



THE CATHOLIC UNIVERSITY OF KOREA
CATHOLIC MEDICAL CENTER

HAP/VAP 에서 비정형 폐렴균의 임상적 의미

서울성모병원
이종민



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면역저하자가 아닌 환자의
HAP/VAP 에서
비정형 폐렴균의 임상적 의미



Contents

1. Bacteria

2. Viral

- Respiratory virus
- Herpesviridae

3. Pulmonary tuberculosis

4. COVID-19



Atypical pneumonia

- **Bacteria**
 - Mycoplasma, Chlamydia, Legionella, (Coxiella ...)
 - Mycobacterium tuberculosis
- **Viral**
 - Respiratory virus
 - HSV, CMV
- **Fungus**



Bacteria

- **Legionella**
 - 1990s: 10% of nosocomial infection
 - After 2010s: 10 – 15 cases / 1,000,000
- **Mycoplasma, Chlamydia : rare in HAP/VAP**



Legionella pneumonia

- **9,933 cases in 2018**
 - ~ 25%: health care-associated cases
- **Portable water contamination: most common source**
 - Via inhalation of legionella in aerosolized water
 - Shower heads, Hot water-faucets
- **Investigation**
 - Single case of presumptive legionella HAP
 - 2 cases of possible legionella HAP



| Variable | Value (n=526) |
|--|---------------------|
| Classification of pneumonia | |
| Hospital-acquired pneumonia | 419 (79.7) |
| Ventilator-associated pneumonia | 107 (20.3) |
| Location of diagnosis | |
| General ward | 379 (72.1) |
| Intensive care unit | 147 (27.9) |
| Prior IV antibiotic use within 90 days | |
| Used | 381 (72.4) |
| Not used | 141 (26.8) |
| No data | 4 (0.8) |
| Artificial airway | |
| None | 377 (71.7) |
| Endotracheal tube | 104 (19.8) |
| Tracheostomy | 42 (8.0) |
| Other | 3 (0.6) |
| Risk of aspiration | |
| Impaired swallowing | 223 |
| Impaired consciousness | 171 |
| Increased chance of gastric contents reaching the lung | 202 |
| Impaired cough reflex | 156 |
| SOFA score | 4.0 (2.0–7.0) |
| Sepsis | 336 (63.9) |
| Septic shock | 56 (10.6) |
| Specimen for bacterial cultures | |
| Respiratory samples | 434 (82.5) |
| Sputum | 287 (54.6) |
| Transtracheal aspirates | 168 (31.9) |
| Bronchial washing fluid | 34 (6.5) |
| Bronchoalveolar lavage | 9 (1.7) |
| Blood | 417 (79.3) |
| Pleural fluid | 32 (6.1) |
| Serological test for atypical pathogen | |
| Respiratory virus test | 130 (24.7) |
| AFB stain and culture | 163 (31.0) |
| Laboratory test | |
| White blood cell, $\times 10^3/L$ | 10.2 (7.1–14.5) |
| Hemoglobin, g/dL | 10.0 (8.8–11.5) |
| Platelet count, $\times 10^3/L$ | 175.0 (95.0–252.0) |
| Sodium, mmol/L | 137.0 (133.0–140.0) |
| Chloride, mmol/L | 101.0 (98.0–105.0) |

| Variable | No. (n=211) |
|--|-------------|
| Gram-positive pathogens | |
| <i>Staphylococcus aureus</i> | 24 |
| <i>Streptococcus pneumoniae</i> | 7 |
| <i>Enterococcus faecium</i> | 5 |
| <i>Nonstaphylococcus aureus Staphylococcus species</i> | 4 |
| Others* | 5 |
| Gram-negative pathogens | |
| <i>Acinetobacter baumannii</i> | 68 |
| <i>Pseudomonas aeruginosa</i> | 36 |
| <i>Klebsiella pneumoniae</i> | 35 |
| <i>Escherichia coli</i> | 11 |
| <i>Sternotrophomonas maltophilia</i> | 11 |
| <i>Enterobacter cloacae</i> | 10 |
| <i>Serratia marcescens</i> | 5 |
| <i>Proteus species</i> | 4 |
| <i>Klebsiella aerogenes</i> | 3 |
| <i>Moraxella catarrhalis</i> | 2 |
| <i>Burkholderia cephalica</i> | 2 |
| <i>Citrobacter species</i> | 2 |
| Others† | 2 |
| MDR pathogen identified‡, n (%) | |
| <i>Acinetobacter species</i> | 67 |
| <i>Pseudomonas aeruginosa</i> | 30 |
| <i>Enterobacteriaceae</i> | 27 |
| <i>Staphylococcus aureus</i> | 19 |
| <i>Enterococcus species</i> | 4 |



