Acute Kidney Injury in Acute Liver Failure

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“Update on the management of Acute Liver Failure”
Rome, February 17th 2016
Outline

• Diagnostic criteria

• Epidemiology

• Pathophysiology

• Prognostic implications

• Management
**Definition and staging of Acute Kidney Injury (AKI)**

KDIGO creatinine criteria = an abrupt (within 48 hours) reduction in kidney function currently defined as an absolute increase in serum creatinine of more than or equal to 0.3 mg/dl ($\geq 26.4 \mu mol/l$), or a percentage increase in serum creatinine of more or equal to 50 % (1.5-fold from baseline) in less than 7 days.

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>Increase in serum creatinine of more than or equal to 0.3 mg/dl ($\geq 26.4 \mu mol/l$) or a percentage increase in serum creatinine of more or equal to 50 % (&lt; 2 fold from baseline).</td>
</tr>
<tr>
<td>2°</td>
<td>Increase in serum creatinine to more than 200% to 300% (&gt; 2- to 3-fold) from baseline</td>
</tr>
<tr>
<td>3°</td>
<td>Increase in serum creatinine to more than 300 % (&gt; 3-fold) from baseline or serum creatinine of more or equal to 4.0 mg/dl ($\geq 354 \mu mol/l$) with an acute increase of at least 0.5 mg/dl (44 μmol/l) or need for renal replacement therapy</td>
</tr>
</tbody>
</table>

*P. Angeli et al. Gut 2015; 64: 531-537*
Definition and staging of Acute Kidney Injury (AKI)

KDIGO urine output criteria = an urinary output < 0.5 ml/kg B.W./hr x 6-12 hours

<table>
<thead>
<tr>
<th>Stage</th>
<th>Serum creatinine criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>1°</td>
<td>an urinary output &lt; 0.5 ml/kg B.W./hr x 6-12 hours</td>
</tr>
<tr>
<td>2°</td>
<td>an urinary output &lt; 0.5 ml/kg B.W./hr x 12 hours</td>
</tr>
<tr>
<td>3°</td>
<td>an urinary output &lt; 0.5 ml/kg B.W./hr x 24 hours or anuria per 12 hr</td>
</tr>
</tbody>
</table>

Patient classification by KDIGO criteria

- Patients: 75
- AKI sCr or UO: 45
- AKI only sCr: 4
- AKI sCr and UO: 17
- AKI only UO: 24

E. Macedo Nephrol. Dial. Transplant 2011; 26: 509-515 (modified)
Relationship between n° of hours of oliguria in ICU and hospital mortality

E. Macedo Nephrol. Dial. Transplant 2011; 26: 509-515 (modified)
Relationship between combination of UO and sCr criteria and hospital survival

Group 1 (green): no AKI by either criterion;
Group 2 (blue): stages 1–2 by UO criteria but no AKI by SC or stage 1 by SC and no AKI by UO;
Group 3 (yellow): stages 1–2 by UO plus stage 1 by SC or stages 2–3 by SC alone;
Group 4 (orange): stages 1–2 by UO plus stage 2 by SC or stage 3 by UO alone;
Group 5 (red): stage 3 by UO plus stages 1–2 by SC or stage 3 by SC plus stages 1–2 by UO;
Group 6 (dark red): stage 3 by both criteria.

Outline

• Diagnostic criteria

• Epidemiology

• Pathophysiology

• Prognostic implications

• Management
Incidence of AKI in hospitalized patients

<table>
<thead>
<tr>
<th></th>
<th>General population</th>
<th>Patients with ALF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of AKI</td>
<td>5-7%</td>
<td>40-80%</td>
</tr>
<tr>
<td>Need of RRT</td>
<td>4-15%</td>
<td>30-70%</td>
</tr>
</tbody>
</table>


Incidence of AKI in patients with ALF

<table>
<thead>
<tr>
<th></th>
<th>Acetaminophen-induced ALF</th>
<th>Non acetaminophen-induced ALF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence of AKI</td>
<td>80%</td>
<td>51%</td>
</tr>
<tr>
<td>Need of RRT</td>
<td>34-60%</td>
<td>25-38%</td>
</tr>
</tbody>
</table>


Outline

• Diagnostic criteria

• Epidemiology

• Pathophysiology

• Prognostic implications

• Management
Independent predictors of AKI in patients with ALF

- Age
- Severity of ALF
- SIRS
- Arterial hypotension
- Superimposed infection
- Acetaminophen as cause of ALF

