Practical Trends in Anesthesia and Intensive Care 2020-2021

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Perioperative Management of Patients Affected by Ischemic Cardiomyopathy

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Franco Cavaliere and Carlo Cavaliere

The incidence of myocardial infarction after surgery is relatively high. In a recent multicenter study, 3904 out of 21,842 patients over 45 years of age (18%) presented the diagnostic criteria for myocardial injury of ischemic origin in the first three postoperative days after noncardiac surgery [1]. This complication was particularly insidious because it is associated with a 30-day mortality of 4.1%, against 0.6% in the remaining patients, and because the characteristic symptoms of myocardial ischemia were absent in over 90% of cases.

To prevent perioperative myocardial infarction, it is of primary importance to identify patients at the most significant risk, i.e., those suffering from known ischemic heart disease or presenting symptoms suggestive of it. For this purpose, the anesthetist should always look for anginal signs in patients at risk and possibly ask for an evaluation by the cardiologist. In the presence of positive medical history, anesthetists should frame ischemic heart disease based on clinical symptoms and their evolution over time, coronary lesions documented by instrumental examinations, and relics left by previous heart attacks. The management during the intervention and postoperative period is based on the knowledge of the pathophysiological mechanisms underlying myocardial ischemia and on the adoption of careful monitoring to highlight the ischemic suffering when it is still reversible and prevent the evolution toward tissue necrosis. Finally, it is necessary to arrange all the instruments needed to treat a possible myocardial infarction.

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1.1 Classification

Patients affected by known ischemic heart disease come to the pre-anesthetic visit with a medical history of symptoms attributable to angina pectoris or one or more myocardial infarctions. These conditions are associated with different levels of risk.

Stable angina generally arises after exertion, is accompanied by transient electrocardiographic changes, and regresses after 3–10 min, with rest or with the administration of nitrates. The pathological lesion is an atherosclerotic plaque that partially occludes the lumen of an artery of the coronary circulation. Lumen stenosis limits the increase in blood supply to the myocardium during exercise. The stenosis can worsen with slow plaque build-up but is relatively stable. In general, its severity is inversely proportional to the magnitude of the effort that triggers the attack. The Canadian Cardiovascular Society grading scale (CCS) classifies angina into four classes based on the patient's physical activity (Table 1.1). The maximum physical activity that the patient can perform without the onset of stenocardial pain can be expressed in metabolic equivalents. In the perioperative period, myocardial ischemia usually results from increased cardiac oxygen consumption or reduced oxygen supply, as in anemization. However, the presence of a plaque can be the substrate for thrombus formation and the occlusion of the affected coronary branch.

Variant angina or Prinzmetal's angina occurs at rest, often at night. Like the previous one, it causes transient electrocardiographic changes and generally regresses with the intake of nitrates. Coronary arteries often do not have hemodynamically significant stenosis because angina originates from vasospasm. The spasm can be triggered by cold, exercise, hyperventilation, drugs, drugs of abuse, and cardiac catheterization and is inducible for diagnostic purposes with substances such as ergonovine, methylergonovine, and acetylcholine. Myocardial ischemia that occurs in the anginal attacks, if prolonged, can cause severe arrhythmias (including ventricular tachycardia and ventricular fibrillation), intracardiac blocks, and myocardial infarction. In the perioperative period, vasospasm may appear due to sympathetic hypertonicity or the administration of sympathomimetics [2, 3]. A particularly delicate phase is the induction of general anesthesia, but coronary vasospasms have also been described during regional or neuraxial anesthesia. The drug of choice for the treatment of vasospasm is nitroglycerin, either sublingually or intravenously; prevention is carried out with long-acting nitrates and with calcium antagonists as nifedipine, amlodipine, verapamil, and diltiazem. Intraoperative coronary spasm has also been observed in patients with a negative history.

Table 1.1 Canadian Cardiovascular Society grading scale for the classification of the severity of angina pectoris

Class I—Angina only during strenuous or prolonged physical activity
Class II—Slight limitation, with angina only during vigorous physical activity
Class III—Symptoms with everyday living activities, i.e., moderate limitation
Class IV—Inability to perform any activity without angina or angina at rest, i.e., severe limitation

An alteration of the microcirculation causes *microvascular angina or cardiac syndrome X* [4]. The painful symptoms are induced by effort, last for 15–20 min, and generally do not respond to the administration of nitrates. Coronary arteries may not have hemodynamically significant stenosis, and vasospasm provocation tests are usually negative. Some drugs, including beta-blockers, appear to reduce the frequency and severity of episodes.

Acute coronary syndromes include unstable angina and myocardial infarction [5].

Unstable angina is characterized by at least one of the following characters: (a) angina that occurs at rest and lasts for a long time, usually more than 20 min; (b) angina of new-onset (less than 2 months) and high severity (CCS class III or IV); (c) angina that has changed its characteristics, increasing in frequency, duration, or intensity. The anatomical substrate is generally the ulceration of an atherosclerotic plaque with thrombotic apposition that does not completely occlude the lumen of the coronary artery. The residual blood flow is sufficient to prevent myocardial necrosis, but the risk of the vessel's complete occlusion is very high. Unstable angina is a contraindication to elective noncardiac surgery. In the case of urgent interventions, it is necessary to evaluate case by case the possibility of treating coronary artery disease preventively, by surgical or intravascular route; if the treatment involves stent placement, subsequent therapy with double anti-platelet aggregation entails an increased risk of surgical bleeding, which should also be evaluated.

Myocardial infarction is a condition characterized by necrosis of part of the myocardium due to an ischemic mechanism [6]. Diagnosis is based on the increase in specific biomarkers with at least one value above the 99 percentile of the upper reference limit and one of the following criteria:

- Corresponding clinical symptoms.
- Significant electrocardiographic changes in the ST segment or T wave or the onset of a left branch block.
- Appearance of pathological Q waves.
- Imaging indicative of recent loss of viable myocardium or the appearance of abnormal segmental myocardial contractility.
- Evidence of coronary thrombosis on coronary angiography or post-mortem examination.

Based on the etiopathogenesis of ischemic damage, myocardial infarction has been classified into five categories [7]:

- Type 1: Occlusion of a coronary artery due to thrombus formation on an ulcerated atherosclerotic plaque.
- Type 2: Discrepancy between myocardial oxygen supply and need in the absence of phenomena related to plaque instability. This type of heart attack includes ischemia from coronary vasospasm, alterations in the microcirculation, arrhythmias, arterial hypotension and hypertension, anemia, hypoxemia, and drugs.
- Type 3: Myocardial infarction resulted in patient death without the availability of biomarker values.

- Type 4: Myocardial infarction secondary to percutaneous angioplasty.
- Type 5: Myocardial infarction secondary to myocardial revascularization surgery.

Finally, myocardial infarction is traditionally divided into STEMI (ST-elevation myocardial infarction) and non-STEMI (non-ST elevation myocardial infarction) [8, 9]. In the first case, clinical symptoms are accompanied by a significant elevation of the ST segment in two or more contiguous leads or by the acute onset of a left branch block; in the second, such alterations are missing. These two categories have multiple characteristics in common. The main difference is the indication for revascularization, which is the only accepted therapy in STEMI, and must be performed as quickly as possible; conversely, it could be replaced by medical treatment in non-STEMI, at least initially.

1.2 Preoperative Evaluation

The preoperative evaluation aims to determine the risk of myocardial infarction or heart failure in the perioperative period. Quantifying this risk has several purposes: correct patient information, optimization of preoperative conditions, planning surgery time and technique, anesthetic technique, and postoperative management. The evaluation is based on anamnestic and instrumental data and the dosage of biomarkers, considering the type of surgery the patient will be subjected to. Preoperative drug therapy should be confirmed or not on the day of surgery and in the following days.

1.2.1 Anamnesis

Unstable angina and recent myocardial infarction (less than 6 months) are associated with an increased risk of perioperative myocardial ischemia. The first six weeks after myocardial infarction are at high risk because they correspond to the period of wound healing; the next six are considered intermediate risk. Between 3 and 6 months, the risk remains more elevated than usual when arrhythmias or ventricular dysfunction complicated the infarction [10].

Also, recent coronary, endovascular procedures increase the risk of cardiac complications [11]. Surgery should be postponed for at least 2 weeks after plain old balloon angioplasty (POBA), 3 months after angioplasty with bare-metal stents, 6 months after angioplasty with drug-eluting stents, and 1 year after procedures performed during an acute ischemic syndrome. On the contrary, in the absence of new anginal symptoms and signs of ventricular dysfunction, myocardial revascularization surgery should be considered protective against perioperative cardiac risk for the next 6 years. These data are particularly important in planning elective surgeries.

Outside of these conditions, some scoring systems allow for the quantification of perioperative cardiac risk. Lee's index or revised cardiac index is based on the presence of six conditions (high-risk surgery, history of ischemic heart disease, history

Table 1.2 Perioperative incidence of cardiovascular complications (myocardial infarction, acute pulmonary edema, cardiac arrest, complete AV block) based on Lee's index or revised cardiac index [12]

Revised cardiac risk index for preoperative risk assessment		
	Criteria	
1	Elevated-risk surgery	
2	History of ischemic heart disease	
3	History of congestive heart failure	
4	History of cerebrovascular disease	
5	Pre-operative treatment with insulin	
6	Pre-operative creatinine >2 mg/dL or 176.8 μmol/L	
Class	Number of criteria	Risk of major complications (%)
I	0	0.4
II	1	0.9
III	2	6.6
IV	3 or more	11

of heart failure, diabetes on insulin therapy, creatinine above 1.2 mg/dL) (Table 1.2) for predicting the incidence of complications that include myocardial infarction, pulmonary edema, ventricular fibrillation, primary cardiac arrest, and complete atrioventricular block in patients over the age of 50 who undergo noncardiac surgery [12]. The American College of Surgeons National Surgical Quality Improvement Program has developed a score aimed at quantifying cardiac risk by providing an estimated percentage of new myocardial infarctions and cardiac arrests in the perioperative period starting from five factors: type of surgery, functional status, preoperative creatininemia greater than 1.5 mg/dL, ASA class, and age [13]. More recently, a more complex version of the program estimates noncardiac complications too [14].

In assessing the risk, it is of course necessary to consider the type of surgical procedure the patient will undergo. Proportional to its invasiveness, surgery causes stress that induces a neuroendocrine response and an increase in sympathetic tone. The risk of myocardial ischemia is greatly increased by tachycardia, arterial hypertension due to sympathetic hyperactivity, arterial hypotension caused by blood loss and fluid shifts in the body, anemia, and a hypercoagulable condition that results from the unbalance between thrombogenic and fibrinolytic factors. Traditionally, interventions are classified on the basis of the incidence of cardiac complications in low risk (less than 1%), intermediate risk (1–5%), and high risk (over 5%) [15]. Emergencies in themselves increase the risk.

Finally, it is important to include in the preoperative assessment the evaluation of the patient's cardiorespiratory functional reserve because this provides useful information on the degree of preoperative cardiac dysfunction and the extent of effort associated with the onset of anginal symptoms. Moreover, the two components can interact because cardiac dysfunction can favor the onset of tachycardia or arterial hypotension, which in turn can induce myocardial ischemia. Exercise spirometry allows to quantify functional reserve but involves an increase in costs and

preoperative hospitalization length. A less precise but in many cases adequate assessment can be performed during the preoperative visit, asking patients if in daily life they are able to perform some physical activities associated with different levels of cardiorespiratory work. Specific tables provide a list of physical activities such as doing housework, moving a piece of furniture, walking, running, and playing sports with the corresponding oxygen consumption expressed in metabolic equivalents (METs) [16]. One MET corresponds to the basal oxygen consumption; it is defined as the amount of oxygen consumed while sitting at rest and is equal to about 3.5 ml O_2/kg body weight/min. If patients are unable to climb two flights of stairs or run a short distance (activities that roughly correspond to 4 METs), they have poor functional capacity and are at increased risk of perioperative cardiac events.

1.2.2 Instrumental Tests

Preoperative ECG may be normal but often provides valuable information, such as the signs of previous myocardial infarctions or the presence of conduction disturbances (left branch block). According to the guidelines, its execution is indicated in patients who have risk factors for ischemic heart disease and who undergo interventions with high and intermediate risk (class I recommendation) or low risk (class IIb) and in subjects older than 65 years undergoing interventions with high and intermediate risk (class IIb) [11].

The resting transthoracic echocardiogram can provide important information on ventricular and valve function and highlights the presence of segmental alterations in contractility suggestive of ischemic suffering or damage. It is indicated in patients with symptoms or signs suggestive of heart disease. Its execution could also be helpful in the absence of risk factors in patients undergoing high-risk surgery (class IIb) [11].

Performing an exercise stress test with a cycle ergometer or treadmill allows detecting myocardial ischemia through the electrocardiographic and ultrasound changes that appear under stress. The indication is well-coded for patients with more than two Lee index factors undergoing high-risk interventions but may be extended to patients with one factor undergoing intermediate- or high-risk surgery [11]. An exercise stress test also assesses the subject's functional capacity because the maximal effort is required and is indicative of the heart rate and blood pressure values associated with the onset of cardiac ischemia. In patients who cannot perform a valid exercise test due to gait deficiency or functional reserve impairment (patients with the maximal activity of three METs or less), myocardial scintigraphy or transthoracic echocardiogram under drug stimulation with dipyridamole, adenosine, or dopamine can replace the test.

The indications for preoperative coronary angiography are the same as those for non-surgical patients. They mainly consist of recent STEMI, non-STEMI, and unstable angina with pain at rest or mild exertion [11]. In other words, surgery does not in itself constitute a reason to perform the examination but rather a contraindication in emergency/urgent conditions.

1.2.3 Biomarkers

The determination of some biomarkers can integrate instrumental tests. The main ones are cardiac troponins and the atrial natriuretic factor.

Cardiac troponins T and I are proteins present in actin filaments that play an essential role in controlling muscle contraction [17]. Both have isoforms specific to the heart muscle, making them superior to other markers (creatinine kinase and creatine kinase-myocardial band, lactate dehydrogenase, and aspartate aminotransferase) as indicators of myocardial ischemia, necrosis, and inflammation. The new high sensitivity methods allow detecting troponins T and I in the plasma of 50–90% of healthy subjects against 20–50% of low sensitivity techniques. This possibility could extend the use of these biomarkers from the diagnosis of acute cardiac events to the stratification of the risk of future events in the general population. The results of some recent studies appear promising in this regard [18]. Guidelines suggest that dosing before surgery and 48–72 h afterward could be helpful in high-risk patients undergoing major surgery, while there is no indication outside this group [11]. An increase beyond the 99th percentile in the healthy population is consistent with the diagnosis of myocardial ischemia. In evaluating the results, it should be considered that values increase in renal insufficiency and other cardiac pathologies.

The NT-proBNP factor (N - terminus of the B-type natriuretic peptide) is an index of the dilation of the atrial cavities because cardiomyocytes secrete it as a response to wall stress. It increases in states of heart failure, regardless of the presence of ischemia. Guidelines suggest that its dosage could be helpful as a prognostic factor in high-risk patients [11].

