



## Covid-19/Influenza-Associated Pulmonary Aspergillosis - Management

Philipp Koehler, FECMM<sup>1,2,3</sup>, Jacques F. Meis, FECMM<sup>4</sup>, Luis Ostrosky-Zeichner, FECMM<sup>5</sup>, Boris Böll<sup>1,3</sup>, Martin Hoeningl, FECMM<sup>6,7</sup>, Oliver A. Cornely, FECMM<sup>1,2,8\*</sup>, and Dennis A. Eichenauer<sup>1,3\*</sup>

<sup>1</sup>Univ. of Cologne, Faculty of Medicine and Univ. Hospital Cologne, Dep. I of Internal Medicine, Excellence Center for Medical Mycology (ECMM), Cologne, Germany. <sup>2</sup>Univ. of Cologne, Cologne Excellence Cluster on Cellular Stress Responses in Aging-Associated Diseases (CECAD), Cologne, Germany. <sup>3</sup>Univ. Hospital Cologne, Dep. I of Internal Medicine, Intensive Care Medicine, Cologne, Germany <sup>4</sup>Dep. of Medical Microbiology and Infectious Diseases, Excellence Center for Medical Mycology (ECMM), Center of Expertise in Mycology Radboudumc/CWZ, Canisius Wilhelm Hospital, Nijmegen, The Netherlands. <sup>5</sup>Div. of Infectious Diseases, McGovern Medical School, Houston, Texas, USA. <sup>6</sup>Division of Infectious Diseases and Global Public Health, Univ. of California San Diego, La Jolla, California. <sup>7</sup>Section of Infectious Diseases and Tropical Medicine, Medical Univ. of Graz, Austria <sup>8</sup>German Centre for Infection Research, Partner Site Bonn-Cologne, Cologne, Germany. \* these authors contributed equally

### References

1. Koehler et al. CMI 2019. 2. Koehler et al. Mycoses 2020. 3. Mercier et al. CID 2020. 4. Vergidis et al. CMI 2019.
5. Schauwvlieghe et al. Lancet Respir Med 2018. 6. Beigel et al. NEJM 2020. 7. Goldmann et al. NEJM 2020. 8. Uyeke et al. CID 2019. 9. Ullmann et al. CMI 2018. 10. Cornely et al. Mycoses 2019. 11. ARDS: Berlin Definition JAMA 2012. 12. Fan et al. AJRCCM 2017. 13. Berlin et al. NEJM 2020. 14. Guerin et al. NEJM 2013. 15. Bellani et al. JAMA 2016.

## Patients with acute respiratory distress syndrome (ARDS) and/or ICU treatment under mechanical ventilation due to suspected pneumonia<sup>1,2</sup>

### DIAGNOSIS BUNDLE

- ✓ Day (D)0+2 – Chest CT (if feasible)
- ✓ D0 – Bronchoalveolar lavage (BAL) → inspection of trachea and bronchi (consider risk of aerosolization of SARS-CoV-2) or tracheal aspirate (TA)
  - Virology: Respiratory viruses incl. SARS-CoV-2 & Influenza A/B
  - Microbiology: direct microscopy, culture, susceptibility, bacterial & fungal (*Aspergillus* spp.) specific PCR, galactomannan (GM) from BAL/TA fluid, if available: IMMY™ *Aspergillus* lateral flow assay (LFA)
- ✓ If SARS-CoV-2 or Influenza A/B positive → serum GM, IMMY™ *Aspergillus* LFA and β-D-glucan screening (if available)<sup>3</sup> 3x/week until discharge from ICU or defervescence for ≥7 days with improved lung function
- D7±3 w/o improvement: BAL → inspection of trachea and bronchi (consider risk of aerosolization of SARS-CoV-2)
  - ✓ Microbiology: direct microscopy, high volume culture, susceptibility testing of min. 5 isolates or use screening agar with azoles plus specific fungal PCR (*Aspergillus* spp.); GM from BAL/TA fluid<sup>4</sup>

### One of the following signs or symptoms triggers a repeat chest CT after 7 days<sup>5</sup>

- Infiltrates or specific invasive Aspergillosis (IA) signs on prior chest CT
- Microbiological findings indicative of IA
- Refractory fever ≥3 days of appropriate antibiotic therapy
- New fever after a period of defervescence of ≥48 hours while still on antibiotics without other cause
- Haemoptysis
- Pleural friction rub or chest pain
- Worsening respiratory insufficiency despite appropriate antibiotic therapy and ventilator support

## TREATMENT BUNDLE

### COVID-19<sup>6,7</sup>

- ✓ Remdesivir 200mg loading dose, followed by 100mg QD iv can be considered on a case-by-case basis. Alternatively use local standard of care

### INFLUENZA A/B<sup>8</sup>

- ✓ Oseltamivir 75mg BID po –  $\geq 5$  days
- ✓ Oseltamivir 105mg or 150mg BID po can be considered during pregnancy
- ✓ Steroids for influenza treatment have been associated with increased mortality → not recommended unless indicated for known adrenal insufficiency

### COVID-19/INFLUENZA-ASSOCIATED PULMONARY ASPERGILLOSIS (CAPA/IAPA)<sup>9, 10</sup>

- ✓ 1<sup>st</sup>-line options: voriconazole (loading dose 6mg/kg BW BID, iv on D1; D2 4mg/kg BW BID, iv) or isavuconazole (loading dose 200mg TID, iv D1+2 (6 doses); D3 200mg QD, iv)
- ✓ Consider local resistance situation
- ✓ 2<sup>nd</sup>-line options in refractory cases or when 1<sup>st</sup>-line options contraindicated/not feasible: liposomal amphotericin B (3mg/kg BW QD, iv), posaconazole (300mg BID, iv on D1; D2 300mg QD, iv), echinocandins
- ✓ Refractory disease: switch or add antifungal class

### THERAPEUTIC DRUG MONITORING (TDM) – weekly (2x in first week)<sup>9</sup>

- ✓ Voriconazole: Target plasma trough concentration: 1-5.5mg/L
- ✓ Posaconazole: Target plasma trough concentration:  $> 1$ mg/L
- ✓ Isavuconazole: No target level available, but TDM may help explain failure

### ARDS-MANAGEMENT<sup>11-13</sup>

- ✓ Use lung protective ventilation
- ✓ Sufficient positive end-expiratory pressure (PEEP) on the ventilator may prevent alveolar collapse and facilitate the recruitment of unstable lung regions
  - ✓ CAVEAT: PEEP decreases venous return to the heart and can cause hemodynamic instability. Alveolar overdistention can be caused by excessive PEEP, that furthermore reduces respiratory-system compliance
- ✓ Consider prone positioning during mechanical ventilation in patients with severe ARDS ( $\geq 16$  hours per day)<sup>14, 15</sup>
- ✓ Consider vVECMO as rescue strategy in patients with refractory respiratory failure. However, it is currently unknown if it is beneficial during COVID-19 triggered cytokine storm or hypercoagulability