

Medicine

Query paper:

Title: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China

Abstract: The SARS-CoV-2 pandemic and its unprecedented global societal and economic disruptive impact has marked the third zoonotic introduction of a highly pathogenic coronavirus into the human population. Although the previous coronavirus SARS-CoV and MERS-CoV epidemics raised awareness of the need for clinically available therapeutic or preventive interventions, to date, no treatments with proven efficacy are available. The development of effective intervention strategies relies on the knowledge of molecular and cellular mechanisms of coronavirus infections, which highlights the significance of studying virus–host interactions at the molecular level to identify targets for antiviral intervention and to elucidate critical viral and host determinants that are decisive for the development of severe disease. In this Review, we summarize the first discoveries that shape our current understanding of SARS-CoV-2 infection throughout the intracellular viral life cycle and relate that to our knowledge of coronavirus biology. The elucidation of similarities and differences between SARS-CoV-2 and other coronaviruses will support future preparedness and strategies to combat coronavirus infections.

Candidate papers:

1. **Title:** A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome

Abstract: A worldwide outbreak of severe acute respiratory syndrome (SARS) has been associated with exposures originating from a single ill health care worker from Guangdong Province, China. We conducted studies to identify the etiologic agent of this outbreak. We received clinical specimens from patients in seven countries and tested them, using virus-isolation techniques, electron-microscopical and histologic studies, and molecular and serologic assays, in an attempt to identify a wide range of potential pathogens. None of the previously described respiratory pathogens were consistently identified. However, a novel coronavirus was isolated from patients who met the case definition of SARS. Cytopathological features were noted in Vero E6 cells inoculated with a throat-swab specimen. Electron-microscopical examination revealed ultrastructural features characteristic of coronaviruses. Immunohistochemical and immunofluorescence staining revealed reactivity with group I coronavirus polyclonal antibodies. Consensus coronavirus primers designed to amplify a fragment of the polymerase gene by reverse transcription–polymerase chain reaction (RT-PCR) were used to obtain a sequence that clearly identified the isolate as a unique coronavirus only distantly related to previously sequenced coronaviruses. With specific diagnostic RT-PCR primers we identified several identical nucleotide sequences in 12 patients from several locations, a finding consistent with a point-source outbreak. This virus may never before have circulated in the U.S. population.

2. **Title:** Origin and evolution of pathogenic coronaviruses.

Abstract: Severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) are two highly transmissible and pathogenic viruses that emerged in humans at the beginning of the 21st century. Both viruses likely originated in bats, and genetically diverse coronaviruses that are related to SARS-CoV and

MERS-CoV were discovered in bats worldwide. In this Review, we summarize the current knowledge on the origin and evolution of these two pathogenic coronaviruses and discuss their receptor usage; we also highlight the diversity and potential of spillover of bat-borne coronaviruses, as evidenced by the recent spillover of swine acute diarrhoea syndrome coronavirus (SADS-CoV) to pigs.

3. **Title:** Distinct Immune Response in Two MERS-CoV-Infected Patients: Can We Go from Bench to Bedside?

Abstract: One year after the occurrence of the first case of infection by the Middle East Respiratory Syndrome coronavirus (MERS-CoV) there is no clear consensus on the best treatment to propose. We compared innate and adaptive immune responses of two patients infected with MERS-CoV to understand the underlying mechanisms involved in the response and propose potential therapeutic approaches. Broncho-alveolar lavage (BAL) of the first week and sera of the first month from the two patients were used in this study. Quantitative polymerase chain reaction (qRT-PCR) was performed after extraction of RNA from BAL cells of MERS-CoV infected patients and control patients. BAL supernatants and sera were used to assess cytokines and chemokines secretion by enzyme-linked immunosorbent assay. The first patient died rapidly after 3 weeks in the intensive care unit, the second patient still recovers from infection. We confirm previous in vitro findings that MERS-CoV can drive IL-17 production in humans. Host recognition of viral dsRNA determines outcome in the early stage of MERS-CoV infection. We highlight the critical role of IFN α in this initial stage to orchestrate a robust immune response and bring substantial arguments for the indication of early IFN α treatment during MERS-CoV infection.

4. **Title:** SCDC definitions for nosocomial infections, 1988

Abstract: The Centers for Disease Control (CDC) has developed a new set of definitions for surveillance of nosocomial infections. The new definitions combine specific clinical findings with results of laboratory and other tests that include recent advances in diagnostic technology; they are formulated as algorithm. For certain infections in which the clinical or laboratory manifestations are different in neonates and infants than in older persons, specific criteria are included. The definitions include criteria for common nosocomial infections as well as infections that occur infrequently but have serious consequences. The definitions were introduced into hospitals participating in the CDC National Nosocomial Infections Surveillance System (NNIS) in 1987 and were modified based on comments from infection control personnel in NNIS hospitals and others involved in surveillance, prevention, and control of nosocomial infections. The definitions were implemented for surveillance of nosocomial infections in NNIS hospitals in January 1988 and are the current CDC definitions for nosocomial infections. Other hospitals may wish to adopt or modify them for use in their nosocomial infections surveillance programs.