1.2.4 Pharmacological Therapy

Drug therapy aimed at preventing ischemia should be confirmed or not on the day of the surgery and in the following days.

1.2.4.1 Beta-Blockers

The rationale for using beta-blockers in ischemic heart disease consists of reducing myocardial oxygen consumption, mainly by decreasing arterial pressure, heart rate, and contractility, and increasing oxygen supply to the heart by prolonging the duration of the diastole. On the other hand, these drugs can cause bradycardia and arterial hypotension to the extent of increasing the incidence of stroke. The indication for treatment should consequently take into account the risk/benefit ratio [11].

In the preoperative evaluation, patients already under treatment should be distinguished from those who could benefit from taking these drugs. In the former, the administration of beta-blockers should be continued on the day of surgery when the indication is angina pectoris, heart failure, or cardiac arrhythmias. At the same time, it should be evaluated based on the risk/benefit ratio when the indication is the treatment of hypertension. In any case, the dosage can be reduced on the day of surgery and the following ones to avoid the risk of arterial hypotension and low output, especially in patients with reduced cardiac function.

Some patients are not on beta-blocker medication, but they may benefit from it. Literature indicates that the risk/benefit ratio of starting therapy before surgery is favorable in high-risk patients, unfavorable in low-risk patients, and doubtful in intermediate-risk patients. In any case, beta-blockers without sympathomimetic effect (atenolol, bisoprolol) should be preferred over those with sympathomimetic effect (metoprolol). In addition, therapy should be started at least one day before surgery, but better a week before. Finally, the initial dosage should be low (e.g., atenolol 50 mg/day) and then titrated, targeting a heart rate between 60 and 70 beats per minute and systolic blood pressure greater than 100 mmHg [19]. This approach is not feasible in patients who undergo urgent or emergency interventions, in whom the use of beta-blockers should be symptomatic only to control heart rate during surgery and in the postoperative period.

1.2.4.2 Acetylsalicylic Acid

Acetylsalicylic acid (ASA) inhibits platelet aggregation by irreversibly blocking the cyclooxygenase enzyme and the formation of thromboxane A2. The intake would increase the number of bleeding episodes in the perioperative period, but not their severity [21]. Discontinuation of ASA therapy is indicated only in certain types of surgery, such as neurosurgical and ophthalmic surgery, in which the bleeding risk exceeds the benefits expected from platelet anti-aggregation. In these cases, the restoration of normal platelet aggregation occurs with platelet turnover, quantifiable at 10% per day, and requires a suspension of the administration of the drug for 4 or 5 days [22, 23].

1.2.4.3 Platelet Glycoprotein Inhibitors (Clopidogrel, Tigaclogrel, Prasugrel)

The treatment of coronary heart disease through transluminal angioplasty with naked (BMS) or medicated (DES) stent placement involves the use of antiplatelet therapy with two active drugs (cyclooxygenase inhibitor + P2Y12 platelet receptor inhibitor) for a time that varies according to the procedure and the characteristics of the coronary stent [11]. Double anti-aggregation should be continued for 3 months in BMS carriers, 6 months in DES carriers, and 1 year if BMS or DES have been placed for an acute coronary syndrome. If the intervention, although elective, cannot be postponed for such a long time, the time intervals can be reduced to 1 month, 3 months, and 3 months, respectively. In this case, ASA therapy should be continued, and it would be desirable that the surgery be performed in a hospital equipped with a hemodynamics laboratory to treat any stent occlusion immediately. Finally, in cases where the surgery can be postponed for only a few days, therapy with ASA is continued, and the administration of clopidogrel or ticagrelor is suspended 5 days before surgery or prasugrel 7 days before. Double anti-aggregation should be resumed in the postoperative period as soon as possible, generally within the first 48 postoperative hours. In patients at particularly high thrombotic risk, reversible inhibitors of the GPIIb/IIIa receptor such as eptifibatide or tirofiban can be used, while in the case of severe perioperative bleeding in an anti-aggregated patient, platelet preparations can be infused.

1.2.4.4 Statins

Statins reduce the plasma concentration of cholesterol by inhibiting the enzyme HMG-CoA reductase, which intervenes in the conversion of 3-hydroxy-3-methyl-glutaryl coenzyme A to mevalonic acid. They are drugs widely used in subjects suffering from ischemic heart disease, in which they would also play a stabilizing action on the atherosclerotic plaque, preventing ulceration and thrombosis. The results of some studies suggest that statin therapy would reduce the mortality and incidence of perioperative myocardial infarction [20].

Patients already on therapy should continue statins during the perioperative period. The unavailability of injectable preparations can make it difficult to administer them in the immediate postoperative period of some types of surgery. In this case, preparations with a longer half-life (atorvastatin, prolonged-release lovastatin) can be used. Data on the efficacy of statin therapy started shortly before surgery in normocholesterolemic patients are discordant. Guidelines suggest the possible usefulness in vascular surgery, starting treatment at least 2 weeks before surgery [11].

1.2.4.5 Nitrates

The use of nitrates outside of an acute ischemic condition has no positive effects on perioperative mortality and morbidity, while it carries the risk of arterial hypotension from relative hypovolemia. Therefore, the administration of these preparations should be suspended before surgery [11].

1.2.5 Premedication

Premedication aims to reduce anxiety and, consequently, tachycardia and arterial hypertension. Benzodiazepines (diazepam, midazolam) are generally a good choice. The dosage should be reduced in elderly or hypovolemic patients due to the possible hypotensive effect, even if generally modest. Opioid administration may be indicated in some patients due to the presence of preoperative pain. In these cases, morphine (0.05–0.1 mg/kg) can be administered intramuscularly or fentanyl (25–50 mcg) intravenously in an environment with adequate monitoring for the risk of respiratory depression.

1.3 Intraoperative Management

1.3.1 Specific Issues

The patient with ischemic heart disease has an increased risk of developing acute myocardial ischemia in the perioperative period. The prevention of this complication must start from its pathophysiology. Autopsy studies have shown that the majority of patients who died from perioperative myocardial infarction had coronary artery disease with significant stenosis of one or more coronary vessels, but that in most cases there was neither thrombosis of the coronary vessels nor fissure

of an atherosclerotic plaque. This suggests that the majority of perioperative heart attacks are type 2 that is linked to a discrepancy between the need and the supply of oxygen to the myocardium.

Myocardial oxygen consumption mainly depends on three factors: heart rate, contractility, and wall tension [24, 25]. The latter depends on afterload, i.e., on systemic blood pressure during systole, and on preload, i.e., on ventricular pressure during diastole. These components have a different bearing on oxygen consumption. In experimental models, myocardial oxygen consumption increases by 50% for a 50% increase in contraction rate or contractility (expressed as dP/dT), by 45% for a 50% increase in afterload, and only by 4% for a 50% increase in preload. The main factors that can cause an increase in myocardial oxygen consumption in the perioperative period are therefore sympathetic hyperactivity, tachycardia, arterial hypertension, and the use of positive inotropic drugs.

The supply of oxygen to the myocardium depends, in addition to local factors related to the patency and caliber of the coronary vessels, on systemic arterial pressure and the oxygen content of the blood and therefore on the concentration and saturation of hemoglobin. The subendocardial portion of the myocardium is particularly subject to ischemia because it is directly exposed to the pressure present inside the heart cavities, which exerts a compression effect. Consequently, the perfusion of these areas of the myocardium occurs exclusively during diastole, the duration of which is reduced exponentially with the increase in heart rate; ventricular end-diastolic pressure also has a negative effect on perfusion during diastole [26]. The main factors that can reduce the supply of oxygen to the tissues are therefore tachycardia, arterial hypotension, anemia, hypoxia, and high preload.

The goals of perioperative management in the ischemic heart patient should be [27]:

- To maintain adequate anesthesia depth and analgesia level. A too deep anesthesia causes arterial hypotension; a too superficial one can be associated with sympathetic hypertonia, tachycardia, and arterial hypertension.
- To maintain an adequate blood volume. Hypovolemia causes tachycardia and hypotension; hypervolemia causes hypertension and an increase in the left ventricle end-diastolic pressure.
- To maintain a heart rate between 50 and 80, using if necessary the administration of beta-blockers such as esmolol or metoprolol or, alternatively, amiodarone.
- To avoid arterial hypotension. In addition to maintaining an adequate volume, possible pharmacological interventions consist in the administration of alpha1 stimulants (etilefrine, noradrenaline).
- To avoid arterial hypertension. Possible pharmacological interventions include the administration of beta-blockers, clonidine, and nitroglycerin.
- To ensure adequate arterial oxygen saturation and avoid anemia, maintaining hemoglobin levels not lower than 8 g/dL.

1.3.2 Anesthesia

Studies on the subject failed to show a superiority of locoregional anesthesia over general anesthesia. A mixed technique could offer more excellent cardiovascular stability, allowing to decrease the dosages of general anesthetics and offering better postoperative analgesia [27].

The induction of general anesthesia is a particularly delicate phase because it can easily be associated with arterial hypertension and tachycardia (increased myocardial oxygen consumption) or hypotension (reduced myocardial perfusion). The drugs commonly used are propofol, midazolam, and etomidate, which differ concerning hemodynamic effects and the ability to inhibit the sympathetic response to endotracheal intubation. The dosage and rate of administration are critical as they influence the peak plasma concentration. A slow or split injection is often better tolerated. Ketamine is rarely used for the risk of hypertensive crises.

Tracheal intubation is a maneuver that can induce a marked sympathetic response. It is crucial to perform it after reaching an adequate anesthetic plan, possibly associating opioids or lidocaine with hypnotics. Extubation can also induce a sympathetic reaction and should be performed at the end of the operation with the patient still not fully awake.

Maintaining the state of anesthesia can be achieved with inhaled or intravenous drugs. The former could contribute to the prevention of myocardial ischemia due to myocardial preconditioning, that is, by inducing biomolecular changes that make myocytes more resistant to ischemia. However, myocardial preconditioning has been well documented in the laboratory, but its benefits on perioperative complications in clinical practice have not yet been proven with certainty [28].

1.3.2.1 Monitoring

The choice of parameters to be monitored in patients suffering from ischemic heart disease is based on standard criteria and does not present peculiarities [27].

The ECG is the fundamental tool for highlighting the onset of myocardial ischemia. For this purpose, leads II and V5 should be continuously displayed, which can reveal about 90% of ischemic episodes if examined simultaneously. Monitors providing continuous ST-segment analysis are particularly effective for this purpose.

Invasive blood pressure monitoring and placement of a central venous catheter are generally indicated in major surgery, when there may be acute changes in blood volume, significant impairment of cardiac function, and use of inotropic and vasopressor drugs.

Pulmonary catheterization is generally not indicated outside cardiac surgery or any cardiogenic shock following an acute myocardial infarction.

The transesophageal echocardiogram provides complete monitoring of heart function. It is rarely indicated as initial monitoring but can provide valuable information in acute myocardial ischemia. In particular, the appearance of hypokinesia, dyskinesia, and akinesia allows identifying the affected coronary vessel and the

evolution of ischemia with reasonable precision. The comparison with a preoperative echocardiogram, which highlights the pre-existing segmental alterations of myocardial contractility, is very useful in these cases.

1.3.3 Postoperative Period

Myocardial infarction occurs in the first 48 h after surgery in more than 90% of cases. According to a series, this complication arises in 44% of patients on the operating day, 34% on the first postoperative day, and 16% on the second [29]. Consequently, it is essential to continue to apply precautions to optimize myocardial oxygen consumption and intake for at least 2 days after surgery.

Adequate postoperative analgesia is significant to reduce sympathetic hypertonia. A multimodal approach is preferred, in which locoregional techniques and systemic analgesia are joined. Guidelines recommend cautious use of NSAIDs and COX2 inhibitors for possible side effects, particularly on clotting and renal function [11].

Admission to an intensive care unit allows for the monitoring and optimizing of cardiorespiratory parameters in high-risk patients and offers continuous ECG recording, but it increases costs and is subject to the availability of beds. Additional resources are made up of sub-intensive units and wards equipped with telemetry. Admission to intensive care should be planned preoperatively based on the degree of risk, but the intraoperative course may require changes. The surgical Apgar score (APGAR) can object the changes in the risk of complications that occur during surgery and provide the new expected mortality and morbidity [30].

1.3.4 Treatment of Acute Myocardial Ischemia

It is essential to quickly recognize the onset of myocardial ischemia to treat it and prevent its infarct evolution. It is also necessary to maintain a high clinical suspicion in the presence of arrhythmias or hypotensive episodes because clinical symptoms of myocardial ischemia are often absent (over 90% of cases in the VISION study) [1]. ECG monitoring is also feasible outside the intensive care unit, for example, by telemetry and using automatic analysis systems of the ST segment and arrhythmias. In patients at increased risk or based on clinical parameters, serial troponin dosing may be indicated. A transthoracic echocardiogram can confirm the presence of changes in segmental contractility in previously normal areas.

Treatment of myocardial ischemia is based on the optimization of blood oxygenation (oxygen therapy, high flow nasal cannulae oxygen therapy, continuous airway pressure (CPAP), mechanical ventilation), oxygen transport capacity (correction of anemia by blood transfusion), heart rate control (adequate anesthesia depth, beta-blockers, amiodarone), and blood pressure control (fluids, vasoconstrictors). The administration of nitrates intravenously or sublingually can quickly resolve the situation. The cardiologist consultant will decide whether to indicate a coronary angiography if the signs of ischemia persist or recur.

1.4 Conclusions

The surgical patient who has a history of ischemic heart disease is at greater risk of developing myocardial infarction in the perioperative period. Preoperative evaluation should be accurate to quantify risk, plan surgical and anesthetic techniques, and confirm or modify drug therapy. Perioperative management is based on the stability of hemodynamic conditions, the maintenance of an adequate anesthetic depth, and effective analgesia. Early recognition of ischemia is essential for effective treatment.

