ARDS during Neutropenia

D Mokart
DAR IPC
GRRRRROH 2010
Definitions

- Neutropenia is a decrease in circulating neutrophil white cells in the peripheral blood.
  - neutrophil count of 1,000–1,500 cells/ml = mild neutropenia
  - 500–1,000 cells/ml = moderate neutropenia
  - 500 cells/ml or less = severe neutropenia
Definitions

- Consensus 1994

Panel 2: Simplified consensus definition of acute lung injury

- Acute onset (less than 7 days)
- Severe hypoxaemia (\(\text{PaO}_2/\text{FiO}_2<300\) for acute lung injury, or 200 for acute respiratory distress syndrome)
- Diffuse bilateral pulmonary infiltrates on frontal radiograph consistent with pulmonary oedema (these can be patchy and asymmetric, and pleural effusions can be present)
- Absence of left atrial hypertension (pulmonary-artery wedge pressure <18 mm Hg if measured)
Patients with severe neutropenia exhibit lung infiltrates in 20% of cases

Most frequent causes:
- bacteria
- filamentous fungi, Pneumocystis jiroveci and viruses
- alveolar haemorrhage
- infiltration by the underlying malignancy
- organising pneumonia
- lesions caused by chemotherapy or radiation

In these situations ARDS has been described
Neutrophils and acute lung injury

Edward Abraham, MD

LPS

→ PI3-K/Akt, p38 activation

→ NF-κB nuclear translocation

↑ IL-1β

↑ TNF-α

↑ Chemotaxis

↓ Apoptosis

ACUTE LUNG INJURY
ARDS during neutropenia

- **The first descriptions:**

- **Hypothesis:**
  - a neutrophil-independent mechanism for lung injury?
ARDS during neutropenia

- Histological
  - As in the general population:
    - Exudative phase
    - Proliferative phase
    - Fibrotic phase
  - Neutrophil sequestration did not appear nor as thromboemboli processes.

ARDS in a neutropenic patient at the exudative phase

- Diffuse alveolar damage, early phase (Hematoxylin and eosine x 100). Alveolar septa are thickened by oedema and scant mononuclear inflammation. Pneumocyte Hyperplasia (red arrows) and Hyaline membranes (black arrows) are seen.
ARDS in a neutropenic patient at the proliferative phase

- Diffuse alveolar damage, organizing phase (H&E x 100). Alveolar septa are still thickened by congestion, mononuclear infiltrate and scant interstitial fibrosis. Fibrosis is more prominent into the alveolar lumen (black stars). Note the alveolar pneumocyte hyperplasia (black arrows).
ARDS in a neutropenic patient at the fibrotic phase

- ARDS occurring in a neutropenic patient, the lung biopsy was made at the fibrotic phase of ARDS and 12 days after the neutropenia recovery.
- Diffuse alveolar damage, late organizing phase, showing thickening of alveolar septa by extensive fibrosis and scant mononuclear inflammation (H&E x 100). Despite the absence of neutropenia at this time, there is no obvious neutrophilic infiltration.
Epidemiology

- No data in neutropenic patients
- ARF in cancer patients:
  - In 5% of patients with solid tumors
  - 50% of patients with hematological malignancies
  - 30% of neutropenic patients
- When MV is used: 75% of mortality
Epidemiology

- In ICU (Minimax):
  - 35% of cancer patients with ARF are neutropenic
  - 70% of cancer patients with ARF need MV
  - 83% of them developed an ARDS
  - the mortality rate of ARDS = 70%
  - From our experience the mortality rate of ARDS in neutropenic patients = 74%
Pathophysiology

- Only few human studies
  - Histological
  - BAL
  - Inflammatory mediators in blood
BAL

- **Pneumonia**
  - Cordonnier C, 1994, ERJ
  - Von Eiff M, 1995, Lung
  - Kiehl MG, 1997, Chest

- **ARDS**
  - Kiehl MG, 1998, CCM
  - Mokart D, 2003, Chest

- **Cellularity**
  - Low cellularity
  - Alveolar macrophages are predominant
  - Low concentrations of neutrophils
Inflammatory Mediators in BAL Fluid as Markers of Evolving Pneumonia in Leukocytopenic Patients*

Michael G. Kiehl, MD; Helmut Ostermann, MD; Michael Thomas, MD; Traute Birksellner, MD; and Joachim Kienast, MD

