GDMT FOR HFREF PATIENTS: UNMET NEEDS AND HOW DO WE ADDRESS THEM?

**Dr Gregg C Fonarow, USA**

- Despite evidence-based, guideline-recommended, life-prolonging therapies being available, many eligible patients are not being optimally treated.
- The four pillars of comprehensive disease modifying medical therapy (quadruple therapy) for heart failure with reduced ejection fraction (HFrEF) are: angiotensin receptor neprilysin inhibitor (sacubitril/valsartan), β-blockers, mineralocorticoid receptor antagonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors.
- First-line use of sacubitril/valsartan, rather than starting with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB), then switching, results in improvement in health status, and greater reductions in CV death/HF hospitalizations.
- A strategy of in-hospital initiation of all 4 therapies at the low guideline-recommended starting doses in patients hospitalized with HFrEF can improve treatment rates, adherence, overcome inertia and lead to large clinical benefits within 30 days.

## INTRACORONARY THROMBOLYSIS – WHEN, WHAT AND HOW?

**Dr Jayagopal PB, Palakkad**

Intracoronary thrombolysis is indicated in: Patients with huge thrombus burden who present early. Young patients with thrombus during primary angioplasty in myocardial infarction (PAMI) and plaque erosion. Patients with ectatic coronaries, large vessels and failed thrombectomy. Patients with a large vessel with failed thrombectomy at the ostium of left anterior descending artery (LAD), either prolapsing into left main coronary artery/left circumflex (LMCA/LCx) and at danger of retrograde migration. Patients with stent thrombosis as an adjunctive during PCI. As an adjunctive in selected cases of PAMI. Intracoronary tenecteplase (TNK), alteplase and streptokinase are all effective. Can be administered through export, clearway and even a guiding catheter. TNK is preferred because of 5-second bolus, ease of administration, efficacy and data.

## CAN YOU PREDICT STROKE IN YOUR ACS PATIENTS?

**Prof Yash Paul Sharma, Chandigarh**

ACS is associated with increased stroke risk, especially in the first 4 weeks. The occurrence of stroke in ACS increases the morbidity and mortality associated with ACS. The key risk factors are older age, atrial fibrillation, female sex, diabetes and heart failure. The pathophysiology is multifactorial, involving LV dysfunction and thrombus, atrial dysfunction, systemic inflammation, accelerated atherosclerosis, carotid plaque instability, etc. STEMI and NSTEMI are associated with heightened risk compared to unstable angina. Cardiogenic shock increases the risk of stroke in ACS; Hemorrhagic stroke during ACS is related to various drugs like antiplatelet, anticoagulants, fibrinolytic, etc. Risk scores that can be used easily to predict risk irrespective of atrial fibrillation are $CHADS_2$, $CHA_2DS_2VAS$, GRACE scores, etc. Anticoagulation and antiplatelets can reduce the risk of stroke; however, their use increases the risk of bleeding complications; hence, prescriptions to each patient need to be personalized based on individual risk, and close monitoring needs to be done.

■■■■

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# News and Views

## COVID-19 Hospitalizations 3-fold Higher in US States with Less Than Half of Residents Vaccinated

Average coronavirus disease 2019 (COVID-19) hospitalization rates seem to be around 3-fold higher in states where less than half of the residents are fully vaccinated compared to the average in the states that have vaccinated over half of their residents, revealed a CNN analysis.

Additionally, the COVID-19 case and fatality rates have been over twice as high in states that have vaccinated less than half of their residents. As per data obtained from the US Department of Health and Human Services, average current hospitalizations among states with less than half of residents vaccinated was 14.4 per 1,00,000 residents, while that in states that have vaccinated more than half of their residents stood at 4.9 per 1,00,000 residents. Daily COVID-19 case rate as per Johns Hopkins University data, was 23.7 per 1,00,000 residents in states that have vaccinated less than half of residents compared to 9.3 per 1,00,000 residents among states with more than half of residents vaccinated… (*CNN, July 29, 2021*)

## Some Gut Bacteria Linked to Lower Diabetes Risk

More diverse gut bacteria and higher abundance of 12 butyrate-producing bacteria have been found to be tied to less insulin resistance and less type 2 diabetes in a population-based observational study.

The study published in *JAMA Network Open* also identified several bacteria that ferment dietary fiber in the gut to produce butyrate, which may contribute to the protection against type 2 diabetes.