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2 Acute Liver Failure: Definition, Epidemiology and Management – Update 2022

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Diseases desperate grown, by desperate appliance are relieved. Or not at all.—William Shakespeare, Hamlet, Act IV, Scene iii

2.1 Introduction

Acute liver failure (ALF, known from the early 1970s as fulminant hepatic failure, FHF or fulminant hepatitis) is a rare syndrome characterised by acute and massive hepatocellular necrosis in individuals without chronic or pre-existing liver disease [1–6]. ALF is characterised by different degrees of altered mentation (*encephalopathy*) and impaired coagulation (INR, international normalised ratio of prothrombin time > 1.5, secondary to impaired synthetic function): hyperbilirubinemia, reported in non-hyperacute presentation, is less common in rapidly evolving cases [1–3]. The incidence is 1–8 cases per million population in developed countries (2000–3000 cases per year in the USA, 400–600 in the UK and 150–200 in Italy), even more in developing countries [1–7]. In spite of very different aetiologies, clinical features of ALF are similar. Its presentation varies according to the rate of evolution of illness, classified as hyperacute (<7 days), acute (>7 to 21 days) and subacute (> 21 to 26 weeks), according to emergence of encephalopathy following the start of clinical symptoms [1–6]. Over the course of days or weeks, ALF can evolve into devastating forms of multiple organ dysfunction/failure (MODS/MOF): cerebral oedema (frequent in the hyperacute forms, rarely reported in subacute cases), coma (these latter often) characterised by renal failure and portal hypertension [1–6]. Counterintuitively,

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better prognosis is usually associated with the hyperacute forms of ALF, in spite of extrahepatic organ dysfunction, cerebral oedema and the risk for intracranial hypertension [1–6]. As emphasised by Stravitz and Lee [1], the rarity of ALF is at the base of the many (unsuccessful) attempts to build international well-structured databases. This is the main reason guidelines and position papers reflect mainly authoritative expert opinions and not, at least so far, evidence-based medicine [1, 2]. ALF should not be confused with the acute-on-chronic form of liver failure (ACLF) and the acute hepatic decompensation of a chronic liver disease associated with the failure of extrahepatic organ systems [1, 8]. Even if frequently acute in their presentation, Wilson's disease, hepatitis B virus (HBV) reactivation, autoimmune hepatitis and Budd-Chiari syndrome have stigmata of unrecognised/unknown chronicity, to be thoroughly tracked in all the forms of unexplained presentation of ALF cases [1–3, 9–11]. In the most recent European guidelines on ALF, there is place also for the acute liver injury condition (ALI), a relevant biochemical liver injury without alteration of consciousness [2, 10].

2.2 ALF Aetiology and the Impact of Geographical Distribution

The aetiology of ALF recognises multiple causes, with different modes of presentation and potentially different management solutions: the most recent analysis, ranging from January 1990 to March 2019, is reported in the American Registry of Fulminant Hepatitis [1]. In short, 2614 patients were included. Paracetamol caused 46% of cases, 12% of cases had an undetermined aetiology, and drug-induced liver damage was responsible for 11% of cases. Patients with acute hepatitis of undetermined cause were only 5.5% [1]. According to Jayalakshmi and Bernal [4], grouping ALF into *primary* and *secondary* causes should ease the appropriate indication to urgent/emergent liver transplant (ELTx), the last solution when the maximal intensive treatments are not enough and the outcome is poor [1–6, 11–13]. Primary ALF caused by direct injury from drugs, toxins, viruses, autoimmune-mediated hepatitis, pregnancy-related liver dysfunction and vascular insult (Budd-Chiari) are indications for ETLx: Wilson disease and HBV reactivation are also to be included among the "primary" forms of ALF and to be considered for ELTx [4]. On the contrary, the so-called "secondary" forms of ALF (hypoxic hepatitis, haemophagocytic lymphohistiocytosis, dengue, malaria or leptospirosis) should represent a contraindication to ELTx, due to the systemic involvement which makes the transplant futile [1, 2, 10].

The geographical distribution of ALF [6, 7] deserves, according to the prognosis and the treatment, a particular attention [1–7]. The five most prevalent causes in developed countries are paracetamol toxicity, ischaemia, drug-induced liver injury, hepatitis B virus and autoimmunity (nearly 80% of cases) [1–6, 9–14]. Paracetamol is the most frequent cause of ALF in the USA, Canada and the UK, viral aetiology being more common in Europe (Italy and Southern Europe) and Asia [12, 13]. On the contrary, viral hepatitis A, B and E are the main causes of

ALF in developing countries [6]. ALF due to hepatitis B virus is now less frequent in developed countries due to vaccination campaign, but this aetiology should be considered if and when vaccination is not present. Relevant is the impact immigration might have today in Europe, with cases of ALF due to HEV. Herpes simplex and varicella zoster viruses, non-hepatotropic viruses, have been associated with rare but devastating and rapidly lethal forms of ALF [1–4]. Much rarer are forms associated with cytomegalovirus (CMV) and Epstein-Barr (EB) viruses. Less common causes of ALF are pregnancy-associated microangiopathic liver injury (HELLP, haemolysis, elevated liver enzyme and low platelet count; acute fatty liver of pregnancy). ALF, as already underlined, might be the acute presentation of Wilson disease, always to be considered in case of unexplained ALF in young individuals: acute kidney injury and intravascular haemolysis are peculiar stigmata, to be considered to speed up the diagnosis. A thorough aggressive, updated research in the clinical history is today able to reduce the "indeterminate causes" to close to 5% of the cases [1–3].

The clinical patterns of liver injury associated with ischaemia and paracetamol are similar: high to very high plasma aminotransferase concentrations (AST/ALT) and pathological INR peak at approximately 72 h after the insult, bilirubin being either normal or only slightly elevated. Quite predictable is the subsequent effect of cytokine cascade and the evolution of injury towards extrahepatic multiple organ dysfunction and damage [1–3, 13, 15–17]. In case of paracetamol ingestion, due to the quite short half-life, plasma level of the parent compound is present in less than half of the cases but could constitute a reliable confirmatory test as the acute cause of the ALF. N-Acetylcysteine, taken within 12 hours after the ingestion, is able to prevent liver injury and might be beneficial if administered with 48 hours [1, 3]. However, ELTx is sometimes the only solution if liver recovery/regeneration is not expected [1–6]. Inadequate perfusion and oxygenation to the liver (hypoxic hepatitis, shock hepatitis) might have various causes, critical hypotension being usually the hallmark: heart failure/cardiogenic shock, septic shock and hypovolemic shock are among the most common conditions leading to a hyperacute but (usually) self-limited liver injury. Hypoxia secondary to acute, very severe respiratory failure is a possible alternative cause. Short-term prognosis of the hepatic ischaemia is good, if the haemodynamic profile is rapidly assessed and appropriately managed. Liver transplant is usually not necessary unless in case of inadvertent, prolonged surgical occlusion of the hepatic artery. Rather different is the drug-induced liver injury (DILI), often due to an idiosyncratic response, usually immune-based, with a genetic predisposition and with a more insidious and indolent course. Antibiotics are quite frequently involved and, among others, the amoxicillin-clavulanate combination [18]. In DILI forms of ALF, AST/ALT are usually not very high, bilirubin concentration is high, and encephalopathy, often present, is an ominous prognostic marker, with a mortality rate close to 70% without if ELTX. The acute-to-subacute insidious course is also typical of the so-called autoimmune hepatitis, frequently recorded in women and requiring biopsy to support an often difficult diagnosis. Outcomes are poor and LTx is frequently required.

2.3 Clinical Manifestations of ALF

The main manifestations of ALF are varying degrees of altered mentation/altered consciousness (hepatic encephalopathy, see stages according to West Haven (WH) classification (I–IV), the FOUR (Full Outline of Unresponsiveness) classification and the correlation with Glasgow Coma scale) [19] associated with severe coagulopathy, elevation of transaminases and hyperbilirubinemia: these are observed over a period ranging from 2–5 days (hyperacute form) to 26 weeks (subacute form) after an acute hepatic insult of various aetiologies [1–6, 11, 19]. Patients with mild hepatic encephalopathy (West Haven Grade I) have *covert* encephalopathy, *overt* encephalopathy being present with grade II or higher. The clinical scale to define encephalopathy according to the FOUR score is based on four neurological aspects. The score ranges from 0 to 16; the lower the scores, the lower the level of consciousness [19]. As already mentioned, according to the time lag from the onset of symptoms to the onset of the encephalopathy, the syndrome is usually classified as hyperacute (<7 days), acute (8–28 days) and subacute (28 days–26 weeks) [1–6]. Recently, Stravitz and Lee [1] proposed, as more logical, to group acute and subacute forms into a single syndromic entity, due to an overlap of the speed of evolution (days to weeks), while recognising to the hyperacute liver failure (within hours) a distinct disease pattern. Thus, two large groups (hyperacute and acute/subacute) would be maintained that differ in evolution and aetiology. The hyperacute form (usually associated with paracetamol intake and ischaemic hepatitis) evolves within 36–48 h of the insult and presents high "liver injury" (high transaminases), low bilirubin concentration and resolution in 4–5 days, while the acute and subacute forms (defined as slowly evolving) develop over 1–24 weeks and are often associated with hepatitis B, autoimmune hepatitis or drug intake. To be underlined, recent and authoritative reviews did not consider or did not agree with this hypothesis [5, 10, 11] (Fig. 2.1).

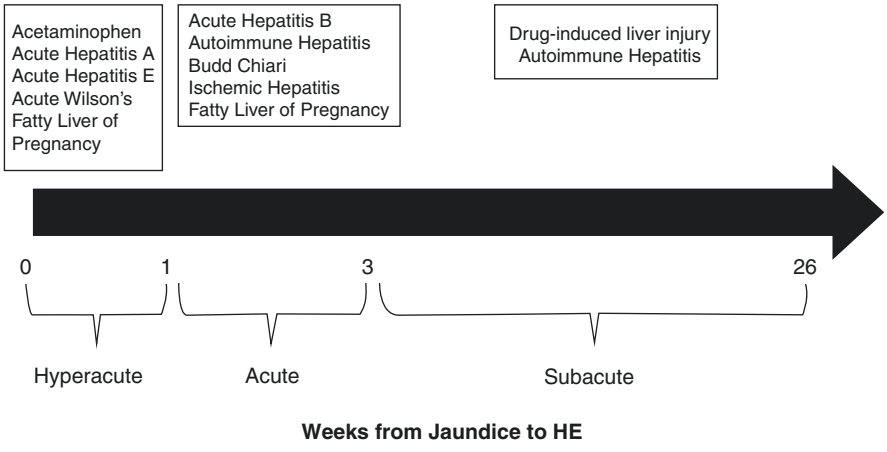

Fig. 2.1 Classification and causes of ALF From Tafesh ZH and Pyrsopoulos in Liver Failure, N Pyrsopoulos Ed. Springer © 2020 with permission

In general, the evolution of ALF depends on the aetiology, making efficient and rapid diagnostic tool(s) key for an appropriate and prompt intensive treatment or for the indication to ELTx, the real game changer of the natural course of the disease, (very poor) in specific cases [11]. In fact, ELTx has changed the natural history of ALF in the last 30 years [1–13]: it is the recognised form of treatment and cure for ALF, able to revert both MODS/MOF and their systemic consequences, with a significant impact on the prognosis [1, 2, 4, 10–13]. In fact, mortality, ranging between 70% and 90% in the pre-transplant era (1970s), has been drastically reduced, reaching now figures well above 70% in the medium and long term [1–5, 11]. Relevant to be underlined, in some forms of ALF (acute hepatitis associated with hepatitis A virus, ischaemic damage, pregnancy or from paracetamol), aggressive, updated intensive treatment has led to survival of over 60%, even in the absence of transplantation (previous figures between 20 and 25%) [3, 11].

As previously highlighted, ALF has a complex aetiology and develops following *cytotoxic* or *cytopathic* damage [1, 11–16]. Depending on the aetiology, mortality, early if associated with cerebral oedema and acute hyperdynamic circulatory failure, or late, if associated with sepsis or septic shock and MOF, is still very high, ranging from 30% to 40% [1–11, 15–17, 20–22]. A direct *cytotoxic* effect on hepatocytes is associated with viral aetiology (hepatitis A virus, HAV), drugs (paracetamol, amoxicillin-clavulanate, nimesulide, flutamide, cyproterone, the latter two in some cases with off-label indications) [18], toxins (mushrooms, carbon tetrachloride), the so-called recreational excitatory drugs (3,4-methylenedioxymeth amphetamine, better known as ecstasy, a synthetic amphetamine) [14] or in dietary regimes (turmeric, unpublished, personal case). A *cytopathic* effect is associated with the immune-mediated response of hepatocytes in the presence of hepatitis B virus (HBV) due to abnormal expression of surface antigens. Hepatitis C (HCV) has not yet been shown to be related to ALF [15–17].

In ALF, the prognosis varies according to aetiology but also to age: better in subjects <65 years, in case of ALF from HAV, paracetamol or associated with pregnancy, it is really poor (mortality >70%) in case of idiosyncratic aetiology, if associated with HBV or in the presence of unknown cause. The severity of hepatic encephalopathy significantly affects outcome (WH I–II, survival 77%, vs grades III–IV, survival 54%) [19]. In a study of 315 ALF patients [15], the immediate cause of death in 35% of the cases was cerebral herniation secondary to endocranial hypertension, while refractory hypotension associated with septic shock and multiple organ failure (often one the consequence of the other) contributed to death in the large majority of the cases [1–6, 11, 20]. Dead hepatocytes trigger release of DAMPS (*damage-associated molecular patterns*) able to activate immune cells and the release from monocytes and neutrophils of pro-inflammatory cytokines, nitric oxide and ROS [17]. The acute, massive loss of hepatic function is responsible for the increase of water-soluble toxic substances (ammonium and mercaptans) and of hydrophobic substances carried by albumin (bilirubin, aromatic amino acids, endogenous benzodiazepines, bile salts, short-chain fatty acids). This complex immune dysregulation leads to MOF, the systemic manifestations of ALF [1, 11, 16, 17, 20–22]. Among others, hepatic encephalopathy (and potentially cerebral oedema),

respiratory consequences of capillary leak syndrome, cardiocirculatory alterations (including the hyperdynamic syndrome, the hepatorenal syndrome and the acute renal failure), haemostatic imbalance and changes in the metabolic profile (hypoglycaemia and acidosis, almost always lactic) depict a full-blown MOF syndrome [1, 11, 16, 17, 20–22]. Globally, substances and mediators involved in the generation/maintenance of the oxidative stress are associated with increased microvascular permeability, altered immune response(s) and, as a consequence, increased infections, particularly bacterial and fungal [1–4, 11].

2.4 Indications for ICU Admission and Referral to a Transplant Centre

In case of ALF, it has to be recommended the early referral to a critical care facility, possibly part of a Liver Transplant Centre, to optimise the multi-organ vital support and to speed up the indication for ELTX if appropriate [1, 2, 4, 11–13, 17, 19]. In fact, if the appropriate indication of ELTx has changed the natural history of ALF in the last 30 years [11–13], survival in ALF improved due to the important results achieved with the intensive medical treatment, including extracorporeal modalities [17, 20–22], in particular the high-volume plasmapheresis [22], in cases where, for various reasons including social ones, there is no indication for ELTx [1, 2]. Aims of the ICU management of ALF are aggressive support of vital functions and their continuous optimisation [1, 2, 4, 17–20], both to contrast/contain/solve the onset of MOF in the event of non-irreversible liver necrosis and to buy time while bridging the patient to ELTx (usually in case of an inadequate liver regeneration in spite of the aggressive medical treatment) [1–4, 11, 17, 20]. In this context, the role of early high-dose N-acetylcysteine (NAC) to treat ALF, known for decades [1, 4], has to be stressed [4, 23–25]. NAC should be started immediately in case of paracetamol overdose and very early (within 24–48 h from the exposure) also in case of non-paracetamol drug-induced liver injury (DILI) or hypoxic hepatitis [3, 4, 23–25]. NAC should prevent liver damage and promote liver regeneration. The effects are a reduction in the incidence and severity of encephalopathy, a reduced need for ICU and a reduced incidence of MOF: the latter effects deserve of course further confirmation. The usual schedule is as follows: NAC infusion for 72 hours (load dose of 150 mg/kg in 1 h, followed by 12.5 mg/kg/h for 4 h and a continuous infusion of 6.25 mg/kg/h for the remaining 67 hours) [23–25].

