COVID-19 and the Kidney

American Society Of Nephrology and Indian Society of Nephrology Webinar

June 3, 2020

Welcome & Opening Statement

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PRESIDENT, AMERICAN SOCIETY OF NEPHROLOGY

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Pathophysiology of COVID-19–associated Kidney Injury

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Pathophysiology of COVID-19–associated Kidney Injury

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COVID-19 Pathogenesis

• SARS-CoV-2 — gains entry to host cells via angiotensin-converting enzyme 2 (ACE2).

• The affinity of SARS-CoV-2 for ACE2 is 10–20-fold higher than that of SARS-CoV—explain its higher transmissibility.

• Binding of the spike protein to ACE2, and proteolytic cleavage of ACE2 by transmembrane serine protease 2 (TMPRSS2), facilitates viral entry, replication and cell-to-cell transmission.

• ACE2 is a crucial counter-regulatory component of the RAS with approximately 60% homology with ACE. ACE2 converts angiotensin II (Ang II) into Ang-(1–7), which acts on the Mas receptor.


Marquez et al. Acta Physiologica 2020
Single-cell RNA of SARS-COV-2 receptor (ACE2) and known priming proteases in the kidney.

There is no clear correspondence in single-cell RNA between ACE2 and TMPRSS2. It remains to be determined if other TMPRSS such as TMPRSS 4, 5, or 9 in the proximal tubule can mediate the priming step. Tropism of SARS-CoV-2 might be expanded by the unique furin cleavage site in the Spike protein that is processed during biogenesis.

Batlle, D….Swaminathan, S et al. JASN doi:10.1681/ASN.2020040419

SARS CoV-2 Pathogenesis

No evidence of Harm with use of ACE inhibitors or ARB in COVID-19. But observational evidence is still susceptible to selection bias and residual confounding, and hence, RCT is needed.

Epidemiology of AKI in COVID-19

• 20-35% incidence of AKI on hospitalized COVID-19 patients in China, Europe, and the US
• Potential risk factors: CKD, DM, Male gender, African-American
• Lower incidence reported in some studies
• Manifestations also vary significantly between ethnicity and geography- reasons unclear
• Lower incidence observed in some studies- likely due to inclusion of large number of asymptomatic and milder COVID19 patients


Renal involvement and early prognosis in patients with COVID-19 pneumonia

METHODS

- 333 patients
- confirmed COVID-19
- 198 patients
- renal involvement in cohort
- 12 days
- the median observation

OUTCOME

- Remission of proteinuria
- Remission of hematuria
- Recovery of AKI
- Pneumonia remission
- 75.4% hematuria, proteinuria or AKI.
- 59.6% pneumonia remission
- 68.5% patients had remission of proteinuria
- Among 35 patients who developed AKI, 16 (47.5%) patients achieved recovery of kidney function
- Patients with renal involvement had higher overall mortality (11.2% vs 1.2%), compared to patients without
- Severity of pneumonia was the common negative risk factor in the remission of renal involvement

CONCLUSION

Remission of proteinuria and hematuria is common in patients with COVID-19 pneumonia, but renal involvement is associated with higher mortality.

Guangchang Pei et al. JASN 2020;31:1157-1165
Acute kidney injury (AKI) in patients hospitalized with COVID-19

Methods & Cohort
- Retrospective cohort
- 13 hospitals in New York
- SARS-CoV-2 positive
- N = 5449
  Age = 64 (52, 75)
- March 1 – April 5, 2020

Results
- All AKI 1,993 (37%)
- Stage 1: 47%
- Stage 2: 22%
- Stage 3: 31%

Independent risk factors for AKI
- Older age
- Black race
- Hypertension
- Diabetes mellitus
- Cardiovascular disease
- Vasopressor use
- Need for ventilation*
  *OR=10.7 (99%CI 6.8 -16.7)

Disposition of patients with AKI
- Still admitted 780 (39%)
- Discharged 519 (26%)
- Died 694 (35%)

CONCLUSION:
AKI occurs frequently among patients with COVID-19. It occurs early and in temporal association with respiratory failure. AKI in COVID-19 is associated with a poor prognosis.