### Independent predictors of AKI in patients with ALF (1)

<table>
<thead>
<tr>
<th></th>
<th>No AKI</th>
<th>Intermediate</th>
<th>AKI stages 1-2</th>
<th>AKI stages 3 and RRT</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>34.7 (17-78)</td>
<td>40.0 (17-81)</td>
<td>34.0 (21-72)</td>
<td>37.1 (18-78)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>INR</td>
<td>2.5 (1.2-15.8)</td>
<td>2.9 (1.0-20.0)</td>
<td>3.3 (1.2-24.1)</td>
<td>3.1 (0.9-27.1)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Coma grade III/IV</td>
<td>35.7%</td>
<td>56.4%</td>
<td>56.1%</td>
<td>62.4%</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>MAP</td>
<td>78.5 (46-118)</td>
<td>75.0 (31-125)</td>
<td>77.0 (33-114)</td>
<td>73.0 (30-118)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Need of vasopressors</td>
<td>11.5%</td>
<td>36.9%</td>
<td>24.6 %</td>
<td>54.4 %</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Independent predictors of AKI development in patients with ALF (2)

<table>
<thead>
<tr>
<th></th>
<th>No AKI (n=243)</th>
<th>AKI (n=121)</th>
<th>Multivariate analysis</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline MELD (mean ± SD)</td>
<td>20 (4.2)</td>
<td>23 (5.5)</td>
<td>1.1 (1.04-1.15)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Presence of HE (%)</td>
<td>22 (9)</td>
<td>29 (22.8)</td>
<td>2.94 (1.5-5.5)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>SIRS (%)</td>
<td>139 (57)</td>
<td>97 (76)</td>
<td>2.9 (1.7-4.8)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

R. Maiwall et al. Dig. Dis. Sci 2015 ; [Epub ahead of print]
Survival rate according to the presence of SIRS

R. Maiwall et al. Dig. Dis. Sci 2015 ; [Epub ahead of print]
Survival rate according to the type of SIRS

R. Maiwall et al. Dig. Dis. Sci 2015; [Epub ahead of print]
Danger and stranger models

Nuclear DNA damage and release of DNA fragments into the plasma after the administration of APAP (300 mg/kg) in mice

C. Cover et al. J. Pharmacol. Exp. Ther. 2005; 315; 879-887
Serum total HMGB1 5 hours after the administration of APAP (530 mg/kg) in mice

*D.l. Antoine et al. Toxicol. Sci. 2009; 112; 521-531*
Serum total TNF-α after the administration of APAP (500 mg/kg) in mice

$P < 0.01$

ACUTE LIVER FAILURE

BACTERIAL TRANSLOCATION/INFECTIONS
PAMPS release

ACTIVATION OF INNATE PATTERN RECOGNITION
RECEPTORS

RELEASE OF PRO-INFLAMMATORY MOLECULES
(ROS/RNS)

SPLANCHNIC ARTERIoLAR VASODILATION
& CARDIOVASCULAR DYSFUNCTION

Other potential mechanisms?
(i.e. Portal hypertension)

M. Bernardi et al. J. Hepatol. 2015; 6: 1272-1284 (modified)
Mechanisms of renal injury potentially involved in AKI in patients with ALF

- Renal hypoperfusion
- Danger signal/Inflammation
- Direct tubular damage
- Microvascular dysfunction
Mechanisms of renal injury potentially involved in AKI in patients with ALF

Renal hypoperfusion
Mean arterial pressure (MAP), Renal Blood Flow (RBF) and Renal Vascular Resistance (RVR) of studies in animals with sepsis

Mechanisms of renal injury potentially involved in AKI in patients with ALF
Microvascular dysfunction in sepsis

Peritubular vessels with continuous flow (% vessels per 200 μ)

Peritubular vessels with no flow (% vessels per 200 μ)

Mechanisms of renal injury potentially involved in AKI in patients with ALF

Danger signal/Inflammation
The “danger signal” amplification (1)

H. Gomez et al. Shock. 2014; 41: 3–11
Endotoxin uptake in S1 segments of WT mice and TLR4 KO mice

The “danger signal” amplification (2)

H. Gomez et al. Shock. 2014; 41: 3–11
The “danger signal” amplification (3)

H. Gomez et al. Shock. 2014; 41: 3–11
The “danger signal” amplification (4)

H. Gomez et al. Shock. 2014; 41: 3–11
The “danger signal” amplification (5)


)
Mechanisms of renal injury potentially involved in AKI in patients with ALF

Direct tubular damage
Mechanisms of acute tubular necrosis (ATN) in patients with ALF

Potential mechanisms

Direct nephrotoxicity

HEPATOTOXINS
• Acetaminophen
• Amanita poisoning
• Trimethoprim/sulfamethoxazole
• Bile salts, Bilirubin (?)

