SUPERINFECTIONS AND COINFECTIONS IN COVID-19

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SUPERINFECTIONS AND COINFECTIONS IN COVID-19

Definitions

- According to the CDC, a **superinfection** is an "infection following a previous infection especially when caused by microorganisms that are resistant or have become resistant to the antibiotics used earlier
- **coinfection** is an infection concurrent with the initial infectioninitial infection
- The difference is **temporal** ►►►►

*coinfections occur simultaneously

*superinfections develop following the initial infection

Superinfection is diagnosed when the patients exhibited clinical signs and symptoms of pneumonia or bacteremia **+** a positive culture of a new pathogen from a lower respiratory tract samples or blood samples taken **≥48 h** after admission

VAP is identified based on 3 criteria:

- new or progressive persistent radiographic infiltrates
- clinical observations suggesting infection (new onset of fever, purulent sputum, leukocytosis, increased minute ventilation, arterial oxygenation decline and/or need of vasopressors, and high PCT/CRP
- positive microbiological culture

- Superinfections and coinfections are common in respiratory viral illnesses
- up to 65% of laboratory-confirmed cases of influenza infection are complicated by bacterial co/superinfections with the majority ranging between 11- 35% in a meta-analysis
- Preliminary studies from high-burden COVID-19 areas suggest that superinfections are common, particularly in severe cases
- ***Streptococcus pneumoniae, Haemophilus influenzae***, and ***Staphylococcus aureus*** being the most frequently reported pathogens

- definite incidence of bacterial superinfections in **COVID-19** is not known so far; it seems to be lower than in severe influenza cases
- A few reports, mostly from China, have reported secondary infections in range of 5–27% of SARS-CoV-2 infected adults in several hospitals, which included 50–100% of those who died
- These infections are more commonly seen in **severe disease** who are critically ill and in ICU receiving **MV**
- reported incidence of super added infection in ICU cases ranges between 13.5 and 44%
- most frequent type of infection is **VAP** due to bacterial or fungal, followed by **bacteremia** with sepsis and **UTIs**

- A study among 150 COVID-19 cases in Wuhan reported that of 68 deaths, 11/68 (16%) had secondary infections
- In another Wuhan study of 41 patients, secondary infections (defined as positive respiratory or blood culture along with compatible clinical syndrome) were a reported complication in 31% of ICU patients and 10% of patients overall
- A brief report of 3,200 COVID-19-related deaths from numerous regions of Italy reported "superinfection in 8.5%" of cases
- Notably, patients with severe illness were 10 times more likely to have superinfections with bacteria or fungi than non-severe cases, and twice as likely to have viral superinfections.

