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EVOLVING CONCEPTS IN ACUTE-ON-CHRONIC LIVER FAILURE

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Most patients with liver cirrhosis remain in a compensated stage for more than 10 years, regardless of the aetiology of the liver disease. The progression to decompensated cirrhosis is defined by the occurrence of a major complication such as ascites, variceal bleeding and/or hepatic encephalopathy. From here on most patients will not die because of a progressive, irreversible decrease in liver function, but because of a relatively sudden event that precipitates an acute deterioration in their clinical condition, a syndrome termed acute-on-chronic liver failure (ACLF). For many intensive care specialists, ACLF stands for a critically ill patient who is suffering from an intra- or extrahepatic acute insult with serious repercussions on both an existing chronic liver disease and on other organ functions. It also means that, as compared to the average intensive care unit (ICU) patient, the patient has an unusually high risk of death.

Concepts about cirrhosis have evolved significantly in recent years, and major advances have been made in defining the natural history of ACLF (for general reviews see Arroyo et al. 2016; Bernal et al. 2015; Sarin and Choudhury 2016). The syndrome is highly challenging for intensivists and poses difficult questions related to the recognition of precipitating factors, pathogenesis of extrahepatic organ failures, accurate prognosis, medical management, evaluation for urgent liver transplantation and finally the identification of those situations that may render intensive care futile. The present appraisal will focus on recent insights and their potential repercussions on the way intensivists should understand and manage patients with ACLF.

Definition and Natural History of Acute-on-Chronic Liver Failure

There is no uncontested universal definition for ACLF and the two most widely used definitions depend on the origin of the hepatologists—West versus East (Arroyo et al 2015; Sarin et al. 2014). For the purpose of this text we will use the definition of the European Association for the Study of the Liver – Chronic Liver Failure (EASL-CLIF) Consortium, because extrahepatic organ failure(s) and short-term mortality are central to the definition and therefore more closely mimic circumstances in the ICU. This definition is based on a prospective, multicentre, observational study (CANONIC study) of 1343 patients who were hospitalised for acute decompensation of cirrhosis (Moreau et al 2013). ACLF is thus defined as a specific syndrome comprising acute decompensation of cirrhosis (development of ascites, variceal bleeding, hepatic encephalopathy and/or bacterial infections), organ failure and high short-term mortality (by definition 28-day mortality rate ≥15%) (Arroyo et al 2015).

> ACLF is not necessarily the final event in a progressive course of decompensating liver disease, but may occur at any point in time after diagnosis of cirrhotic liver disease

Based on the chronic liver failure (CLIF) Acute-on-Chronic Liver Failure in Cirrhosis (CANONIC) study a new grading system for severity of ACLF (grade 0 to 4) has been introduced built on a modified Sequential Organ Failure Assessment (SOFA) score (**Tables 1 and 2**). This new grading system is proving useful to diagnose the condition, to study the natural history of ACLF, to stratify patients in interventional trials and for prognostication (Gustot et al 2015; Silva et al. 2015; Shi et al. 2016).

In the CANONIC study the prevalence of ACLF in patients presenting to the hospital with acute decompensation of cirrhosis was 31%. Twenty-three percent had ACLF at the time of admission and another 11% developed ACLF during hospitalisation. Twenty-four percent of the patients required care in the ICU with one in three not fulfilling criteria for ACLF at the time of admission to the ICU. A similar prevalence ranging from 24 to 34% has been reported in other large studies from China, North America and Scandinavia (Li et al 2016; Bajaj et al. 2014a; Sargenti et al. 2015). Almost half of the patients with ACLF did not have a prior history of acute decompensation, or had developed the first decompensating event within the three months prior to the diagnosis of ACLF. This observation is relevant to the extent that ACLF is not necessarily the final event in a progressive course of decompensating liver disease, but may occur at any point in time after diagnosis of cirrhotic liver disease.

The clinical course of the condition is very dynamic. One study observed resolution of ACLF in 42.5% of patients across all grades of ACLF, 53.5% in ACLF-1, 34.6% in ACLF-2 and 16% in ACLF-3 (**Table 1**) (Gustot et al. 2015). In the CANONIC study the overall 28-day and 90-day mortality rates for patients with ACLF, who did not undergo liver transplantation, were 32.8% and 51.2%. Similar rates have

Table 1. Chronic Liver Failure (CLIF)-Sequential Organ Failure Assessment (CLIF-SOFA) Score