Urine sediment in COVID-19 associated AKI

Granular casts
Waxy casts
Muddy brown casts
Leukocyturia
Hematuria
(occasionally acanthocytes)
Proteinuria

Urine sediment most commonly suggestive of ATN

Human Kidney as a target in COVID-19

- 27.06% (23/85) patients exhibited acute renal failure (ARF).
- Patients with comorbidities (hypertension and heart failure) more often developed ARF (65.22% vs 24.19%, p< 0.001; 69.57% vs 11.29%, p< 0.001, respectively).
- Severe ATN and lymphocyte infiltration.
- Immunohistochemistry showed that SARS-CoV-2 NP antigen in kidney tubules.
- EM observation of viruses- like particles are visible in the kidneys.
- CD68+ macrophages infiltration tubulo-interstitium
- Complement C5b-9 deposition on tubules

Diao, B et al. 2020.03.04.20031120; doi: https://doi.org/10.1101/2020.03.04.20031120
Pathogenic Pathways in COVID19 AKI

• Direct viral invasion
• Angiotensin system activation
• **Immune system:** (increased neutrophils, Lymphopenia, macrophage activation, cytokine storm (high IL-6, but still lower than seen with other cytokine storm syndromes) and high IL-1-b) and Complement activation
• Coagulation: Hypercoagulation, microangiopathy
• Pathologic angiogenesis (**intussusceptive**)
• Hypoxia, hypotension, sepsis
• Organ cross-talk

Not all Crowns Are Coronas!

• Multivesicular bodies (MVB) and Clarithrin coated vesicles can mimic Coronavirus (50-80nm).
• Even viral arrays are reported.
• Caution is required.

2. Evan A. Farkash, Allecia M. Wilson, Jeffrey M. Jentzen. JASN May 2020, ASN.2020040432; **DOI:** 10.1681/ASN.2020040432
ACE and ACE2 colocalize in the apical border of the proximal tubule. ACE2 is present in podocytes while ACE is endothelial.

Immune responses in viral infections: Therapeutic approach

Vardhana, SA et al. J. Exp. Med. 2020 Vol. 217 No. 6 e20200678

Neutrophil extracellular Traps (NETs) and Severity of COVID-19

Zuo, Y et al. JCI Insight. 2020. https://doi.org/10.1172/jci.insight.138999

Cytokine Storm in COVID-19


Immunopathology in COVID19: Macrophage Activation Syndrome

COVID-19 patients showed decreased circulating T, B and NK cells, and skewing of CD8+ T cells towards a senescent phenotype.

Reduced cytotoxic potential in COVID-19 patients, particularly in those that required intensive care.

Serum IL-6 levels correlated to the frequency of granzyme-expressing NK cells.

Off-label treatment with tocilizumab restored the cytotoxic potential of NK cells.

Anakinra has shown benefit

Zheng, M et al. Cellular & Molecular Immunology. 2020: 17; 533–535

Renal manifestations of Hemophagocytic Syndrome

Collapsing glomerulopathy

Thrombotic microangiopathy

Severe ATN

Tubulointerstitial inflammation

Cytokine storm. A central role for Interferon gamma, and high CXCL9 & 10

Interferon implicated in Collapsing glomerulopathy

Buatois, V et al. Translational Research. 2017: 80; 37-52.e2

COVID19 associated with Collapsing Glomerulopathy

Images by Dr. Chris Larsen, Arkana Laboratory

Severe podocyte effacement
Tubulo-reticular inclusions

Four patients presenting with cFSGS and Nephrotic proteinuria after COVID19 – All of them were African American and carry APOL1 High Risk allele.


COVID-19–associated Collapsing Glomerulopathy - Biopsy study

Serum Ferritin: 4254 mcg/l, high CXCL10
Serum sC5b-9: 526 ng/ml (HIGH)
Urine sC5b-9: 53 ng/mg (HIGH)
Patient was homozygous for the at-risk apolipoprotein A (APOL1) G1 variant (A342G and I348M)
Complement activation in COVID-19

SARS-CoV-2 spike glycoprotein co-localization with C4d in multiple organs of different patients who presented with microvascular thrombosis


Complement activation in COVID-19

- N proteins of SARS-CoV, MERS-CoV and SARS-CoV-2 were found to bind to MASP-2, the key serine protease in the lectin pathway of complement activation, resulting in aberrant complement activation.
- Complement hyper-activation was also observed in COVID-19 patients
- Promising benefit was observed when the deteriorating patients treated with anti-C5a monoclonal antibody.

1. Gao, T. medRxiv preprint doi: https://doi.org/10.1101/2020.03.29.20041962

Angiotensin II– and Heme–mediated microvascular injury and Complement activation

Complement Activation in Angiotensin II–Induced Organ Damage

Hypertension. 2010: 56; 1089-95.

