Acute Respiratory Distress Syndrome in Immunocompromised Patients

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Critical Care Canada Forum
November 2018

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Toronto, Canada
Disclosures:

No Relevant Financial Disclosures
Acute Respiratory Failure is the Leading Cause of Critical Illness in Immunocompromised Patients

- Wide spectrum of conditions that can render a patient immunocompromised

- Number of living IC patients increasing

- Increasingly they are presenting to ICU

- Historic skepticism surrounding utility of ICU should be changing given marked improvement in ICU survival

ICU Mortality Across Immunocompromised Patients Over Time

Median period of ICU admission

Mokart et al ICM 2014
While Mortality is Improving, It Remains High in ARDS

Improved ICU Outcomes Attributable to:

- Advancements in cancer, rheumatologic disease, transplant and ICU care
- Infection control and infection disease practices
- Better patient selection
- Mortality remains HIGH

- IC ARDS Mortality 52%
- General ICU ARDS Mortality 36%

Cortegiani et al ICM 2014
OBJECTIVES:

1. Classification of Immunocompromised Patients
2. Etiologies of AHRF and ARDS
3. Challenges Surrounding Diagnostic Work Up
4. Management and Prognosis
No Consensus Exists Surrounding Categorization of Immunosuppressed Conditions

<table>
<thead>
<tr>
<th>Mechanisms of Immunodeficiency</th>
<th>Neutropenia</th>
<th>Impaired B-cell mediated immunity</th>
<th>Impaired T cell-mediated immunity (cell mediated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leukemia Chemotherapy HSCT</td>
<td></td>
<td></td>
<td>Corticosteroids (transplant/autoimmune) HIV</td>
</tr>
<tr>
<td>GNB MSSA Fungal Infections</td>
<td></td>
<td></td>
<td>Intracellular (Mycobacteria, Legionella, Nocardia) Fungal infections/PJP Cytomegalovirus</td>
</tr>
</tbody>
</table>

Cancer and Cancer treatment remains the leading cause of immunosuppression in critically ill patients.
Unique Features of Immunocompromised Patients

Critical illness may develop as a consequence of definitive treatment of underlying disease (curative intent).

A large proportion tends to be young with few comorbidities.

Etiology of AHRF/ARDS not always easily identified.

Unusual disease processes can complication their treatment.

Concurrent infections/non infections AHRF.
ETIOLOGY of ARDS: What about the neutrophil??

Alveolar Macrophages

Tafoya et al Can Ther Advisor 2017
Etiologies

Disease Induced vs. Treatment Induced Acute Hypoxemic Respiratory Failure

ARDS
Causes of **AHRF** in Immunocompromised Patients

- **Immunosuppression**
- **Treatment**
- **Direct Lung Toxicity**

Infectious Complications
- Bacterial Pneumonia
- Opportunistic/Fungal
- Reactivation Latent Infections
- Viral Infections

CRS
- DAH
- Cardiogenic
- IPS

Neutrophil Recovery

**Undetermined ARDS**
# EMERGING THERAPIES THAT CAN INDUCE ARDS

<table>
<thead>
<tr>
<th>Immune-Check Point Inhibitors</th>
<th>Chimeric Antigen Receptor T Cell Therapy</th>
</tr>
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<tbody>
<tr>
<td><strong>What they do</strong></td>
<td></td>
</tr>
<tr>
<td><strong>Reprogram T cells to recognize cancer cells</strong></td>
<td></td>
</tr>
<tr>
<td>Target monoclonal Ab directed against regulatory immune check point molecules that inhibit T cell activity</td>
<td>T cells collected and engineered to recognize proteins on cancer cells, reinfused into patient</td>
</tr>
<tr>
<td><strong>Efficacy</strong></td>
<td></td>
</tr>
<tr>
<td>Remarkable results in eliminating or sustaining cancer control (melanoma/lung)</td>
<td>50-90% rates of complete remission reported in B cell ALL and Adult LBCL</td>
</tr>
<tr>
<td><strong>Toxicities – on target off tumor</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary pneumonitis &lt;10% Neurotoxicity</td>
<td>Severe Cytokine Release Syndrome/ARDS Neurotoxicity</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td></td>
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<tr>
<td>Corticosteroids</td>
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AHRF/ARDS Following Hematopoietic Stem Cell Transplantation