(CHEST 1997; 112:1214-20)
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Deactivation of alveolar macrophages and circulating monocytes

Deactivation of Alveolar Macrophages in Septic Neutropenic ARDS*

Djamel Mokart, MD; Benoit P. Guery, MD, PhD; Reda Bouabdallah, MD; Claude Martin, MD; Jean-Louis Blache, MD; Christine Arnoulet, MD; and Jean-Louis Mege, MD, PhD

(CHEST 2003; 124:644–652)

Monocyte deactivation in neutropenic acute respiratory distress syndrome patients treated with granulocyte colony-stimulating factor

Djamel Mokart1, Eric Kipnis2, Pierre Guerre-Berthelot1, Norbert Vey4, Christian Capo3, Antoine Sannini1, Jean-Paul Brun1, Jean-Louis Blache1, Jean-Louis Mege9, Didier Blaise4 and Benoit P Guery2

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Inflammatory response in neutropenic patients with ARDS

- Low cellularity
- No neutrophils (BAL, histological)
- AM are predominant cells
- Monocytes and AM are deactivated
- Pro and anti-inflammatory responses are suppressed
- Mortality = 75%
- A different inflammatory response?
Anti-inflammatory response

AM and ARDS in general population

- Steinberg K, AJRCCM, 1994
  - AM are only predominant during resolution of lung injury and not before
Inflammatory response in non neutropenic patients with ARDS

- High cellularity
- Neutrophilic infiltration (BAL, histological)
- Neutrophils are predominant cells at the early phase
- Important pro-inflammatory response at the early phase
- Important anti-inflammatory response at the resolution
- Monocytes and AM are activated
- Mortality = 40%
A different inflammatory response with therapeutic consequences?

- Despite such discrepancies, neutropenic patients with sepsis or ARDS are treated according to the standard guidelines devised for non-neutropenic patients.
- Some recommendations need probably a reappraisal.
G-CSF?

- Neutropenia recovery could worsen a pre-existing acute lung injury when G-CSF is used

- G-CSF-induced neutropenia recovery is associated with a risk of respiratory status deterioration
  - Karlin L, Bone Marrow Transplant 36: 245-50, 2005.

- G-CSF could promote the development of infectious pneumonia-related ARDS in neutropenic patients

- G-CSF could participate in monocyte/macrophage deactivation during ARDS in neutropenic patients
Corticosteroids?

- Immunocompromised patients may develop acute noninfectious parenchymal lung diseases that often meet ALI/ARDS criteria

“Imitators” of the ARDS*
Implications for Diagnosis and Treatment

Marcin I. Schwarz, MD, FCCP; and Richard K. Albert, MD, FCCP

(CHEST 2004; 125:1530-1535)
Corticosteroids?

- Around neutropenia and neutropenia recovery
  - Intra pulmonary lysis
  - Pre-engraftment syndrome
  - Neutropenia recovery
  - Engraftment syndrome
  - Immune Reconstitution Inflammatory Syndrome
Ventilator-associated lung injury (VALI)?

Pathogenetic Significance of Biological Markers of Ventilator-Associated Lung Injury in Experimental and Clinical Studies*

James A. Frank, MD; Polly E. Parsons, MD, FCCP; and Michael A. Matthay, MD, FCCP

Since neutropenic patients presenting ALI/ARDS appear to develop uncharacteristic inflammatory response, this population should be evaluated in order to determine subgroups of patients in whom VALI is more likely and protective ventilation strategies most useful.
What must we do?

VENTILATION WITH LOWER TIDAL VOLUMES AS COMPARED WITH TRADITIONAL TIDAL VOLUMES FOR ACUTE LUNG INJURY AND THE ACUTE RESPIRATORY DISTRESS SYNDROME

Surviving Sepsis Campaign: International guidelines for management of severe sepsis and septic shock: 2008


The NEW ENGLAND JOURNAL of MEDICINE

Efficacy and Safety of Corticosteroids for Persistent Acute Respiratory Distress Syndrome
Our experience...