Complement activation via cell-free heme and heme-loaded microvesicles

Merle, N et al. JCI Insight DOI: 10.1172/jci.insight.96910

NY-Northwell Renal Biopsy Experience in COVID-19

• ATN is the most common pathology.
• Thrombotic microangiopathy
• FSGS- classic and collapsing
• Pauci-immune vasculitis and glomerulonephritis

Thrombotic Microangiopathy and Collapsing glomerulopathy are associated; both are linked to VEGF


TMA in COVID-19

Data provided by Kaner Jhaveri


Angiogenesis, TMA, and FSGS

Increased angiogenesis in COVID-19 lungs


VEGF-A 164 overexpression in podocytes leads to collapsing glomerulopathy


Estrada, CC et al. JASN February 2019, 30 (2) 187-200

Thromboembolic complications in COVID-19

Renal Infarction

Renal and Spleen Infarction

Klok, FA et al. Thrombosis Research 191 (2020) 145–147


   DOI: https://doi.org/10.1053/j.ajkd.2020.05.004

**Immunothrombosis** - An innate immune defense in COVID-19

![Diagram of blood coagulation and immunothrombosis]

- Hypoxia
- Hif-1α
- Protein S
- Angiotensin II
- PAI-1

Anti-phospholipid antibodies are also described in COVID-19: Causal role uncertain.


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**Skeletal muscle damage in COVID-19**

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<td>CPK</td>
<td>20 - 200 U/L</td>
<td>6.1 AM</td>
<td>2.08 PM</td>
<td>12.78 (H)</td>
<td>7.576 (H)</td>
<td>7.45 (H)</td>
<td>4.119 (H)</td>
<td>1.415 (H)</td>
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<td></td>
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<td></td>
<td></td>
<td>5.08 AM</td>
<td>11.10 PM</td>
<td>368 (H)</td>
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</tbody>
</table>

Patients with skeletal muscle injury had higher neutrophil counts, decreased lymphocyte counts, elevated D-dimer, and more serious liver and kidney injuries.

**Summary 1**: Clinical and Laboratory Features of AKI in COVID-19

- Asymptomatic urine abnormalities (glycosuria, microhematuria)
- Acute Kidney Injury - Acute tubular necrosis and Acute interstitial nephritis
- Rhabdomyolysis - pigment nephropathy
- Thrombotic microangiopathy
- Proteinuria - collapsing glomerulopathy
- Rare reports of crescentic glomerulonephritis
- Renal infarction
- AKI and Progression of CKD to ESRD

**Summary 2**

- COVID-19 results from a complex pathophysiology that involves activation of innate immune system, complement pathway, hypercoagulation, and endothelial injury, which are worsened further by systemic hypoxia, hypotension, and Sepsis.
- Angiotensin pathway perturbation (high Angiotensin II and low Angiotensin 1-7) likely plays an important role in the pathophysiology.
- There is suggestion of direct viral infection of the kidney but further confirmatory studies in human biopsy tissues are needed.
- Renal manifestations can include ATN, AIN, TMA, collapsing glomerulopathy, and renal infarction.
- *Interaction with susceptibility genes likely determine manifestations and severity*: APOL1 G1/G2. NK cell variants and complement regulation are of interest
- Therapies targeting angiotensin (rACE2), anticoagulation, complement inhibition, and anti-cytokine therapies in combination with antivirals hold promise.
Pathogenesis of COVID-19–associated AKI

Battle, D.....Swaminathan, S JASN May 2020, ASN.2020040419; DOI: https://doi.org/10.1681/ASN.2020040419

Acknowledgements

- COVID-19 and ACE2 in Cardiovascular, Lung, and Kidney Working Group
- University of Virginia
- American Society of Nephrology
- Indian Society of Nephrology
- My Family
Management of AKI Associated with COVID-19

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OUTLINE

• Overview of COVID-19 associated AKI in US
• Non-RRT management of AKI
• RRT in AKI
  • Dose, Modality, Timing
  • Management of scarce/finite resources
AKI AND RRT REQUIREMENT IN ICU

815 ICU patients
1395 ICU patients
257 ICU patients
173 ICU patients

Chan et al, https://www.medrxiv.org/content/10.1101/2020.05.04.20090944v1
Hirsch et al, Kidney international (in press)

MECHANICAL VENTILATION AND AKI

Van den Akker et al, Crit Care 2013
Hepokoski et al, Nephron 2018
Non RRT management