OTHER TOXINS
• Contrast media
• Myoglobin

Ischemia/Inflammation

CAUSES
• Conditions inducing persistent macro- or micro-vascular dysfunction and inflammation in the kidney
Mechanisms of acute tubular necrosis (ATN) in mice with CBDL: Bile salts

We estimate that Fxr\(^{-/-}\) mice, with a mean urinary bile acid excretion rate of \(\sim2\ \mu\text{mol/day}\) during the first 7 days after CBDL, eliminate \(\sim50\%\) of the bile acid load during obstructive cholestasis into urine.

**Legend**: FXR = Farnesoid X receptor

*P. Fickert et al. Hepatology 2013;58:2056-2069*
Effect of bilirubin on the citotoxic effect of Chlorodinitrobenzene (CDNB) and Haemoglobin (HB) in LLK-PK1 cells (kidney cell line)

N. Leung et al. Kidney Int. 2001; 60: 1047-1057
Effects of cholestasis on bacterial translocation

Mesenteric lymph nodes

- Sham
- BDL

Days

CFUs

Mechanisms of acute tubular necrosis (ATN) in patients with ALF

Potential mechanisms

Direct nephrotoxicity

HEPATOTOXINS
- Acetaminophen
- Amanita poisoning
- Trimethoprim/sulfamethoxazole
- Bile salts

OTHER TOXINS
- Contrast media
- Myoglobin

Ischemia/Inflammation

CAUSES
- Conditions inducing persistent macro- or micro-vascular dysfunction and inflammation in the kidney
- Cholestasis
Outline

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• Management
Outcomes of AKI in patients with ALF: free LT survival

Outcomes of AKI in patients with ALF; survival after LT

21.1% of patients had stage 3–5 CKD by at 12 months. The cumulative incidence of stage 3–5, and stage 4–5 CKD by 5 years was 41.5% and 2.6%, respectively.

Outcomes of AKI in patients with ALF; independent predictors of normal GFR 12 months after LT

<table>
<thead>
<tr>
<th>Variable</th>
<th>RC</th>
<th>(95 CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>-0.51</td>
<td>(-0.91,-0.11)</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>Female gender</td>
<td>-14.5</td>
<td>(-24.3,-4.6)</td>
<td>&lt; 0.005</td>
</tr>
<tr>
<td>Preoperative AKI</td>
<td>-10.20</td>
<td>(-22.36, 1.96)</td>
<td>N.S.</td>
</tr>
<tr>
<td>APAP-induced AKI</td>
<td>16.17</td>
<td>(1.88-30.46)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Preoperative SIRS</td>
<td>-12.78</td>
<td>(-24.99,-0.57)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>CNI (cyclosporine)</td>
<td>-12.46</td>
<td>(-22.94,-1.98)</td>
<td>&lt; 0.025</td>
</tr>
</tbody>
</table>

Outline

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• Prognostic implications

• Management
  • Differential diagnosis
  • Prevention
  • Treatment
    • General supportive measures
    • Specific therapeutic measures
Differential diagnosis of AKI in patients with ALF

- Prerenal-AKI
- HRS-AKI
- Intrinsic AKI (ATN-AKI)
- Postrenal-AKI
### Values of urinary biomarkers in patients categorized according to the absence or presence of AKI and phenotype of AKI

