The medical laboratory prosecution of Covid – 19: pathogenesis and diagnosis

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ABSTRACT

The outbreak of Covid – 19 is now a pandemic affecting population pan continentally. It has challenged the health system at various levels such as case identification, diagnostic laboratory workup, management and treatment and the epidemiological aspects of preventive interventions. It is so because this viral infection has never ever been encountered in past. The coronavirus is a single stranded RNA virus with a few peculiarities of structure such as spike glycoprotein (S). This structural protein has been attributed to pathogenesis of Covid – 19 infections. The transmission of Covid - 19 is by droplets and aerosol. It primarily affects lungs, and its binding sites are cellular receptor of ACE II of pneumocytes. The morbidities and fatalities associated to Covid-19 infection are attributed to cytokine storm. It chiefly affects lungs producing pneumonitis. There are other manifestations of Covid – 19 infections. The diagnosis of Covid – 19 infection is by PCR of nasopharyngeal swab and samples from trachea and bronchi. The antibody (IgM and IgG) testing too is advised but as a auxiliary methods in support of diagnosis .The hematological manifestations and biochemistry of the blood helps in suspecting and predicting the course of Covid – 19 infection. The present review imbibes within it, the various scientific nuances of novel corona virus that introduces Covid -19 infection and explains the characteristics of the virus, pathogenesis and cytokine storm, immune evasion , lung injury , histological alteration , laboratory diagnosis, biosafety, parameters of significance in laboratory, rRT-PCR of viral RNA and the proposed model of laboratory evaluation of Covid – 19 infection. The review provides a model for resource limited hospital at screening and confirmation of Covid – 19 infections which will simplify, augment and enable the necessary hospital services and corrective therapeutic interventions.

INTRODUCTION

Never before such a calamity loomed large over the humanity like recent outbreak of COVID – 19, which has achieved the proportion of monstrous pandemic (Sun et al., 2020; Gao et al., 2020; Chen et al., 2020).

This is happening as a new learning for medical community in the backdrop of recently known outbreaks which has affected sizeable population by SARS and MERS (Mousavizadeh and Ghasemi, 2020; WHO, 2020).
The novel corona virus, whose transmission to human, pathogenesis, laboratory diagnosis and treatment is under the hammer for exploring the pan-continental deaths (ul Qamar et al., 2020; Haveri et al., 2020; Li et al., 2020).

Novel corona virus known as Covid – 19 is RNA virus with meta-typical biological behavior, for its fatality not seen before except of Spanish flu. The published literature concludes that the route of transmission of infection is from human to human through droplets, aerosols and foams (Fan et al., 2020; Lee et al., 2016; Mason et al., 2020). The symptomatic patients of Covid – 19 remains the source of infection and temporary reservoirs (Rothan and Byrareddy, 2020; Woo et al., 2010; Yaqian et al., 2020).

There are several aspects related to this new RNA virus, which are required to be scrutinized for its novelty that includes its structure, the pathogenesis, laboratory diagnosis and treatment (Woo et al., 2010; Pung et al., 2020; Xu et al., 2020). The present review is basically a medical prosecution of the virus for its laboratory diagnosis which could suggest a local model to be adopted for diagnostic stratification for prophylactic preventions (quarantine), early laboratory suspicion and diagnosis and pave the way for proper therapeutic interventions.

Virus

Corona viruses are enveloped viruses with a positive single stranded RNA genome (26 – 32 kbs). Four corona virus genera (α, β, γ, δ) are identified in human corona viruses and the present one belongs to corona virus genera much in similarity to SARS like corona viruses (Bhatraju et al., 2020). The virus is described on its various aspects in the following items.

Viral Structure

Corona group of viruses have often affected human in the past and has bought out the mild to fatal manifestations of pneumonitis. (Zhang et al., 2020; Coleman and Frierman, 2014). The genome of corona virus is a single stranded positive - sense RNA (+ ss RNA) with S’ cap structure and 3’ poly-A tail. Replication transcription process is through genomic RNA that encodes non-structural proteins (nsps). A discontinuous transcription too is synthesized for nested set of sub-genomic RNAs (Mousavizadeh and Ghasemi, 2020; Bhatraju et al., 2020)