- Appropriate volume resuscitation
- Judicious use of diuretics
- Potassium binding resins
  - Sodium zirconium cyclosilicate is faster acting than others
- IV bicarbonate
  - BICARB ICU trial. Jaber et al, Lancet, 932: 10141 7-13, July 2018

45

46
ACUTE KIDNEY INJURY

- Presence of life threatening complications?
- Not responding to medical management?
- Initiate RRT if a suitable candidate

MANAGEMENT OF COVID-19 PATIENTS WITH AKI

Indications to start RRT
- Volume overload/Respiratory failure
- Hyperkalemia
- Metabolic acidosis
- Uremia
- Severe oligoanuria
RRT IN COVID-19 ASSOCIATED AKI

- Timing
  - No data to support early initiation in COVID AKI
- Dose
- Modality
- Management of Scarce/Finite Resources

MODALITIES OF RRT

- CRRT
  - CVVH
  - CVVHD
  - CVVHDF
- PIRRT (prolonged intermittent renal replacement therapy)
  - Various terminologies – SLED, AVVH, (Others)
- Intermittent HD
- Peritoneal Dialysis
CRRT

• Preferred modality of RRT in hemodynamically unstable patients (2012 KDIGO)
• Convective clearance – hypothetical benefit in sepsis/SIRS
• No data to suggest convective (CVVH) over diffusive (CVVHD) clearance for patient outcomes
• Diffusive clearance (CVVHD) is associated with less clotting

AVAILABLE MACHINES IN US FOR CRRT

No need to buy a different kind of machine from what is used at your center
You may need more machines based on COVID projections for your city and your hospital
**PIRRT/SLED**

- Hybrid therapy
- Can be performed either with IHD or CRRT machines
- Does not need 1:1 hemodialysis nursing
- **Allows one CRRT machine to be used for 2 patients**


c/o Juan Carlos Velez, Ochsner Health, LA
DOSING OF PIRRT

- Dose (simple calculation)
  - 20 ml/kg/hour dose for 24 hours, divided by # hours on treatment
- Duration - 10 hours or shorter
  - Allows time for cleaning, then using it for another 1-2 patients


SLED PRESCRIPTION

- Fresenius 2008 T
- Blood flow: 200 ml/min
- Dialysate flow: 100-200 ml/min
- 8-10 hours
Anticoagulation during CRRT/PIRRT in COVID-19 patients with AKI is essential
• Heparin
  • Via machine circuit
    • Our heparin protocol PTT 60-80 secs
  • Systemic
    • Our heparin protocol PTT 60 – 90 secs
• Citrate
  • ACD-A or Tri-sodium citrate
  • Multiple citrate protocols
  • Nursing intensive
  • Risk for patient safety issues if implemented hastily

If your center is NOT using citrate already, do not recommend starting new protocol urgently.
Need nephrologist/intensivists/nursing/pharmacy input to develop citrate protocol
Consider working on citrate protocol to prepare for next surge

IHD in AKI
• Standard
  • 3 times/week, Kt/Vurea 1.3/treatment (per KDIGO)

Considerations during COVID-19 pandemic
• Not every patient needs 4 hour HD
• Consider shortest duration that achieves metabolic and volume control
• Minimize 1:1 RN time in room
Hemodialysis Catheter

- Temporary HD catheters are usually placed by nephrologists and intensivists.
- During pandemic, additional physicians/providers are being recruited to place catheters.
- Catheter lengths are extremely important to ensure adequate blood flow and reduce clotting.

  - RIGHT IJ (preferred): length 15 -20 cm
  - Femoral: length 24-30 cm
  - LEFT IJ: length 20 -24 cm
  - Last resort – Subclavian: length 20 cm
Managing resources

- Delay RRT (if possible) in COVID PUI (conserves PPE)
  - If COVID-19 results are available within 24 hours
  - High dose diuretics (not feasible in ESRD)
  - Medications to lower K
- Decrease flow rates in CRRT
  - Consider 15 ml/kg/hour once metabolic control is achieved?
- Pharmacy compounding CRRT fluids?
- Using HD machine to do SLED (conserve fluids)
- Cross training others to help with nursing