Organ/system	0	1	2	3	4
Liver (Bilirubin, mg/dl)	<1.2	≥1.2 - ≤2.0	≥2.0 - <6.0	≥6.0 - <12.0	≥12.0
Kidney (Creatinine, mg/dl)	<1.2	≥1.2 - <2.0	≥2.0 - <3.5 or use of renal replacement therapy	≥3.5 - <5.0	≥5.0
Cerebral (HE grade)	No HE	I	II	III	IV
Coagulation (INR)	<1.1	≥1.1 – <1.25	≥1.25 - <1.5	≥1.5 – <2.5	≥2.5 or Platelets≤20x10^9/l
Circulation (MAP mm Hg)	≥70	<70	Dopamine ≤5 or Dobutamine or Terlipressin	Dopamine >5 or E ≤ 0.1 or NE ≤ 0.1	Dopamine >15 or E > 0.1 or NE > 0.1
Lungs PaO/FiO_2: or SpO^2/FiO_2	>400 >512	>300 - ≤400 >357 - ≤512	>200 - ≤300 >214 - ≤357	>100 - ≤200 or >8 - ≤214	≤100 ≤89

HE hepatic encephalopathy INR international normalised ratio MAP mean arterial pressure E epinephrine NE norepinephrine PaO_2 partial pressure of arterial oxygen; FIO_2 fraction of inspired oxygen SpO_2 pulse oximetric saturation. The highlighted areas in grey show the diagnostic criteria for organ failures.

been reported in other studies (Li et al. 2016). These mortality rates are clearly different from those in patients with acute decompensation of liver cirrhosis but not fulfilling criteria for ACLF (1.9% and 9.3%, respectively). The most frequent cause of death in patients with ACLF was multiple organ failure without septic or hypovolaemic shock (40%), followed by septic shock in approximately 25% of cases. The aetiology of cirrhosis does not seem to be determinant of outcome, but patients with gastrointestinal haemorrhage as a precipitating factor do better than patients who were not bleeding at admission (McPhail et al. 2014).

It is often assumed that acute decompensation of liver function is triggered by a clinically identifiable, precipitating event. The trigger may have a hepatic origin, such as drug-induced liver injury, viral or ischaemic hepatitis, liver surgery or undue alcohol consumption. It can also have an extrahepatic origin such as acute bacterial infection, major surgery or paracentesis. Interestingly, in the CANONIC study, in 43.6% of the patients with ACLF, no precipitating event could be identified (Moreau et al. 2013). This observation underscores the fact that in the majority of patients we are not yet able to diagnose the pathogenetic mechanism leading to acute decompensation. Acute bacterial infection was the most frequent precipitating event in 33% of the patients (Moreau et al. 2013).

Prevalence and Pathogenesis of Organ Dysfunctions Associated With ACLF

Organ dysfunction or failure is highly prevalent in ACLF. Hepatic, renal, cerebral, coagulation and circulatory dysfunctions are well known, but important derangements in the function of the heart, immune system, adrenal glands and muscle have been also well documented. In ACLF patients in the CANONIC study kidney failure (56%) was the most frequent organ failure followed by liver failure (44%), coagulation (28%), cerebral (24%), circulation (17%) and lung failure with 9%. The number of failing organs correlates with increasing white cell count and C-reactive protein (CRP) levels (Jalan and Williams 2002).

Two pathogenetic mechanisms seem to be important drivers of both intra- and extrahepatic organ dysfunction: systemic inflammation and dysbiosis of the microbiome (Bernardi M. et al. 2015). Systemic inflammation may be induced by bacterial pathogen-associated molecular patterns (PAMPs) or by virulence factors produced by bacteria. Patients with cirrhosis have increased permeability of the gut related to portal hypertension, inflammation-mediated damage to the gut barrier and altered gut flora. The result is increased translocation of particularly Gram-negative bacteria, PAMPs or virulence factors from the intestinal lumen to the systemic circulation. The prevalence of translocation of enteric organisms to mesenteric lymph nodes in cirrhotic patients is significantly increased according to the Child-Pugh classification: 3.4% in Child A, 8.1% in Child B and 30.8% in Child C patients (Cirera et al. 2001). Systemic inflammation may also be induced by ongoing necrosis of hepatocytes or damage to the extracellular matrix caused by alcohol, viral disease or any other aetiopathogenetic mechanisms of cirrhosis. In this case the molecules inducing inflammation are called damage-associated molecular patterns (DAMPs). How inflammation contributes to organ dysfunction in ACLF has not yet been fully elucidated. Besides the well-described severe immune dysfunction associated with cirrhosis with increased susceptibility to infection, the following concepts are likely to be important (Verbeke et al. 2011):