The study confirmed that low diversity in gut microbiome is linked with a heightened risk of obesity and type 2 diabetes. A higher abundance of each of seven types of butyrate-producing bacteria, namely *Christensenellaceae, Christensenellaceae R7* group, *Marvinbryantia, Ruminococcaceae UCG005, Ruminococcaceae UCG008, Ruminococcaceae UCG010* and *Ruminococcaceae NK4A214* group, was shown to be tied to lower insulin resistance, after adjusting for confounders like diet and drugs. Additionally, a higher abundance of each of five types of butyrate-producing bacteria, including *Clostridiaceae 1, Peptostreptococcaceae, C sensustricto 1, Intestinibacter* and *Romboutsia*, was linked with less type 2 diabetes… (*Medscape*)

## US FDA Agrees to Extend Shelf-life of J&J COVID-19 Vaccine, Says Company

Johnson & Johnson (J&J) has stated that the US Food and Drug Administration (FDA) extended the shelf-life of its COVID-19 vaccine from 4½ to 6 months. The decision came after the data obtained from ongoing studies indicated that the vaccine is stable at 6 months while refrigerated at 2-8°C or 36-46°F. The agency stated, in a letter to the company, that it had reviewed the data provided by J&J, and on the basis of the information provided, it agrees with the extension of the vaccine's shelf-life. The extension also applies to the vaccine batches that might have expired before the letter was issued, under the condition that they were stored at the suggested temperature, said the agency… (*Reuters*)

## Pfizer Third Dose Strongly Boosts Protection Against Delta Variant, Shows Data Released by Company

A third dose of the Pfizer/BioNTech vaccine against COVID-19 has the potential to strongly improve protection against the Delta variant, more than the protection provided by the standard two dose regimen, suggest latest data released by Pfizer.

The data indicate that the levels of antibodies that protect against the Delta variant increase by about 5 times in individuals aged 18 to 55 years who receive a third dose of the vaccine. Additionally, among people aged 65 to 85 years, antibody levels that protect against Delta variant rise by 11-fold more than that after the second vaccine dose.

The data have not yet been peer-reviewed and it is unclear if the improved antibody levels actually correlate to better protection… (*CNN*)

## Shorter Antibiotic Regimen Better in Men with UTI

Seven days of antibiotic treatment among afebrile men with suspected urinary tract infections (UTI) was found to be as effective as a 14-day regimen in a randomized, double-blind trial published in *JAMA*.

Among more than 250 men with suspected symptomatic UTI included in the as-treated analysis, 93.1% of the patients in the 7-day group had resolution of symptoms by 14 days after completing the antibiotic treatment, compared to 90.2% of the patients in the

14-day group. There was a difference of 2.9%, meeting the noninferiority criterion of 10%. A secondary as-randomized analysis conducted among more than 270 men revealed that symptom resolution was noted in 91.9% of the patients in the 7-day regimen group vs. 90.4% in the 14-day regimen group, with a difference of 1.5%... (*Medpage Today*)

### Pfizer, AstraZeneca Vaccine Antibody Levels Start Decreasing After 6 Weeks

The antibody levels start decreasing 6 weeks after complete inoculation with Pfizer and AstraZeneca COVID-19 vaccines, and can decrease by over 50% over 10 weeks, suggests a study published in *The Lancet*.

Investigators from University College London (UCL), UK noted that if the antibody levels continue to decline at this rate, the protective effects of the vaccines may also start to dwindle, especially against the new variants. The UCL Virus Watch study noted that antibody levels were considerably higher after two doses of the Pfizer vaccine compared to the AstraZeneca vaccine. Additionally, the levels of antibodies were higher in vaccinated individuals compared to those who had a previous severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection… (*ET Healthworld – PTI*)

### US Urged Fully Vaccinated to Wear Masks Indoors in Some Places

People of America who have been fully vaccinated against COVID-19 must start wearing masks again in indoor public places in areas where the infection is showing a rapid spread, stated US health authorities.