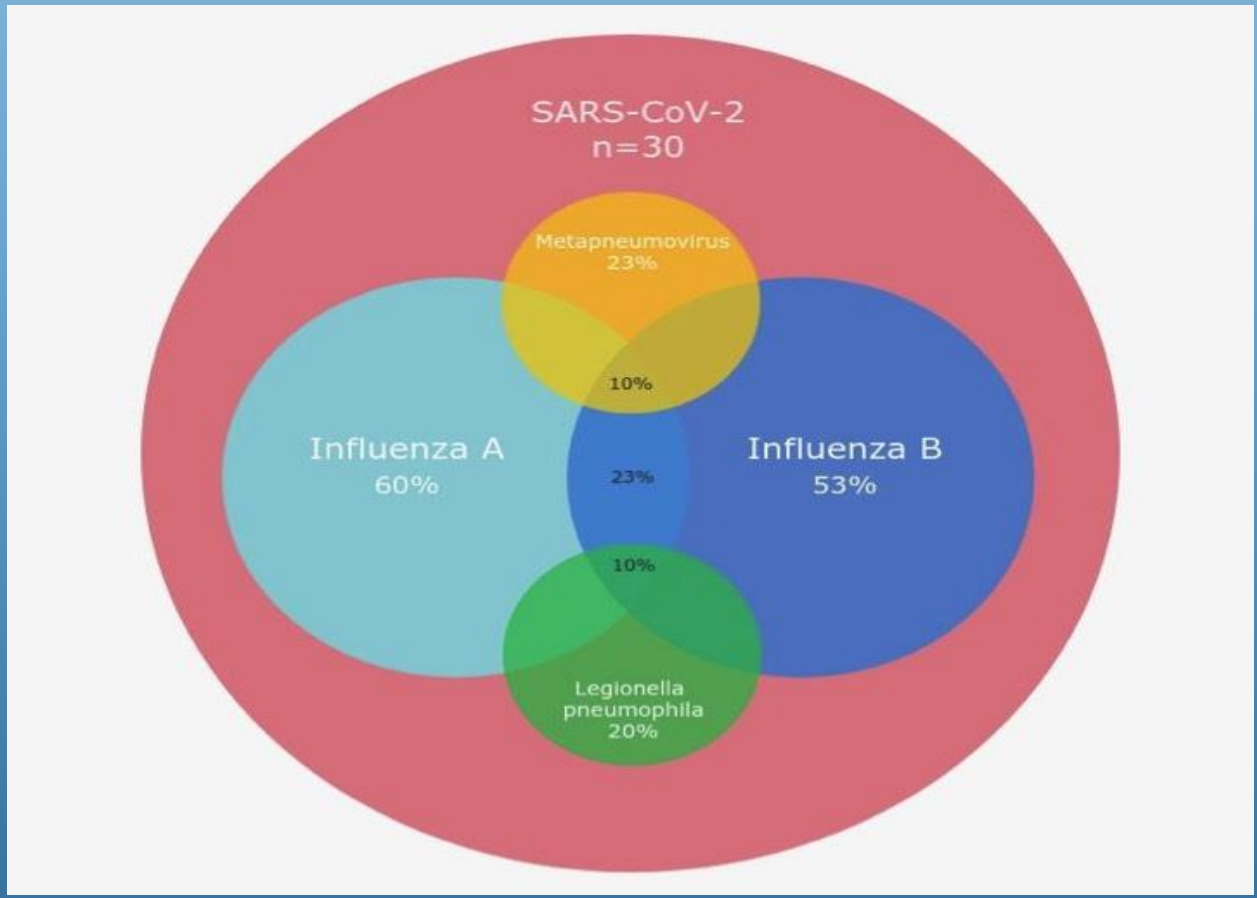
- Notably, among COVID-19 ICU cases in Zhongnan Hospital, there was a high reported frequency of secondary infections with carbapenem-resistant *Acinetobacter baumannii,* particularly among ICU deaths (55.6% or 5/9) versus ICU patients ultimately transferred to the ward (17.4% or 4/23)

- Recent limited observations suggest that coinfections in COVID-19 patients are more frequently viral than bacterial, and rates of viral coinfections in COVID-19 illness are consistent with what is seen with other respiratory viral illnesses

- A study of 30 COVID-19 patients in Qingdao suggested a high proportion of coinfections with other respiratory pathogens based on serum IgM antibody detection

- Provided these limitations, 24 (80%) of these patients showed evidence of coinfection with at least one respiratory pathogen; the most commonly detected co-pathogens were influenza A (60%) and influenza B (53%), followed by *M. pneumoniae* (23%) and *L. pneumophila* (20%)

TYPES OF CO-INFECTIONS AMONG COVID-19 PATIENTS QINGDAO, CHINA. 2020.



Recent data from hospital at Stanford support high rates of coinfection among COVID-19 patients in Northern California:

- 1,217 samples from symptomatic patients from multiple Northern California locations tested for SARS-CoV-2 and other respiratory pathogens:
- 9.5% tested positive for ***SARS-CoV-2*** and 90.5% tested negative
- 26.1% were positive for ***other respiratory viruses*** by multiplex PCR testing
- 20.7% of SARS-CoV-2-positive cases had a ***respiratory coinfection***, compared with 26.7% of SARS-CoV-2-negative cases

Statistically, there was no difference in rates of respiratory coinfections comparing SARS-CoV-2 and non-SARS-CoV-2 cases