1. The effects caused by immunopathology, a term that describes the potential negative impact of an excessive immune response (Iwasaki and Medzhitov 2015). Either PAMPs or DAMPs can cause immunopathology that in turn may cause organ dysfunction. In this case defence mechanisms directed at controlling infection or immunopathology are insufficient. This is the likely mechanism in ACLF precipitated by acute bacterial infection or severe alcoholic hepatitis.
2. Failed tolerance, a concept that describes the incapacity to develop tolerance mechanisms to persistent infection–mediated inflammation (Medzhitov et al 2012). In this case persistent 'low-grade' systemic exposure to PAMPs or DAMPs may be the reason for ongoing 'sterile' inflammation for which no tolerance can be developed. This concept provides an array of potential new therapeutic targets aimed at increasing tolerance.

Recent evidence points to gut dysbiosis as a second important pathogenetic driver of organ dysfunction in ACLF (Bajaj et al. 2014b; Chen et al. 2015; Rai et al. 2014). Several factors contribute to altered microbiota in cirrhosis, including increased intestinal permeability, abnormal small intestinal motility, impaired antimicrobial defence, small intestinal bacterial overgrowth, decreased bile acid production and compromised enterohepatic circulation (Rai et al. 2014). In stable cirrhosis there is a clear change in diversity and composition of gut microbiota with progressive dysbiosis in the setting of decompensation. Similar changes

Table 2. ACLF Grades, Mortality and Disease Course Patterns

ACLF grades	28 day mortality (%)	90 day mortality (%)	Disease Course Patterns
No ACLF This category includes patients who either: • Do not have any organ failure • Have a single organ failure that does not involve the kidneys with a serum creatinine level of <1.5 mg per dl and no hepatic encephalopathy • Have single brain failure with a serum creatinine level of <1.5 mg per dl	1.9	10	
ACLF grade 1 ACLF grade 1 is diagnosed with one of the following: • Single kidney failure • Single liver, coagulation, circulatory or lung failure that is associated with a serum creatinine level of 1.5-1.9 mg per dl and/or hepatic encephalopathy grade 1 or grade 2 • Single brain failure with a serum creatinine level of 1.5-1.9 mg per dl	33	51	54% improve to ACLF-0 24% remain at ACLF-1 8.9% progress to ACLF-2 12.4% progress to ACLF-3
ACLF grade 2 • ACLF grade 2 is diagnosed when there are two organ failures of any combination	31	55	34.6% improve to ACLF-0 14% improve to ACLF-1 25.7% remain ACLF-2 25.7% progress to ACLF-3 ACLF grade 3
ACLF grade 3 • ACLF grade 3 is diagnosed when there are three or more organ failures of any combination	74	78	16% improve to ACLF-0 4% improve to ACLF-1 12% improve to ACLF-2 68% remain at ACLF-3

have been reported in ACLF. In a recent trial a relative abundance of *Pasteurellacae* was an independent predictor for mortality and, interestingly, the use of antibiotics had only moderate impact on the gut flora (Chen et al. 2015). Robust correlations were also observed between specific bacterial families and inflammatory cytokines such as interleukin-6 and TNF-alpha. A clear mechanistic link between pathogenic colonic mucosal microbiota and poor cognition has been demonstrated for hepatic encephalopathy (Rai et al. 2014; Bajaj et al. 2012). Remarkably, treatment with lactulose in patients with hepatic encephalopathy did not change faecal flora composition. It remains unclear how gut dysbiosis contributes to organ dysfunction. Current findings suggest that relative gut overgrowth of one type of bacteria or metabolites of certain bacteria species can contribute to inflammation and thereby to organ dysfunction.

Potential New Therapeutic Approaches

In specific situations early treatment of precipitating events such as alcoholic hepatitis with steroids or reactivation of hepatitis B with antivirals can reduce mortality. However, and for the most part, medical management of organ failure in ACLF remains supportive. Randomised trials with extracorporeal liver support systems aimed at blood purification did not result in survival benefits (Banares et al. 2013; Kribben et al. 2012).

A recent observational study reported improved clinical outcome with plasma exchange in hepatitis B-related ACLF (Chen 2016). High hopes are placed in regenerative therapy of cirrhosis including the use of growth factors, the combination of G-CSF and erythropoietin, hepatocyte and stem cell transplantation (King et al. 2015; Kedarisetty et al. 2015, Shiota and Itaba 2016; Duan et al. 2013; Garg et al. 2012; Zekri et al. 2015). Granulocyte-colony stimulating factor (G-CSF) therapy in ACLF reduced organ dysfunction and improved survival (Chavez-Tapia et al. 2015). It is unclear if the positive results obtained in randomised trials with administration of G-SCF in ACLF patients will be applicable in more severe forms of ACLF in the ICU (Duan et al. 2013; Garg et al. 2012).

