Fungal Infections in ECMO

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What is ECMO?

• Extracorporeal membrane oxygenation

• Indication is acute severe pulmonary or heart failure considered reversible but non-responsive to conventional treatment
  • E.g. severe pneumonia, cardiac arrest, post cardiac surgery, bridge to heart transplant

• Blood circulated outside the body, passes through oxygenator and heat exchanger

• Two types: VV-VA
Some critically ill patients have suffered such severe heart and lung failure that a ventilator (breathing machine) is not enough to keep them alive. Our ECMO (extracorporeal membrane oxygenation) unit uses a cutting edge technique to take over patients’ heart and lung functions to allow these organs to recover.
Venovenous (VV) ECMO for isolated respiratory failure

Diagram of venovenous ECMO for respiratory failure. When there is no native lung function the arterial saturation will be 75 to 85 percent. VV access: Blood is withdrawn from the IVC, circulated through the artificial membrane, and returned via the SVC to the RA.

ECMO: extracorporeal membrane oxygenation; AO: aorta; PV: pulmonary vein; PA: pulmonary artery; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle; VV: venovenous; IVC: inferior vena cava; SVC: superior vena cava.

Veno-arterial (VA) ECMO for cardiac and/or respiratory failure

Demonstrated here with right internal jugular vein drainage and right carotid artery infusion.
ECMO outcomes

- Randomised study of ECMO vs conventional management (CESAR trial) (Peek et al, Lancet 2009)
  - 180 patients in UK
  - 63% vs 47% survival without disability at 6 months
- Cohort study: 75 matched pairs of patients with H1N1 flu
  - Lower hospital mortality with ECMO (24% vs 53%) (Noah et al, JAMA 2011)
- Observational studies in heart failure
ECMO and fungal infection

- ECMO as treatment for fungal infections
- Fungal infections as complications of ECMO
- Antifungal drug levels during ECMO
ECMO and fungal infection

• ECMO as treatment for fungal infections
• Fungal infections as complications of ECMO
• Antifungal drug levels during ECMO
ECMO for PCP

Table 1. Patients with Respiratory Failure Caused by *Pneumocystis jirovecii* Pneumonia Treated with ECMO

<table>
<thead>
<tr>
<th>Patient (Ref)</th>
<th>Age (y)/Sex</th>
<th>CD4 (cells/ml)</th>
<th>HIV Viral Load (copies/ml)</th>
<th>Timing of ART Initiation (Pre-, On-, Post-ECMO)</th>
<th>PaO2 (mmHg)/FiO2 (%)</th>
<th>ECMO Initiation (hospital day)/Duration (days)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (our patient)</td>
<td>45/M</td>
<td>33</td>
<td>113,000</td>
<td>Pre</td>
<td>59/60</td>
<td>5/57</td>
<td>Died in hospital, after decannulation</td>
</tr>
<tr>
<td>2 (Goodman et al)(^{11})</td>
<td>30/F</td>
<td>13</td>
<td>976,631</td>
<td>Post</td>
<td>50.1/100</td>
<td>3/7</td>
<td>Survived to hospital discharge</td>
</tr>
<tr>
<td>3 (Gutermann et al)(^{12})</td>
<td>55/M</td>
<td>9</td>
<td>80,235</td>
<td>Post</td>
<td>NR/NR</td>
<td>4/4</td>
<td>Survived to hospital discharge</td>
</tr>
<tr>
<td>4 (Steppan)(^{13})</td>
<td>39/M</td>
<td>69</td>
<td>6297</td>
<td>Pre</td>
<td>NR/100</td>
<td>12/14</td>
<td>Died on ECMO</td>
</tr>
<tr>
<td>5 (Goodman et al)(^{11})</td>
<td>25/M</td>
<td>36</td>
<td>622,234</td>
<td>Pre</td>
<td>63.6/100</td>
<td>18/69</td>
<td>Died on ECMO</td>
</tr>
</tbody>
</table>

ART, antiretroviral therapy; ECMO, extracorporeal membrane oxygenation; NR, not reported.
ECMO for Blastomycosis

Extracorporeal membrane oxygenation for blastomycosis-related acute respiratory distress syndrome: a case series

Oxygé nation par membrane extracorporelle pour un syndrome de détresse respiratoire aiguë liée à une blastomycose: une série de cas

Joseph M. Bednarczyk, MD · Shravan Kethireddy, MD · Christopher W. White, MD · Darren H. Freed, MD, PhD · Rohit K. Singal, MD · Dean Bell, MD · Syed Zaki Ahmed, MD · Anand Kumar, MD · Bruce Light, MD
ECMO for Blastomycosis