The US Centers for Disease Control and Prevention (CDC) also recommended that all students, teachers and staff at schools for kindergarten up to 12th grade should wear masks, irrespective of their vaccination status. COVID-19 cases have been on the rise in the country owing to the highly transmissible Delta variant, which is accountable for over 80% of the cases in the US. President Joe Biden stated that ramping up vaccination and wearing masks would help the country evade lockdowns and closure of schools… (*Reuters*)

### Diabetes Duration Tied to Increasing Heart Failure Risk

Longer the duration of diabetes, greater the risk for developing heart failure, stated an analysis of around 10,000 US adults followed for about 23 years. A multivariable analysis revealed that there was a steady and significant escalation in the rate of incident heart failure with increase in diabetes duration. Among 168 study subjects, constituting 2% of the total study group, who had diabetes for at least 15 years, the incidence of heart failure was shown to be around three times higher than among 4,802 individuals (49%) who never had diabetes or prediabetes, reported researchers in *JACC Heart Failure*.

Individuals with prediabetes, who constituted 32% of the study population, demonstrated a significant yet modest increase in the rate of incident heart failure - 16% higher than control group that never developed diabetes. People with diabetes for duration of 0-4.9 years, 5.0-9.9 years or 10-14.9 years, demonstrated a steady rise in relative incident heart failure rates of 29%, 97% and 210%, respectively, compared to controls… (*Medscape*)

### Patients with Hypertension Most Likely to Develop Post-COVID Complications

A recent analysis of medical records of more than 1,800 patients admitted to hospitals run by the Mayo Clinic in the United States has shown that patients with hypertension have the greatest odds of developing complications after COVID-19 infection.

Another study involving 18,000 COVID-19 patients conducted by Max Healthcare has also found a role of hypertension in complications. The study conducted in the US revealed that hypertension was tied to 10 complications, including acute respiratory distress syndrome, improper beating of the heart and anemia. In the analysis conducted with the help of an artificial intelligence (AI) platform developed by nference Labs, the other most significant factors that predicted complication in early COVID-19 infection included cardiovascular chronic disease, such as heart failure, coronary artery disease, cardiomyopathy and chronic kidney disease… (*ET Healthworld – TNN*)

### COVID-19 has Considerable Impact on Intelligence in Recovered Patients, Says Study

A severe COVID-19 infection that involves hospital admission and ventilator support can have a considerable impact on a recovered patient's intelligence as part of long-COVID symptoms, reported a UK study. Investigators assessed 81,337 participants from January through December 2020 as part of the Great British Intelligence Test. The questionnaire items included self-report of suspected and confirmed COVID-19 infection and respiratory symptoms. The results agree with the reports of long-COVID, where brain fog, difficulty in concentrating and difficulty finding the correct words

are common, stated the study. Recovered individuals had significant cognitive deficits compared to controls after controlling for age, gender, education level, racial-ethnic group, pre-existing medical disorders, tiredness, depression and anxiety, and income.

The findings are published in *The Lancet - EclinicalMedicine*… (*NDTV – PTI*)

## Safe to Take Second mRNA Vaccine Dose After Allergic Reaction to First

Individuals who had an allergic reaction to a first dose of the Pfizer/BioNTech or Moderna mRNA COVID-19 vaccine tolerated a second dose safely, reported a retrospective, multicenter study.

Overall, 17% of the 189 individuals with initial allergic reactions had anaphylaxis. Other reactions to the first dose included erythema, dizziness, tingling, throat tightness, hives and wheezing or shortness of breath. Among the 189 people with initial allergic reactions, researchers assessed 159 (84%) who took the second dose. All the individuals, including 19 people with first-dose anaphylaxis, tolerated the second dose. Thirty-two people who took a second dose developed immediate and potentially allergic symptoms. About 20% of the individuals had symptoms with the second dose, but they were manageable and not anaphylactic, noted researchers. The findings are published in *JAMA Internal Medicine*… (*Medscape*)

## A New Treatment Option for Children with Type 2 Diabetes

Exenatide extended-release has now been accorded US FDA approval for use in children aged ≥10 years with type 2 diabetes in addition to diet and exercise to improve glycemic control. This makes it the second glucagon-like peptide-1 receptor agonist approved for use in pediatric type 2 diabetes, after liraglutide, which was approved in 2019.

This injectable formulation is not recommended as a first treatment option for patients whose disease is not adequately controlled through diet and exercise. It is not to be used for children with type 1 diabetes.

Exenatide extended-release has earlier been approved to treat adults with type 2 diabetes.