Prognosis, Futility and Eligibility for Liver Transplantation

Many intensivists take a reserved attitude towards the admission of ACLF patients because of the dim prognosis of the syndrome. However, several new facts have emerged in recent years that defend a change in attitude and justify a full evaluation for transplant for every patient with ACLF admitted to the ICU. First, new data show that liver fibrosis and even cirrhosis are potentially reversible if the underlying cause is removed, with significant improvement in long-term survival (Ramachandran 2015). Second, the outcome of ACLF in the ICU has improved considerably. In expert ICUs survival of patients with cirrhosis and organ failure improved from 40% in the year 2000 to 63% in the year 2010 (McPhail et al. 2014). Similarly, ICU mortality of cirrhotic patients with septic shock has decreased from 74% in 1998 to 65.5% in 2010 (Galbois et al. 2014). Third, the course of the disease is very dynamic with resolution or improvement of ACLF in 4.2% of patients. Eighty-one precent reach their final ACLF grade at one week after admission, and it is now clear that for most patients prognostication will be considerably more accurate if done towards the end of the first week of ICU stay (Gustot et al. 2015). Fourth, prognostication for these patients has improved. New scoring systems, such as the Chronic Liver Failure Consortium Acute-on-Chronic Liver Failure score (CLIF-C ACLF) score that incorporates a modified SOFA-score (CLIF-Organ Failure [OF] score), age and white blood cell count can be calculated on a daily base in order to monitor evolution/resolution of ACLF and provide a significantly better estimate of risk for mortality than the model for end-stage liver disease (MELD) or Child-Pugh score (Jalan et al. 2014).

Considering the above, indiscriminate refusal of ICU admission of ACLF patients is not acceptable any more, since no specific group of patients can be identified at the time of diagnosis for which medical ICU treatment may be considered futile. However, intensivists also need to acknowledge that patients with four or more organ failures or a CLIF-C ACLF score > 64 after one week of ICU care have 28-day mortality rates in the range of 90 to 100%. If ineligible for transplantation withdrawal of care is a reasonable option for these patients.

Liver transplantation in ACLF is controversial and fraught with uncertainties regarding case selection and timing (Pamecha et al. 2015; Reddy et al. 2015). Only 15-25 % of patients are actually transplanted (Gustot et al. 2015, Finkenstedt et al. 2013). Recent series have reported encouraging results with 1- and 5-year survival of 80-90% (Finkenstedt et al. 2013; Chan et al. 2009). Even patients with ACLF-3 may expect a 1-year survival probability of 78% (Gustot et al. 2015).

Summary

Major progress has been made in defining the natural history and prognosis of ACLF. Regenerative therapies and liver transplantation in selected cases hold promise for the future. ■

Conflict of Interest

Philippe Meersseman and Alexander Wilmer declare that they have no conflict of interest.

Abbreviations

ACLF acute-on-chronic liver failure
CANONIC CLIF Acute-on-Chronic Liver Failure in Cirrhosis
CLIF chronic liver failure
CLIF-C Chronic Liver Failure Consortium
CRP c-reactive protein
DAMP damage-associated molecular patterns
G-CSF Granulocyte-colony stimulating factor
ICU intensive care unit
MELD model for end-stage liver disease
OF organ failure
PAMP pathogen-associated molecular patterns
SOFA sequential organ failure assessment

References

Arroyo V, Moreau R, Jalan R et al. (2015) Acute-on-chronic liver failure: a new syndrome that will re-classify cirrhosis. J Hepatol, 62(1 Suppl): S131-43.

Arroyo V, Moreau R, Kamath PS et al. (2016) Acute-on-chronic liver failure in cirrhosis. Nat Rev Dis Primers, 2: 16041.

Bajaj JS, Hylemon PB, Ridlon JM et al. (2012) Colonic mucosal microbiome differs from stool microbiome in cirrhosis and hepatic encephalopathy and is linked to cognition and inflammation. Am J Physiol Gastrontest Liver Physiol, 303 (6): G675-85.

Bajaj JS, O'Leary JG, Reddy KR et al. (2014a) Survival in infection-related acute-on-chronic liver failure is defined by extrahepatic organ failures. Hepatology, 60(1): 250-6.

Bajaj JS, Heuman DM, Hylemon PB et al. (2014b) Altered profile of human gut microbiome is associated with cirrhosis and its complications. J Hepatol, 60(5): 940-7.