Extracorporeal membrane oxygenation for overwhelming *Blastomyces dermatitidis* pneumonia
Heidi J Dalton, James H Hertzog, Robert L Hannan*, Phyllis Vezza†
and Gabriel J Hauser
ECMO for acute aspergillus pneumonia

CASE REPORT

Gardening can induce pulmonary failure: Aspergillus ARDS in an immunocompetent patient, a case report

Nina Jung¹, Slike Mraona¹, Susanne Schroth¹, Timon Vassiliou², Frank Sommer³, Eduard Walthers⁴, Christian Aeplinus⁵, Andreas Jerentrup⁶, Claus Vogelmeier⁷, Angelique Holland⁸ and Rembert Koczulla⁹

Early diagnosis of invasive pulmonary aspergillosis in a young immunocompetent patient

Rosanna Vaschetto¹, Vesselina Kroumova², Carlo Olivieri¹, Valentina Bergamaschi¹, Laura Cancelliere¹, Silvio Borri³, Giacomo Fortina³, Paolo Navalesi¹, Francesco Della Corte¹

¹Università del Piemonte Orientale “Amedeo Avogadro” Alessandria-Novara-Vercelli, Dipartimento di Medicina Clinica e Sperimentale, Anestesia e Terapia Intensiva, Azienda Ospedaliero Universitaria “Maggiore della Carità”, Novara, Italy; ²Dipartimento di Microbiologia, Azienda Ospedaliero Universitaria “Maggiore della Carità”, Novara, Italy; ³Dipartimento di Malattie Infettive, Ospedale San Andrea, Vercelli, Italy
ECMO and fungal infection

• ECMO as treatment for fungal infections
• Fungal infections as complications of ECMO
• Antifungal drug levels during ECMO
Epidemiology of nosocomial fungal infections

• Candida infection
  • 5th most common cause of nosocomial infection (Richards et al, Pediatrics 1999)
  • 3rd most common cause of catheter related bloodstream infection (Wisplinghoff et al, Pediatr Infect Dis J 2003)

• Healthcare associated invasive aspergillosis
  • In ICU, COPD patients on steroids and broad spectrum antibiotics
  • 7% of consecutive ICU admissions have AF isolated (Meersemann et al, Am J Resp Med Crit Care 2004)
  • Positive predictive value of AF isolated in hospitalised COPD patients: 22% (Guinea Clin Microbiol Infect 2010)
The Morbidity and Mortality of Patients with Fungal Infections Before and During Extracorporeal Membrane Oxygenation Support

Thomas Pluim, MD¹, Natasha Halasa, MD, MPH², Sharon E. Phillips, MSPH³, and Geoffrey Fleming, MD¹

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²Department of Pediatrics, Division of Infectious Diseases, Vanderbilt University School of Medicine, Nashville, TN

³Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN

<table>
<thead>
<tr>
<th></th>
<th>Neonate</th>
<th>Pediatric</th>
<th>Adult</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total N</td>
<td>12933</td>
<td>6073</td>
<td>2067</td>
</tr>
<tr>
<td>VA Support % (N)</td>
<td>74% (9542)</td>
<td>83% (5014)</td>
<td>61% (1260)</td>
</tr>
<tr>
<td>VV Support % (N)</td>
<td>26% (3391)</td>
<td>17% (1059)</td>
<td>39% (807)</td>
</tr>
<tr>
<td>Mean Age</td>
<td>4.1 (days)</td>
<td>3.7 (yrs)</td>
<td>44.6 (yrs)</td>
</tr>
<tr>
<td>Male % (N)</td>
<td>58% (7514)</td>
<td>53% (3205)</td>
<td>60% (1246)</td>
</tr>
<tr>
<td>Mean Duration of Support (hrs)</td>
<td>187.7</td>
<td>206.7</td>
<td>185.2</td>
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Prevalence and mortality of fungal infection on ECMO