Creative RRT maneuvers during pandemic

- Minimize exposure to nurses and physicians
- Conserve PPE

PATIENT SAFETY FIRST
CAUTION USING NON-MANUFACTURER RECOMMENDED EXTENSION TUBING
**COORDINATION OF CARE**

- Multi-disciplinary rounds at specified time
  - Nephrologist, ICU physician, ID physician, Cardiologist
- Review plan for day
- Ultrafiltration goals
- Metabolic control
- Medication dose adjustments
- Goals of care – escalation vs de-escalation
  - ?ECMO

**MANAGEMENT OF AKI IN COVID 19**

**Summary**

- High incidence of AKI in COVID-19, especially in critically ill patients
- CRRT/PIRRT is preferred in hemodynamically unstable patients
- PIRRT using CRRT and SLED using IHD equipment will free up machines/nursing
- IHD and PD are also appropriate if CRRT/PIRRT are not available
- Anticoagulation is essential (based on expertise at your institution)
- Creative ways to minimize nursing exposure WITHOUT compromising PATIENT SAFETY
- Management of finite resources is critical to provide RRT to as many people as possible
- Collaboration with other specialties is essential
Effect of COVID-related Lockdown on Renal Services in India

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Effect of COVID-related Lockdown on Renal Services in India

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MD, FASN, FRCP
Professor of Nephrology
Sanjay Gandhi Postgraduate Institute of Medical Sciences,
Lucknow, India
Email: narayan.nephro@gmail.com
Lockdown: an action for mass quarantine

• GOI - lockdown for 3-weeks on 24th March 2020

• Lockdown affected 1.3 billion people at a time when COVID cases were only 500.

• Henk Bekedam (WHO) – timely, comprehensive and robust intervention

Impact of lockdown: importance of contact and non-contact transmission

Effective Lockdown: Both contact and non-contact transmission rates over a long period

Lockdown measures can suppress the primary infection peak, but will lead to a secondary peak


Global GDP growth-3% worst since 1930s: A collateral damage

International Monetary Fund (IMF):
Global and Indian economy Effect of COVID and lockdown

**Global GDP Growth Jan and April**

**USA**: 2.00 and -5.90

**China**: 6.00 and 1.20

**India**: 5.80 and 1.90

"the economic danger > health risks".

Energy, Agriculture, Manufacturing, Stock markets and E-commerce
Mathematical models used in the USA or the UK to India

Points to a possible 300 million cases in India

Out of which 100 million will face severe COVID infection

Looking at the incidence of 5.1% of AKI in severe cases

There may be the potential of 5.1 million AKI patients in India

Collateral damage - Impact on dialysis services

Public and private transports were shut down, which prevented patients from reaching dialysis centers.

The impact was felt almost immediately by patients on dialysis.
Effect on dialysis in first lockdown (3 weeks)

19 centres-8 public (all major tertiary care institute AIIMS,PGIMER,SGPGIMS) and 11 Pvt

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Hospitals</th>
<th>Public N =972</th>
<th>Private N =1545</th>
<th>Total N =2517</th>
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<td>dialysis stations before</td>
<td></td>
<td>209</td>
<td>314</td>
<td>523</td>
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<tr>
<td>dialysis stations after</td>
<td></td>
<td>200</td>
<td>296</td>
<td>496</td>
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<tr>
<td>No of MHD patients</td>
<td></td>
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<tr>
<td>a. before lockdown</td>
<td></td>
<td>972</td>
<td>1545</td>
<td>2517</td>
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<td>a. after lockdown</td>
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<td>928</td>
<td>1476</td>
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Impact on dialysis service: missing dialysis and emergency dialysis

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<th>Missing one or more HD sessions</th>
<th>Public</th>
<th>Private</th>
<th>Total</th>
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<tbody>
<tr>
<td>1. Missing HD with information</td>
<td>198 (20.37%)</td>
<td>133 (8.6%)</td>
<td>331 (13.15%)</td>
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<tr>
<td>2. Missing HD without information</td>
<td>105 (10.8%)</td>
<td>84 (5.4%)</td>
<td>189 (7.51%)</td>
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<tr>
<td>3. Nephrologists per se reduced HD</td>
<td>47 (4.83%)</td>
<td>30 (1.94%)</td>
<td>77 (3.06%)</td>
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**Effect of missing dialysis and emergency dialysis**

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<tr>
<th>Number of patients missing one or more HD</th>
<th>Public (47.25%)</th>
<th>Private (18.83%)</th>
<th>Total (28.20%)</th>
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<tr>
<td>419</td>
<td>63 (6.48%)</td>
<td>41 (2.65%)</td>
<td>104 (4.13%)</td>
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<td>291</td>
<td>41 (2.65%)</td>
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<td>710</td>
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**4. Permanently missing**