Banares R, Nevens F, Larsen FS et al. (2013) Extracorporeal albumin dialysis with the molecular adsorbent recirculating system in acute-on-chronic liver failure: the RELEF trial. Hepatology, 57(3): 1153-62.

Bernal W, Jalan R, Quaglia A et al. (2015) Acute-on-chronic liver failure. Lancet, 386(10003): 1576-87.

Bernardi M, Moreau R, Angeli P et al. (2015) Mechanisms of decompensation and organ failure in cirrhosis: from peripheral arterial vasodilation to systemic inflammation hypothesis. J Hepatol, 63(5): 1272-84.

Chan AC, Fan ST, Lo CM et al. (2009) Liver transplantation for acute-on-chronic liver failure. Hepatol Int, 3(4): 571-81.

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UPDATE ON INTRA-ABDOMINAL HYPERTENSION

Knowledge of intra-abdominal hypertension (IAH) and abdominal compartment syndrome (ACS) is crucial for successful treatment of critically ill patients, whether medical or surgical, young or old (Kirkpatrick et al. 2013). Today we understand that IAH and ACS are frequent causes of increased morbidity and mortality (De Waele et al. 2016). More importantly, we now also know that IAH and ACS have correctable causes, can easily be diagnosed and effectively treated, but only if the clinician is aware of these conditions and pursues their recognition (Wise et al. 2015). A monograph has recently been published on this topic, as despite the increasing interest unanswered questions still cloud the understanding of the pathophysiology of IAH and ACS (Malbrain and De Waele 2013). In this article we will try to provide at least some answers.

Understanding Intra-Abdominal Hypertension: What to Worry About?

The abdomen can be considered as a closed anatomical space with the abdominal contents being primarily fluid in character, following Pascal's Law: any change in pressure applied at any given point is transmitted undiminished throughout the abdomen (Malbrain 2004). This means that intra-abdominal pressure (IAP) can be measured by way of different direct and indirect routes via the stomach, bladder, uterus or rectum (Malbrain 2004). The intra-abdominal volume (IAV) will exert a certain force on the abdominal compartment walls, resulting in a baseline IAP that will be mainly determined by the abdominal compliance (Cab) (Malbrain 2016). The relationship between IAV and IAP is curvilinear, with an initial linear part followed by an exponential increase once a critical volume is reached (Malbrain et al. 2014a; Malbrain et al. 2014b). IAP is an important physiological parameter and the recent updated consensus definitions must be used (**Table 1**) (Kirkpatrick 2013). IAH is defined as a sustained increase in IAP ≥ 12 mmHg and ACS is an IAP > 20 mmHg with new-onset organ failure (Kirkpatrick et al. 2013). While IAH is a graded continuum, ACS is an all-or-nothing phenomenon (**Table 2**) (Kirkpatrick et al. 2013). IAP should be measured at end-expiration, with the patient in the supine position and ensuring that there is no abdominal muscle activity. Intravesicular IAP measurement is convenient, most widely used and considered the gold standard technique (Kirkpatrick et al. 2013; Malbrain 2004). Where the mid-axillary line crosses the iliac crest is the recommended reference level for transvesicular IAP measurement and marking this level on the patient increases reproducibility of IAP measurement (Kirkpatrick et al. 2013; De Waele et al. 2008). Instillation volume (maximal 25 ml) and temperature (above room temperature) may affect IAP readings, and the head of the bed elevation above 30° increases IAP while PEEP only minimally affects IAP (Cheatham et al. 2009; Verzilli et al. 2010). Protocols for IAP measurement should be developed for each intensive care unit (ICU) based on the locally available tools and equipment, and the ICU physician should pick the technique that the nurses are going to use. Pitfalls in IAP measurement are multiple, and thorough knowledge is essential, e.g. absence of abdominal muscle activity should be checked, particularly in awake patients.

Underlying Predisposing Conditions: When to Worry?

1. Decreased Cab

Clinicians should worry about patients in whom Cab is decreased. The major problem is that Cab is not routinely measured in clinical practice (Malbrain 2014a). However, some indirect measures of Cab are available in mechanically ventilated patients: the ΔIAP (= IAP at end-inspiration minus IAP at end-expiration) and the abdominal pressure variation (APV = mean IAP divided by ΔIAP) are such parameters and they are inversely correlated with Cab, i.e. the higher the ΔIAP or APV, the lower the Cab (Malbrain 2014a). True Cab can only be measured in case of addition or removal of a known abdominal volume (e.g. laparoscopic insufflation, paracenthesis etc.) with simultaneous measurement of the change in IAP. Cab is defined as the ease with which abdominal expansion can occur, and is determined by the elasticity of the abdominal wall and diaphragm (Malbrain 2014a). It should be expressed as the change in IAV per change in IAP (ml/mmHg). Cab helps to understand the pathophysiological mechanisms and possible therapeutic targets (Malbrain et al. 2014a). Increased compliance indicates a loss of elastic recoil of the abdominal wall. Decreased compliance (e.g. in obesity, fluid overload, burn eschars, young age etc.) means that the same change in IAV will result in a greater change in IAP, and this can be a major contributor to secondary IAH.