A boxed warning has been added to prescribing information about the increased risk of thyroid C-cell tumors. The FDA has cautioned that patients with family history of medullary thyroid carcinoma, patients with multiple endocrine neoplasia syndrome type 2 or a history of drug-induced immune mediated thrombocytopenia or those with previous hypersensitivity to exenatide or any of its components should avoid the therapy.

While the overall side effects reported (injection site reactions, headaches and gastrointestinal discomfort) were similar to those seen in adults, warnings about hypoglycemia when used with insulin or insulin secretagogues, acute kidney injury, gastrointestinal disease, immunogenicity, allergic reactions (such as anaphylaxis and angioedema) and drug-induced immune-mediated thrombocytopenia have been included. Type 2 diabetes mellitus was earlier perceived as adult-onset diabetes. But, its prevalence in children and adolescents has increased in recent years. Therefore, it is important to screen children at high risk such as positive family history of type 2 diabetes mellitus and/or clinical features of insulin resistance (such as hypertension, dyslipidemia, polycystic ovarian syndrome or acanthosis nigricans). Type 2 diabetes mellitus is emerging as a new clinical problem within pediatric practice. Recent reports indicate an increasing prevalence of type 2 diabetes mellitus in children and adolescents around the world in all ethnicities, even if the prevalence of obesity is not rising. Therefore, a screening seems meaningful especially in high risk groups such as children and adolescents with obesity, relatives with type 2 diabetes mellitus, and clinical features of insulin resistance (hypertension, dyslipidemia, polycystic ovarian syndrome or acanthosis nigricans).

The American Diabetes Association (ADA) Standards of Medical Care in Diabetes—2021 recommends risk-based screening for prediabetes and/type 2 diabetes after the onset of puberty or after 10 years of age, whichever occurs earlier, in children and adolescents with overweight (body mass index [BMI] ≥85th percentile) or obesity (BMI ≥95th percentile) and who have one or more risk factor for diabetes.

Metformin is the only oral antidiabetic drug approved for use in children with type 2 diabetes, while the approved injectables include insulin, liraglutide and now exenatide.

(*Source: FDA OKs extended-release exenatide for children with type 2 diabetes - Medscape - Jul 23, 2021; https://content.govdelivery.com/accounts/USFDA/bulletins/2e98d66; ADA Standards of Medical Care 2021*)

## France Approves Bill to Handle Fourth Wave of COVID-19

French lawmakers have approved a bill recently which will mandate COVID-19 vaccinations for healthcare

workers and require a health pass in several social venues as the country fights the fourth wave of COVID infections.

People visiting museums, cinemas or swimming pools are already denied access if they fail to show a pass that confirms that they have been vaccinated against COVID-19 or have had a recent negative test. The pass has been needed for large-scale festivals or for clubbing. From August, the pass will be required to access restaurants and bars and for long-distance travel by train and plane as well. These measures will end on November 15. A final approval from the constitutional court is needed for the law to come into effect… (*Reuters*)

### Low-income Countries Acquired Only 0.27% of COVID Vaccine Doses Administered Thus Far

Low-income countries have received a mere 0.27% of the COVID-19 vaccine doses administered globally thus far, while high-income countries and upper-middle-income countries have received over 80% of the doses.

Among the 27 low-income countries, 23 are in Africa. Owing to the wide inequality in vaccine distribution, out of the 52 African countries, 38 have been able to administer at least one dose of a COVID vaccine to less than 5% of the population. Several countries in Africa have also recorded a recent rise in COVID-19 infections, mostly accountable to the highly contagious Delta variant. Around 27% of the global population has been administered at least one vaccine dose, while in Africa, only 3.13% of the population has received at least one dose… (*The Hindu*)

### Flu Activity During the Pandemic: CDC Report

The circulation of influenza and several other respiratory viruses diminished during the pandemic in 2020; however, it was found to increase during the spring of 2021, noted researchers. Flu activity was shown to reduce in March 2020, and continued to remain low until May 2021, as <0.4% of respiratory samples tested positive for influenza per week of the flu season. The patterns were similar for several other respiratory pathogens, including respiratory syncytial virus, parainfluenza viruses, and common human coronaviruses, reported researchers in *Morbidity and Mortality Weekly Report*. Human metapneumovirus and respiratory adenovirus were found to be circulating at low levels from 2020 to 2021. Rhinovirus and enterovirus were low till May 2020 before they rose to near pre-pandemic levels. Experts had warned of a COVID and flu 'twindemic' in the fall of 2020. However, from October 2020 to May 2021, circulating influenza had the lowest activity since 1997… (*Medpage Today*)

### EMA Approves Moderna Vaccine for 12 to 17 Years Age Group

The European medicines regulator has granted approval for the use of Moderna COVID-19 vaccine in children aged 12 to 17 years. This is the second vaccine that has been approved for use in adolescents in Europe.