Legionella pneumonia – hospital outbreaks

| Year | Country | Source | Cases | Death |
|------|---------------|----------------|-------|------------|
| 2001 | Spain | Cooling Towers | 800+ | 6 (0.8%) |
| 2004 | Spain | Cooling tower | 127 | 21 (16.5%) |
| 2007 | Portland | Water system | 4 | 3 (75%) |
| 2008 | United States | Drinking water | 6 | 2 (33.3%) |
| 2012 | United States | Unknown | 22 | 6 (27%) |
| 2017 | Portugal | Cooling tower | 56 | 6 (11%) |



Legionella pneumonia

- **Legionella pneumophila serogroup 1**
 - 50 – 80% of Legionnaires' disease
 - Excrete antigen in urine
 - ~ 8% of diseases: serogroup 4, 6, longbeachae, micadadei



Legionella pneumonia

- **Diagnosis**
 - **Urinary antigen test**
 - Currently 97% of clinical diagnoses
 - For *L. pneumophila* serogroup 1
 - Sensitivity: 69 – 100% / Specificity: 99 – 100%
 - **Culture of respiratory tract specimen: Gold standard**
 - 3 days – 2 weeks
 - **Direct Fluorescent Antibody**



Legionella pneumonia

- **Treatment**

- **Macrolide / Fluoroquinolone: Treatment of choice**

- **Duration**

- **Minimum 5 days until clinically stable**
- **Severe pneumonia: 7 – 10 days**
- **Lung abscess / Empyema / Immunocompromised: extend**



Virus in HAP/VAP

- Mainly in immunosuppressed patients
- Underscored significance of importance in HAP/VAP?
- Respiratory virus
- Herpesviridae



Respiratory virus in HAP/VAP

- Common pathogen in CAP
- 2,488 patients from 2010 - 2012
- Pathogen detected: 38%
 - **Virus (23%)** Bacteria (11%) Both (3%) Fungal (1%)

Community-Acquired Pneumonia Requiring Hospitalization among U.S. Adults

| Pathogen detected | No. of cases per 10,000 |
|-----------------------|-------------------------|
| Viruses | |
| Human rhinovirus | 2.0 (1.7 – 2.3) |
| Influenza A or B | 1.5 (1.3 – 1.8) |
| Human metapneumovirus | 1.2 (1.0 – 1.4) |
| Parainfluenza virus | 0.8 (0.6 – 1.0) |
| Coronavirus | 0.6 (0.4 – 0.7) |
| Adenovirus | 0.4 (0.2 – 0.5) |
| Bacteria | |
| <i>S. pneumoniae</i> | 1.2 (1.0 – 1.4) |
| <i>S. aureus</i> | 0.4 (0.3 – 0.6) |
| <i>L. pneumophila</i> | 0.4 (0.2 – 0.5) |

Severe pneumonia from the hospital (n=262)

Mechanical ventilated:
251 (95.8%)

Bronchoscopic BAL performed (n=107)

- BAL fluid RT-PCR performed (n=93)
- BAL fluid shell vial culture performed (n=87)
- NP specimen RT-PCR performed (n=75)

Viral pathogen identified (n=42)

- BAL fluid test (+) (n=37)
 - RT-PCR (+) (n=34)
 - Shell vial culture (+) (n=13)
- Nasopharyngeal specimen RT-PCR (+) (n=24)

Immunocompromised: 36.4%
Immunocompetent: 11.1%

Viral pathogen not identified (n=65)

Bronchoscopic BAL not performed (n=155)

- Nasopharyngeal specimen RT-PCR performed (n=99)

Viral pathogen identified (n=17)

- Nasopharyngeal specimen RT-PCR (+) (n=17)

Viral pathogen identified (n=59) (22.5%)