<table>
<thead>
<tr>
<th>Period</th>
<th>Early (Pre-engraftment)</th>
<th>Early Post-engraftment (~1 month)</th>
<th>Late (&gt;100 days)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infectious</td>
<td></td>
<td></td>
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<tr>
<td>Bacterial</td>
<td>Drug-associated pulmonary toxicity* (pre-conditioning agents/previous chemotherapy)</td>
<td>Engraftment Syndrome</td>
<td>Acute GVHD**</td>
</tr>
<tr>
<td>Fungal</td>
<td>Hyperacute GVHD** (rare &lt;14 days)</td>
<td>Bacterial Fungal</td>
<td>Idiopathic pneumonia</td>
</tr>
<tr>
<td>Viral</td>
<td>Diffuse alveolar hemorrhage typically within first 30 days, median 11 days</td>
<td>Viral PJP</td>
<td>Syndrome typically within first 4 months</td>
</tr>
<tr>
<td>Non-Infectious</td>
<td>Drug-associated pulmonary toxicity* (pre-conditioning agents/previous chemotherapy)</td>
<td>Engraftment Syndrome</td>
<td>Radiation pneumonitis typically months 1-3</td>
</tr>
<tr>
<td>Peri-Engraftment</td>
<td>Drug-associated pulmonary toxicity* (pre-conditioning agents/previous chemotherapy)</td>
<td>Bacterial Fungal</td>
<td>Diffuse alveolar hemorrhage</td>
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<td>Cardiogenic</td>
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* particularly in the presence of GVHD requiring immunosuppressants

INFECTIOUS (HIGHER RISK FOR FUNGAL)
Undetermined ARDS Represents 15-20% of Immunocompromised Patients with ARDS

- Atypical Presentations
- Atypical Infectious Organisms
- Concurrent Infectious Processes
- Concurrent Infectious/Non Infectious

? Undetermined Infectious/Disease or Treatment Associated Condition

Familiarity with Unique Non-Infectious Etiologies for Condition is Necessary

? Separate Entity of Lung Injury with Targeted Treatment
Risk of death higher when cause of respiratory failure unknown; however diagnostic approach has remained controversial.

314 cancer patients admitted to the ICU with Acute Respiratory Failure (ARF)

- 49 patients intubated at admission
- 11 patients refused to participate
- 34 patients with a known cause of ARF at ICU admission (9 with cardiac pulmonary edema)

No difference in rates of diagnosis or adverse events in diagnostic strategy with FOB and without FOB

113 patients in the Invasive Diagnostic Strategy (early FO-BAL)
- No diagnosis: N=23 (20.3%)
- 101 diagnoses in 90 patients
  - Established by FOBAL, n=18 (17.8%)
  - Established by noninvasive tests, n=63 (62.3%)
  - Established by both techniques, n=20 (19.8%)
- Intubation: N=41 (36.3%)
- Death before day 28: N=33 (29.2%)

106 patients in the Noninvasive diagnostic strategy (no early FO-BAL)
- No diagnosis: N=23 (21.7%)
- 93 diagnoses in 83 patients
  - Established by FOBAL, n=2 (2.2%)
  - Established by noninvasive tests, n=80 (96.1%)
  - Established by both techniques, n=11 (11.8%)
- Intubation: N=41 (38.7%)
- Death before day 28: N=35 (33%)

Management

Do we manage immunocompromised patients differently?

Should we manage immunocompromised patients differently?
Differences in Acute Respiratory Distress Syndrome Management in Immunocompromised Patients

Antonelli & Hilbert
2000/2001

NI compared to COT in IC was found to decrease need for IMV/Mort.
Increased enthusiasm for NIV in IC (pulmonary edema/small/mortality).

- **High Flow Nasal Cannula**
  - **Non Invasive Ventilation**
  - **Non Invasive Ventilation**

- **ECLS**
- **ECO2-R**
- **HFO**
- **Prone Position**

- **Adapted from Ferguson, N et al Intensive Care Med 2012**

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**Lemiale et al**
2015

INVICTUS Study
374 patients
NIV vs. COT in IC patients
Early AHRF
No differences in IMV or Mortality

**Frat et al**
2015

FLORALI Study
310 patients
HFNC vs. COT vs NIV
Early AHRF
HFNC lower death at 90 days compared to COT/NIV
Post Hoc - IC patients
HFNC > NIV but not COT

**Azoulay et al**
2018

HIGH Study
778! Patients
HFNC vs. COT in IC patients
Early AHRF
No differences in IMV or Mortality

Adapted from Ferguson, N et al Intensive Care Med 2012
Across NIV Patients, NIV Failure in 48%
Historically NIV failure was associated with an increased mortality