2.5 Intensive Care Treatment Aimed at Supporting Organ Function

For a rational multidisciplinary treatment of ALF-associated MODS/MOF, extensive, finalised multimodal monitoring is required and should include the control of cerebral, cardiovascular, respiratory and renal systems and metabolic (in particular control of glycaemia, ammonia, lactate, electrolytes, arterial blood gases,

acid-base equilibrium) and haemostatic functions [1–6, 10, 11, 17, 19, 21, 26, 27]. Liver function monitoring should include both "static" laboratory (coagulation profile; lactate trend; metabolic profile) and dynamic parameters [26–30]. Among the latters, Indocyanine green clearance (PDR_{ICG} clearance, Limon Maquet) might be considered, [28–30] being long used in the critically ill patient and in the perioperative period of both major liver surgery and liver transplant (preoperative assessment; intraoperative evaluation; recovery of postoperative liver function). Pathological PDR_{ICG} values are <8–10%/min [29, 30]. However, experience in ALF is limited and its use deserves caution. In fact pathologically low values are not mandatorily associated with a poor outcome: unreliable results are reported with bilirubin >6 mg dl^{-1}, due to the competition of bilirubin and ICG for the same carrier [29].

Encephalopathy, severe coagulopathy, acidosis and changes in renal function mandate the referral of the patient to a Liver Transplant Centre: stringent criteria for the ICU admission and the aggressive immediate treatment are since long available and should be followed [1, 2, 4, 10, 11, 17, 26, 27, 31, 32]. Hepatic encephalopathy progressing to WH III 3 is a criterion for intubation to protect the airways (mandatory in case of transfer to the Liver Transplant Centre) [1, 4, 11, 31, 32]. Often but not always, haemodynamic instability, progressive worsening of coagulopathy with possible thrombocytopenia, acute respiratory failure and acute renal failure concur to compose the full-blown MOF, the case for the rapid referral to a transplant centre [1, 4, 11, 31, 32]. The King's College Criteria (KCC) prognostic criteria for paracetamol and "non-paracetamol" ALF are also widely used for ELTX indication [4, 11, 26, 27]. In addition to the pH, the coagulation profile, the creatinine value, the degree of encephalopathy and the arterial lactate value before or after volemic resuscitation 4 or 5 mmol/l now form part of the prognostic criteria for paracetamol and non-paracetamol ALF [23–25]: in spite of that, while specificity was close to 79%, sensitivity was below 60%, a performance substantially not different from MELD score [4, 33]. Recently, the substantial improvement in the intensive medical care and the limitations of KCC have led to a replacement of the timely honoured KCC criteria with new dynamic models [4, 27, 34–36]. Among them is the UK revised criteria (UKRC) (Table 2.1) [27, 34, 35] a better predictor of mortality if compared to KCC in a recent report from Australia (sensitivity 92% and specificity 80%) [4]. In Table 2.1, the recently revised UK criteria are presented (From 4). Other alternative prognostic criteria have been developed both in Europe (Clichy criteria) and in the USA (USA-ALF Study Group Index) [4, 31, 36], the latter being one of the novel web-based dynamic models, whose role in clinical practice is still to be confirmed [4].

The MELD score, a score indicating the severity of the patient, has also been included in order to finalise the allocation of the available organ with priority criteria for transplantation [4, 33]. The criteria used in France for the indication for hepatic transplant (Clichy criteria) are based on the degree of encephalopathy (grades III–IV) and monitoring of factor V levels, which becomes a criterion for values <20% in subjects aged <30 years and for values <30% in subjects aged >30 years [4, 11, 31].

Table 2.1 UK revised criteria (UKRC) for urgent ELTx listing in case of paracetamol and non-paracetamol ALF. From Jajalakshimi VT, Bernal W, Update on the management of acute liver failure Curr Opin Crit Care 2020;26: 163–70 with permission

Current ALF indications for superurgent registration: paracetamol	Current ALF indications for superurgent registration: nonparacetamol
1. pH <7.25 more than 24h after overdose and after fluid resuscitation	Favourable causes (ecstasy/viral) with hepatic encephalopathy (any grade) • INR > 6.5 (PT> 100s) • 3 of: INR > 3.5 (PT > 50s), age <10 or >40, bilirubin >300 μmol/l,J–E > 7 days
2. Coexisting INR >6.5 (PT > 100s), creatinine > 300 μmol/l, hepatic encephalopathy grade ≥3	Unfavourable causes (idiosyncratic DILI, indeterminate) • INR > 6.5 (PT > 100 s) • In absence of hepatic encephalopathy: INR > 3.5 and age <10 or >40 • In presence of hepatic encephalopathy: J–E >7 days and bilirubin > 300 μmol/l
3. Liver injury, coagulopathy and hepatic encephalopathy with • Arterial lactate > 5 mmol/l on admission • Arterial lactate > 4mmol/l> 24h after admission • Exclusion of other causes of elevated lactate	Acute presentation of Wilson or Bold–Chiari syndrome • Combination of coagulopathy and any grade of encephalopathy
4. Two of three criteria from category 2 with other evidence of deterioration in organ failure in the absence of clinical sepsis	

DILI, Drug-induced liver injury; INR, International normalized ratio; J-E, jaundice to encephalopathy time.

2.6 Multi-Organ Failure Syndrome and the Multimodal Intensive Medical Treatment

According to the most recent advices, the management of patients with ALF in the ICU relies upon the aggressive and prompt multimodal medical treatment (including extracorporeal replacement therapies), able to positively impact on the outcomes. Prompt recognition of ALF, appropriate care setting (semi-intensive or intensive care setting, constant communication with a transplant centre), early and aggressive restoration of haemodynamic stability, wise use of both fluid resuscitation and pressors driven by an appropriate monitoring and airway protection in case of deteriorating consciousness are keys in preventing/controlling/improving hepatic and extrahepatic organ failure(s) [1–6, 11]. In a recent report from a single-centre experience, spontaneous survivors had better long-term outcome compared to liver-transplanted patients, underpinning once again the relevance of an updated, aggressive, intensive multimodal medical treatment for the modern management of ALF [37].

2.7 Central Nervous System: Hepatic Encephalopathy, Intracranial Pressure and their Management

Hepatic encephalopathy (HE), the neurological impairment of ALF, has a major prognostic significance. It is characterised by a wide range of neurological and behavioural changes, fluctuating from modest obnubilation, uninhibited behaviour and cognitive decline to deep areflexic coma, the onset being gradual or abrupt. Headache, vomiting, asterixis, agitation and clonus may be additional manifestations. Relevant to be excluded are other causes of neurological deterioration

Table 2.2 West Haven Classification of hepatic encephalopathy. From Glass DM, Khafaji AA in Liver Failure, N Pyrsopoulos Ed. Springer © 2020 with permission

Grade	Behavior/arousal	Abnormal movement	EEC/seizure	Pupillary changes	Cerebral edema
I	Alert with subtle irritability, sleep disturbances, mild confusion	Asterixis mild	Usually normal	None	Uncommon
II	Lethargy, disorientation, inappropriate behavior	Asterixis easily elicited	Slowing	None or hyperrespreksive	Uncommon
III	Sleeping most of the time but arousable, incoherent speech, marked confusion	Asterixis present if patient cooperative	Possible subclinical or convulsive seizure	Hyperrespoasive to sluggish	Possible
IV	Unarousable possibly responds to pain	Asterixis usually absent, posturing may be present	Possible subclinical or convulsive seizure	Sluggish to fixed and dilated	Likely

(metabolic infective, pharmacological in origin) [2]. In Table 2.2, the WEST HAVEN classification (WH) is presented [2, 19, 38].

The overall prognosis, favourable with stable HE (WH grades I–II, risk of cerebral oedema 25–35%), is more severe in WH stages III–IV: in these two latter stages, in particular in stage IV, cerebral oedema is common (70–80%) and may be heralded by bradycardia, hypertension and pathological respiratory patterns and pathological brain stem reflexes, among them are changes in pupillary reactivity (usually dilatation), abnormal oculovestibular reflexes, decerebrate posturing and seizures. WH grade III is a strict indication to intubation (airways protection) and appropriate mechanical ventilation (main aim the optimisation of PaO_2 and $PaCO_2$) (vide infra). In case of ICH, mortality is high due to the risk of transtentorial herniation and brain death [1–6, 11, 19].

Cerebral oedema, the most feared complication of ALF because of the high risk of death from cerebral herniation, has a multifactorial aetiology, only partially understood, so far. Cerebral oedema may be associated with intracranial hypertension (ICH), indeed reduced in the last 15–20 years due to the aggressive medical intensive treatment (20% in the most recent data, compared with values >60% in the past), but still associated with high mortality [1–6, 11, 19]. Cerebral oedema is thought to be correlated to high levels of ammonia [1–6, 19, 38–44], its monitoring being considered by many authorities key for risk stratification [44]. Ammonia, generated in the hepato-splanchnic compartment and not metabolised by the liver, crosses the blood-brain barrier and reacts with glutamate forming glutamine, which accumulates within cerebral astrocytes: the large quantity of intracellular glutamine is responsible for the osmotic shift of fluid into astrocytes, the astrocytes swelling and the formation of cerebral oedema [1, 4, 19, 38–44]. A relevant role is also

played by the production of ROS (reactive oxygen species) causing cerebral vasodilation and loss of blood-brain barrier regulation. The level of ammonia and the cerebral concentration of glutamine have been correlated with the development of cerebral oedema, increased intracranial pressure (ICP) and the possible evolution towards intracranial hypertension [1–6, 11, 17, 19, 38]. An elevated ammonia value (>200 umol/L or > 300 micrograms/dL) is considered a risk factor for the development of severe encephalopathy, cerebral oedema, ICH and poor outcome [17, 38–44]. Even if considered a specific and sensitive prognostic parameter, the correlation between ammonia and the severity of HE is not linear and the correlation, strong in case of ALF, is much less evident in ACLF [19, 38]. Relevant to be considered, brain imaging by CT has no sensitivity for cerebral oedema, brain MRI being the right choice: indirect signs on CT are poor differentiation/loss of demarcation of the grey and white matter, flattening of sulci and swollen gyri and markers of CNS oedema [1]. Hyponatremia (< 125 mmol/L) and hyperglycaemia are two other metabolic parameters able to influence the CNS damage, the formation of cerebral oedema (hyponatremia) and outcome (hyperglycaemia) [1, 4, 11, 19, 38–44].

HE monitoring should include (i) repeated clinical assessments focusing WH, GCS and, even if not widely used, the FOUR classification [19]; (ii) neuroelectrophysiological modalities; (iii) invasive or noninvasive intracranial pressure monitoring; and (iv) imaging including ultrasounds (US). Electroencephalography (EEG) is still considered in clinical practice [19, 45, 46], in spite of its lack of specificity: progressive worsening of HE is characterised by a particular pattern of cerebral electrical activity with increased dysrhythmias, progressive slowing (*delta waves*) and the presence of *triphasic waves* [46]. EEG could be indicated in case of abrupt changes of HE (deepening), in case of WH grades III–IV, to exclude the presence of irritative activity (non-convulsive epileptic state) [19]. Electrophysiological monitoring might be completed with somatosensory evoked potentials [19]. Invasive Intracranial pressure monitoring (ICPM) is used but still under hot debate due to the lack of clinical and survival benefits [1, 2, 4, 11, 19, 44]: the main advantages are continuous monitoring and prompt interventions in case of ICH. However, in recent years its role has been challenged due to the intracranial bleeding risk and the absence of a clear improvement in patient survival [1, 2, 4, 11, 19, 44]. In fact, invasive monitoring should allow targeted therapeutic interventions to maintain ICP close to 20–25 mmHg (target <25 mm Hg) to avoid prolonged periods of cerebral hypoperfusion (CPP < 50 mm Hg or ICP > 25 mmHg) and potential permanent brain damage and an ominous outcome. However, when used, in spite of more cerebral oedema—driven interventions/therapies—there is no clear demonstration that the use of invasive ICP monitoring impacts survival rate, while the procedure-associated risks are still relevant (intracranial haemorrhage, 10–20%, mortality 1–8%) [40]. The indications of ICPM, usually restricted to high-volume very expert centres, are worsening HE (WH stages III to IV) and brain imaging suggesting evolving cerebral oedema: its value should rely upon identification of futile ELTx in case of low cerebral perfusion pressure, predicting poor or no neurological recovery [1]. According to various reports, ICPM is now seldom used worldwide [47–53] and indications reported in a recent international survey are not univocal at best [47]. To

be reported the very recent, positive US experience with the use of ICPM: Jinadasa et al. were able to report a safe and clinically effective use of invasive ICP monitoring in a series of ALF patients with no symptomatic and few asymptomatic haemorrhagic complications and a better management of ALF patients with cerebral oedema while buying time to transplantation or to spontaneous recovery [53]. Instead, on the rise are noninvasive monitoring techniques, in particular transcranial Doppler ultrasound and jugular venous oximetry [44, 51, 52], potentially useful both in identifying evolving cerebral oedema and cerebral perfusion and also serving as tools for risk stratification [44]. Reduced blood flow on TCD can indicate cerebral oedema, although it may be inaccurate for mild-to-moderate ICP elevations. Optic nerve sonography and pupillometry, even if potentially interesting, are not validated in ALF, so far [52].

Recommended general measures are derived from the neurosurgical critical care, mandatory in patients with HE WH grade III ICU management. The main aims are to minimise/zeroing the risk of increased ICP, implementing neuroprotective measures while providing (multi)organ support using intensive haemodynamic, respiratory, metabolic and haemostatic monitoring. Measures include (i) elevated head posture (15°–30°); (ii) tracheal intubation for airway protection; (iii) controlled ventilation (vide infra); (iv) deep sedation (propofol, 3–4 mg/kg/h) to reduce agitation and possible increases in cerebral metabolism, intracranial pressure and cerebral oxygen consumption; (v) osmotic agents (mannitol or hypertonic saline, 3.5%) [1–6, 11, 19, 44, 50–53]. Other measures include circulatory equilibrium (mean arterial pressure 65–75 mm Hg), normoxia and normocapnia (no indication for hyperventilation and hypocapnia, useful only for treating refractory crises of ICP) and the use of mannitol to reduce cerebral oedema, normoglycaemia and mild hypernatremia (natremia 140–145 mMol/L). Even if mild-moderate hypothermia, (T < 33 °C), is able to reduce hyperammonaemia, side effects (changes of the coagulation profile, alteration of metabolism, increased incidence of infections) outweigh the potential advantages and has therefore been abandoned except in severe rescue cases [54]. To maintain intracranial perfusion pressure (ICPP), hypotension should be avoided: the vasopressor of choice is noradrenaline [1, 4, 11], even if recent studies, contrary to older reports, support also the use of terlipressin. Recently, Eefesen et al. have reported no changes in ICP in spite a documented increase in cerebral blood flow, restoration of cerebral autoregulation and, using cerebral micro-dialysis for lactate and lactate/pyruvate ratio, no cellular toxicity [55]. In recent years, the overall proposed approach has been associated with a remarkable fall in the incidence of ICH noted.