Polyprotein 1a/1ab (pp1a/pp1ab) is translated through a template of genomic RNA. The subsequent acquisition of leader RNA happens at transcription regulatory sequences located between open reading frames (ORFs) (Mousavizadeh and Ghasemi, 2020; ul Qamar et al., 2020). The genome and sub genome of typical corona virus contains atleast 6 ORFs. Corona viruses possess the largest genome (26.4 to 31.7 kb). The major structural proteins of corona virus such as S, E, M and N occurs in the 5’-3’ ends of the gene. COVID – 19 which is a spherical or pleomorphic envelope particle belongs to Beta corona-virdiae family, taxonomically called as SARS –COV – 2. Through their ORF – a and ORF – 1b produces 2 polypeptide pp1a and pp1ab (Mousavizadeh and Ghasemi, 2020; Li et al., 2020; Coleman and Frierman, 2014).

The structural protein contains spikes (S), membrane (M), envelope (E) and nucleocapsid (N) which is encoded by ORFs 10 and 11. Beside these other special and accessory proteins are – HE protein, 3a/b protein, and 4a/b protein. These mature proteins are responsible for several functions in genome functions and virus replication. The abundant structural protein found in virus is a membrane glycoprotein (M) and spike protein (S) as a type 1 membrane glycoprotein. The main inducer of neutralizing antibody is the S – protein (Mousavizadeh and Ghasemi, 2020; Woo et al., 2010).

The comparison of COVID – 19 with SARS - CoV and MERS – CoV is by their sizes, spike protein and by arrangement of nucleo-capsid protein (N), envelope protein (E) and membrane protein (M) (Mousavizadeh and Ghasemi, 2020). The Figure 1 (Mousavizadeh and Ghasemi, 2020) - shows the basic schematic structure of corona virus.

Figure 1: Basic structure of Covid – 19

Viral Culture and Electron Microscopy

Though the viral culture and electron microscopy do not form the laboratory diagnostic protocol for Covid – 19 but it produces typical changes in infected cells and observations and electron microscopy as described in the following (Figure 2) (Mason et al., 2020).
Human alveolar type II cells cultured in-vitro and later infected with corona virus is seen in Figure 2a and Figure 2b. Figure 2a shows double membrane viral particle and Figure 2b show the apical microvilli.

**Structural peculiarity of COVID – 19 causing human pathology and tropism**

The sequence analysis of virus as previously described in under the item 2.1 that can pave the way for antiviral therapies. The S protein which is a peculiarity with Covid -19 virus is a target RBD/ACE2 blockers, S cleavage inhibitors, fusion core blockers, neutralizing antibodies, protease inhibitors, S protein inhibitors, and small interfering RNAs. The corona virus has higher affinity for S2 receptors. The adaptations in Covid -19 sequence make it more efficient in transmitting virus and boost its virulence. The genetic bottle neck for RNA viruses often occurs at respiratory droplet transmission. Therefore, it is assumed that Covid -19 will become less virulent over a period of time (Mason et al., 2020; Woo et al., 2010).

**Case characteristics as of underlying pathogenesis**

Patients with Covid-19 show manifestation of fever, myalgia, dyspnea, non productive cough, normal or decreased leukocyte count (Fan et al., 2020). There is a radiographic evidence of pneumonia. These are similar to symptoms of SARS-CoV and MERS-CoV infections (Yaqian et al., 2020). There are vascular and dermatological manifestations reported with Covid -19 infections. Though pathogenesis of Covid 19 is yet not perfectly revealed but is proposed to be similar to SARS-CoV and MERS-CoV. This has enabled the recognition of Covid-19 by laboratory methods (NHS, 2020; WHO, 2014).

**Corona virus: transmission, incubation and duplication**

The corona virus is known to enter the host cell with its S protein which is a determinant of entry. Cellular receptor of ACE2 is binding sites for the envelope spike glycoprotein. Cleavage event occurs at...
CoV S protein at position of S 20 which is a critical proteolysis responsible for membrane fusion and viral infectivity. Besides membrane fusion the clathrin-dependent and –independent endocytosis too mediates SARS-CoV entry. Polyproteins and structural proteins are translated in the cytoplasm once the viral genome is released to it. The viral genome begins to replicate after it. The newly formed enveloped glycoproteins inserts into the membrane of endoplasmic reticulum or Golgi apparatus. The nucleocapsid is formed by combination of genomic RNA and nucleocapsidprotein which germinates into the endoplasmic reticulum–Golgi intermediate compartment (ERGIC). The vesicles that contain the virus particles fuse with the plasma membrane along its release (Li et al., 2020; Rothan and Byrareddy, 2020).