<table>
<thead>
<tr>
<th>Biomarkers</th>
<th>No AKI</th>
<th>Prerenal AKI</th>
<th>HRS-AKI</th>
<th>ATN-AKI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NGAL (μg/g sCr)</td>
<td>30 (17-41)</td>
<td>36 (26-125)</td>
<td>104 (58-208)</td>
<td>1807 (494-3716)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>IL-18 (ng/g sCr)</td>
<td>21 (16-35)</td>
<td>16 (14-36)</td>
<td>18 (10-29)</td>
<td>150 (58-259)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Albumin (mg/g sCr)</td>
<td>3 (1-7)</td>
<td>9 (1-77)</td>
<td>16 (8-46)</td>
<td>324 (53-380)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TFF-3 (μg/g sCr)</td>
<td>582 (367-1665)</td>
<td>2300 (323-2720)</td>
<td>1893 (840-2715)</td>
<td>5810 (4019-14466)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>MCP-1 (μg/g sCr)</td>
<td>0.2 (0.1-1.4)</td>
<td>0.9 (0.2-2.5)</td>
<td>3 (1-6)</td>
<td>4 (1-14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Osteopontin (μg/g sCr)</td>
<td>1456 (715-3210)</td>
<td>2914 (1847-8382)</td>
<td>5471 (2959-11983)</td>
<td>83337 (4019-14466)</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Calbindin (μg/g sCr)</td>
<td>71 (26-150)</td>
<td>5 (2-34)</td>
<td>25 (8-58)</td>
<td>118 (37-324)</td>
<td>0.010</td>
</tr>
<tr>
<td>GST-TT (μg/g sCr)</td>
<td>3 (1-16)</td>
<td>3 (1-7)</td>
<td>4 (2-21)</td>
<td>50 (9-169)</td>
<td>0.012</td>
</tr>
<tr>
<td>KIM-1 (μg/g sCr)</td>
<td>0.5 (0.3-1.4)</td>
<td>0.5 (0.1-1.1)</td>
<td>1.2 (0.5-2.8)</td>
<td>1.7 (0.9-5.1)</td>
<td>0.015</td>
</tr>
<tr>
<td>Cistatin C (μg/g sCr)</td>
<td>24 (12-435)</td>
<td>21 (15-53)</td>
<td>27 (10-47)</td>
<td>115 (39-1552)</td>
<td>0.023</td>
</tr>
</tbody>
</table>

X. Ariza et al. Plos One 2015 ; 10 [Epub ahead of print]
Percentage of patients with prerenal- (PRE-), hepatorenal syndrome (HRS-), and acute tubular necrosis- (ATN-) AKI by the number of biomarkers of structural injury above their optimal cutoff for the diagnosis of ATN

J.M. Belcher et al. Hepatology 2014; 60: 622-632
Prevention of AKI

• Close monitoring of hemodynamic parameters

• Close monitoring of parameters of renal function, electrolytes, acid base-status

• Minimizing intravenous contrast and, in case, considering the use of NAC

• Prompt diagnosis and treatment of infections

• Adequate nutrition

• Use of pentoxyfilline (PTX) in acute alcoholic hepatitis
Effects of pentoxyfilline (PTX) in patients with acute alcoholic hepatitis

<table>
<thead>
<tr>
<th>Variable</th>
<th>PTX (n° = 49)</th>
<th>Placebo (n°=52)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts who developed HRS (%)</td>
<td>4 (8.2%)</td>
<td>18 (34.5%)</td>
<td>&lt; 0.0025</td>
</tr>
<tr>
<td>PTS who died (%)</td>
<td>12(24.5%)</td>
<td>24 (46.1%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Pts who died with HRS (%)</td>
<td>6/12 (50%)</td>
<td>22/24 (91.7%)</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

Treatment of AKI: general supportive measures

- Maintaining MAP > 75 mm Hg
  - Use a chloride-restriction intravenous fluid or/and albumin for fluid management avoiding saline and artificial colloids
### Composition of intravenous fluids

<table>
<thead>
<tr>
<th></th>
<th>0.9% Saline</th>
<th>Ringer’s Lactate sol.</th>
<th>Hartmann sol.</th>
<th>4% Gelatin</th>
<th>Plasma-lyte 148</th>
<th>4 % Albumin</th>
<th>20 % Albumin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sodium</td>
<td>150</td>
<td>130</td>
<td>129</td>
<td>154</td>
<td>140</td>
<td>140</td>
<td>48-100</td>
</tr>
<tr>
<td>Potassium</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chloride</td>
<td>150</td>
<td>109</td>
<td>109</td>
<td>120</td>
<td>98</td>
<td>128</td>
<td>19</td>
</tr>
<tr>
<td>Calcium</td>
<td>0</td>
<td>1.5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Magnesium</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Lactate</td>
<td>0</td>
<td>28</td>
<td>29</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Actate</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>27</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*N. M. Yunos et al. JAMA 2012; 308:1566-1567 (modified)
**Chloride-liberal versus chloride-restrictive intravenous fluid administration in critically ill patients**