2.8 Cardiovascular Profile

ALF is very often associated with a deranged haemodynamic profile, very similar to late stages of septic shock. Described as hyperdynamic, it is characterised by high cardiac index (often above 5 L min^{-1} m^{-2}), low mean arterial pressure (MAP) (lower normal limits), low systemic vascular resistances (SVR, <600–800 dynes sec^{-1} cm^{-5})

and low-normal filling pressures. The increase in cardiac output is associated with an increased stroke volume and an increased heart rate. Cardiac function (e.g. ejection fraction) is almost always maintained and heart failure in non-cardiac patients becomes evident only in the late stages of the disease. Modifications in cardiac rhythm (bradyarrhythmias, AV blocks of various degrees, ectopic beats and forms of supraventricular tachyarrhythmias) or alterations in the ST segment could be associated with hypoxia, hypovolaemia or cerebral oedema [1, 2, 4, 5, 11, 56–61]. The systemic vasodilation of the early stages of ALF (well documented in the renal and musculocutaneous circulatory districts) is closely correlated with an increased release/reduced clearance of cytokines and/or vasoactive mediators by the diseased liver, with increased NO and cyclic guanosine monophosphate (cGMP) production within a framework of severe SIRS [1, 4, 11, 57–59]. This is associated with a significant neuroendocrine response leading, in the late stages of ALF, to a regional vasoconstriction [1–6, 11, 57–59]. Advanced multimodal haemodynamic monitoring (invasive or minimally or noninvasive, implementing also the use of transthoracic echocardiography and ultrasounds) is therefore mandatory [57, 58, 61]. The effective circulating volume is often reduced by relative hypovolaemia due to fluid loss, vasodilation, peripheral pooling and capillary damage [4, 59]. While nitric oxide (NO) and cGMP seem to be significantly involved in the phases following the initial phase, the genesis of the vasodilation is not yet fully clarified [15, 56]. The interpretation of lactate levels in this setting could be challenging [59]: hyperlactatemia may reflect both peripheral hypoperfusion and reduced hepatic clearance capacity. Clearance capacity (or on the contrary the persistence of hyperlactatemia) after circulatory optimisation efforts might be considered an outcome indicator in ALF [26, 34]. In fact, maintenance of an acceptable circulatory profile involves the use of crystalloids (saline or balanced solutions) and vasopressors [4]. The use of albumin as a colloid, even if widely reported, is not yet considered evidence-based: every intervention should be guided by advanced haemodynamic monitoring [1–6, 56–61]. The use of filling pressures may be unreliable, central venous pressure (CVP) in particular being altered by a number of confounders. Passive leg raising, Trendelenburg position or end-expiratory hold during controlled ventilation, possibly opening to the risk of increased intracranial pressure or unreliable due to an increased intra-abdominal pressure (IAP), should not be considered to assess volume status in the ALF setting [59]. On the other hand, haemodynamic assessments using cardiac output (Swan-Ganz catheter, SGC) or volumetric methods (PiCCO Pulsion/EV1000 Edwards Hemosphere, these latter able to provide intrathoracic blood volume, ITBVi and extra vascular lung water, EVLWi) is mandatory in this setting [57–60]. A common target for ALF treatment is to maintain MAP >70–75 mmHg aiming at an adequate systemic perfusion (including cerebral perfusion while avoiding the risk of cerebral hyperperfusion) [1–6, 57–60]. The use of fluid challenge and dynamic fluid responsiveness parameters during protective controlled ventilation might be considered as reliable, at least in part of the ALF patients [58, 59]. In a recent experience, one third of patients were fluid responders and fluid responsiveness was well predicted by pulse pressure variation (PPV) > 15%, but not by stroke volume variation (SVV) [59, 60]. Alternatives include the use of US to

measure inferior vena cava diameter (IVC), even if a parameter is still under debate [61]. The use of vasoconstrictors (noradrenaline, 0.1–0.7 gamma/kg/min; terlipressin in case of non-response to noradrenaline and vasopressin in case of absence of response to the first two) must be considered after having optimised the circulating volume and in the presence of at least a "simplified" invasive haemodynamic monitoring including arterial blood pressure and CVP (with the abovementioned limitations). $ScvO_2$ and SvO_2 may be considered but could be biased by the hyperdynamic circulation and the microvascular shunting: trend however could be useful [59, 60]. Cardiac output monitoring, mandatory in cases of refractory hypotension, involves the use of PiCCO or Swan-Ganz catheter [1, 2, 4–6, 11, 57–60]. Cardiac output with minimally invasive techniques (Vigileo Edwards, LiDCO, MOSTCARE) in hyperkinetic conditions should not be used, being unreliable at best. Transthoracic echocardiography is useful to assess cardiac contractility (even if only inspective), chambers filling, pericardial effusion if present and changes in IVC diameter during ventilation [57, 58, 60]. The use of transthoracic echocardiography, to be improved and implemented in this setting, may be useful, possibly shedding further light on the troponin I elevations during ALF, a phenomenon not yet completely understood [62]. A latent/subclinical adrenal insufficiency responding to steroid treatment is often reported [1–6, 11, 57, 58, 61, 63]. Doses of 200–300 mg of hydrocortisone per day for 5–7 days (often on an empirical basis, without the Synacthen stimulation) were able to reduce pressors dosage during ALF (as observed in septic shock). No survival benefit, however, has been proven [1, 4, 11, 58, 63].

2.9 Management of Respiratory Failure: Ventilation and Associated Procedures

The use of intubation (possibly elective) and mechanical ventilation in ALF is pivotal for airway management (aspiration prevention), in case of worsening encephalopathy (WH > II) [1, 2, 4, 5, 11, 57, 58, 63–66]. Invasive haemodynamic monitoring as above described should ease the interpretation of the hypoxemic acute respiratory failure associated with ALF (< 20% with the current intensive care approach): common features are pulmonary interstitial oedema due to, among other causes, vasoactive mediators causing increased vascular permeability and capillary leak, but also worsen by fluid accumulation due to excessive fluid load [1, 2, 4, 5, 57, 58]. Monitoring includes serial blood gas and acid-base equilibrium assessments in addition to the EVLWi if available [57]. Due to possible mechanical alterations associated with pleural effusion, atelectasis, reduced lung compliance and increased IAP, a balanced ventilatory approach (neuroprotective ventilation) is crucial: it should combine lung protective ventilation strategy (tidal volume 6–8 ml/kg; plateau <30 cm H_2O; PEEP 8–10 cm H_2O); alveolar recruitment manoeuvres should be avoided, to avoid obstruction of cerebral venous outflow and ICH worsening [4, 58, 63–66]. Normocapnia should be strictly maintained to avoid unfavourable consequences on cerebral perfusion [1, 4, 5, 11, 58, 63–65]. Invasive diagnostic and therapeutic manoeuvres such as bronchoscopy or BAL should be limited [58]. Among

nursing manoeuvres, head elevation at 30° and minimal and gentle turning are essential to avoid ICH exacerbation, while subglottic suction could reduce VAP incidence, often sustained by Gram-negative microorganisms [4, 58]. Lung ultrasounds, today easily available and reproducible, should be mandatorily implemented as the standard diagnostic modality in the ICU: main targets are assessment of interstitial oedema, pleural effusion, areas of atelectasis or dysventilation and could constitute the guide for invasive manoeuvres if and when needed [61, 67, 68]. In recent years, after the implementation of the new intensive medical approach, the presence of acute respiratory failure does not have a negative impact on the outcome [68]. The possible contribution of increased intra-abdominal pressure on intrathoracic pressures, lung function and mechanics has to be strongly considered: monitoring has to be implemented [58, 69–71]. Extracorporeal membrane oxygenation (ECMO) might be considered in the peritransplant period in case of refractory respiratory and/or cardiac failure [1, 4, 58, 72, 73]. During the recovery phase, possible after resolution of the acute phase of ALF or in the postoperative period of the ELTx, problematic emergence should be anticipated, due to (among others) slow recovery of ICP autoregulation mechanisms, sedation, delirium, muscular weakness (critically ill polyneuropathy, CIP) and difficult respiratory weaning: percutaneous tracheostomy (except for anatomical contraindications, also assessed using bedside ultrasound) can be safely performed despite the presence of altered haemostasis, with additional safety provided by bedside US control [4, 58, 61, 74].

2.10 Renal Failure

Renal failure is present in 40–75% of in ALF cases and is multifactorial in origin, main causes being the consequences of renal hypoperfusion (acute tubular necrosis) and functional haemodynamic derangements [1, 2, 4, 5, 11, 75–78]. The presence of acute kidney injury (AKI) stage 3 (300% increase in sCreat) [77] has been associated with a poor prognosis and is one of the criteria for referral to LTx centres [1, 2, 4, 5, 75]. Renal hypoperfusion associated with systemic vasodilation and selective renal vasoconstriction (as is in septic shock) [77] is frequently associated with hypovolaemia, either absolute or more frequently relative. Monitoring should include hourly diuresis and urinary electrolytes (when present), the haemodynamic profile (invasive haemodynamic monitoring, SGC or PICCO/HEMOSPHERE), dynamic parameters, IAP (abdominal hypertension in case of IAP > 16 cm H_2O, able to impact renal perfusion pressure) [69] and US. Ascites, oedema of the abdominal wall abd oedema of the intestinal canal are among the conditions contributing to an abdominal compartment syndrome [69–71]. Treatment involves restoration of circulatory volume and tissue perfusion to maintain (if possible) renal blood flow with the wise use of volume and pressors (noradrenaline being the reference drug): the main aim is to raise glomerular perfusion pressure. The use of

terlipressin, very frequently administered in the ACLF-associated hepatorenal syndrome [78–81], is not, as yet, evidence based in ALF. However, very recent observations, already discussed above, modify these statements [55]. The "renal" effect of terlipressin, mediated by splanchnic V_1 receptors, relies upon a selective vasoconstriction of the efferent renal arteriole and the increase in glomerular filtration; at cerebral level, on the other hand, the effect, mediated by V_2 receptors, is vasodilation, with an increased cerebral blood flow and a potential increase in intracranial pressure, but not of cerebral oedema [5, 55]. Extracorporeal replacement therapy with continuous techniques (continuous renal replacement therapy, CRRT), used in close to 30% of the ALF cases, is preferred to intermittent techniques due to a better haemodynamic stability, including cerebral perfusion pressure, and more continuous and consistent systemic effects. Improved survival has been also reported [1–5, 11, 82–85]. Together with standard indications for the critically ill patients, in ALF patients CRRT rationale includes control of acidosis, hyponatremia, hyperammonaemia, temperature control and potential treatment of hepatic encephalopathy (CRRT are defined by EASL guidelines as "metabolic replacement therapy") [2]. CRRT (usually venovenous haemodiafiltration) should be started early [1–5, 11, 17, 82–84] (criteria are not fully standardized, so far) and is an integral part of measures aiming at reducing cerebral oedema due to its ability to remove ammonia [17, 84, 85]. In recent years, with dedicated monitors able to optimise its use, the use of citrate for regional anticoagulation is expanding: careful monitoring of the total calcium/ionised calcium ratio is mandatory to avoid citrate toxicity. Results are of extreme interest both in adult and paediatric patients [86–89]. There is no place, instead, for the use of dopamine or fenoldopam.

2.11 Infections

The changes induced by acute liver injury on immunological competence induce an "immune dysregulation" [1–5, 17], making ALF patients particularly prone to infectious complications, frequently evolving to septic shock. Critical in this specific setting are major defects in opsonisation due to reduced levels of complement and markedly reduced phagocytic function of macrophages [1–5, 11, 17, 90–99]. ALF is associated with an acute, massive release from necrotic hepatocytes of DAMPS and pro- (and anti)-inflammatory cytokines by macrophages and monocytes ("cytokine storm") [16, 17]. The release of TNF is associated with the development of a "sepsis-like" syndrome, while the release of IL_6 correlates with the development of MOF and mortality [17, 91–94]. Infections are in large part bacterial in origin (>80%) and are frequently sustained by Gram-negative bacilli, even if *methicillin-resistant Staphylococcus aureus* (MRSA) and *vancomycin-resistant Enterococcus faecium* (VREF) are increasingly reported, with multidrug-resistant (MDR) bugs on the rise [1–5,

90–94]. Fungal infections range from 5% to 10%, with an increased incidence of *Aspergillus* spp. and *Candida* spp. [95–99]. Respiratory tract infection including ventilator-associated pneumonia (VAP) (50%), urinary tract infections (20%), primary bacteraemia (16%) and central catheter-related bacteraemia (12%) are the most frequently reported infections [1–5, 94–97]. Worsening hepatic encephalopathy, worsening renal function and the rapid rise in the use of vasopressors are sensible markers of impending septic shock, often rapidly evolving to MOF [1–5, 17]: the above clinical signs should start a prompt, thorough, intensive research aiming at "source tracking and control" and an appropriate antibiotic therapy [2, 11]. EASL guidelines support the wise use of surveillance cultures (including indwelling devices) for the best indication and use of antibiotics and antifungals [1–5, 11]. This specific point is still a matter of discussion. The use of molecular tests for the early determination of MDR bug colonisation (*Acinetobacter baumannii, Klebsiella Pn Carbapenemase producing, Pseudomonas aeruginosa, ESBL Escherichia coli or* carbapenem-resistant *Enterobacteriaceae*) is key for an appropriate use of empirical antibiotic therapy. To anticipate fungal infections, much rarer but with very high mortality, and to avoid delay in therapy, the use of colonisation index and prediction rules for *Candida* infections and the use of biomarkers (beta D glucan and galactomannan, the latter for *Aspergillus*) are among the best possible choices [96–99], keeping in mind the strong negative predictive power of these tests. Universal hygiene measures are obviously the first and indispensable cornerstone of infection prevention in every setting, but particularly in the ICU [100]. The early administration of broad-spectrum empirical antibiotic therapy in the presence of active infection (signs of sepsis or septic shock) is recommended [1–5, 11] and should be followed by targeted therapy as soon as culture results are available (including *de-escalation therapy* if and when needed); in case of low likelihood/absence of infection, the suggestion is to defer/stop antimicrobials while continuing a close monitoring of the patient, as per 2021 Surviving Sepsis Campaign Guidelines [101]. Recent EASL GLs and recent reviews [1–5, 11] suggest empirical antibacterial and antifungal treatment in case of ELTx or in case of conditions at high risk for septic shock: among others are SIRS, isolation of MDR bugs in surveillance cultures, progression towards encephalopathy WH III to IV and refractory hypotension. There are no evidence-based recommendations for the choice of antibiotics or antifungals, but it may be wise to refer to surveillance cultures, wards and hospital "ecology" and patient risk factors for bacterial or fungal infections. Echinocandins and liposomal formulation of amphotericin B are of choice if the risk is aspergillosis [102]. Along with microbiological criteria (including "local and hospital ecology"), pharmacokinetic and pharmacodynamic profiles should always be considered as a priority in the choice of anti-infective drugs [103, 104].