The European Medicines Agency (EMA) announced that the use of the Moderna vaccine, named Spikevax, in children aged between 12 and 17 years, will be the same as in individuals 18 years of age and above. Two shots will be given at an interval of 4 weeks. The Pfizer/BioNTech vaccine was approved for youngsters in Europe in May.

The agency stated that the Moderna vaccine was evaluated in 3,732 children aged 12 to 17 years. The vaccine led to a comparable antibody response in 12- to 17-year-old age group as that noted in young adults, 18 to 25 years of age… (*NDTV – AFP*)

### Countries Promote Mix-and-Match COVID Vaccines

Despite preliminary data, certain countries are going ahead with mixing and matching mRNA and adenoviral vector COVID-19 vaccines, usually guided by supply constraints.

Germany has made an official recommendation to mix-and-match vaccines, encouraging people to get a dose of an mRNA vaccine after their AstraZeneca jab. Chancellor Angela Merkel had followed her initial AstraZeneca shot with a Moderna jab in June. Canada and Thailand have also started administering COVID-19 shots on a heterologous schedule. While the EMA and the European Centre for Disease Prevention and Control (ECDC) did not issue any specific recommendation, but they promoted mix-and-match approach in a press release which stated that good scientific grounds exist to expect that this approach would be safe and effective when used in vaccination against COVID-19… (*Medpage Today, July 22, 2021*)

### J&J COVID-19 Vaccine Recipients may Need a Booster

Individuals who have been administered the single-dose J&J COVID-19 vaccine may require a booster jab to tackle some of the concerning coronavirus variants, suggests a new study.

A significant proportion of blood samples taken from people who had received the J&J vaccine showed low

Indian Journal of Clinical Practice, Vol. 32, No. 3, August 2021

# The Spiritual Heart: Your Heart and My Heart are One

"Tat tvam asi" is a mahavakya in the ancient Sanskrit texts of the Upanishads. It translates as "I am that" and means "You and I are same" or "**your heart and my heart are one**".

Whenever we point to our own self, we put our hand on our heart; we also put our hand on our heart when we say "I love you from the bottom of my heart".

Does the consciousness reside in the celiac plexus (Manipura chakra) or thymus plexus (Anahata chakra)? We do not know. Manipura chakra is associated with fire and the power of transformation. The Anahata chakra manifests unconditional love, forgiveness and patience.

Our ancient scriptures and the Bible say that the heart is the size of a thumb and it is in the heart that our consciousness (soul) resides.

1. **In Svetasvatara Upanishad (5.8, 5.9).** "Soul is the size of a thumb, bright as the sun, when coupled with conception and ego. But with only the qualities of understanding and soul, it appears the size of the point of an awl. This life is the hundredth part of the point of a hair divided a hundred times, and yet in it is infinity". Here the sruti is speaking metaphorically, because actually the soul is atomic in size. Therefore in the next verse (Svet. U. 5.9) the soul is compared to a fraction of the tip of a hair. These comparisons are meant to indicate that the individual soul is atomic rather than all-pervasive.
2. According to **Vedanta Sutra**, the idea that God resides in the physical heart the size of the thumb is for the sake of conceptualization during meditation, and is thus a metaphorical description. The size of the thumb refers to the size of the human heart. God is in reality all pervading and atomic at the same time.
3. **Atharva Veda:** The soul is a particle of God.
4. **Jain metaphysicists** refer to it as of varying sizes, small in a child, big in adults and old people and very big in elephants.
5. **Nemi Chandra in Dravyasangrah-2:** Soul is characterized by knowledge and vision, has the same extent as its own gross body.
6. **Katha Upanishad (1.2.20):** Spirit, the size of a thumb "angush matra", is the inner soul, always seated in the heart of creatures.