<table>
<thead>
<tr>
<th></th>
<th>Candida Sp</th>
<th>Non-Candida Sp</th>
<th>p value</th>
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<tr>
<td><strong>Neonates</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Prevalence of Pre-ECMO Infection</td>
<td>91.2% (31)</td>
<td>8.8% (3)</td>
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<tr>
<td>Mortality of Patients with Pre-ECMO Infection</td>
<td>61% (19/31)</td>
<td>33% (1/3)</td>
<td>0.3475</td>
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<tr>
<td>Prevalence of On-ECMO Infection</td>
<td>84% (99)</td>
<td>16% (19)</td>
<td></td>
</tr>
<tr>
<td>Mortality of Patients with On-ECMO Infection</td>
<td>70% (69/99)</td>
<td>89% (17/19)</td>
<td>0.0757</td>
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<tr>
<td><strong>Pediatrics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence of Pre-ECMO Infection</td>
<td>92% (52)</td>
<td>8% (6)</td>
<td></td>
</tr>
<tr>
<td>Mortality of Patients with Pre-ECMO Infection</td>
<td>69% (36/52)</td>
<td>50% (3/6)</td>
<td>0.3419</td>
</tr>
<tr>
<td>Prevalence of On-ECMO Infection</td>
<td>84% (145)</td>
<td>16% (28)</td>
<td></td>
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<tr>
<td>Mortality of Patients with On-ECMO Infection</td>
<td>58% (84/145)</td>
<td>57% (16/28)</td>
<td>0.9384</td>
</tr>
<tr>
<td><strong>Adults</strong></td>
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<td></td>
<td></td>
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<tr>
<td>Prevalence of Pre-ECMO Infection</td>
<td>82% (27)</td>
<td>18% (6)</td>
<td></td>
</tr>
<tr>
<td>Mortality of Patients with Pre-ECMO Infection</td>
<td>81% (22/27)</td>
<td>67% (4/6)</td>
<td>0.4220</td>
</tr>
<tr>
<td>Prevalence of On-ECMO Infection</td>
<td>81% (86)</td>
<td>19% (20)</td>
<td></td>
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<tr>
<td>Mortality of Patients with On-ECMO Infection</td>
<td>50% (43/86)</td>
<td>35% (7/20)</td>
<td>0.2261</td>
</tr>
</tbody>
</table>

Prevalence of fungal infection

- 0.26%
- 0.9%
- 0.96%
- 2.8%
- 1.6%
- 5%

Pluim et al 2012
### Odds ratio of mortality

<table>
<thead>
<tr>
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<th>Acquired</th>
<th></th>
<th></th>
<th></th>
<th></th>
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<tr>
<td></td>
<td>N</td>
<td>OR (95% CI)</td>
<td>N</td>
<td>OR (95% CI)</td>
<td>N</td>
</tr>
<tr>
<td>Neonates</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>All Neonates</td>
<td>86/118</td>
<td><strong>4.77</strong> (3.18–7.17)</td>
<td>20/34</td>
<td><strong>2.51</strong> (1.26–4.97)</td>
<td>3/5</td>
</tr>
<tr>
<td>VA Support</td>
<td>79/102</td>
<td><strong>4.54</strong> (2.85–7.24)</td>
<td>18/29</td>
<td><strong>2.14</strong> (1.01–4.53)</td>
<td>3/3</td>
</tr>
<tr>
<td>VV Support</td>
<td>7/16</td>
<td><strong>3.97</strong> (1.47–10.7)</td>
<td>2/5</td>
<td><strong>3.38</strong> (0.56–20.27)</td>
<td>0/2</td>
</tr>
<tr>
<td>Pediatrics</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>All Pediatrics</td>
<td>100/173</td>
<td><strong>1.59</strong> (1.17–2.15)</td>
<td>39/58</td>
<td><strong>2.36</strong> (1.36–4.10)</td>
<td>10/13</td>
</tr>
<tr>
<td>VA Support</td>
<td>78/131</td>
<td><strong>1.49</strong> (1.05–2.12)</td>
<td>28/44</td>
<td><strong>1.76</strong> (0.95–3.27)</td>
<td>8/11</td>
</tr>
<tr>
<td>VV Support</td>
<td>22/42</td>
<td><strong>2.51</strong> (1.35–4.66)</td>
<td>11/14</td>
<td><strong>8.27</strong> (2.29–29.84)</td>
<td>2/2</td>
</tr>
<tr>
<td>Adults</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All Adults</td>
<td>50/106</td>
<td>0.72 (0.49–1.06)</td>
<td>26/33</td>
<td><strong>3.09</strong> (1.33–7.14)</td>
<td>3/4</td>
</tr>
<tr>
<td>VA Support</td>
<td>34/59</td>
<td>0.73 (0.43–1.24)</td>
<td>18/19</td>
<td><strong>10.03</strong> (1.33–75.37)</td>
<td>3/3</td>
</tr>
<tr>
<td>VV Support</td>
<td>16/47</td>
<td>0.77 (0.41–1.42)</td>
<td>8/14</td>
<td>2.03 (0.7–5.92)</td>
<td>0/1</td>
</tr>
</tbody>
</table>