Rathi et al, JCC 2017
# Factors Associated with NIV Failure and Mortality

## Risk Factors for Non-Invasive Oxygen Therapy Failure

<table>
<thead>
<tr>
<th>Demographic and Clinical Characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematologic malignancy, Allogeneic hematopoietic stem cell transplantation</td>
</tr>
<tr>
<td>Pulmonary infection</td>
</tr>
<tr>
<td>Prolonged duration of hospitalization prior to admission to ICU</td>
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</table>

## Critical Illness-Associated Features

| Greater severity of illness |
| Worsened severity of ARDS |
| Lack of physiologic response to non-invasive ventilatory therapies |
| Vasopressors/Renal failure |

## Noninvasive Ventilation of Patients with Acute Respiratory Distress Syndrome

*(Bellani et al, Am J Resp Crit Care Med 2017)*

## Insights from the LUNG SAFE Study

## Risk Factors for Mortality after NIV

| PaO₂/FiO₂ < 150; Tidal Volume?? |
Non-Invasive Oxygen Strategies in Acute Respiratory Failure for Immunocompromised Patients

Severity of Acute Respiratory Failure

Dyspnea, Hypoxia, $\text{PaO}_2/\text{FiO}_2$ 300

Early Acute Respiratory Failure

CO²

HFN

C

NIV

Acute Respiratory Distress Syndrome

Mild ARDS

Moderate ARDS

Severe ARDS

Higher severity of illness, shock, vasopressors, renal failure, high tidal volumes on NIV, or $\text{PF} < 150$

Consider HFNC or NIV with a frequent Re-evaluation

Time limited trial of NIV in select patients
Frequent Re-assessment for
Improved FiO₂
Improved P/F Ratio
Improved RR

OR if $\text{PaO}_2/\text{FiO}_2 < 200$ and/or $\text{TV} > 9\text{ml/kg at 1 hour}$ consider intubation (Frat 2018)

Adjuvant Strategies
NMBA
PRONE
INO
ECMO used at Same Frequency in Lung Safe in IC = non IC

IMV
Six-Month Outcome of Immunocompromised Patients with Severe Acute Respiratory Distress Syndrome Rescued by Extracorporeal Membrane Oxygenation

An International Multicenter Retrospective Study

Matthieu Schmidt¹,², Peter Schellongowski³, Nicolò Patroniti⁴, Fabio Silvio Taccone⁵, Dinis Reis Miranda⁶, Jean Reuter⁷, Hélène Prodanovic⁸, Marc Pierrot⁹, Amandine Dorget⁸, Sungmoon Park¹⁰, Martin Balik¹¹, Alexandre Demoule¹², Ilaria Alice Crippa¹³, Alain Mercat¹⁴, Philipp Wohlfarth¹⁵, Romain Sonneville⁷, and Alain Combes¹ for the International ECMO Network (ECMOnet), the REVA Research Network, and the IDEA Study Group

Outcomes and complications of IC patients treated with ECMO for severe ARDS - 203 patients/8 years

- 42% weaned off of ECMO, 34% ICU survival, 30% 6-month survival
- HM significantly poorer outcomes vs. Transplant/Corticosteroids
- ECMO-related major bleeding/infections/VAP were frequent
- Shorter time between ARDS and diagnosis of IC condition, plt, age, driving pressure pre-ECMO associated with 6 mo survival

- Realistic Oncologic/Therapeutic Prognosis, Early in IC state, Adequate Functional Status are imperative for ECMO consideration in this population
Should we manage them differently?  
We don’t know….

**Immunocompromised Status**  
(difficult to treat organisms, unclear etiologies)

**Underlying disease**  
may lead to a lower threshold to limit care in ICU

**ICU Management?**

- More susceptible to VALI?
- More susceptible to develop sarcopenia?
- Should we be more aggressive with investigations?
- Should we have a lower threshold to treat CMV?
- Is there a differential impact of NIV? Or need to prevent IMV?
Prognosis has improved markedly

Historically mortality was high and associated with increased resource use.

Historic reluctance to admit pts to ICU is no longer justified.