**Katha Upanishad Part Fourth XII.** The Purusha (Self), of the size of a thumb, resides in the middle of the body as the lord of the past and the future, (he who knows Him) fears no more. This verily is That. The seat of the Purusha is said to be the heart, hence it "resides in the middle of the body." Although it is limitless and all–pervading, yet in relation to its abiding–place. It is represented as limited in extension, "the size of a thumb". This refers really to the heart, which in shape may be likened to a thumb. Light is everywhere, yet we see it focused in a lamp and believe it to be there only; similarly, although the life-current flows everywhere in the body, the heart is regarded as peculiarly its seat.

1. **Garuda Puran:** Ultimately, the soul, which is not more than the size of a thumb, reluctantly comes out from the body as the attachment with the world exists even after his.
2. **Gaudiyaacharya Sri Baladeva Vidyabhusana** in his Govinda Bhasya commentary on the Vedanta Sutra (1.2.7, 1.3.24-25.): During meditation Paramatma does appear to the yogi or devotee as a localized form in his heart, but in general Paramatma is all-pervasive and all-knowing.
3. **Unknown:** According to some Vedic scholars the soul enters the human form like 4-8 weeks after conception, like when the fetus is the size of a thumb.
4. **Bhagavad Gita 15.15:** "I (soul) am seated in everyone's heart, and from Me come remembrance, knowledge and forgetfulness. By all the Vedas, I am to known. Indeed, I am the compiler of Vedanta, and I am the knower of the Vedas."
5. **Vedanta Sutra II, 6, 17:** The person of the size of a thumb, the inner Self, is always settled in the heart of men. Let a man draw that Self forth from his body with steadiness, as one draws the pith from a reed. Let him know that Self as the Bright, as the Immortal.
6. **Swami Muktananda, Play of Consciousness, p. 85:** "The whole body is like a lotus which has four petals of four kinds, colors and sizes....The first is the gross body, its color is red. The second petal is the subtle body, in which we sleep and experience dreams. It is the size of a thumb, and its color is white. The third petal is the causal body. It is the size of the tip of third finger, and its color is black. The fourth petal is the supracausal body, which is as small as a sesame seed. Its color is blue.... It is very brilliant; it is the foundation of sadhana; it is the highest inner vision."
7. **Matthew 5; 8:** Soul resided in the heart: "Blessed are the pure in heart, for they shall see God."

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# The Seed of Honesty

A successful business man was growing old and knew it was time to choose a successor to take over the business. Instead of choosing one of his Directors or his children, he decided to do something different. He called all the young executives in his company together.

He said, "It is time for me to step down and choose the next CEO. I have decided to choose one of you."

The young executives were shocked, but the boss continued. "I am going to give each one of you a SEED today – one very special SEED. I want you to plant the seed, water it, and come back here 1 year from today with what you have grown from the seed I have given you. I will then judge the plants that you bring, and the one I choose will be the next CEO."

One man, named Jim, was there that day and he, like the others, received a seed. He went home and excitedly, told his wife the story. She helped him get a pot, soil and compost and he planted the seed. Every day, he would water it and watch to see if it had grown. After about 3 weeks, some of the other executives began to talk about their seeds and the plants that were beginning to grow.

Jim kept checking his seed, but nothing ever grew. Three weeks, 4 weeks, 5 weeks went by, still nothing. By now, others were talking about their plants, but Jim didn't have a plant and he felt like a failure.

Six months went by — still nothing in Jim's pot. He just knew he had killed his seed. Everyone else had trees and tall plants, but he had nothing. Jim didn't say anything to his colleagues, however… He just kept watering and fertilizing the soil – He so wanted the seed to grow.

A year finally went by and all the young executives of the company brought their plants to the CEO for inspection. Jim told his wife that he wasn't going to take an empty pot. But she asked him to be honest about what happened. Jim felt sick to his stomach, it was going to be the most embarrassing moment of his life, but he knew his wife was right.

He took his empty pot to the board room. When Jim arrived, he was amazed at the variety of plants grown by the other executives. They were beautiful — in all shapes and sizes. Jim put his empty pot on the floor and many of his colleagues laughed, a few felt sorry for him! When the CEO arrived, he surveyed the room and greeted his young executives.

Jim just tried to hide in the back. "My, what great plants, trees and flowers you have grown," said the CEO. "Today one of you will be appointed the next CEO!" All of a sudden, the CEO spotted Jim at the back of the room with his empty pot. He ordered the Financial Director to bring him to the front.