The average incubation during Covid-19 was estimated to be 4.8 +/- 2.6 ranging from 2 – 11 days. As the Covid-19 have the higher levels of transmissibility and therefore its pandemic risk (Yaqian et al., 2020).

**Antigen presentation in coronavirus infection**

The viral antigens are presented by APC (antigen presentation cells) which is a normal first step of antiviral immunity poised against the viruses by the body. Antigenic peptides are presented by major histocompatibility complex and are recognized by virus specific cytotoxic T lymphocytes.

The antigenic presentation depends on MCH I molecules but MHC II molecules participate for antigenic presentation. Its observed that MHC II molecules, such as HLA-DRB1*11:01 and HLA-DQB1*02:0are associated with the susceptibility to MERS-CoV infection.

HLA polymorphism has also been found to be susceptible with HLA-B*4601, HLA-B*0703, HLA-DR B1*1202 and HLA-Cw*0801. The HLA-DR0301, HLA-Cw1502 and HLA-A*0201 alleles have protective effect from SARS infection. Gene polymorphism of MBL too is found related to the risk of SARS CoV infection (Mousavizadeh and Ghasemi, 2020; Li et al., 2020; Mason et al., 2020).

**Humoral and cellular immunity**

The immunity elicited against CoV virus is both humoral and cellular. This is initiated by virus specific B anticells. There is a production of IgM and IgG antibodies in regular manner.

By 12 week, SARS specific IgM antibodies disappear. The IgG antibodies last long in protective role. It observed that CD4 and CD8 T cells are reduced in SARS CoV 2 infected patient. But the activation of the cells processing HLA DR and CD 38 are activated in excess. Specific T memory responses are known to be existing to the SARS CoV S peptide for long time. This finding forms the rationale for designing the vaccine against SARS-CoV-2 (Haveri et al., 2020; Woo et al., 2010; Coleman and Frieman, 2014).

**Cytokine storm in COVID-19**

Morbidities and fatalities in Covid – 19 infected patients is attributed to cytokine storm that produces deadly and controlled systemic and inflammatory response. Large amounts of pro inflammatory cytokines of IFN-a, IFN-g, IL-1b, IL-6, IL-12, IL-18, IL-33, TNF-a and TGFβ are released. The chemokines of CCL2, CCL3, CCL5, CXCL8, CXCL9 and CXCL10 too are released by immune affected cells in corona viral infections. The levels of IFN-a, IL-6, and CXCL8, CXCL10, CCL5 in the serum are elevated in the patients suffering from it depending on mild, moderate or aggravated course of the disease. Cytokine storm triggers the ARDS and multiple organ failure. Therefore, the pathogenesis of Covid – 19 is concluded to be brought out by excessive response by cells of immune systems (Lippi and Plebani, 2020; Henry et al., 2020; Tan et al., 2020).

**Coronavirus immune evasion**

Immune response by the body against the corona virus is known to be evaded by virus itself through multiple strategies. The pathogen associated molecular pattern (PAMS) which is a conserved microbial structure can be recognized by patter recognition receptors (PRRs). The corona viruses induce the production of double membrane vesicle that lacks PRRs. Thereby, it avoids the host detection of their RNA. Interferon – 1 is known to bear the protective effect on corona virus infection, but it’s observed that INF – 1 pathway is inhibited in infected mice. Besides, ORF4a, ORF4b, ORF5, and membrane proteins of MERS CoV inhibit nuclear transport of IFN regulatory factor 3 (IRF3) and activation of IFN b promoter. There is a down regulation of gene expression related to antigen in corona virus infection (Mousavizadeh and Ghasemi, 2020; Li et al., 2020).