2.12 Haemostatic Profile

The definition of ALF includes the "severe coagulopathy" (PT INR > 1.5, values >5 being not uncommon), while the presence of thrombocytopenia or thrombocytopathy is variable but indeed clinically more relevant [1–5, 11, 105–111]. According to Stravitz, haemodynamic instability, renal failure, consumption of factors with short half-life, infections and the related release of endogenous heparinoids, gut-derived endotoxin able to induce vWF and FVIII release and thrombosis, endothelial dysfunction associated with SIRS, prothrombotic microparticles (pro-thrombotic) and qualitative platelet dysfunction all are "destabilising factors" on the "rebalanced" haemostatic profile of ALF [110, 111]. Since the liver is the site of the synthesis of coagulation factors (except for VIII) and of natural anticoagulants, there is, to varying degrees, an imbalance between procoagulant and anticoagulant factors [1–5, 11, 105–111]. The severity of the coagulation derangements is associated with the aetiology of ALF and in particular with the extent of the systemic inflammatory response. Reduced coagulation factor synthesis (in particular vitamin K-dependent factors II, VII, IX, X and V), increased consumption, reduced natural anticoagulants (AT, protein C, protein S), reduced clearance of activated coagulation factors and factor-inhibitor complexes (a condition associated with the dysfunction of the reticuloendothelial system) and reduced regulating proteases ADAMTS13 all contribute to the condition of "rebalanced haemostasis" present in liver failure [105–111]. In fact, in spite of severe laboratory test derangements, functional viscoelastic tests (VETs, viscoelastic thromboelastography, TEG/thromboelastometry, ROTEM) may reveal mild disturbances if not a "near normal" haemostatic profile, bleeding complications being infrequent and/or clinically not relevant [1–5, 11, 105, 106]. Interestingly enough, in the most recent experience with ROTEM in ALF [111], patients with the more severe systemic complications (WH III to IV and CRRT) had the highest incidence of deranged ROTEM parameters. The recent EASL GLs and some available reports [2, 109, 110] refer to a possible prothrombotic state, despite the lengthening of conventional lab coagulation parameters (INR/aPTT): VETs are able to support this statement [2, 105–110]. The problem of fibrinolysis is controversial in ALF, since a significant increase in tissue plasminogen activator (tPA) (at the base of the *hyperfibrinolytic* state) is sometimes associated to an even greater increase in plasminogen activator inhibitor 1 (PAI-1), able to shift the balance towards *hypofibrinolysis* [105–107]. The presence of hyperfibrinolysis (documented by fibrin degradation products and d-dimer, FDP, or better by VET tracings) causes inhibition of procoagulant factors and a tendency towards bleeding. Recent evidences report of increased endogenous heparinoids (anticoagulants) and procoagulant factors (FVIII/von Willebrand factor) [2, 105–110]. As evident, the optimal management of

haemostatic derangements present in ALF includes some solid statements and some controversial points [109, 110]. Spontaneous bleeding is not frequent, and according to the most recent US data, close to 11% in a retrospective series of 1770 patients [108]. Mortality due to major haemorrhage is <5%, major bleeding tendency being associated with the extent of the systemic inflammatory response (SIRS) [108]. Interestingly enough, in bleeding and non-bleeding patients the INR value is substantially the same (2.8 vs. 2.7), but significantly different is the platelet count (128,000 vs. 96,000/microlitre), thrombocytopenia again paralleling the severity of SIRS [108]. The "prophylactic" administration of fresh frozen plasma (FFP), platelets and cryoprecipitates is unequivocally discouraged in all the most recent guidelines [1–5, 11], even if considered by some in case of severe bleeding [110]: recent observations document the tendency to administer FFP and platelets, with a short-lived, ill-defined haemostatic effect and exposure to the risk of overload, TRALI, prothrombotic complications and increased cerebral oedema [1–5, 105–110]. On the other hand, the administration of FFP (10–15 ml/kg), platelets (1 unit per 10 kg to reach values >60,000/microlitre), cryoprecipitates or fibrinogen (25–50 mg/kg) is recommended [2, 110] in case of fibrinogenemia <100 mg/dl and/or in the presence of patients with significant bleeding or in case of high-risk invasive manoeuvres. Administration should rely upon VETs [1–5, 109, 111] and not on static lab tests (PT, aPTT, fibrinogenemia, platelet count, d-dimer) [109–111]. In this sense, the administration of FFP, platelets and cryoprecipitates should be guided by VETs whose parameters and morphologies are able to provide information for the specific components to be administered, avoiding unnecessary/harmful blood components (the case of prothrombotic attitudes despite extremely long INR values). Interestingly enough, and very recently, Stravitz et al. [111] concluded that "the need and indications for the repletion of FFP remains unclear despite universal hypoprothrombinemia in ALF patients". Further data are then needed. The use of antifibrinolytics (AFs) has been proposed by some: even if a solid rationale is still lacking, in some cases AF administration was able to reduce or stop bleeding [2]. VETs should again drive the clinical decisions [109]. The use of recombinant activated factor VII (rFVIIa), also reported in the literature prior to risky invasive procedures (ICP monitoring) or before transplant surgery, lacks evidence of positive outcomes [109–112].

In Table 2.3 (from [4]), the main issues for the clinical management of ALF are summarised.

Table 2.3 Main issues for the clinical management of ALF. From Jajalakshimi VT, Bernal W, Update on the management of acute liver failure Curr Opin Crit Care 2020;26:163–70 with permission

Initial steps in ALF management at presentation
Fluid resuscitation
Airway protection
Correction of gfoss metabolic disarray
NAC infusion without delay in suspected or confirmed cases of paracetamol overdose
Elective endotracheal intubtion for encephalopathy >grade 2 and initiation of early neuroprotective measures for safe transfer
Prophylactic antibiotics at onset of organ failure and encephalopathy
Avoid correction of coagulopathy unless actively bleeding or prior to invasive procedures
Early discussion with specialist liver unita
Postinitial critical care management
Airway: elective intubation for airway protection in encephalopathy, subglottic suction, head-end elevation
Breathing: balance lung protective ventilation strategies and neuroprotective ventilulion
Circulation: Fluid resuscitation, vasopressors-noradrenaline ± terlipressin ± steroids in septic shock dose. Hemodynamic monitoring individualized
Disability: neuroprotective measures similar to TBI RAAS-5, T36, head-end elevation up to 30°, PaO_2> 11, normocapnoea, MAP to maintain CPP 55–60 mmHg, normoglycoemia, hypertonic sodium (30%) infusion to maintain sodium 145–155. Early CRRT to reduce ammonia below 100 μmol/l as below
External/Electrolytes: temperature and electrolytes as above
Fluid management: CVVHDF for oligo-anuria, ammonia levels >150 μmol/l, increasing ammonia levels, worsening encephalopathy and standard indications of renal replacement therapy
GIT: IV dextrose infusion; early enteral feeding; prepyloric feeds; temporary suspension of feeds if ammonia levels are high or worsening encephalopathy; PPI for stress ulcer prophylaxis; prokinetics; multivitamin and trace element supplementation
Hoemostasis: avoid correction of coagulopathy unless actively bleeding or prior to invasive procedures
Infection: prophylactic broad spectrum antibiotics and antifungals in multiorgan failure

NAC, *N*-acetyl cysteine; GIT, gastro-in testinal tract.

2.13 Novel Therapies: The Artificial Liver Support

Severe ALF leads to relevant alterations of all liver functions (synthetic, excretory, depurative, metabolic functions), and it is often complicated by MOF [1–6, 11, 21, 22]. Liver detoxification capacities are lost, while many toxic substances bound to or carried by albumin (bilirubin, aromatic amino acids, bile acids, endogenous benzodiazepines, prostacyclins, tryptophan and nitric oxide) together with DAMPS and cytokines released by the massive hepatic necrosis are increased: haemodynamic and renal derangements induced by these toxins are relevant [113–117]. While CVVHD techniques have place to remove hydrophilic substances (ammonia) [113], a dedicated adsorber is required for albumin-bound substances [113–117]. The intensive treatment of the ALF patient may include *artificial (non-cell-based systems)* or *bioartificial* (living hepatocytes or hepatic tissue) extracorporeal support devices (ECLSDs) [1–6, 11, 21, 22, 113–117]: extracorporeal liver support devices (ECLSDs) have a role both as a bridge to ELTx, when medical therapy fails, and to support the spontaneous regeneration of the native liver [4, 117]. Three are the main functions ECLSDs should theoretically provide [117]: (i) detoxification (toxins remotion); (ii) restoration of the physiological profile; and (iii) biosynthetic capacities (production of albumin and coagulation factors mimicking hepatic function) [114–117]. *Artificial ECLSDs* use column chromatography, with selective membranes of various size pores and adsorbent affinities to filter specific serum toxins [117]. *Bioartificial ECLSDs* are hybrid devices combining artificial ECLS system technology with living hepatocytes in a bioactive platform (*bioreactor*) "to mimic both the natural hepatic detoxification and some synthetic functions" [117–125]. Current bioreactors incorporate human (hepatoblastoma) or porcine hepatocytes "in a manner promoting cell survival and provide a level for filtrate transport similar to that seen in vivo" [117].

The most recent and most widely used applications of acellular artificial support involve the use of albumin as a scavenger molecule able to bind (acceptor or adsorber) toxic molecules often water-soluble, but much more frequently bound to albumin and therefore insoluble in water ("albumin dialisis") [1–6, 116, 118–125]: albumin and/or plasma are transporter to remove protein-bound toxins. Albumin dialysis is a "detoxifying" system that uses albumin as a solution in the dialysis circuit and membranes with high flow, high selectivity (pores <50 kDa) and high permeability. Toxins in the blood are removed by diffusion from the blood to the dialysis circuit bound to the albumin in the dialysate. *MARS* (Molecular Adsorbent Recirculating System, Edwards) and SPAD (single-pass albumin dialysis) are now available [116, 118–123]. *Prometheus* (Fresenius) [116, 124, 125] and *high-volume plasmapheresis* (HVP) [21, 22] use less selective membranes (250 kDa pores) and do not have a parallel circuit with albumin as dialysate.

2.13.1 Mars [114–120]

The MARS system, developed in the 1990s by Stange and Mitzner [114], includes a blood circuit, an albumin circuit and a "kidney" circuit. The blood is circulated in a dialysis module with hollow fibres covered by an albumin-impregnated

polysulfone high flux membrane with a cut-off of less than 50–60 kD to avoid loss of endogenous albumin, hormones, growth factors and carrier proteins. The dialysate solution is 20% albumin 600 ml in a continuous flow circulating in the extracapillary compartment. The ability to bind molecules usually carried by albumin is the rationale for the use of albumin as a dialyser. Toxic substances bound to albumin are adsorbed on the membrane albumin. Water-soluble molecules and protein-bound toxins are removed immediately by binding to the albumin attached on one side of the filter membrane and subsequently removed by albumin circulating in countercurrent on the other side of the filter membrane. The albumin dialysate is then circulated through a charcoal filter to be regenerated, passing through a low-flux membrane against a traditional dialysis circuit to clear hydrophilic toxins and provide electrolyte/acid-base balance. Initial enthusiastic reports of the potentials of MARS included improved neurological profile, haemodynamics and in some cases better coagulation profile, reduction of ammonia, bilirubin and lactate: the improvement was hypothesised to be associated with the elimination of albumin-bound circulating vasoactive factors. However, there is currently no evidence that MARS is able to impact mortality when used in the treatment of ALF, especially if urgent liver transplantation is not expected soon [1–5, 116, 118–120].

2.13.2 SPAD (Single-Pass Albumin Dialysis)

SPAD is a more simple technique using conventional CRRT monitors, CVVHD modality and a high-flow hollow fibre dialysis module without additional system of pumps and regeneration modules [114–118]. Blood is dialysed against a 4.4% albumin solution (1000 ml albumin 20% in 3500 ml dialysate) across a highly permeable, high-flux membrane. By diffusion, protein-bound and water-soluble substances pass through the membrane into the albumin solution and are eliminated. The albumin solution is eliminated after passing through the filter. A recent in vitro study comparing MARS and SPAD was able to confirm the identical detoxifying capacity of SPAD and MARS [121]. Canadian studies in ALF from paracetamol using standard maximal treatment and SPAD revealed no advantage on mortality and little if any on biochemistry [122].

2.13.3 Prometheus (FPSA) [116, 123, 124]

Fractionated plasma separation and adsorption (FPSA) with high-flow dialysis is a variant of albumin dialysis [123, 124] and is the Prometheus System, Fresenius Medical Care AG. Patient plasma is fractionated and then passed through an albumin-permeable membrane with pore cut-off of 250 kDa into a proprietary FPSA albumin circuit. Native albumin passes through an adsorbent resin and an anion exchange column that remove serum toxins. The “cleansed” albumin-rich plasma fraction is returned to the blood circuit: the blood is then filtered against conventional high-flow haemodialysis. Studies were conducted mainly on ACLF

(Helios study) [124]. Even for this system, after initial enthusiasms mainly in ACLF cases, no advantage was demonstrated on mortality [114–116].

Generally speaking, as recently proposed by Fisher and Wendon although there are, particularly for ACLF and apparently using Prometheus, potential benefits of the artificial treatment on mortality, there is currently no evidence that the treatment changes outcomes for ALF [115]. Unfortunately the results, of the meta-analyses, are so far completely contradictory and opposite: the use of these methods, indeed costly and sometimes cumbersome, should be proposed for high-volume, very expert centres and in a research context [1–5, 9, 114–117].

2.13.4 High-Volume Plasma Exchange (PE)/Plasmapheresis (HVP)

HPV is the only purification modality able to modify the outcome in ALF with an increase in transplant-free survival [1–5, 21, 22, 114–118]. HVP is defined as exchange of 15% ideal weight (8–12 l) with FFP. After small studies in which improvements in HE and haemodynamics were observed, Larsen et al. in a randomised study of 182 patients (maximal standard intensive treatment [TSM] vs. TSM + HVP) lasting approximately 11 years with a median number of treatments of 2.4/patient was able to document both statistically (59 vs. 48%) and clinically an increase in survival without transplantation [22]. Primary endpoint was survival to hospital discharge, regardless of LT. Survival to hospital discharge was 58.7% for patients treated with HVP versus 47.8% for patients who received SMT alone ($p = 0.0083$). Biochemically, bilirubin, INR and ammonia levels all significantly decreased following HVP treatment. Interestingly, in a subgroup of 30 patients, a reduction in all mediators of the "cytokine storm" was documented, suggesting a potential role for HPV [22] to remove DAMPs, cytokines, TNF and interleukins 6 and 8 [4, 21, 22, 114–117]. According to very recent experiences, low-volume PE (LV-PE) in ALF cases showed improved surrogate parameters comparable with the effects reported with HV-TPE [125, 126]. These data are retrospective and to be interpreted with caution, but further controlled studies in this context should be strongly considered. According to the most recent review on the item, therapeutic plasma exchange (TPE) is emerging as an attractive extracorporeal blood purification technique in patients with ALF (and ACLF) [127]. TPE is able to impact the "cytokine storm" removing toxic substances and allowing, if and when possible, the recovery of native liver or as a bridge to ELTx [127].