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<tr>
<td>75</td>
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**5. Death**

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<th>Private (18.83%)</th>
<th>Total (28.20%)</th>
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<td>76</td>
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**Emergency dialysis**

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**PD patients**

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<th>Public</th>
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<td>637</td>
<td>496</td>
<td>141</td>
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**Reported with disturbances in supplies of PD fluid**
Guidelines for Dialysis with reference to COVID-19 Infection

Guidelines for Dialysis of COVID – 19 patients

Effect of lockdown on Outpatient Department during COVID pandemic

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<th>Total</th>
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<td>New patients OPD per day before</td>
<td>920</td>
<td>321</td>
<td>1241</td>
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<td>per day after</td>
<td>75</td>
<td>20</td>
<td>95</td>
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<tr>
<td>Telemedicine Uses</td>
<td>8</td>
<td>9</td>
<td>17</td>
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### Effect of lockdown on IPD services during COVID pandemic

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<tr>
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<td>IPD services</td>
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<tr>
<td>Number of admitted patients before lockdown</td>
<td>359</td>
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<tr>
<td>Number of patients in IPD services on the day of reporting</td>
<td>159</td>
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### Case fatality in India

- **Fatality rate - reduced from 3.3% to 2.87% in a month**
- **Lowest in the world, says Health Ministry,**

**Govt of India**

Economic Times | 27 May, 2020 | 12.32AM IST

India has, so far, reported 2,01,007 Cases and 5,628 deaths (including 98,834 active cases, 96,534 cured/migrated. 02 Jun, 6:25 PM IST
Lower case fatality in India and South Asia

• **Early implementation of lockdown** (The Lancet. Editorial. 25th April 2020).

• **Universal BCG vaccination in childhood** (non-specific protection mediated via the induction of innate immune memory).


Lower case fatality in India and South Asia

• **Hot and humid environment** - high fatality in latitude band with temp below 17 Celsius

• **Both one unit increase of temp and absolute humidity were associated with the decreased COVID-19 death.** (Ma Y et al. Sci Total Environ 2020;724:138226, A China study)

• **Individual host immunity and virulence factor**

• **Proportionately lower elderly population** than the western world
Take home message

• Lockdown- caused significant collateral damage
• Caused death, and required emergency dialysis
• OPD by 92.3% and IPD by 60% declined
• Lack of preparedness before lockdown posed these patients at risk

Stay safe and healthy

Thank you!
Renal Transplantation during the COVID Pandemic

DR. (PROF.) DINESH KHULLAR D.M (NEPHROLOGY), FACP

CHAIRMAN & HEAD OF DEPARTMENT
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NEW DELHI

Renal Transplantation During COVID Pandemic

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Outline of the talk

- Issues/concerns regarding transplantation during COVID pandemic.
- Strategies to ensure safe renal transplantation during present times.
- Managing patient who becomes COVID positive post renal transplant.
- Experience from our centre and other centres across the country.
- Conclusions.

Issues

- Should renal transplantation activities be suspended? (Fears due to Immunosuppression/comorbidities).
- How to rule out Corona virus infection in donor & recipient?
- Relative paucity of classical symptoms in transplant recipients.
- Impact on immunosuppression protocol.
- Drug interactions between immunosuppressant drugs & COVID therapeutics. QTc prolongation, ACEi/ARBs.
- Poorer outcomes in transplant recipients?
UNITED KINGDOM

- Study of 7 patients from St. George university hospital, London, UK.
- 1 recipient died (14%) and significant AKI was observed.
- Five required admission & four in ICU.
- Immunosuppression reduced in six, anti-viral drugs in all, anti-bacterial agents in four.
- Lymphopenia, very high ferritin and D dimer levels, and raised troponin levels are seen in severe disease and may be of prognostic value.

**Suggested:**
- Suspending kidney transplantation during the COVID-19 pandemic particularly for high-risk & older recipients with comorbidities.

NEW YORK

- Fifteen post transplant (deceased donor) patients requiring hospitalization with confirmed COVID.
- Symptoms – fever, cough, myalgia, diarrhea.
- Most had B/L chest infiltrates, 33% had no radiographic findings.
- Five required mechanical ventilation, two died

**Conclusions:**
- Overall presentation was similar to that reported for the general population.
- But the treatment protocols differed from institution to institution.
- Larger studies with longer follow up are required to further understand the prognosis and sequelae of COVID-19 infection in immunosuppressed renal transplant patients.
Why to continue transplants?