Pluim et al 2012
Frequency of candidaemia in ECMO

• ELSO database:
  • Blood stream infections in 11.7% of cases or 15.4 / 1000 ECMO days (30.6% in adults)
  • Highest rate in VA vs. VV ECMO
  • Candida second cause (12.7%)

• 146 patients
  • 24 cases of BSI, 9 were Candida (Aubron et al 2013)
IA in ECMO

• Retrospective review of ELSO registry:
  • 46 patients (19 adults)
  • 42% survival to hospital discharge in adults
  • median age 30.2 years
  • Mostly immunocompetent

• Case report: combination therapy (voriconazole and anidulafungin)+IFNgamma (Parcell et al 2014)
Aspergillus isolated in patients on ECMO (Aubron et al 2013)

• 11/151 (7.2%) had Aspergillus isolated (vs. 1.7% in general ICU admissions)
• Median age 48 years
• 5/11 had no risk factors
• Mortality 74%
Difficulties in diagnosing IA in ECMO

• Non specific radiology- underlying disease (pneumonia/heart failure)
• Biopsy usually impossible (bleeding risk)
• Poor sensitivity of respiratory culture
Clinical algorithm to diagnose IA in ICU (Blot et al, Am J Resp Crit Care Med 2012)

Proven invasive pulmonary aspergillosis
Idem EORTC/MSG criteria

Putative invasive pulmonary aspergillosis (all four criteria must be met)
1. *Aspergillus*-positive lower respiratory tract specimen culture (= entry criterion)
2. Compatible signs and symptoms (one of the following)
   - Fever refractory to at least 3 d of appropriate antibiotic therapy
   - Recrudescent fever after a period of defervescence of at least 48 h while still on antibiotics and without other apparent cause
   - Pleuritic chest pain
   - Pleuritic rub
   - Dyspnea
   - Hemoptysis
   - Worsening respiratory insufficiency in spite of appropriate antibiotic therapy and ventilatory support
3. Abnormal medical imaging by portable chest X-ray or CT scan of the lungs
4. Either 4a or 4b
   4a. Host risk factors (one of the following conditions)
      - Neutropenia (absolute neutrophil count <500/mm³) preceding or at the time of ICU admission
      - Underlying hematological or oncological malignancy treated with cytotoxic agents
      - Glucocorticoid treatment (prednisone equivalent, ≥20 mg/d)
      - Congenital or acquired immunodeficiency
   4b. Semiquantitative *Aspergillus*-positive culture of BAL fluid (+ or ++), without bacterial growth together with a positive cytological smear showing branching hyphae

*Aspergillus* respiratory tract colonization
When ≥1 criterion necessary for a diagnosis of putative IPA is not met, the case is classified as *Aspergillus* colonization.
Prevention of fungal infection in ECMO

• ELSO infectious diseases task force recommendation
  • ‘Cautious but aggressive’ use of prophylaxis in high risk patients
• Parenteral nutrition through dedicated line
• Remove unnecessary lines
Aspergillus infection in patients on ECMO at UHSM (Rodriguez-Goncer 2017, submitted)

• 64 patients, mean age 36.3 years
• Asthma most common underlying disease
• 15.6% had microbiological evidence of aspergillus
• 60% of patients with aspergillus evidence were considered to have IA
• 70% lacked classical risk factors
• 83.3% had influenza
• Mortality for IA was 50%
ECMO and fungal infection

• ECMO as treatment for fungal infections
• Fungal infections as complications of ECMO
• Antifungal drug levels during ECMO
Fluconazole

- Higher volume of distribution but no change in clearance in children. Higher loading doses recommended (35mg/kg) (Watt et al 2015)
- A dose of 25mg/kg weekly achieves adequate exposure for prophylaxis

Voriconazole

- Early sequestration on ECMO circuit.
- This may result in difficulties achieving therapeutic levels early on.
- Higher doses are given initially, with the risk of reaching toxic levels later on with saturation of binding sites of the ECMO circuit (Spriet et al 2009)
Micafungin

• In infants, clearance and volume of distribution higher. Recommended dose 5mg/kg for candidaemia (Autmizquine et al 2016)

• 10 patients on ECMO: micafungin is minimally sequestered in ECMO circuit. No dosage adjustment needed (Sanchez et al, ECCMID 2016)

Caspofungin

• Insufficient levels on paediatric patient on ECMO: After dose of 78mg/m2, AUC was considered subtherapeutic (Koch et al, Med Mycol Case Rep 2013)

• Sequestration in ECMO circuit unlikely as caspofungin water soluble. Adequate caspofungin levels in adult patient (Spriet et al 2009)
Thank you