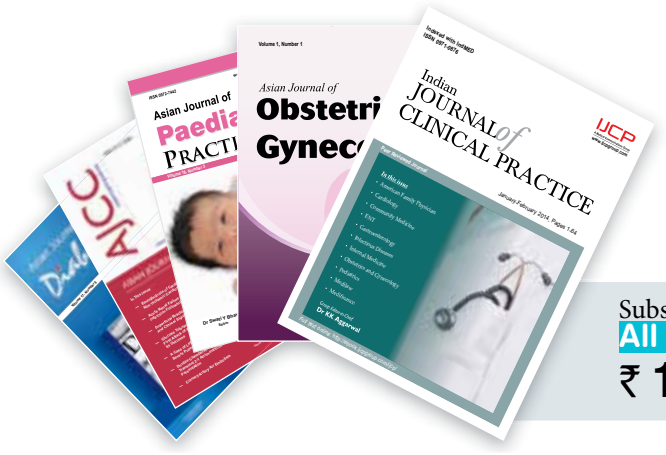
Jim was terrified. He thought, "The CEO knows I'm a failure! May be he will have me fired!" When Jim got to the front, the CEO asked him what had happened to his seed – Jim told him the story.

The CEO asked everyone to sit down except Jim. He looked at Jim, and then announced to the young executives, "Behold your next Chief Executive Officer! His name is Jim!" Jim couldn't believe it. Jim couldn't even grow his seed. "How could he be the new CEO?" the others said.

Then the CEO said, "One year ago today, I gave everyone in this room a seed. I told you to take the seed, plant it, water it, and bring it back to me today. But I gave you all boiled seeds; they were dead – it was not possible for them to grow. All of you, except Jim, have brought me trees and plants and flowers. When you found that the seed would not grow, you substituted another seed for the one I gave you. Jim was the only one with the courage and honesty to bring me a pot with my seed in it. Therefore, he is the one who will be the new Chief Executive Officer!"

- If you plant honesty, you will reap trust.
- If you plant goodness, you will reap friends.
- If you plant humility, you will reap greatness.
- If you plant perseverance, you will reap contentment.
- If you plant consideration, you will reap perspective.
- If you plant hard work, you will reap success.
- If you plant forgiveness, you will reap reconciliation.
- If you plant faith in God, you will reap a harvest.

So, be careful what you plant now; it will determine what you will reap later. "Whatever You Give To Life, Life Gives You Back"



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# Lighter Side of Medicine

HUMOR

Doctor, doctor, will I be able to play the violin after the operation?"

"Yes, of course."

"Great! I never could before!"

Why did the Dalmatian go to the eye doctor?

He kept seeing spots.

Patient: "Doctor, what should I do if my temperature goes up a point or more?"

Doctor: "Sell!"

A man walks into a doctor's office. He has a cucumber up his nose, a carrot in his left ear, and a banana in his right ear.

"What's the matter with me?" he asks the doctor.

The doctor replies, "You're not eating properly."

What did one tonsil say to the other tonsil?

"Get dressed up — the doctor is taking us out!"

Patient: "I always see spots before my eyes."

Doctor: "Didn't the new glasses help?"

Patient: "Sure, now I see the spots much clearer."

Doctor: "Nurse, how is that little girl doing who swallowed 10 quarters last night?"

Nurse: "No change yet."

Patient: "Doctor, I get heartburn every time I eat birthday cake."

Doctor: "Next time, take off the candles."

Does an apple a day keep the doctor away?

Only if you aim it well enough.

Why did the doctor tell the nurses to be quiet when walking past the medicine cabinet?

So they wouldn't wake the sleeping pills!

Why did the mattress go to the doctor?

It had spring fever.

Did you hear about the guy who lost his whole left side?

He's all right now!

Doctor: "You are very sick."

Patient: "Can I get a second opinion?"

Doctor: "Yes, of course! You are very ugly too."

Who do you call when you need a doctor immediately?

The nearest golf course.

Patient: "Doctor, I've swallowed a spoon."

Doctor: "Sit down and don't stir."

## Dr. Good and Dr. Bad

**SITUATION:** A 54-year-old obese male recently diagnosed with type 2 diabetes was advised 2D echocardiography for assessing LA volume and function.


**LESSON:** It has been suggested that LA function may be impaired in patients with newly diagnosed type 2 diabetes. Moreover, BMI and advancing age are likely to have an effect on LA enlargement and LA volumes, independent of the effects of hypertension and type 2 diabetes.