- BAL fluid test (+) (n=37)
 - RT-PCR (+) (n=34)
 - Shell vial culture (+) (n=13)
- Nasopharyngeal specimen RT-PCR (+) (n=41)

Viral pathogen not identified (n=138)

| | HAP patients (n = 262) (%) |
|-----------------------------|----------------------------|
| Virus | 59 (22.5) |
| Respiratory syncytial virus | 16 (6.1) |
| Type A | 11 (4.2) |
| Type B | 5 (1.9) |
| Parainfluenza virus | 16 (6.1) |
| Type 3 | 15 (5.7) |
| Type 1 | 2 (0.8) |
| Rhinovirus | 15 (5.7) |
| Influenza virus | 10 (3.8) |
| Influenza A | 9 (3.4) |
| Influenza B | 1 (0.4) |
| Cytomegalovirus | 5 (1.9) |
| Human coronavirus | 4 (1.5) |
| Human coronavirus OC43 | 2 (0.8) |
| Human coronavirus 229E/NL63 | 2 (0.8) |
| Bocavirus | 2 (0.8) |
| Human metapneumovirus | 2 (0.8) |
| Adenovirus | 1 (0.4) |



Respiratory virus in Non-ventilated HAP

| Variable | Undetermined (55%) | Virus isolated (22.7%) | Bacteria isolated (23.8%) | P value |
|---------------------------|-----------------------|---------------------------|------------------------------|---------|
| Age | 59.9 ± 14.5 | 54.5 ± 14.4 | 56.3 ± 15.9 | 0.234 |
| Co-morbidities | | | | |
| Collagen Vascular Disease | 14.1% | 5.1% | 9.3% | 0.120 |
| Metastatic malignancy | 7.4% | 15.4% | 12.2% | 0.153 |
| HIV | 1.1% | 0% | 2.4% | 0.454 |
| Hospital mortality | 16.0% | 15.4% | 14.6% | 0.905 |



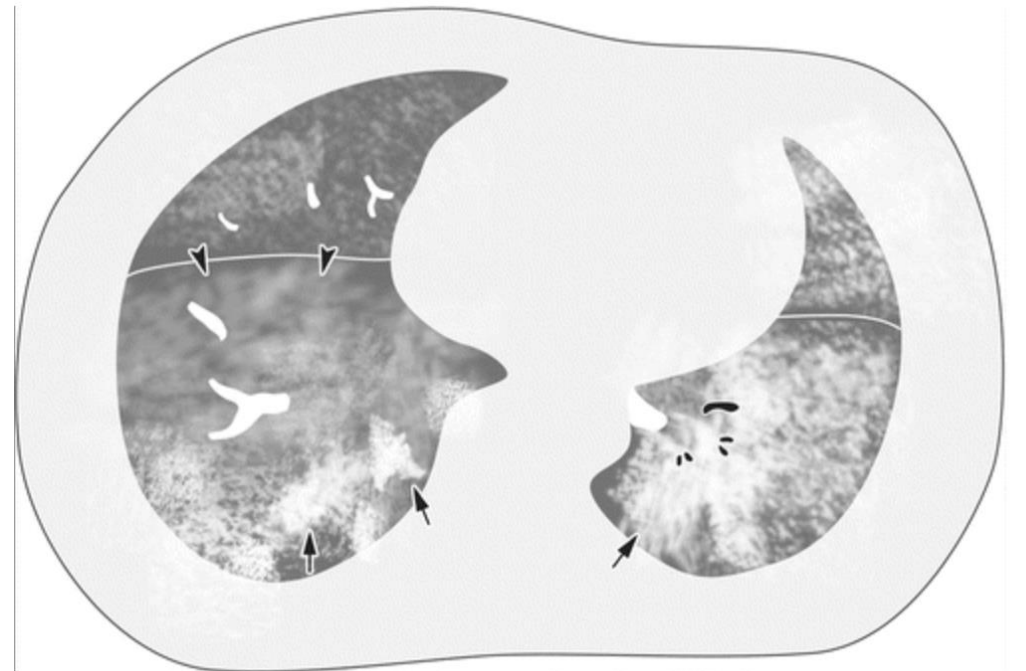
Meaning of respiratory virus in HAP/VAP

- **Specific treatment**
 - Conservative care – most of RVs
 - Influenza virus – oseltamivir, peramivir ...
 - Adenovirus – cidofovir ...
- **Risk of co-infection**
 - Bacteria, Fungus (IPA) ...
- **Antibiotics de-escalation**