This observation might open to the use of other sorbent systems able to absorb cytokines, DAMPS, TNF, etc.: CytoSorb (CytoSorbents, USA), particularly in cases where CRRT is in use [4, 128, 129], is now explored in ALF. In addition CytoSorb may remove circulating bilirubin, bile acid and (personal unpublished data) ammonia when CRRT is not able to lower the blood levels.

Bioartificial or hybrid support involves the use of viable human (human-derived hepatoblastoma cells, ELAD) or porcine liver cells (freshly harvested) or preserved by cryoprecipitation integrated into an extracorporeal support [1, 4, 114–117, 130].

Bioartificial systems (BAL, ELAD) are composed of a "bioreactor", consisting of a hollow container housing hollow fibre capillaries onto which human or porcine hepatocytes are immobilised, grown and induced to perform native hepatic functions on the blood/plasma of ALF patient: the patient's plasma, previously separated, oxygenated and heated, is passed through the bioreactor. The exchange of molecules takes place through a semi-permeable membrane with pores of sufficient size to allow the movement of toxins and carrier proteins (albumin, 66 kD) supposed to be involved in the genesis of ALF, but not of immunoglobulins (100–900kD), complement (200 kD), viruses or cells (a major technical problem to be solved). Hepatocytes, between 6 and 36 × 10^9 to be effective (200–400 g of liver tissue) [114–117], extract oxygen and nutrients and "cleanse" the plasma from toxins. In HepatAssist, the bioreactor is in series with a charcoal column system for purification from toxins able to damage porcine liver cells. In MELS (which uses human hepatocytes from harvested livers unsuitable for transplantation), a dedicated detoxification module allows albumin dialysis and haemodiafiltration. Even if theoretically possible, the risk of zoonosis associated to the use of porcine cells has never been demonstrated, further reaffirming the extreme safety of the method [117, 130]. The same was for the ELAD systems: no dissemination of tumour cells in case of the hepatoblastoma was demonstrated in the late 1990s [116]. The data coming from randomised trials carried out so far (2000–2004), although interesting if taken individually or by case reports (improvement in the neurological profile, reduction in intracranial pressure), did not demonstrate a significant reduction in mortality. The most recent and complete study published on the use of BAL (HEPAT ASSIST) in ALF, [130]· while confirming identical survival in the treated group when compared with the control group, was able to document a trend towards better survival (44%, $p < 0.048$) in subjects with fulminant or subfulminant hepatic failure treated with bioartificial support [130]. Despite the many problems, development and refinement of bioartificial ECLS platforms remain an important focus of future research.

2.14 Conclusions

ALF, despite significant improvements in its treatment, still represents a challenging, high-risk, very severe medical condition. Accumulation of hepatotoxins (among others, vasoactive toxins, endotoxins released from intestinal flora TNF, DAMPs and proinflammatory cytokines) due to the impaired hepatic clearance leads to cellular damage secondary to oxidative stress, increased capillary permeability, immune dysregulation and eventually MOF. Early diagnosis, prompt multidisciplinary approach and multimodal intensive care are key to improve outcomes, while emergent liver transplantation (ELTx) still constitutes the true game changer when maximal intensive medical treatment has failed. All the adopted measures (maximum intensive medical treatment including the use of artificial or bioartificial support methods) aim at promoting either the spontaneous recovery of liver function (if and when possible) or a bridge to ELTx. Criteria to indicate ELTx in ALF cases are

codified since long and rapid referral to Liver Transplant Centres with ICU facilities is mandatory. The deterioration of brain function (HE from WH grades II to III) mandates (i) intensive care management, aiming at "maximum" intensive medical treatment, and (ii) rapid referral and transfer to a Liver Transplant Centre. The transition to WH III mandates endotracheal intubation for airway protection. Multidisciplinary efforts and multimodal treatment at Liver Transplant Centre provide the implementation of the best updated diagnostic and therapeutic measures to prevent/treat MOF or to indicate the ELTx, the only definitive management strategy of ALF in case of failing maximal intensive medical treatment. Extracorporeal artificial and bioartificial liver support (ECLS) devices, although promising, are still supportive and not therapeutic measures in ALF. HVPF has to be strongly considered as an evidence-based tool: new options (CytoSorb, CytoSorbents, USA, as an example) indeed interesting deserve further large prospective RCTs to optimise indications, modality and patient population with the greatest benefit. As a matter of fact, the extremely complex pathways performed by the liver to ensure homeostasis are unlikely to be replaced by artificial ECLSDs performing detoxification alone, while the potential of a biologic ECLS component able to mimic some of the many "synthetic" hepatic functions is, so far, an appealing but long way running.

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Perioperative Medicine: Technical and Organizational Issues

3

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3.1 Introduction

According to its first definition, perioperative medicine (PM) refers to the "medical care of the surgical patient before, during and after a surgical procedure" [1]. Over the years, this definition has not substantially changed. On the other hand, both anesthesiology and surgery have marked many and important steps forward. In particular, responsibilities of the anesthesiologists have expanded rapidly going far beyond the administration of narcotics and including the surveillance, maintenance, and protection of patients' vital functions before, during, and after surgical procedures [2]. Over the last years, PM showed up as rapidly growing "subspecialty," namely, in Northern Europe and in Anglo-Saxon countries. Although not exclusive to a single specialty, PM programs are largely anesthesiologists-led due to their strategic positioning within the surgical pathways. However, it is important to outline that PM pathways are the result of a multidisciplinary collaborative effort aiming to provide a kind of "umbrella" to safeguard all the phases of the journey that patients undertake when they undergo surgery, and that starts at the primary care level and finishes with full recovery at home. From this point of view, PM protocols are of particular interest for those subjects who, due to fragility, comorbidities, or complexity of the planned surgery, are considered as "high-risk patients." In fact, PM aims at the identification and optimization of the perioperative care according to a collaborative multidisciplinary and multiprofessional approach, rather than providing support when complications happen [3]. This intent is not to be overlooked as yearly approximately 230 million people undergo major surgery around the world and more than a million of them die

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within 30 days [4]. Therefore, even a modest reduction in perioperative mortality could save thousands of lives. Hence, the interest in PM is not only clinical but also social and economical.

3.2 Preoperative

3.2.1 Risk Assessment

Risk assessment of the surgical patient is paramount to the concept of PM as it is essential to the process of shared decision-making and informed consent. It also will allow for patient optimization before surgery by addressing patient comorbidities and giving the opportunity to suggest and make preoperative lifestyle and behavioral changes when necessary [5, 6]. Assessment of the risk can be performed in a number of ways and combination of the different methods can allow a more robust framework of interventions. To evaluate patients' overall functional state, methods include the assessment of:

(a) *Anamnesis and physical examination.* During the preoperative evaluation of the patient candidate to surgery, it is necessary to collect the entire medical history in order to identify comorbidities (e.g., COPD, heart disease, neuropathies) and other conditions that can reduce their ability to endure surgical stress. Furthermore, the collection of medical history will allow to prescribe the most appropriate diagnostic investigations (EKG, chest X-ray, Echocardiography, second-level specialist consultations).
(b) *Assessment of biological age.* A still controversial meaning is attributed to biological age. In fact, while for some chronological age does not represent a risk factor per se, according to others it is an objective risk factor due to the possible accumulation of different pathologies.
(c) *Exercise tolerance evaluation.* The cardiopulmonary exercise test (CPET) provides a personalized assessment of patients' cardiorespiratory function and fitness through the use of the cycle ergometer. A treadmill or hand-cranked ergometer can also be used, but these can be less well tolerated by patients with musculoskeletal disorders. Other tests that explore the ability to withstand physical exercise include the 6-min walking test and the stair-climbing test. Although they all are relatively simple to perform, the latter are less commonly used in current practice and have not shown the sensitivity and specificity as CPET [7].
(d) *Identification of systemic diseases.* The identification of any concomitant chronic and/or degenerative disease (e.g., COPD, diabetes, heart disease) is vital in order to stratify the global impact of surgery on thus the patient reserve capacity. The purpose of identifying these pathologies is also to optimize as much as possible before surgery the patient's global health status by therapeutic adjustments aimed at reducing the extent of the perioperative morbidity.

(e) *Risk assessment related to the type of surgery.* A homogeneous classification of the risk related to the specific type of surgery is not available. However, in general, we can summarize the following [5]:
- Emergency surgery exposes you to a greater risk of complications than elective surgery.
- Operations involving the thorax and abdomen are at greater risk than extracavity ones.
- The intraoperative prone position can be associated with some rare but well-documented complications (stroke from vertebral/carotid compression due to head rotation; brachial plexus compression; venous stasis with macroglossia and pharyngeal edema; rare but described event is blindness for increase in intraocular pressure).

(f) *Cardiac risk assessment.* In case of and even suspected heart disease of any kind, a specialist cardiological evaluation should be performed together with the appropriate instrumental evaluation. Of particular importance is the evaluation of the heart systolic-diastolic function and that of its functional capacity [8].

(g) *Scores.* There are several scores which can be used to assess perioperative risk. Their common purpose remains to stratify it through a semiquantitative assessment in order to be able to identify the most vulnerable patients and therefore set up any corrective intervention before surgery and surveillance afterward. It should be noted that no score can predict alone the right level of care required by the single patient and that the clinical examination by the anesthetist is always essential. The detailed description of the available preoperative scores is beyond the scopes of this review. Here we just mention the most frequently used as the *American Society of Anesthesiologists (ASA) Score, the Charlson Comorbidity Index, the Revised Cardiac Risk Index (RCRI*), *the Physiological and Operative Score for enUmeration of Mortality and Morbidity (P-POSSUM-), the Surgical Apgar Score (SAS), and the National Surgical Quality Improvement Project Score (NSQIP)* [9, 10].

3.2.2 Prehabilitation

The term prehabilitation refers to a multimodal process of improving the functional status of a patient before surgery with the aim of increasing her/his ability to cope with a stressful event (surgery), therefore improving outcomes [11]. Thus, prehabilitation shifts the attention of the team toward the preoperative phase. Therefore, patients start their interaction with the caring team much earlier than usual. This is different to the traditional concept of "rehabilitation" which focuses instead on the interventions to be carried out in the postoperative period. Prehabilitation uses the theory of the "marginal gains" whereby a series of small interventions can lead to a reduction in overall morbidity and mortality [11]. The ultimate goal is to increase the patient's physiological, physical, mental, and nutritional endurance and resilience in order to improve the recovery process. Prehabilitation is divided into various lines of intervention which we can summarize as follows:

(a) *Physical exercise programs*. There is significant evidence that physical exercise improves the patient's overall health status and may prevent many and serious medical conditions. The optimal duration of such programs before surgery must be individualized, and clinical improvements may already be evident after as little as 2 weeks. However, setting up successful, personalized, structured physical exercise programs is complex, requires the allocation of resources, and can be made difficult by the necessary coordination between primary and secondary care levels.

(b) *Nutritional optimization*. Malnutrition in patients who are about to undergo surgery is often a direct result of comorbidities and cancer disease. Malnutrition can be associated with sarcopenia, fatigue, impaired immunity, and a tendency to delayed wound healing. For a decade, it has been known that providing nutritional support prior to cancer surgery significantly reduces morbidity [12, 13]. It is also now acknowledged that the prevention of nutritional and metabolic reserves depletion rather than their "reactive" increase protects individuals from the catabolic response to surgical stress. Thus, nutritional optimization should begin as soon as possible along the path that will lead patients to the operating theater. The Society for Enhanced Recovery has recently published a consensus document on this topic highlighting the key role of oral food supplements, the importance of protein intake, and the early start of postoperative nutrition [14]. Figure 3.1 shows a validated decision scheme to initiate patients to nutritional assessment before surgery [3].

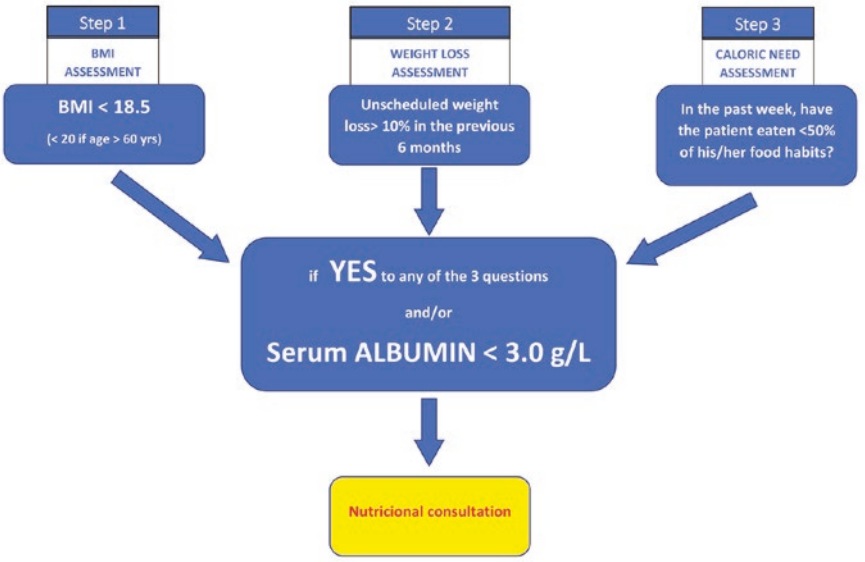

Fig. 3.1 Decision scheme to initiate patients to nutritional assessment before surgery (modified from Schonborn JL, Anderson H. (2019). Perioperative medicine: a changing model of care. *BJA Education* **19**:27–33)

(c) *Psychological intervention*. Anxiety is a major cause of psychological distress before surgery possibly affecting its results with longer hospital stays, impaired immune function, delayed wound healing, and worse functional recovery. If not properly addressed, psychological distress can also compromise patients' motivation to be engaged in the prehabilitation process [11].
(d) *Lifestyle changes*. Smoking, obesity, and alcohol abuse have all been associated with worse outcomes after surgery. Stopping smoking 4–8 weeks prior to surgery has been shown to significantly reduce pulmonary complications. Likewise, 4 weeks of alcohol abstinence can reduce morbidity and shorten hospital stay. Specific actions are also indicated in the management of behavioral abnormalities in relation to obesity [3].

3.2.3 Management of Comorbidities

Optimizing patient comorbidities in the preoperative period is another key component for improving post-surgical outcomes. It may include screening for any undiagnosed disorders. There is now strong evidence that patients with undiagnosed and/or untreated diabetes or with undiagnosed/untreated anemia have significantly worse outcomes and a growing literature supports their identification and clinical management prior to surgery. Fragility is an additional risk factor for worse surgical outcomes. Given the vastness and articulation of all the specific topics, only a brief mention of them is given below as a stimulus for personal study.