2. Increased IAV

Clinicians should also worry when IAV is increased: this can be either related to free abdominal fluids or increased intraluminal

Table 1. WSACS Consensus Definitions Regarding Intra-Abdominal Hypertension and Abdominal Compartment Syndrome (Acs) According to the 2006 and 2013 WSACS Guidelines Update

Def	2006 definitions (Malbrain et al. 2006)	Def	2013 definitions (Kirkpatrick et al. 2013)
1	IAP is the steady-state pressure concealed within the abdominal cavity.	1	IAP is the steady-state pressure concealed within the abdominal cavity.
2	APP = MAP – IAP	2	APP = MAP – IAP
3	FG = GFP – PTP = MAP – 2 * IAP		REJECTED
4	IAP should be expressed in mmHg and measured at end-expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the mid-axillary line.	3	IAP should be expressed in mmHg and measured at end-expiration in the complete supine position after ensuring that abdominal muscle contractions are absent and with the transducer zeroed at the level of the mid-axillary line.
5	The reference standard for intermittent IAP measurement is via the bladder with a maximal instillation volume of 25 mL of sterile saline.	4	The reference standard for intermittent IAP measurements is via the bladder with a maximal instillation volume of 25 mL of sterile saline.
6	Normal IAP is approximately 5-7 mmHg in critically ill adults.	5	IAP is approximately 5-7 mmHg and around 10 mmHg in critically ill adults.
7	IAH is defined by a sustained or repeated pathologic elevation of IAP ≥ 12 mmHg.	6	IAH is defined by a sustained or repeated pathologic elevation of IAP ≥ 12 mmHg.
8	IAH is graded as follows: • Grade I: IAP 12-15 mmHg • Grade II: IAP 16-20 mmHg • Grade III: IAP 21-25 mmHg • Grade IV: IAP > 25 mmHg	7	IAH is graded as follows: • Grade I: IAP 12-15 mmHg • Grade II: IAP 16-20 mmHg • Grade III: IAP 21-25 mmHg • Grade IV: IAP > 25 mmHg
9	ACS is defined as a sustained IAP ≥ 20 mmHg (with or without an APP < 60 mmHg) that is associated with new organ dysfunction/failure.	8	ACS is defined as a sustained IAP ≥ 20 mmHg (with or without an APP < 60 mmHg) that is associated with new organ dysfunction/failure.
10	Primary ACS is a condition associated with injury or disease in the abdomino-pelvic region that frequently requires early surgical or interventional radiological intervention.	9	Primary ACS is a condition associated with injury or disease in the abdomino-pelvic region that frequently requires early surgical or interventional radiological intervention.
11	Secondary ACS refers to conditions that do not originate from the abdomino-pelvic region.	10	Secondary ACS refers to conditions that do not originate from the abdomino-pelvic region.
12	Recurrent ACS refers to the condition in which ACS redevelops following previous surgical or medical treatment of primary or secondary ACS.	11	Recurrent ACS refers to the condition in which ACS redevelops following previous surgical or medical treatment of primary or secondary ACS.
		12	**NEW:** A poly-compartment syndrome is a condition where two or more anatomical compartments have elevated compartmental pressures.
		13	**NEW:** Abdominal compliance quantifies the ease of abdominal expansion, is determined by the elasticity of the abdominal wall and diaphragm, and is expressed as the change in intra-abdominal volume per change in intra-abdominal pressure in L/mmHg.
		14	**NEW:** An open abdomen (OA) is any abdomen requiring a temporary abdominal closure due to the skin and fascia not being closed after laparotomy. The technique of temporary abdominal closure should be explicitly described.
		15	**NEW:** The open abdomen is classified with the following grading system: **1 – No Fixation** 1A: clean, no fixation 1B: contaminated, no fixation 1C: enteric leak, no fixation **2 – Developing Fixation** 2A: clean, developing fixation 2B: contaminated, developing fixation 2C: enteroatmospheric/cutaneous fistula, developing fixation **3 and 4 – Frozen Abdomen** 3: frozen abdomen, no fistula 4: frozen abdomen with enteroatmospheric/cutaneous fistula
		16	**NEW:** Lateralisation of the abdominal wall refers to the phenomenon whereby the musculature and fascia of the abdominal wall, most well seen by the rectus abdominis muscles and their enveloping fascia, move laterally away from the midline with time.