5. **Title:** Coronaviruses post-SARS: update on replication and pathogenesis

Abstract: As the aetiological agent of severe acute respiratory syndrome. Previously these viruses were known to be important agents of respiratory and enteric infections of domestic and companion animals and to cause approximately 15% of all cases of the common cold. This Review focuses on recent advances in our understanding of the mechanisms of coronavirus replication, interactions with the host immune response and disease pathogenesis. It also highlights the recent identification of numerous novel coronaviruses and the propensity of this virus family to cross species barriers.

6. **Title:** Bats as animal reservoirs for the SARS coronavirus: hypothesis proved after 10 years of virus hunting

Abstract: Recently, the team led by Dr. Zhengli Shi from Wuhan Institute of Virology, Chinese Academy of Sciences, and Dr. Peter Daszak from Ecohealth Alliance identified SL-CoVs in Chinese horseshoe bats that were 95% identical to human SARS-CoV and were able to use human angiotensin-converting enzyme 2 (ACE2) receptor for docking and entry. Remarkably, they isolated the first known live bat SL-CoV that replicates in human and related cells. Their findings provide clear evidence that some SL-CoVs circulating in bats are capable of infecting and replicating in human (Ge X Y, et al., 2013).

Exemplary analysis:

1. **Relevance:** The methods used for virus identification, including virus-isolation techniques and molecular assays, are foundational for understanding how SARS-CoV-2 was identified and studied. The query paper aims to build on the knowledge of past coronavirus outbreaks to inform its discussion on SARS-CoV-2.

Reason for Citation: This paper is likely cited because it discusses the identification of a novel coronavirus (SARS-CoV) as the etiological agent behind SARS, marking a significant moment in the history of coronavirus research.

2. **Relevance:** This review paper provides a comprehensive overview of the origins and evolutionary pathways of pathogenic coronaviruses, including SARS-CoV and MERS-CoV.

Reason for Citation: By citing this paper, the authors of the query paper underscore the importance of understanding the zoonotic origins of SARS-CoV-2 and its evolutionary context. This background is crucial for developing strategies to predict, prevent, and combat future zoonotic spillovers.

3. **Relevance:** This study offers insights into the immune responses elicited by MERS-CoV infection, highlighting the variability in patient responses and the potential implications for treatment.

Reason for Citation: The query paper might cite this work to draw parallels between the immune responses to MERS-CoV and SARS-CoV-2, suggesting avenues for research into therapeutic and preventive measures based on immune modulation.

4. **Relevance:** This distinction is vital for infection control and epidemiological studies, which are essential components of managing a pandemic.

Reason for Citation: The inclusion of this citation could seem less directly related at first glance. However, understanding and defining nosocomial infections are critical in the context of a novel virus outbreak, as it helps in identifying hospital-acquired infections versus community-acquired ones.

5. **Relevance:** This review provides an update on coronavirus replication and pathogenesis, focusing on the knowledge gained after the SARS outbreak.

Reason for Citation: By citing this paper, the authors of the query paper connect the dots between past coronavirus research and the current understanding of SARS-CoV-2, particularly in terms of viral replication and the mechanisms driving disease severity.

6. **Relevance:** The discovery that bats harbor coronaviruses closely related to human SARS-CoV provides a foundation for investigating the animal origins of SARS-CoV-2 and underscores the

importance of wildlife surveillance in pandemic preparedness.

Reason for Citation: This paper is cited to support the discussion on the zoonotic origins of coronaviruses, specifically the role of bats as reservoirs.

Exemplary ranking: Ranked order: paper 5, paper 2, paper 1, paper 3, paper 6, paper 4

1. **Explanation:** Offers historical context and methodological insights into the identification and study of novel coronaviruses, which is relevant for research focused on the clinical and molecular features of SARS-CoV-2.
2. **Explanation:** Provides essential background on the evolutionary aspects of coronaviruses, including SARS-CoV-2. This information is foundational for any research that aims to understand the current pandemic in the context of coronavirus evolution.
3. **Explanation:** This paper's insights into the immune responses to MERS-CoV can inform hypotheses and experimental designs for studying the immune response to SARS-CoV-2, making it directly relevant to follow-up research.
4. **Explanation:** Although understanding nosocomial infections is important, especially in the context of a novel virus outbreak, this paper might be less frequently cited in research that is more focused on the virus's molecular biology and clinical features rather than epidemiological aspects of its spread in healthcare settings.
5. **Explanation:** This paper is crucial for understanding the mechanisms of coronavirus replication and pathogenesis, directly relevant to studying the clinical features and molecular mechanisms of SARS-CoV-2 infection.
6. **Explanation:** While the zoonotic origin of SARS-CoV-2 is a critical aspect of understanding the virus, this paper might be slightly less directly cited in research focused specifically on clinical features and molecular mechanisms of the virus unless the research also delves into origins and reservoirs.