• Duration of pandemic is unknown.
• Continuation on haemodialysis poses similar risk.
• Logistic difficulties faced by out of station (including international) patients already fully worked up & approved by authorization committee.
• Benefits of renal transplantation outweigh the risks.

How can safety be ensured?

• Detailed history.
• COVID-19 testing (limitations of RT-PCR). Timing? Frequency?
• Informed Consent.
• Use of proper PPE by all HCWs.
• Immunosuppression adjustment?
• Regular visits to the hospital to be minimized.
Managing Post Renal Transplant Patient Who Becomes COVID Positive

Decision regarding immunosuppression must take into account factors such as:

- Time since transplantation.
- Baseline graft function.
- Prior history of rejection.
- Age.
- Presence of donor specific antibodies.

*Outpatient Management of the Kidney Transplant Recipient during the SARS-CoV-2 Virus Pandemic Gleeson et al CJASN April 2020, CJN.04510420; DOI: https://doi.org/10.2215/CJN.04510420
Asymptomatic/pauci-symptomatic transplant patients (with mild symptoms: fever >37.5°C but <38°C, cough, cold WITHOUT dyspnoea) and negative chest X-ray.

Hospitalization or home management, to be clinically decided on a case-by-case basis. Daily monitoring when at home, of fever and O2 saturation (if possible) with daily telephone visit by the transplant centre.

Immunosuppressive therapy:
- Stop MMF or azathioprine
- Stop calcineurin inhibitor
- Glucocorticoids: initiation of methylprednisolone 16 mg

Resumption after 15 days-first CNIs & later anti-metabolite.

Anti Viral therapy in all.

HCQ dose modified in accordance with GFR.

Transplanted patients with severe symptoms and/or positive chest X-ray

Hospitalization.

Immunosuppressive therapy:
- Stop MMF or azathioprine, Stop calcineurin inhibitor.
- Glucocorticoids: initiation of methylprednisolone 16 mg.
- Antiviral therapy (duration: 5-20 days to be determined based on clinical progression).
- HCQ.

Hospitalised Transplanted/Dialysis Patient with Clinical Deterioration

If Brescia-Covid respiratory severity scale ≥2,

Dexamethasone - 20 mg/day for 5 days, thereafter 10 mg/day for 5 days.

Consider combination with Tocilizumab.
When to de-isolate transplant recipient

- Test based or time based resolution opinion
- Time based only for inpatients who are non-intubated

Indian Experience
(25th March till 25th May 2020)
Pre transplant work up (MSSH protocol)

Special permission from **NOTTO & Hospital Authorization Committee**.

Detailed written informed special consent.

Safety of HCPs. Prevention of transmission of infection/cross infection.

Covid free safe transplant pathway.

Isolation of both donor & recipient at least one week prior to surgery including during hemodialysis.(social distancing, hygiene etiquettes).

More extensive pre transplant immunological workup (in an endeavour to prevent acute rejection).

COVID-19 screening through symptoms & RT-PCR of nasal & nasopharyngeal secretions of donor & recipient as well as HCPs (ET secretions of deceased donor tested twice at an interval of 24 hours). Within 24-72 hours of surgery.

No change in induction therapy/ immunosuppression protocols.

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Transplantation

- **Proper PPE for all involved in the surgery.**
- **Precautions while administering anaesthesia. Minimum pneumo-peritoneum.**
- **Minimizing use of energy devices (diathermy & hormonal).**
- **Suctions to have virus filters & suction bottles to have hypochlorite-like in case of a chest tube.**
- **During laparoscopic & robotic surgery, air-seal & smoke evacuators may be used.**

**Post transplantation:**

- **Special post operative advice in the context of Covid-19.**
- **Strict isolation at home.**
- **Temperature & symptoms monitoring.**
- **Telemedicine.**
- **OPD sampling in a safe environment.**
- **No additional anti-microbial prophylaxis.**
## Indian experience