In contrast, a letter describing clinical experience in Shenzhen (Guangdong province, southeast China) noted that in a group of 186 symptomatic patients admitted to Shenzhen Hospital, 92 patients tested positive for SARS-COV-2 and of these, only 3.2% were coinfected with other respiratory pathogens determined by multiplex PCR testing of respiratory samples

While it is difficult to determine reliable coinfection estimates, most available data have consistently shown that ***viral respiratory coinfections*** with SARS-CoV-2 are common and are more prevalent than bacterial or fungal coinfections, which is expected given the magnitude of co-circulating seasonal respiratory pathogens during the current COVID-19 pandemic

- An association between COVID-19 and superinfection can be possibly attributed to major lung damage caused by viral replication which results in **cytokine storm** and **complex inflammatory processes**

- In developing countries like India, where there is well-established high burden of MDR-organisms in ICU, superinfections in COVID-19 patients can pose a challenge in treatment ►► increase mortality

- Effective antibiotic stewardship has a crucial role in limiting unnecessary use of antimicrobials

MORBIDITY AND MORTALITY

- Super-coinfections can augment pathogenesis, increasing morbidity-mortality of viral infections
- the majority of deaths associated with the Spanish influenza pandemic of 1918 were not thought to be caused by the H1N1 virus itself, but rather by secondary bacterial pneumonia
- Bacterial superinfection was also associated with the higher morbidity and mortality rates seen during the 1957, 1968, and 2009 influenza pandemics
- during 2009 swine flu pandemic, bacterial superinfections were identified in 29-55% of deaths
- Cytokine storm may be provoked or worsened by secondary infections

SUPERINFECTIONS AND COINFECTIONS ARE CHALLENGING TO DIAGNOSE

- Diagnosis of secondary bacterial infections typically requires testing of samples obtained by sputum, naso-oropharyngeal swabs, bronchoscopy, thoracentesis, lung tissue biopsy
- Conventional diagnostic tests have poor sensitivity in identifying the etiologic organisms
- In a review of 5,025 cases of CAP from FDA records from 1996-2007, only 44.7% of cases had a pathogen identified
- Even when conventional culture-based methods are combined with newer molecular techniques such as multiplex PCR and urine antigen testing, 62% of hospitalized patients with pneumonia remain without a microbiologic diagnosis

SUPERINFECTIONS AND RISK FACTORS

- Bacterial-fungal superinfections occur more commonly in critically ill hospitalized patients with risk factors such as:
- advanced age
- underlying systemic diseases
- patients with immunosuppression
- corticosteroid use
- mechanical ventilation
- prolonged hospital and ICU stays
- though relatively uncommon, superinfections can also complicate coronavirus disease in an immunocompetent patient

POSSIBLE PATHOPHYSIOLOGY OF SUPERINFECTIONS

- Following viral infection, mechanical, and immunological mechanisms impair the host defenses of the respiratory tract
- elevated risk for bacterial superinfection may be attributed to lymphopenia in more than 80% reported COVID-19 patients
- Direct infection of T cells and depletion has been studied in SARS and impaired lymphocyte defense resulting in bacterial secondary infections

Two non-exclusive mechanisms, which predispose a patient to superinfection are as follows:

1. Mechanical ventilation
2. Dysregulation of the immune system of the host

- interplay between virus and host cell induces immune response which results in synthesis of pro-inflammatory cytokines such as IL-6, IL-2, soluble IL-2 receptor, TNF-α , and anti-inflammatory cytokines (IL-4 and IL-10), which proves harmful to host cells
- In severe cases, induced cytokine storm, decreased CD4 and CD8 T cells, and suppressed INF-γ production by CD4 T cells have been correlated with disease severity

TYPES OF SUPERINFECTION

- most usual type of infection in hospitalized COVID-19 patients is ***pneumonia*** (VAP), ***bacteremia***, ***UTIs***