Certain subgroups continue to do poorly.
Factors no longer associated with mortality:

1. Neutropenia
2. Autologous bone marrow transplant
3. Type of hematologic malignancy
4. Stage of disease
5. Second line therapies
6. Blood transfusion requirements
7. Multidrug resistant bacteria

Demographics

<table>
<thead>
<tr>
<th>Demographics</th>
<th>Resource(s)</th>
</tr>
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<tbody>
<tr>
<td>Age</td>
<td>Mokart 2015, Nates 2017, Halpern 2017</td>
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</tbody>
</table>

Comorbidity Status

<table>
<thead>
<tr>
<th>Comorbidity Status</th>
<th>Resource(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of comorbidities</td>
<td>Azoulay 2013, Halpern 2017</td>
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</table>

Disease

<table>
<thead>
<tr>
<th>Disease</th>
<th>Resource(s)</th>
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</thead>
<tbody>
<tr>
<td>Allogeneic Hemopoietic Stem Cell Transplant</td>
<td>Azoulay 2013, Mokart 2015</td>
</tr>
<tr>
<td>&gt;1st line chemotherapy/Lack of complete or partial remission</td>
<td>Legrand 2012, Azoulay 2013</td>
</tr>
<tr>
<td>Lack of neutropenia recovery</td>
<td>Darmon 2002, Bouchm 1999</td>
</tr>
<tr>
<td>ECOG 4</td>
<td>Soares 2010, Azoulay, Wheatley</td>
</tr>
<tr>
<td>Lack of lifespan-extending treatment/less than 6 months of life expectancy</td>
<td>Benoit 2015</td>
</tr>
</tbody>
</table>

Causes of critical illness

<table>
<thead>
<tr>
<th>Cause of Critical Illness</th>
<th>Resource(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sepsis</td>
<td>Halpern 2017</td>
</tr>
<tr>
<td>Admission after cardiac arrest</td>
<td>Azoulay 2013</td>
</tr>
<tr>
<td>Invasive Fungal Infections</td>
<td>Azoulay 2013, Agarwal 2015, Halpern 2017</td>
</tr>
<tr>
<td>Neutropenic Enterocolitis</td>
<td>Mokart 2015</td>
</tr>
<tr>
<td>Non-infectious cause of admission</td>
<td>Legrand 2012</td>
</tr>
<tr>
<td>Organ infiltration by malignancy</td>
<td>Azoulay 2013</td>
</tr>
</tbody>
</table>

Management and organ function

<table>
<thead>
<tr>
<th>Management and organ function</th>
<th>Resource(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delay in Antibiotics &gt;1 hour</td>
<td>Mokart 2014</td>
</tr>
<tr>
<td>Delay in catheter removal in sepsis of unknown origin</td>
<td>Legrand 2012</td>
</tr>
<tr>
<td>Continuous Renal Replacement Therapy</td>
<td>Mokart 2015</td>
</tr>
</tbody>
</table>

Consistent factors associated with mortality:

- Age/Comorbid Conditions
- Poor Functional Status/Frailty
- Severe ARDS
- ?NIV Failure
- Treatment Refractory-GVHD
- Organs Failed
- Invasive Fungal Infections
- Non-Solid Tumor
Future Considerations

1. Immunocompromised patients are heterogeneous group

2. Role of biomarkers in delineating categories and response to therapies

3. Improve diagnostic techniques

4. Evaluate differential response to AHRF/ARDS management

5. Better identify who benefits from NIV

6. Understand the impact of critical illness on ongoing care (oncology) and long term outcomes
Conclusions

- **Infectious etiologies dominant** causes of AHRF but need to be **familiar with non-infectious causes of AHRF/ARDS** unique to the population – particularly in newer therapeutic era for cancer.

- **Diagnosis** continues to remain a challenge with a large proportion of persistent undetermined ARDS.

- **NIV used in a higher proportion** of pts than general IC – **while 60% success**, failure may be associated with increased mortality and **more data needed on who may benefit**.

- **Prognosis has markedly improved** – more research is needed to understand if we can **decreased the mortality gap through how we are managing IC patients** and whether it should be different than general ICU population.
Thank you
Non-Invasive Oxygen Selection Across Immunocompromised Patients with AHRF is Variable

Acute hypoxemic respiratory failure in immunocompromised patients: the Efraim multinational prospective cohort study

N=1,611 immunocompromised patients admitted to 62 ICUs in 16 countries for acute respiratory failure

100 with missing data on initial oxygenation strategy

596 (37.0%) received first line intubation and mechanical ventilation (IMV)

915 (56.8%) were not intubated at ICU admission and received standard O2, noninvasive ventilation (NIV) or high flow oxygen through nasal cannula (HFNC)

O2
N=496

HFNC
N=187

HFNC + NIV
N=79

NIV
N=153

N=859 without Do-Not-Intubate order

O2
N=466

HFNC
N=182

HFNC + NIV
N=75

NIV
N=136

IMV: 54 (54%)

IMV: 596 (100%)

IMV: 190 (40.8%)

IMV: 77 (42.3%)

IMV: 32 (42.7%)

IMV: 54 (39.7%)

IMV: 1 (1.8%)