<table>
<thead>
<tr>
<th></th>
<th>Max SSH Saket, Delhi (n=4)</th>
<th>Other Delhi/NCR centres (n=7)</th>
<th>Rest of India (n=7)</th>
<th>Total (n=12)</th>
<th>178</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of Tx</td>
<td>13</td>
<td>43</td>
<td>29</td>
<td>85</td>
<td>(6.8% of expected)</td>
</tr>
<tr>
<td>No. of ABOi Tx (%)</td>
<td>0</td>
<td>04(9.3)</td>
<td>02(6.9)</td>
<td>05(5.9)</td>
<td></td>
</tr>
<tr>
<td>No. of deceased donor Tx(%)</td>
<td>02(15.4)</td>
<td>01(2.3)</td>
<td>09(31.0)</td>
<td>12(14.1)</td>
<td></td>
</tr>
</tbody>
</table>

## Recipient characteristics

<table>
<thead>
<tr>
<th>Recipient characteristics</th>
<th>Max SSH, Saket, Delhi</th>
<th>Other Delhi-NCR centres</th>
<th>Rest of India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Recipient Age(yrs.)</td>
<td>40.4</td>
<td>42</td>
<td>34.8</td>
</tr>
<tr>
<td>Mean Donor Age(yrs.)</td>
<td>45.7</td>
<td>49</td>
<td>45.5</td>
</tr>
<tr>
<td>Male (%)</td>
<td>76.9</td>
<td>64</td>
<td>78</td>
</tr>
<tr>
<td>Mean BMI (kg/m²)</td>
<td>-</td>
<td>-</td>
<td>23.2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Comorbidities (%)</th>
<th>Max Saket, Delhi</th>
<th>Other Delhi-NCR centres</th>
<th>Rest of India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obesity</td>
<td>0</td>
<td>4.7</td>
<td>2.9</td>
</tr>
<tr>
<td>Hypertension</td>
<td>92.3</td>
<td>93.0</td>
<td>97.6</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>46.1</td>
<td>55.8</td>
<td>45.9</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>5.8</td>
<td>13.9</td>
<td>0</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic lung disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Active malignancy</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Auto-immune disease</td>
<td>0</td>
<td>0</td>
<td>0</td>
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</table>
## Immunosuppression

<table>
<thead>
<tr>
<th>Initial IS (%)</th>
<th>Max SSH, Saket, Delhi</th>
<th>Other Delhi-NCR, Centres</th>
<th>Rest of India</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prednisone</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>Cyclosporine</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>93</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>mTOR inhibitor</td>
<td>07</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Azathioprine,</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Induction agent (%)</th>
<th>ATG</th>
<th>Basiliximab</th>
<th>Rituximab</th>
<th>No Induction-</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>80</td>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

## Graft function

<table>
<thead>
<tr>
<th>Graft function</th>
<th>Max SSH, Saket, Delhi</th>
<th>Other Delhi –NCR centres</th>
<th>Rest of India</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (ml/min)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At discharge</td>
<td>83.5</td>
<td>81.4</td>
<td>82.3</td>
</tr>
<tr>
<td>At 1 month</td>
<td>73.4</td>
<td>71.4</td>
<td>70.9</td>
</tr>
<tr>
<td>Proteinuria&gt;500mg at 1 month</td>
<td>NIL</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Covid Positive (when)</td>
<td>NIL</td>
<td>1 (at 1month)-asymptomatic</td>
<td>NIL</td>
</tr>
<tr>
<td>Acute graft dysfunction</td>
<td>NONE</td>
<td>NONE</td>
<td>NONE</td>
</tr>
</tbody>
</table>
Indian experience

- **Total number of transplants**: 85 over two months.
- Good graft function at discharge & one month post transplantation.
- No significant extra evidence of infection.
- COVID-19 only in one recipient - remained asymptomatic.

**Conclusions:**
- COVID-19 did not pose any extra risk to renal transplantation in India at least during initial lockdown period.
- Caveats: Time period & virus virulence in India need to be considered.

Conclusions

- COVID-19 pandemic has significantly impacted renal transplantation programmes world over.
- Since co-existence with COVID-19 could well be the new norm, it may be time now to move on & to strategize.
- Safety of all will always remain the central tenet of any transplant programme.
- Extensive pre transplant workup to prevent graft rejection & no change in routine IS protocol because of fear of COVID-19 being advocated.
- No definite role of routine use of antimicrobial prophylaxis.
- Management of transplanted patient who becomes COVID positive should be done on case by case basis. Watch out for possible drug interactions.
- De-isolation 10-14 days after these patients become asymptomatic may be a reasonable & practical strategy.
- Most important is to share the data with the world.

*Together we will conquer*
Thank you

Questions

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Osmania Medical College and Hospital
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Darlene Rodgers, RN (ASN)
American Society of Nephrology
Closing Remarks

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