Influenza

- CT pattern
 - Multiple **consolidations** along bronchovascular bundle
 - Diffuse GGO
 - Interlobular septal thickening
- Usually seasonal





Influenza

- **Co-infection**
 - **Streptococcus pneumoniae**
 - **Staphylococcus aureus**
 - **Invasive aspergillosis (- 19%)**

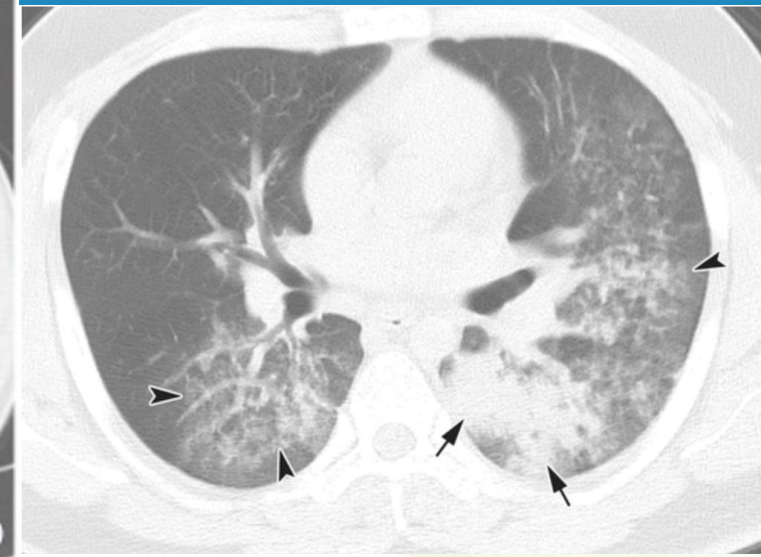
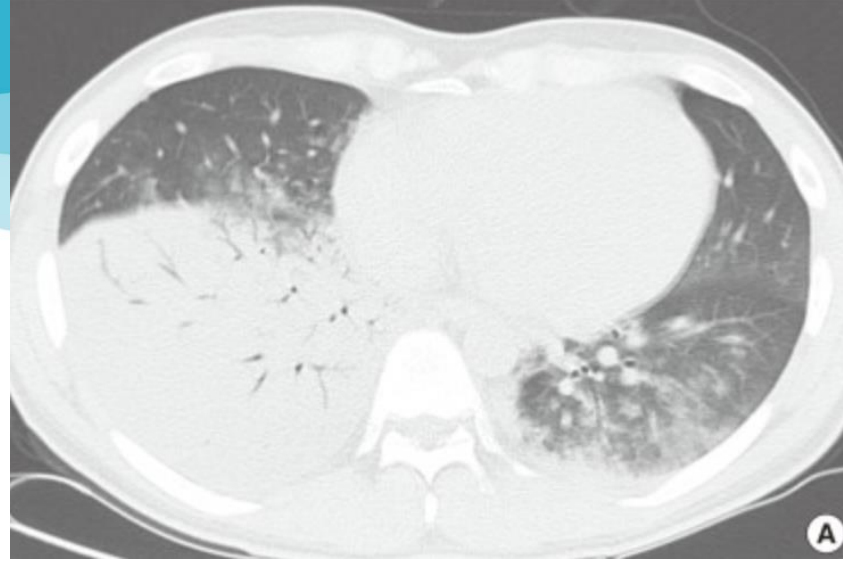
- **Treatment**
 - **Oseltamivir, Peramivir, zanamivir ...**



Adenovirus

- Military trainees
- Psychiatric care facility ...