*Cardiovasc J Afr. 2017;28:1-6.*

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Paintal AS. Impulses in vagal afferent fibres from specific pulmonary deflation receptors. The response of those receptors to phenylguanide, potato S-hydroxytryptamine and their role in respiratory and cardiovascular reflexes. Q. J. Expt. Physiol. 1955;40:89-111.

### Books

Stansfield AG. Lymph Node Biopsy Interpretation Churchill Livingstone, New York 1985.

### Articles in Books

Strong MS. Recurrent respiratory papillomatosis. In: Scott Brown's Otolaryngology. Paediatric Otolaryngology Evans JNG (Ed.), Butterworths, London 1987;6:466-470.

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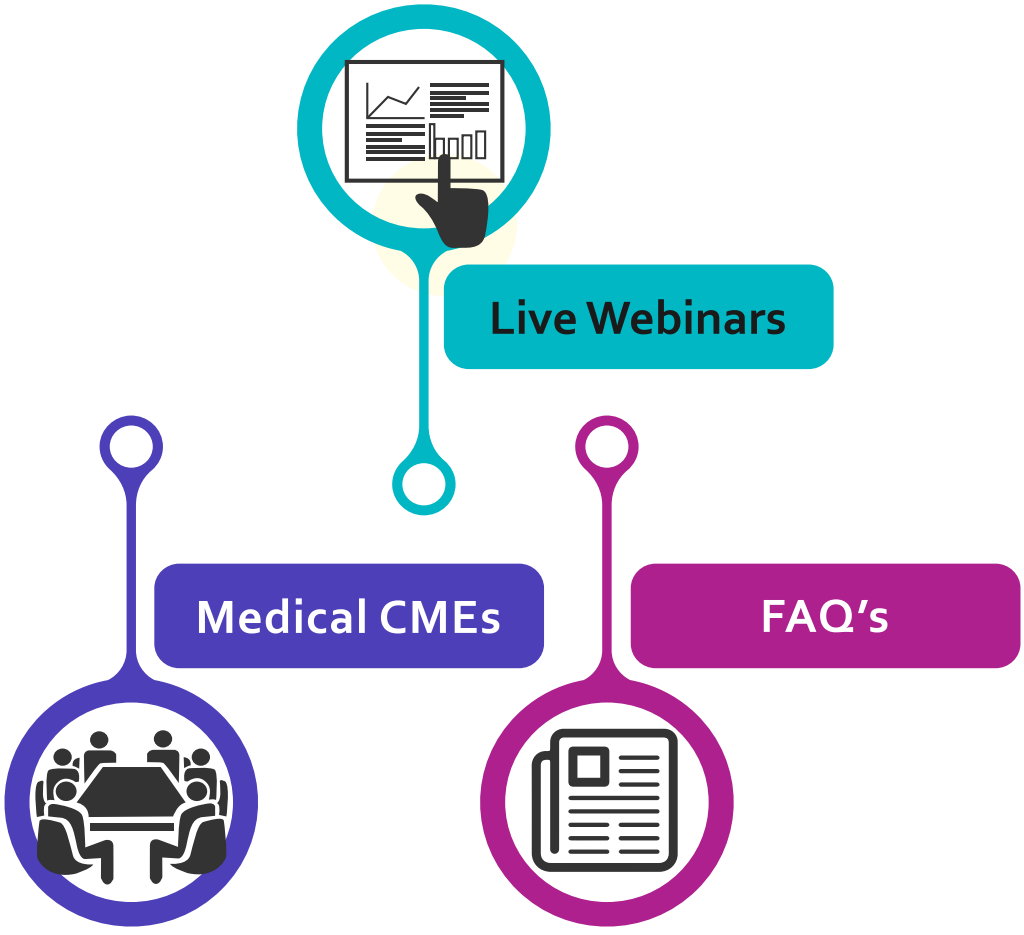


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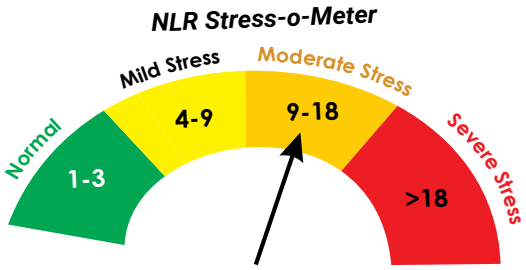


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