**Pathogenesis of the lung injury**

The pathogenesis of the lung injury is influence by cytokine storm generated due to viral infection and participated by complement; reactive oxygen species, defused antioxidant mechanism, Fe^{+2} mediated the parenchymal injuries. Complement associated microvascular injury results in endothelial vascular leaks, and micro thrombi. Rather, these events in the pathogenesis are the targets of the lateral laboratory investigations in the diagnosis of Covid-19 infection. The pathogenesis of lung injury is item-
The cellular attachment of Covid-19 to lung parenchymal cells

The abridged mechanism of Covid-19 attachments to lung parenchymal cells bearing ACE II receptor is shown in Figure 3 (Source: Mousavizadeh et al., 2020). Covid-19 used the same cellular factor ACE II and cellular protease TMPRSS2 for their activation. The attachment of the virus to the cell occurs to attachment spikes (S). The drugs suggested in the treatment of Covid-19 uses these attachment and protein sites for their actions (Mousavizadeh and Ghasemi, 2020; Coleman and Frieman, 2014).

The mechanisms causing ROS and release of toxic Fe’s

Cytokine storm and immune cell infiltrate as a part of intensive immunological reaction is due to long time viral stimulation. The macrophages and neutrophils produce numerous reactive oxygen species ROS that includes $\text{H}_2\text{O}_2, (-\text{O}_2^-), (-\text{OH})$, etc.

A certain level of ROS is critical for regulating immunological responses and clearing viruses. Excessive ROS will oxidize cellular proteins and membrane lipids that will destroy not only virus infected cells but also normal cells in lungs and even the heart resulting in multiple organ failure (Harkin et al., 2020).

Macrophage activating syndrome (MAS) is associated with high levels of ferritin too. Covid-19 attacks one beta chain of hemoglobin. It captures the prophyrin to inhibit human haem metabolism playing a major goal in hypoxia. Terminal complement components of C5b-9 (membrane attack complex), C4d and mannose binding lectins (MBL) – associated serine protease (MASP – 2) are deposited in the microvasculature of the lung which is highly significant pathognomonic feature. These findings suggest the role of activation of the complement activation pathway in systemic inflammatory alterations (Magro et al., 2020; WHO, 2020).

Histopathological alterations in the lung tissue/Autopsy

Histological highlights of lung injury in Covid-19 is similar to alteration in early phase of ARDS. The histological alterations in the lung may be disordered for their features. These histological alterations are enumerated as follows

1. Hyaline membrane formation in the alveoli
2. Desquamation of pneumocytes
3. Pulmonary edema of fluid
4. Thickening of alveolar septa
5. Interstitial infiltrate dominated by lymphocytes, and mononuclear cells
6. Multinucleated giant cells
7. Atypical cells large nuclei, amphophilic granular cytoplasm, and prominent nucleoli in the intra alveolar spaces with viral cytopathic-like changes
8. No obvious intracytoplasmic viral inclusions
9. Micro vascular injury and thrombosis

The immune-histochemical (IHC) study demonstrates the presence of C5b-9, C3b and C4d in the tissue of affected lung (Xu et al., 2020).

Laboratory diagnosis of Covid-19

The basic principle of laboratory diagnosis of Covid-19 is similar to that of other respiratory viral diseases. The workup of Covid-19 for its diagnosis is a little novel as then virus is newly known and therefore, its nucleic acid sequences. However, the ultimate diagnostic test for Covid-19 is polymerase chain reaction. The following paragraphs deals on the specimen collection, handling and diagnostic tests which are educated for Covid-19 (Richardson et al., 2004; ICMR, 2020; World Health Organization, 2020).

Types of specimen and handling of detection test for MERS-COV RNA

Specimen types that could undergo laboratory diagnosis are multiple. Such specimen's bears high risk of transmission to laboratory physicians, therefore
requires a careful and personal protection devices. The protocols are generated for it and required to be followed rigidly.

**Types of specimen**

Both specimens from the upper and lower respiratory tracts are recommended at the same time. Lower respiratory tract specimens: broncho-alveolar-lavage (BAL), sputum, tracheal aspirate, etc.

A careful instruction may be passed to exert at coughing until the secretions from the trachea is collected as a part of sputum specimen. If the specimen of sputum is purulent on gross inspection, no further instructions for forceful coughing are required. Upper respiratory tract specimens which are collected for PCR in the intended for detection of corona virus are combined naso/oropharyngeal swab, nasopharyngeal swab, and nasopharyngeal aspirate.

For a naso/oropharyngeal swab, a flocked swab is used and both specimens are added to the same viral transport medium (this combined specimen has been reported to increase the sensitivity). Blood specimen (Whole blood): To be considered for suspect cases when it is difficult to collect a proper respiratory specimen (children, etc.) Although it is best to test within 3-4 days of symptoms.