- CT pattern
 - Bilateral multifocal GGO with patchy consolidation
 - Lobar / segmental distribution
 - Resembles bacterial pneumonia





Adenovirus

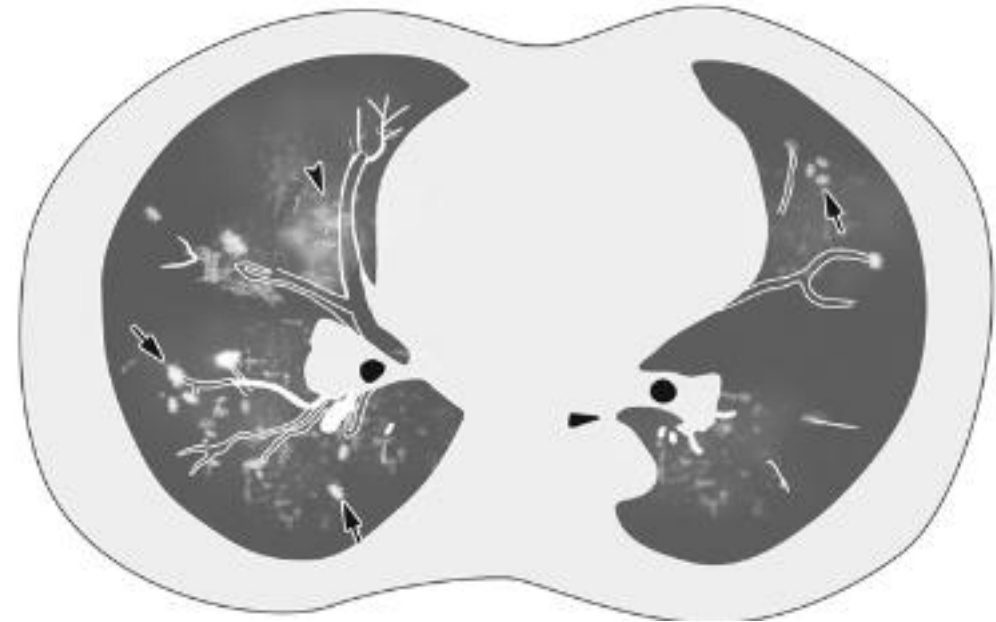
- **Poor outcome**
 - Monocytopenia
 - Multi-lobar infiltration
 - Pleural effusion

- **Treatment**
 - Cidofovir / Ribavirin in severe adenoviral pneumonia



Respiratory Syncytial Virus (RSV)

- **Most common cause of acute respiratory tract infection**
 - Severe infection at childhood / immunocompromised
 - Old age with underlying lung / heart disease
 - Major cause of COPD / Asthma AE
- **CT pattern**
 - Multifocal patchy consolidation
 - GGO
 - Centrilobular nodule





Respiratory Syncytial Virus (RSV)

• Treatment

- Ribavirin (inhaled form)
- FDA approved in infants & young children
- Adults – lack of efficacy data but commonly used

- Monoclonal Antibodies (palivizumab)
- IVIG
 - Asceniv (IVIG with high RSV titer)



Herpesviridae

- Herpes simplex virus (HSV)
- Cytomegalovirus (CMV)
- Epstein-Barr virus (EBV)

- Reactivation after primary infection
 - Immunoparalysis due to proinflammatory response
- Relatively common in immunocompetent patients



HSV

| Author, year | Population | Oropharyngeal reactivation N (%) | Lung reactivation | Virological method |
|-------------------------------------|--|-------------------------------------|-------------------|--------------------|
| Bruynseels et al, 2003 ⁹ | 764 patients (361 on MV) | 169/764 (22%) | 58/361 (19%) | Virus culture |
| Ong et al, 2004 ¹¹ | 393 patients on MV | 106 (27%) | | PCR |
| Luyt et al, 2007 ³ | 201 patients with VAP suspicion, on MV > 4 d | 109 (54%) | 129 (64%) | PCR, virus culture |
| Linssen et al, 2008 ¹⁶ | 260 patients with VAP suspicion | – | 99 (32%) | PCR |
| Costa et al, 2012 ³³ | 127 patients with VAP suspicion | – | 38 (31%) | PCR |



HSV

- HSV bronchopneumonitis
 - Aspiration / Hematogeneous spread
 - No definite diagnostic criteria
 - Clinical deterioration with
 - HSV detection (PCR, culture, nuclear inclusion) in BAL or biopsy
 - HSV viral load > 10^5 copies/million cells
 - Oral / Labial herpetic lesion