- 52,223 medical cancer patients admitted between January 2000 and December 2006
- ICU admission rate between January 2000 and December 2006: 884 medical cancer patients (1.7%)
- ICU admission for ARF between January 2000 and December 2006: 487 patients (55%)
  - ARF with neutropenia: 180 patients (37%)
  - ARF without neutropenia: 307 patients (63%)
    - Neutropenic patients with ARF without ARDS: 110 patients (61%)
  - Neutropenic patients with ARDS: 70 patients (39%)
Pronostic factors

- We conducted the present study to identify early predictive factors (at ICU admission) of 28-day mortality.
- Factors associated with 28-day mortality during ICU stay.
Mortality rates

- 28-day mortality: 66%
- ICU mortality: 74%
- Hospital mortality: 74%
<table>
<thead>
<tr>
<th>Table 1: Patients characteristics at ICU admission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (female)</td>
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<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Underlying malignancy</td>
</tr>
<tr>
<td>Acute Leukemia</td>
</tr>
<tr>
<td>Lymphoma</td>
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<tr>
<td>Myeloma</td>
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<tr>
<td>Solid tumors</td>
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<tr>
<td>Other malignancies</td>
</tr>
<tr>
<td>Time from diagnosis (days)</td>
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<tr>
<td>Status of malignancy</td>
</tr>
<tr>
<td>Delay since neutropenia at ICU admission (days)</td>
</tr>
<tr>
<td>First line chemotherapy</td>
</tr>
<tr>
<td>Complete remission</td>
</tr>
<tr>
<td>Relapse</td>
</tr>
<tr>
<td>Secondary acute leukemia</td>
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<tr>
<td>Allogeneic HSCT</td>
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<tr>
<td>Autologous HSCT</td>
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<tr>
<td>Organ dysfunction at ICU admission</td>
</tr>
<tr>
<td>LOD score on day 1</td>
</tr>
<tr>
<td>SAPSII score on day 1</td>
</tr>
<tr>
<td>Lactates (mmol/L) on day 1</td>
</tr>
<tr>
<td>Causes of ARDS</td>
</tr>
<tr>
<td>Septic ARDS</td>
</tr>
<tr>
<td>Gram-negative bacilli</td>
</tr>
<tr>
<td>Gram-positive cocci</td>
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<tr>
<td>Fungi</td>
</tr>
<tr>
<td>Viruses</td>
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<tr>
<td>Other infections</td>
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<tr>
<td>Non septic ARDS</td>
</tr>
<tr>
<td>Unknown</td>
</tr>
<tr>
<td>Pulmonary ARDS*</td>
</tr>
<tr>
<td>Extra pulmonary ARDS*</td>
</tr>
<tr>
<td>Lung morphology on CT</td>
</tr>
<tr>
<td>Diffuse ARDS</td>
</tr>
<tr>
<td>Lobar ARDS</td>
</tr>
<tr>
<td>Patchy ARDS</td>
</tr>
<tr>
<td>Antimicrobial treatment</td>
</tr>
<tr>
<td>ATB active on DTT bacteria</td>
</tr>
<tr>
<td>Initial adequate antimicrobial treatment**</td>
</tr>
<tr>
<td>Microbiological documentation at ICU admission**</td>
</tr>
</tbody>
</table>

* among the 51 patients with diagnosis
** among the 47 patients with septic ARDS
Factors independently related to day 28 survival

- **Lobar ARDS** (odds ratio 0.10, 95% CI: 0.02 – 0.47, p= 0.0037)
- **ATB active on DTT bacteria at ICU admission** (odds ratio 0.12, 95% CI: 0.03 – 0.55, p= 0.0064)
- **First line chemotherapy** (odds ratio 0.08, 95% CI: 0.02 – 0.45, p= 0.0038)
Initial antibiotic treatment

- until refutation, ARDS in neutropenic patients should be considered as an infectious emergency
- broad-spectrum antibiotic treatment must be initiated promptly considering that data on antibiotic resistance is dynamic and varies from ward to ward.
Lobar ARDS in neutropenic patients

- Similar mortality rate than lobar ARDS in general population
- Strategies which prevent the switch from an initial focal lung injury to a terminal diffuse lung injury
- Early ICU admission of neutropenic patients with focal lung infiltrate(s) should be evaluated
During ICU stay