Ventilator-Associated Pneumonia

- MV along with **heavy sedation, prone positioning,** and **muscle blockers** for prolonged period which can increase the risk of acquiring secondary nosocomial infection mainly VAP
- clinical picture of COVID-19 pneumonia is indistinguishable from VAP; therefore, microbiological evidence from deep respiratory secretions presently remains the sole criterion to support diagnosis
- A retrospective study done on 918 patients in China, reported VAP in 32.3% cases, while Zhou and colleagues documented VAP in 10 of 32 patients needing invasive mechanical ventilation
- Another study reported HAP associated with MV in 20% cases among survivors and 6% cases in non-survivors

BACTEREMIA

- Blood stream infections seem **uncommon** in COVID-19 patients
- A study from New York City hospitals reported very low rate of true bacteremia (1.6%) among COVID-19 patients
- Low rates of bacteremia have also been reported among patients with SARS
- In a study done by Yang et al., bacteremia was seen in 3% cases among non-survivors of COVID-19 patients. In contrast, He et al. documented bacteremia in 24.6% cases

ETIOLOGICAL AGENTS OF SUPERINFECTIONS

- Superinfections related to COVID-19 have been observed to be caused by bacterial and fungal agents as per various studies

Bacterial Agents

- Bacterial superinfections can significantly increase morbidity and mortality of viral infections especially in critically ill patients
- various organisms cultured from COVID-19 patients includes multidrug-resistant *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Serratia marcescens*, *Enterobacter cloacae*, *Acinetobacter baumannii*, *Escherichia coli*, *Staphylococcus aureus*, and *Bacillus cereus*

FUNGAL AGENTS

- Severe COVID-19 patients requiring intensive care may also be at risk of acquiring fungal superinfection
- Alveolar damage facilitating invasion by fungus and acute respiratory distress syndrome are frequently associated with invasive pulmonary aspergillosis in the ICU;
- Invasive aspergillosis is a well-documented complication of severe ***influenza pneumonia***
- In an autopsy-based study, during 2003 ***SARS outbreak***, 10% (2/20) had invasive aspergillosis
- most common fungal agents documented to cause superinfection in COVID-19 patients are *Aspergillus flavus*, *Aspergillus fumigatus, Candida albicans,* and *Candida glabrata*

BIOMARKERS (PCT AND CRP)

- In a meta-analysis, risk of severe COVID-19 infection was seen to be 5 times more in patients with raised PCT
- patients who had raised PCT at time of admission had significantly higher risk of secondary bacterial infection

- In a study involving 1,099 patients, 2 groups were made based on disease severity:

❖ severe (173) and non-severe (926)

❖ MV was required in 61 patients among the severe group

❖ Majority of patients had raised CRP (81.5%) and PCT (13.7%) levels in severe group as compared to CRP (56.4%) and PCT (3.7%) among non-severe group

BIOMARKERS (PCT AND CRP)

- surrogate inflammatory markers such as CRP, and PCT can be done to recognize critically ill patients
- serial PCT measurement plays an important role for predicting evolution towards more severe COVID-19 disease
- Its production and subsequent release into circulation from extra thyroidal sources is tremendously boosted in bacterial infections and actively sustained by interleukin-6 and TNF-α
- biomarker's synthesis is inhibited by **INF-γ**, which is present in high concentrations during viral infections, so PCT value stays within the reference range in uncomplicated COVID-19 patients, and its significant rise would reflect super added bacterial infection or severe form of disease

PCT AND CRP

- CRP lacks specificity for bacterial infections and it rises late in infection
- PCT has better discriminatory ability than CRP and white blood count
- PCT increases promptly within 6–12 h upon stimulation
- PCT can differentiate between:
- ***bacterial and viral systemic infections***
- ***true bacteremia from contaminated blood cultures***

PCT AND CRP

- Randomized controlled trials conducted as per type of infection documents that PCT, when used for diagnosis, can reduce antibiotic exposure in hospitals in VAP and severe sepsis/shock
- measurements of PCT may be an important tool to limit antimicrobial use, the suboptimal specificity of PCT should be considered always as elevated levels, and it may also occur in advanced stages of COVID-19 without proven bacterial co- or superinfection