- Treatment: acyclovir





CMV

| Author, year | Population | Frequency of HSV reactivation | Clinical manifestation of CMV disease | Diagnostic method |
|-------------------------------------|---|-------------------------------|---------------------------------------|--|
| Papazian et al, 1996 ²⁰ | 86 patients with ARF or VAP | 25/86 (29%) | Interstitial lung disease | Histology: autopsy in 60, open lung biopsy in 26 |
| Heininger et al, 2001 ³⁶ | 56 surgical patients with SAPS II score >40 | 7/56 (6%) | NA | Virus culture, PCR |
| Papazian et al, 2007 ²¹ | 100 patients with unexplained ARDS | 30/100 (30%) | Pneumonia, fibrosis | Histology: open-lung biopsy. CMV recovered from lung tissue by virus culture in 10/30 |
| Chiche et al, 2009 ²² | 242 patients on MV ≥2 d | 11/242 | Pneumonia | Rapid shell-vial culture, virus culture |



CMV

- **CMV pneumonia**
 - Clinical deterioration with
 - Definite: surgical lung biopsy
 - Probable: intranuclear inclusion, virus culture (+)

- Negative DNA at BAL: negative predictive value = 100%
- High viral load → High CMV pneumonia likelihood

- Probable disease + proven extra-pulmonary disease



CMV

- **CT findings**
 - Diffuse ill defined patchy GGO
 - Interlobular septal thickening

- **Treatment**
 - First line: Ganciclovir, Foscarnet
 - Second line: Cidofovir





Pulmonary Tb in HAP/VAP

- Rare study about Tb in HAP/VAP
- Activation of LTBI
 - Old age, Comorbidities ...
- Exposure to unrecognized Pul Tb patient



| Variable | Value (n=526) |
|--|---------------|
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| Respiratory virus test | 130 (24.7) |
| AFB stain and culture | 163 (31.0) |

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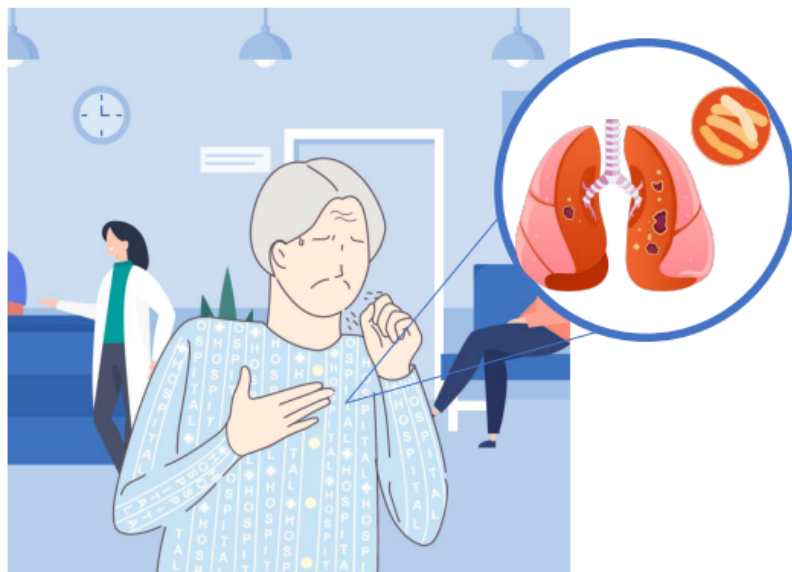
Pulmonary Tb in HAP/VAP

- **Taiwan, 2012, multicenter retrospective**
 - HCAP (n = 701) vs CAP (n = 934)
 - Tb in HCAP: 3% (n = 21) in CAP: 2.7% (n = 25)
- **Risk factors of pulmonary Tbc in HCAP**
 - Previous anti-Tb treatment, High PSI score



Pulmonary Tb in HAP/VAP

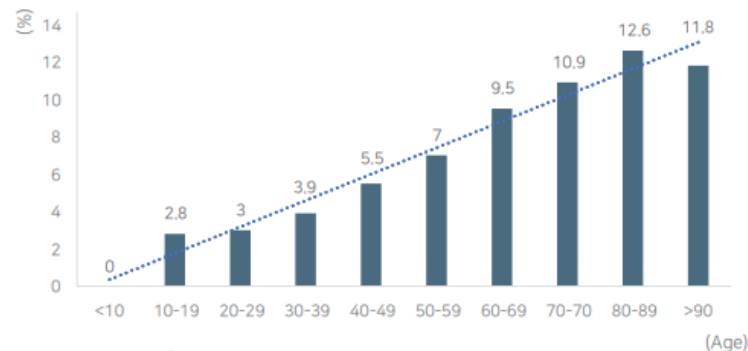
Nosocomial exposure to tuberculosis (TB)
2012 to 2016



2,236 pts in ICU

7,186 Unrecognized active TB cases
94,636 Person-days of hospitalization

Unrecognized by age group



! Patients above 60 accounted for 64%.
Patients in their 80s showed the highest risk.