<table>
<thead>
<tr>
<th></th>
<th>Chloride Liberal</th>
<th>Chloride Restricted</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chloride administration (mmol)/patient</td>
<td>694</td>
<td>496</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>AKI-risk</td>
<td>71 (9.0%)</td>
<td>57 (7.4%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>AKI-Injury</td>
<td>48 (6.3%)</td>
<td>23 (3.0%)</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>AKI-Failure</td>
<td>57 (7.5%)</td>
<td>42 (5.4%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>AKI-Injury+Failure</td>
<td>105 (14%)</td>
<td>65 (8.4%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

**Legend:** RIFLE classification was used for AKI

*N. M. Yunos et al. JAMA 2012; 308: 1566-1567*
Treatment of AKI: general supportive measures

- **Maintaining MAP > 75 mm Hg**
  - Use a chloride-restriction intravenous fluid or/and albumin for fluid management avoiding saline and artificial colloids
  - Consider blood transfusion to maintain HB > 70 g/l
  - When required, terlipressin or norephinephrine is the vasopressor of choice

- **Cautious use of diuretics in case of fluid overload**

- **Careful considerations of drugs which are metabolized or excreted mainly by the kidneys, dose adjustement and monitoring of their plasma levels when considered essential.**
Treatment of AKI: specific therapeutic measures

- Terlipressin plus albumin in case of HRS-AKI
Effects of terlipressin on LPS increase in inducible nitric oxide synthesis (iNOS) mRNA in cirrhotic aortas

* = P < 0.05 vs other groups

Treatment of AKI: specific therapeutic measures

- Terlipressin plus albumin in case of HRS-AKI
- Renal Replacement Therapy (RRT) when indicated
- The traditional indications for RRT are the following:
  - Refractory fluid overload
  - Severe electrolyte imbalance
  - Severe acid-base imbalance
  - Symptomatic azotemia
  - Refractory hepatic encephalopathy
Treatment of AKI in patients with ALF: Renal Replacement Therapy (RRT)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Early RRT (n°=54)</th>
<th>Late RRT (n° = 26)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU mortality</td>
<td>31 (57.4%)</td>
<td>22 (84.6%)</td>
<td>&lt; 0.025</td>
</tr>
<tr>
<td>Hospital mortality</td>
<td>33 (61.1%)</td>
<td>22 (84.6%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>30 day mortality</td>
<td>34 (63%)</td>
<td>22 (84.6%)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Liver recovery</td>
<td>18 (33.3%)</td>
<td>4 (15.4%)</td>
<td>N.S.</td>
</tr>
<tr>
<td>Renal recovery</td>
<td>20 (39.2%)</td>
<td>3 (12.0%)</td>
<td>&lt; 0.025</td>
</tr>
</tbody>
</table>

## Treatment of AKI in patients with ALF: Renal Replacement Therapy (RRT)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late RRT</td>
<td>4.01</td>
<td>(1.05-15.27)</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>APACHE II &gt; 20</td>
<td>6.52</td>
<td>(1.61-26.36)</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>IHD versus CVVH</td>
<td>4.32</td>
<td>(1.26-14.79)</td>
<td>&lt; 0.025</td>
</tr>
</tbody>
</table>

**Legend:** IHD = intermittent hemodialysis, CVVH = continuous venous-venous hemofiltration

*V.C. Wu. J. Am. Coll. Surg. 2007; 205: 266-276*
Summary

• AKI is a common complication in patients with ALF.
• APAP-induced ALF is the most common etiology of ALF associated with AKI.
• AKI in patients with ALF is associated with longer hospital stay and increased mortality but not with an increased risk of CKD.
• The pathophysiology of AKI in patients with ALF is complex and multifactorial. Renal hypoperfusion, danger signal/inflammation and microvascular dysfunction as well as tubular damage are part of it.
• Biomarkers for the differential diagnosis among the phenotypes of AKI in patients with ALF remain an area of research.
• When RRT is indicated, continuous RRT is preferable to intermittent dialysis due to the risk of hypotension and of aggravating intracranial hypertension.