Sources: Adapted from Malbrain et al. (Malbrain et al. 2006) and Kirkpatrick et al. (2013)

ACS abdominal compartment syndrome APP abdominal perfusion pressure FG filtration gradient GFP glomerular filtration pressure IAH intra-abdominal hypertension IAP intra-abdominal pressure MAP mean arterial pressure OA open abdomen PTP proximal tubular pressure

Table 2. Grading of Intra-Abdominal Hypertension

Grade	Range of IAP (mmHg)
1	12–15 mmHg
2	16–20 mmHg
3	21–25 mmHg
4	≥ 25 mmHg

contents (Kirkpatrick et al. 2013). The relationship between IAV and IAP is expressed by Cab (Malbrain 2016). In patients with IAH, a small increase in IAV can lead to life-threatening aggravation of IAH. Vice versa, in the presence of IAH, a small decrease in IAV can lead to a significant decrease in IAP (Malbrain 2014a). So far, attempts to calculate IAV or to define surrogate markers have failed to prove useful in the clinical setting.

3. *Setting of Capillary Leak*

The last situation where clinicians should worry is the setting of capillary leak as a result of the inflammatory response and its diverse triggers, including ischaemia–reperfusion injury (Duchesne et al. 2015). Plasma volume expansion to correct hypoperfusion predictably results in extravascular movement of water, electrolytes and proteins. In the context of global increased permeability syndrome this can lead to IAH and sometimes ACS. A variety of strategies are available to the clinician to reduce the volume of fluids used during resuscitation (e.g. by means of active fluid removal or de-resuscitation) (Malbrain et al. 2014c). This may have beneficial effects on IAP and the occurrence of IAH and its related adverse effects (Regli et al. 2015).

Specific Conditions: When to Worry More?

Normal IAP in mechanically ventilated children is lower than in adults and about 7 mmHg (De Waele et al. 2015). Critical values of IAP that suggest IAH and ACS are also lower in children and an IAP greater than 10 mmHg should be considered as IAH. While IAP above 10 mmHg associated with new organ dysfunction is ACS in children until proven otherwise. IAH and ACS are common in severe acute pancreatitis and one should always suspect IAH in this setting and measure IAP regularly (De Waele et al. 2015). IAP should not be allowed to become greater than 20 mmHg and non-surgical measures should be tried first. However, one should not hesitate to resort to surgical decompression at an early stage if medical management fails (De Keulenaer et al. 2015). IAH will develop in most, if not all, severely burned patients (Wise et al. 2016). One should always suspect IAH and measure the IAP regularly during the initial resuscitation period (Malbrain et al. 2015). The higher the amount of burned surface area and volume of fluid resuscitation the higher the likelihood for developing IAH/ACS. Escharotomy can dramatically reduce IAP in case of circular abdominal burns, while decompressive laparotomy is not a first choice in burn patients. IAH and ACS can occur both in abdominal and extra-abdominal trauma patients. Early recognition in these patients is crucial, and IAP must be measured regularly irrespective of the site of injury. Early bleeding control and avoidance of massive transfusion are key elements in preventing IAH in trauma (Duchesne et al. 2015). Open abdomen treatment should be applied early and liberally in trauma patients at risk for ACS. Medical management strategies to reduce IAP will avoid surgical decompression and complications, and facilitate early closure of the abdomen (De Keulenaer et al. 2015). Baseline IAP is abnormally (chronically) elevated in the morbidly obese patient (Malbrain et al. 2015). Acute elevations in IAP may have similar effects in obese patients, but the threshold before organ dysfunction develops may be higher. Chronic elevations in IAP may, in part, be responsible for the pathogenesis of obesity-related complications (gastro-oesophageal reflux, pulmonary hypertension, pseudotumor cerebri). Pregnancy is another condition with sustained increase in IAP: the higher the IAP, the higher the risk for (pre)eclampsia (Malbrain et al. 2015).

Consequences of Intra-Abdominal Hypertension: Why Worry?