Types of high-risk procedure performed among
unrecognized TB



Bronchoscopy
(28.86%)



Nebulizer therapy
(28.48%)



Endotracheal intubation
(13.02%)

Especially in ICU



COVID-19 in HAP/VAP

- **Nosocomial infection: relatively common**
- **Sx monitoring / Visitor restrictions / Cohort wards ...**
- **Hospital-Onset patients / Visitors / HCW**

Table. Summary of COVID-19 Admissions and Hospital-Onset COVID-19 Rates During the Omicron Winter Surge vs the Prior Winter Surge



| | Winter 1, wild-type variants, Dec 15, 2020-Feb 28, 2021 | Winter 2, Omicron strain, Dec 15, 2021-Feb 28, 2022 |
|--|---|---|
| Cases in Massachusetts | 286 917 | 685 346 |
| Total admissions to Mass General Brigham hospitals | 34 202 | 33 571 |
| Patient-days | 221 587 | 231 630 |
| Admissions with COVID-19 | 3218 | 3820 |
| COVID-19 patient-days | 24 117 | 26 099 |
| Non-COVID-19 patient-days | 197 470 | 205 531 |
| COVID-19-positive employees ^a | 846 | 5798 |
| Patients first diagnosed with COVID-19 on hospital day ≥ 5 , No. (rate/1000 non-COVID-19 patient-days) | 111 (0.56) | 178 (0.87) |
| Relative risk for winter 2 vs 1 (95% CI) | NA | 1.54 (1.22-1.95) |
| Patients first diagnosed with COVID-19 on hospital day ≥ 8 , No. (rate/1000 non-COVID-19 patient-days) | 70 (0.35) | 118 (0.57) |
| Relative risk for winter 2 vs 1 (95% CI) | NA | 1.62 (1.21-2.18) |
| Patients first diagnosed with COVID-19 on hospital day ≥ 15 , No. (rate/1000 non-COVID-19 patient-days) | 32 (0.16) | 77 (0.37) |
| Relative risk for winter 2 vs 1 (95% CI) | NA | 2.31 (1.53-3.49) |



COVID-19 in HAP/VAP

- **Increase risk of HAP/VAP (- 50%)**
 - **High incidence of MDR (- 35%)**
- **Deep sedation, Prolonged MV, Steroids, Anti IL-6 ...**

STUDY DESIGN

Multicenter retrospective study of 774 patients with severe COVID in 8 Italian hospitals from February to May 2020

46% of patients (n=359) developed 759 HAIs

389 Ventilator-associated pneumonia (VAP)

183 Blood stream infections (BSI)

74 Catheter-related blood stream infections

RESULTS

Multivariate Risk Factors for HAI

Younger Age
(HR 0.98; 0.97-0.99)

Higher PEEP
(HR 1.05 (1.01-1.10))

Broad Spectrum Antibiotics at Admission
(HR 0.61; 0.44-0.84)

OUTCOMES

Hospital LOS
Without HAI: 23 days
With HAI: 42 days

ICU LOS
Without HAI: 9 days
With HAI: 24 days

Mechanical Ventilation
Without HAI: 9 days
With HAI: 24 days

Mortality in Those Patients With HAI Complicated by Septic Shock
Without HAI: 29%
With HAI: 52%

■ Without HAI ■ With HAI

Critically-ill patients with COVID-19 are at high risk for HAIs including VAPs, BSI, and CLABSIs. Significant mortality is seen in those who get a HAI.



Summary

- **Atypical pneumonia**
 - Relatively common pathogen in HAP/VAP

- **Viruses**
 - Respiratory virus, CMV, HSV

- **High incidence of HAP/VAP in COVID-19 patients**



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Thank you for your attention!