**Specimen collection**

Infection prevention and control guidelines should be followed while collecting the specimen of sputum, tracheal aspirate and bronchoscopic aspirate. There are separate guidelines in preventing aerosol acquired infections. The samples of blood and other non-respiratory specimen's collection from suspected or confirmed patients, should be carried only after wear personal protective equipment (N95 mask, gloves, long-sleeved gown, goggles, and face shield) (NHS, 2020; World Health Organization, 2020; ICMR, 2020).

**Specimen handling**

Personal protective equipment of level D and gloves should be worn while processing specimens obtained of respiratory system. Class II biosafety cabinet (BSC) are recommended for Aerosol-generating procedures. These procedures are to be carried out only after wearing personal protective equipment. The site of laboratory work requires to be sterilized. Manufacturer guidelines provided with the diagnostic kits should be put to practice. Prevention of cross-contamination during processing of nucleic acid extraction and making aliquots in BSC are as below

1. During pre-treatment of specimens manually, one by one processing is recommended rather than batch of multiple specimens.
2. The automatic nucleic acid extraction equipment devices should be in use with concern of contamination.

In the cases of contamination with specimen, the bench should be disinfected with 70% alcohol immediately, or as soon as the procedure is finished.

**Hematology and coagulation profile**

The following is an excerpt from a published data reviewed for the present work from an onsite laboratory working on multi ethnic inpatients with Covid – 19 for hematological parameters which are abnormally affected for their values as below in Table 1.

**Biochemical alterations**

There are 3 major alterations happening with Covid – 19 infections which are concerned with acute reactant proteins, alterations to the values of the enzymes and cytokines (Lippi and Plebani, 2020; Henry et al., 2020). These are shown in Table 2.

**Role of cytology**

There are few references which have enlisted the cytological alterations observed in the samples of broncho-tracheal aspirations, scrapes and bronchio-alveolar lavages. The virus that infects the epithelial cell shows the changes much similar to the cytopathic effect bought out by RNA respiratory viruses (Harkin et al., 2020).

The commonest alteration those are seen in the smears of above samples is as below

1. Ciliocytophthoria – The process of denuding the cells which shows the ciliary tuft and cytoplasm dissociating from the nucleus. Such a cytoplasm with a ciliary tuft is identified in the background of the smear in suspected cases of these kind of viral infection.
2. The unexplained nucleomegaly and ground glass opacification of nuclei
3. The intranuclear inclusions which morphologically appears much similar to herpes virus nuclear inclusions
4. The presence of polycarrions, i.e. the multinucleated epithelial giant cells with a nucleomegaly and nuclear vesiculation
5. The background shows the fibrinous pink exudate suggesting the vascular legs from the alveoli intermixed with acute inflammatory cells
Table 1: Hematological parameters in Covid – 19 infection

| Blood counts * | Coagulation Profile** | Ferrokinetics*** |
|----------------|-----------------------|------------------|
| Nadir Hemoglobin 13.2(12.5-14) (gm/dl) - Lowered | i.PT – Prolonged, | Abnormal values of ferrokinetic profile in plasma |
| AMC 0.3 (0.2-0.5) (x109/L) - Lowered | ii. aPTT – Prolonged | Others |
| ANC 4.2 (2.1-6.9) (x109/L) – Raised | iii.D-dimer and FDP – Significantly present | Others |
| ESR – Raised | | |
| WBC 5.1 (3.5-8.2) (x109/L) – Raised | | |
| ALC 0.5 (0.48-0.8) (x109/L) – Lowered | | |
| Platelet count 217 (154-301) (x109/L) - Lowered | | |
| | | |

(*) – stands for standard reference values of individual laboratories

Table 2: Hematological parameters in Covid – 19 infection

| Acute reactant proteins* | Enzymes ** | Blood Analysts *** |
|-------------------------|------------|-------------------|
| Serum Ferritin - Raised | AST – Raised | Total bilirubin – Raised |
| CRP levels – Raised | ALT – Raised | BUN – Raised |
| Fibrin levels – Raised | LDH - Raised | Creatinine – Raised |
| Pro-calcitonin – Raised | CK – Raised | Myoglobin – Raised |
| Others | Others | Cardiac Troponins–Raised |
| | | Interleukins (IL-2R , IL- 6, IL – 8, IL- 10) - Raised |

(*) – stands for standard reference values of individual laboratories

contrary to the lymphoid cells population but with alveolar macrophages “A source of reactive oxygen species”.