The effects of IAH on dfferent organs within and outside the abdomen are well recognised. IAH leads to increased intrathoracic pressure, increased central venous pressure and decreased venous return from the brain (De laet et al. 2007a). As a consequence, increased IAP can lead to increased intracranial pressure in all patients. Prevention of IAH therefore is essential in patients with intracranial hypertension. Cardiovascular dysfunction and failure are common in IAH or ACS (Malbrain et al. 2015b). Accurate assessment of preload, contractility and afterload is therefore essential to restore end-organ perfusion and function. Because pressure-based estimates of intravascular volume are erroneously increased in IAH/ACS, transmural filling pressures and volumetric preload indicators may better reflect true intravascular preload (Malbrain and Wilmer 2007). IAP also affects chest wall mechanics, and this has clinical relevance during lung protective ventilation (Pelosi et al. 2007). Opening and closing pressures are altered in such a way that a recruitment manoeuvre needs higher pressures and PEEP setting must be adapted to counteract the effects of increased IAP at the level of the diaphragm. IAH is a frequent cause of acute kidney injury (AKI); the relationship between IAP and kidney function seems to be dose-dependent (De Waele et al. 2011; De laet et al. 2007b). Clinically relevant kidney dysfunction may occur at IAP levels as low as 10–12 mmHg, and the best way to prevent IAH-induced AKI is to prevent IAH. Fluid overload should be treated early and aggressively in patients with IAH and AKI, and peritoneal dialysis should be avoided in patients diagnosed with, or at risk for, IAH. Recently the term polycompartment syndrome has been coined alluding to simultaneously increased pressures in different compartments (head, chest, abdomen, extremities etc.) (Malbrain and Wilmer 2007; Malbrain et al. 2014d). Increased compartment pressures are independently associated with morbidity and mortality and clinicians need to be aware of the existence of the polycompartment syndrome and the interactions of increased compartmental pressures between compartments.

> “treatment should always be based equally on the level of IAP, the underlying aetiology, the presence of comorbidities and the degree and magnitude of organ dysfunction”

Management: How to Stop Worrying?

Based on the underlying conditions that promote IAH and ACS medical management addresses four therapeutic targets:

1. Improving Cab
2. Reducing IAV (either by removing free abdominal or intraluminal fluid)
3. Correcting capillary leak and
4. Correcting fluid balance.

It is beyond the scope of this article to give an extensive overview of the different medical management strategies as these can be found elsewhere (Regli et al. 2015; De Keulenaer et al. 2015). The bottom line is that treatment should always be based equally on the level of IAP, the underlying aetiology, the presence of comorbidities and the degree and magnitude of organ dysfunction.

Conclusions

In 2013 the World Society of the Abdominal Compartment Syndrome (WSACS) published evidence-based guidelines on the definitions, diagnosis and management of IAH and ACS (Kirkpatrick et al. 2013). However, bedside decisions regarding correct management in individual patients with IAH or ACS remain difficult. The clinician should be aware of the polycompartment syndrome and interactions between different compartmental pressures. Cab is one of the most neglected parameters in critically ill patients, although it plays a key role in understanding organ-organ interactions and the deleterious effects of unadapted IAV on IAP and end-organ perfusion. ■

Abbreviations

ACS abdominal compartment syndrome
AKI acute kidney injury
Cab abdominal compliance
IAH intra-abdominal hypertension
IAV intra-abdominal volume
ICU intensive care unit

References

Cheatham ML, De Waele JJ, De Laet I et al. (2009) The impact of body position on intra-abdominal pressure measurement: a multi-center analysis. Crit Care Med, 37(7): 2187-90.

De laet I, Citerio G, Malbrain ML (2007a) The influence of intraabdominal hypertension on the central nervous system: current insights and clinical recommendations, is it all in the head? Acta Clin Belg Suppl, 62(1): 89-97.

De laet I, Malbrain ML, Jadoul JL et al. (2007b) Renal implications of increased intra-abdominal pressure: are the kidneys the canary for abdominal hypertension? Acta Clin Belg Suppl, 62(1): 119-30.

De Waele JJ, De Laet I, De Keulenaer B et al. (2008) The effect of different reference transducer positions on intra-abdominal pressure measurement: a multicenter analysis. Intensive Care Med, 34(7): 1299-303.

De Waele JJ, De Laet I, Kirkpatrick AW et al. (2011) Intra-abdominal hypertension and abdominal compartment syndrome. Am J Kidney Dis, 57(1): 159-69.

De Waele JJ, Ejike JC, Leppaniemi A et al. (2015) Intra-abdominal hypertension and abdominal compartment syndrome in pancreatitis, paediatrics, and trauma. Anaesthesiol Intensive Ther, 47(3): 219-27.

De Waele JJ, De Laet I, Malbrain ML (2016) Understanding abdominal compartment syndrome. Intensive Care Med, 42(6): 1068-70.

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