<table>
<thead>
<tr>
<th>Fluid expansion (ral)</th>
<th>Survivors (n = 26)</th>
<th>Non survivors (n = 44)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crystalloid on day 1</td>
<td>3200 [2000 - 3900]</td>
<td>3000 [2000 - 4500]</td>
<td>1</td>
</tr>
<tr>
<td>Colloid on day 1</td>
<td>0 [0 - 400]</td>
<td>275 [0 - 925]</td>
<td>0.08</td>
</tr>
<tr>
<td>Total fluid expansion on day 1</td>
<td>3875 [2875 - 4437]</td>
<td>3575 [3450 - 5312]</td>
<td>0.82</td>
</tr>
<tr>
<td>Crystalloid during the first 3 days</td>
<td>7750 [6813 - 10750]</td>
<td>8000 [6563 - 10725]</td>
<td>0.73</td>
</tr>
<tr>
<td>Colloid during the first 3 days</td>
<td>0 [0 - 500]</td>
<td>550 [0 - 1300]</td>
<td>0.020</td>
</tr>
<tr>
<td>Blood products transfusion (unit)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RBC during the first three days</td>
<td>3 [1 - 4]</td>
<td>2 [2 - 3]</td>
<td>0.55</td>
</tr>
<tr>
<td>Plasma during the first three days</td>
<td>0 [0 - 0]</td>
<td>0 [0 - 0]</td>
<td>0.089</td>
</tr>
<tr>
<td>Platelets during the first three days</td>
<td>1 [1 - 2]</td>
<td>2 [1 - 3]</td>
<td>0.12</td>
</tr>
<tr>
<td>Respiratory support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NIMV</td>
<td>16 (62%)</td>
<td>23 (52%)</td>
<td>0.47</td>
</tr>
<tr>
<td>Conventional MV</td>
<td>22 (88%)</td>
<td>44 (100%)</td>
<td>0.016</td>
</tr>
<tr>
<td>Almitrine</td>
<td>0 (0%)</td>
<td>4 (9%)</td>
<td>0.29</td>
</tr>
<tr>
<td>Prone position</td>
<td>3 (12%)</td>
<td>3 (7%)</td>
<td>0.66</td>
</tr>
<tr>
<td>Nitric oxide inhalation</td>
<td>4 (15%)</td>
<td>10 (23%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Hemodynamic support</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Need for vasopressors</td>
<td>18 (69%)</td>
<td>43 (98%)</td>
<td>0.0011</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>7 (27%)</td>
<td>22 (50%)</td>
<td>0.080</td>
</tr>
<tr>
<td>Organ dysfunction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LOD score (day 3)**</td>
<td>7.5 [6.75 - 9]</td>
<td>9 [8 - 11]</td>
<td>0.0049</td>
</tr>
<tr>
<td>LOD score (day 7)**</td>
<td>7 [5 - 9]</td>
<td>10 [8 - 11]</td>
<td>0.0027</td>
</tr>
<tr>
<td>LOD score - 2 days after neutropenia recovery</td>
<td>6 [4 - 7]</td>
<td>10 [9 - 11]</td>
<td>0.000037</td>
</tr>
<tr>
<td>Other treatments</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>G-CSF</td>
<td>13 (50%)</td>
<td>25 (57%)</td>
<td>0.63</td>
</tr>
<tr>
<td>Stress-dose corticoids</td>
<td>17 (65%)</td>
<td>25 (57%)</td>
<td>0.62</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>7 (27%)</td>
<td>12 (27%)</td>
<td>1</td>
</tr>
<tr>
<td>Neuromuscular blocking agents</td>
<td>5 (20%)</td>
<td>17 (39%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Evolution of sepsis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sepsis</td>
<td>13 (50%)</td>
<td>14 (32%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Septic shock</td>
<td>15 (65%)</td>
<td>43 (98%)</td>
<td>0.00036</td>
</tr>
<tr>
<td>DIC</td>
<td>1 (4%)</td>
<td>8 (18%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Neutropenia recovery</td>
<td>23 (88%)</td>
<td>14 (32%)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

** among the 61 patients alive at day 3
*** among the 52 patients alive at day 7
**** among the 38 patients with neutropenia recovery
During ICU stay

- In general population
  - outcome is determined in 10 days, by which time about half of patients have died or have been weaned off treatment

- In neutropenic patients
  - 90% of survivors were still in ICU after 10 days
  - in ICU and during the first month, for a given patient, there was no more risk to die the first 10 days than after.
  - 88% of survivors showed neutropenia recovery

Weeler AP, Lancet, 369:1553-64. 2007
During ICU stay

- Full-code management followed by a reappraisal around neutropenia recovery should be considered in these patients.