Serology

Serological test in the course of Covid -19 infection in detection of IgM and IgG antibodies by techniques of ELISA, Western blot, Immunodot, IFA and neutralization are the options. However, the exertion of the serological tests are yet not confirmatory and are not backed by WHO and many other health authorities across the globe as the ultimate diagnostic test of Covid – 19 is PCR (Li et al., 2020; Richardson et al., 2004; World Health Organization, 2020).

Nucleic acid detection technology (polymerase chain reaction, PCR)

The rRT-PCR remains the standard diagnostic investigation of novel corona virus (Covid - 19). The suggested target in the diagnosis of Covid – 19 by WHO which is to be followed worldwide in this time of epidemics, are – ORF 1ab (RdRP) gene and E gene. Routine confirmation of cases of COVID-19 is based on detection of unique sequences of virus RNA by NAAT such as real-time reverse-transcription polymerase chain reaction (rRT-PCR) with confirmation by nucleic acid sequencing when necessary. The viral genes targeted so far include the N, E, S and RdRP genes. RNA extraction should be done in a biosafety cabinet in a BSL-2 or equivalent facility. Heat treatment of samples before RNA extraction is not recommended.

Real-time quantitative polymerase chain reaction (RT-qPCR) and high-throughput sequencing are two commonly used nucleic acid detection technologies for SARS-CoV-2. High-throughput sequencing of the viral genome is ultimate authoritative method of SARS CoV 2. However, equipment dependency and high cost is a limiting factor in diagnostic workup of corona virus. RT-qPCR is an effective, dependable and easy to perform and interpret. The molecular laboratories world over are equipped with it. Therefore, RT-qPCR is a laboratory modality of choice for diagnosis of Covid 19 irrespective of sample types. Covid 19 virus can be detected by using specific primers and probes of corona virus. The commonly used primers are targeted against ORF1ab and N gene regions for SARS-CoV-2. The confirmation of Covid 19 infection is reported when both targets show amplification over a given Ct values. (NHS, 2020; WHO, 2014, 2020). Resource poor laboratories, molecular diagnosis viral RNA PCRs may be car-
ried out as a pooled sample processing which will cut the cost per test and is recommended recently.

**Laboratory diagnostic surveillance of Covid – 19 in a suspected case**

The guidelines of ICMR, WHO, NHS and others have been proposed for the diagnosis of Covid – 19 in clinically suspected patients (ICMR, 2020; NHS, 2020; WHO, 2020).

The following diagnostic algorithm (Figure 4) may be useful for the laboratory and laboratory parameters of prognosis for Covid – 19 infection adhering to ICMR directives which is a statutory body issuing the guidelines for registered Covid – 19 labs. Timely visits to ICMR website for updated guidelines in laboratory diagnosis of Covid 19 is advised and to be followed (ICMR, 2020).

**Laboratory based strategic interventions for Covid – 19 workup suggested for resource limited hospital**

The basic model proposed in Figure 4 is ideal for resource limited hospital which is close to the suggested guidelines of ICMR, WHO and NHS. This will bring about higher rate of detection as well as lowering the rate of hospitalization. This model will also suggest the likely complications and outcome of Covid – 19 infections through the laboratory parameters lumped in three groups of:

1. Pro inflammatory cytokines and acute reactant proteins
2. Enzymes related to liver
3. Coagulation profile

This will enable the clinicians and laboratory physicians to diagnose and predict the Covid – 19 complications and crisis. This will also give guidelines to health organizations working on Covid – 19 on the laboratory medicine aspect. This article is an attempt to explain the diagnostic endeavors for Covid – 19; a sort of laboratory prosecution.

**CONCLUSION**

India is a populous nation. It requires its own laboratory strategies for handling Covid – 19 infections enabling to take the decisions at screening and diagnostic workup of patients suspected of Covid – 19 infection which is expected to be cost effective and banally executed. The present review offers the itemized insight for a model of laboratory medicine.
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Conflict of Interest
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