(a) *Frailty.* The concept of frailty has been adopted especially for elderly patients in order to provide a broader perspective of their global health status than that allowed by the different organ-specific assessment tools. Frailty is therefore defined as a state of high propensity for negative health outcomes, including disability, addiction, falls, need for long-term care, and, consequently, mortality [15, 16]. Thus, frailty can be considered as a progressive global decline related to age and the progressive exhaustion of the physiological reserve overall. This translates into less resilience, loss of adaptability, and therefore greater vulnerability to stressors [17]. Therefore, it is not surprising that frailty has been associated with adverse postoperative outcomes, including medical and surgical complications, prolonged hospitalization, admission to rehabilitation units, and hospital readmission with both short- and long-term increased mortality. Unfortunately, given the relative novelty of the topic, there is still not a large amount of evidence that frailty and its consequences can be limited, mitigated, or cured once it is identified, whereas a growing body of data supports physical training programs supervised by competent personnel before surgery as important tools that can improve mobility and functional ability in selected cases [18, 19].
(b) *Sarcopenia*. The European Working Group on Sarcopenia in the Elderly (EWGSOP) defines sarcopenia as a syndrome characterized by a progressive and generalized loss of muscle mass and strength with a risk of adverse outcomes such as physical disability, poor quality of, life and death [20]. Sarcopenia

is common in the elderly and is capable to globally worsen the global state of health with objective negative consequences on the health system. Therefore, its identification has been suggested at least in frail patients and in those at increased risk of surgical complications and mortality [21]. Although there is no standardized approach to diagnosing sarcopenia, the EWGSOP has proposed a screening algorithm for patients aged 65 and over [20]. The diagnosis of sarcopenia is based on the detection of reduced muscle mass along with decreased muscle strength and physical performance, the latter assessed by the speed of the gait: the lower the speed, the lower the physical function (cut-off of 0.8 s/m). Muscle strength can be evaluated by measuring the hand-grip strength (hand-grip test) with a dynamometer (cut-off: <30 kg for men and < 20 kg for women). Finally, muscle mass can be nowadays evaluated with computed tomography or magnetic resonance imaging. This method is particularly useful for staging sarcopenia in cancer patients. The treatment of sarcopenia makes use of coordinated interventions where nutrition and physical exercise are employed synergistically [22].

(c) *Anemia*. Anemia is a common and serious problem in patients undergoing surgery. In fact, it has been estimated that approximately 40% of patients undergoing major surgery are anemic and that this condition is associated with significantly higher morbidity and mortality rates [23]. Thus, it is essential to identify and treat anemic patients before they undergo surgery [3]. However, there is still considerable variability between countries and hospitals in the perioperative management of anemia and an international group of experts has tried to remedy this indicating the need to treat iron deficiency and iron deficiency-related anemia through the administration of oral or i.v. martial supplements [24]. In general, all patients undergoing elective surgery with an expected blood loss of >500 ml should have their hemoglobin checked prior to surgery and should have specialist evaluation if they are found anemic. The measurement of the preoperative hemoglobin must be performed as soon as possible and, in any case, at least 14 days, preferably more than 30 days, before of the planned surgery [23]. Treatment of iron deficiency-related anemia should be undertaken under medical outpatient supervision, and there is good evidence that this practice will result in higher hemoglobin concentrations, lower perioperative transfusion rates, and improved quality of life [23]. Routine use of erythropoietin is not recommended and, although it can reduce the number of patients transfused, the total number of red blood cell transfusions and the length of hospitalization are not affected. In addition, a potential increased risk of thrombosis has been reported [23]. Therefore, since the risks of erythropoietin therapy seem to outweigh its benefits, it use should be restricted to patients who refuse red blood cell transfusions (e.g., Jehovah's Witnesses) or those with rare blood types. In summary, the management of preoperative anemia requires a multidisciplinary effort on various levels of care, and it must start far before patients' admission to hospital for the planned intervention (Fig. 3.2).

(d) *Diabetes*. Perioperative hyperglycemia, regardless of whether the cause is undiagnosed diabetes or stress hyperglycemia, is an important risk factor for post-

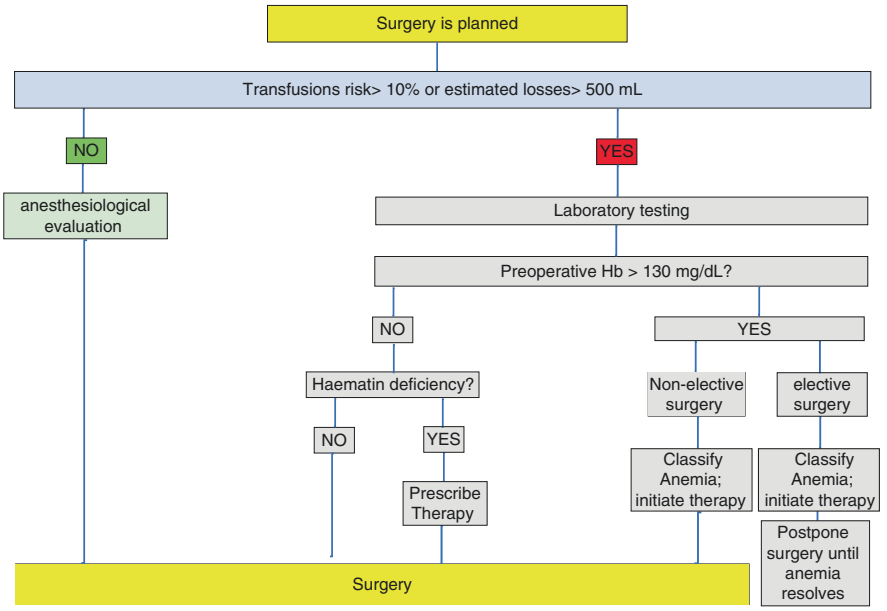

Fig. 3.2 Suggested management of preoperative anemia (modified from Munting KE, Klein AA. Optimisation of pre-operative anaemia in patients before elective major surgery – why, who, when and how? (2019) *Anaesthesia* **74** (Suppl. 1): 49–57)

operative complications, increased length of hospital stay, and death [25]. However, it should be emphasized it is modifiable. Therefore, many of the interventions needed to improve be undertaken before hospitalization for planned surgery. Diabetes affects 10–15% of the candidates to surgery and its perioperative management begins with its early identification and concomitant optimization of glycated hemoglobin. Perioperative management with insulin therapy should also be considered.

3.3 Intraoperative

In a 2009 publication entitled "WHO guidelines for safe surgery: safe surgery saves lives" [26], the World Health Organization clearly underlined the central role of the anesthesiologists in promoting safety of surgical patients and improving their outcomes after surgery. Over time, a series of interventions to be implemented during the intervention have also been identified that can influence the quality of care provided to the patient, including maintenance of normothermia, adequate fluid management, reduction of blood transfusions, and implementation of standardized care bundles aimed at early postoperative recovery [3]. The negative relationship between intraoperative hypotension and different postoperative outcomes was also quite well defined. For example, Sessler and colleagues described the so-called triple effect

whereby a low mean arterial pressure in the presence of a low alveolar concentration of halogenated anesthetics and a low value of the bi-spectral index constitutes a negative predictor for morbidity and mortality [27].

One area where considerable progress has been made is that of hemodynamic management. In fact, the progressive increase in the complexity of the surgical procedures and of the comorbidities affecting the candidates to surgery has prompted anesthesiologists to seek intraoperative hemodynamic management strategies that could guarantee the best organs perfusion. To this end, the goal-directed therapy (GDT) approach is fast becoming a routine practice with a growing body of evidence showing that its use can result in a reduction in postoperative complications and the length of hospital stay compared to other strategies (e.g., liberal or restrictive) of fluid therapy. GDT, defined as the administration of fluids (with or without inotropes or vasoactive agents) on the basis of well-identified hemodynamic flow objectives with the aim of optimizing (or increasing) tissue perfusion, has been the subject of many randomized studies in recent years. A very recent meta-analysis included all clinical studies published on various platforms (CENTRAL, MEDLINE, EMBASE) up to January 2020 including all RCTs reporting pulmonary outcomes. The primary outcome was the generic presence of postoperative pulmonary complications. The authors identified 66 RCTs with 9548 participants. The use of GDT resulted in a significant reduction in total pulmonary complications (OR 0.74, 95% CI 0.59–0.92). The incidence of lung infections, reported in 45 studies with 6969 participants, was significantly lower in the GDT group (OR 0.72, CI 0.60–0.86). Pulmonary edema was recorded in 23 studies with 3205 participants and was also less common in the GDT group (OR 0.47, CI 0.30–0.73). No differences were found in the incidence of pulmonary embolism or acute respiratory distress syndrome. Subgroup analyses demonstrated the following: (i) a benefit of GDT in general/abdominal/mixed and cardiothoracic surgery but not in orthopedic or vascular surgery; (ii) a benefit of the combined use of fluids with inotropes and/or vasopressors to achieve the hemodynamic objectives of GDT vs. the use of fluids alone. Finally, the GDT group received more colloidal solutions (+280 mL) and fewer crystalloid solutions (−375 mL) than the control group [28]. However, the authors warn that the interpretation of these data must take into account the clinical and statistical heterogeneity of the available studies. Finally, it should be emphasized that the key to obtaining the benefits related to the use of GDT lies in the algorithms and its correct application to the type of patient rather than the specific type of parameter or monitor used [29].

3.4 Postoperative

Over the years, there has been a progressive paradigm shift in the postoperative approach to the surgical patient. In fact, we have moved from a “reactive” management of postoperative complications (i.e., the complication is first diagnosed and then treated) to a model that, based on the planning of postoperative care, has prevention as its cornerstone. From this point of view, a key role is that of creating

individualized preoperative care plans through the identification of different levels of care depending on the characteristics of the patients and the surgical interventions they undergo. This approach is emphasized in the Enhanced Recovery After Surgery (ERAS) protocol which was conceived and developed in the early 2000s. The concept of ERAS is based on several components: (a) a multidisciplinary team that works together having the individual patient as its central reference; (b) a multimodal approach to solve problems that may delay recovery and cause complications; (c) an evidence-based scientific approach to care protocols; and (d) an adjustment of the care process through continuous auditing activities [30]. The description of the different interventions that make up an ERAS protocol, its benefits, and difficulties are beyond the scope of this review. However, here we want to emphasize that ERAS programs are now widely established in many surgical subspecialties as procedure-specific paths articulated in "multimodal packages" of assistance from the preoperative period to patients discharge. One of the recognized benefits of the ERAS approach is the reduction of variations in their clinical management and the improvement of the quality of care through adherence to a set of evidence-based standards which, if applied all together, improve and speed up postoperative recovery. It cannot be excluded that, with further future developments, the ultimate goal of positively influencing also long-term outcome and not only short- and medium-term outcomes may be achieved [31]. In summary, ERAS programs represent a paradigm shift in which surgical patient care is provided based essentially on teamwork, auditing, and continuous improvement of procedures which are selected on the strongest evidence available. The final aim is to optimize the postsurgical recovery of patients in view of both short- and long-term benefits (clinical and also economic).

3.5 Organizational Issues

Patient engagement with anesthetists occurs quite relatively late in traditional surgical pathways. This limits the ability not only to identify those who are at high risk for surgery but also to prepare patients adequately affecting changes in their decision-making, expectation, behavior, and physiological reserve (through comorbidity management) in a collaborative way. Although today's evidence shows that and adequate preparation of patients before major surgery plays a fundamental role in improving postoperative outcomes, there is currently no general consensus about which of the above described interventions/strategies brings the greatest clinical benefits. This is due to different factors: (a) a lack of standardization of the different experiences available; (b) the heterogeneity of the patient populations studied so far; and (c) the time-gap between the implementation of corrective interventions and the surgical procedures. Another issue still to be fully evaluated is whether delaying surgery in order to carry out and complete preoperative optimization can be justified on a clinical level, especially in the case of oncologic patients. Moreover, it is becoming more and more clear that preparation for surgery still takes place relatively too late, at least in traditional surgical pathways [3]. In this regard, it has been

proposed a redesign of the existing process with much earlier patient engagement and risk stratification, allowing effective triage and resource utilization [3]. This implies the creation of specialized clinics for high-risk subjects who are involved in a shared decision-making process where the risks and benefits of the proposed intervention can be fully presented and understood by the patient within the context of their own lives.

Conceptually, this model aims to reduce variability in perioperative care as variability increases the likelihood of errors and complications. One way to achieve this is to ensure continuity of care for each individual patient rather than managing it in different stages by applying the best evidence/practices in a consistent and standardized way. When best evidence/best practice does not exist or is not clear, the PM team should develop an agreement for the standardization of a particular practice that will be applied. At every stage of this continuum, from the decision to undergo surgery up to 30 days after surgery, patients will be informed, educated, and involved in decision-making and treatment planning [31]. Applying these concepts, anesthesiologists have a unique opportunity to improve outcomes, reduce length of stay and other parameters, and improve patient satisfaction.

3.6 Future Developments

The increasing complexity of surgical procedures associated with that of the patients require the creation of more and more personalized and tailored paths of care and stimulate interest in hi-tech solutions and automated treatment processes. Digital technology is likely to play an increasingly important role in shaping perioperative care in the near future. In this regard, a series of possible advances relevant for improved postoperative care have been studied such as software applications aimed at supporting patients in the necessary lifestyle changes and in prehabilitating them before surgery. Also, noninvasive sensors have been designed to recognize any cardiopulmonary complications and track their physical activity in the aim to monitor postoperative recovery [31]. An exciting frontier that lies ahead in future years is the combination of big data analysis with artificial intelligence to guide patients' perioperative management. To date, there is evidence that artificial neural networks and machine learning programs may outperform conventional models in diagnosing acute appendicitis, selecting patients for surgery, predicting quality of life after breast cancer surgery, and long-term mortality after surgery for hepatocellular carcinoma [31]. Another area of great potential is that of machine learning. These are mathematical-computational methodologies aimed at learning information directly from data, without mathematical models and predetermined equations in order to create algorithms that will improve their performance in an "automatic and adaptive" way as they come into contact with the data as they as "learned." There are already some experiences where these algorithms are used to PM. For example, multilayer perception neural networks have been used to calculate the best time windows to apply individualized pre-habilitation care and also to calculate the probabilities of delayed discharge and hospital readmission [32, 33]. A wide

implementation of these technological aids could revolutionize the management of surgical patients within the next 20 years when the collection of clinical data from computerized medical records, their combination with those collected prospectively during the perioperative period, and the integration of all the information from automatic learning programs will lead to a continuous updating of therapies and care interventions that will as tailored to the individual patient. Finally, with regard to both the evaluation of performance and outcomes, until now the focus has been almost exclusively on static parameters such as the length of hospitalization, the readmission rate, and the morbidity and mortality at 30 days. However, these measures fail to reflect the complex multidimensional recovery process after surgery. Therefore, in the future, in order to better describe the post-surgery period, it will be important to also include indicators and a more detailed assessment of physical, emotional, functional, and cognitive recovery.

3.7 Conclusion

The progress achieved over the years by anesthesiology both in terms of clinical practice and the quality of the results is impressive. Although these advances have much contributed to the increase in the overall quality of care and safety of the surgical patient, there is a broad consensus that significant margins still exist to expand the breadth and scope of research in anesthesiology. Perioperative medicine is a rapidly growing and evolving specialty that places the patient at the center of its processes. It aims to build a sort of physical, physiological, and emotional resilience to the surgery and to the stress response that it entails through the involvement of multiple professional figures throughout all the phases of the surgical path. There is still no defined and definitive organizational and operational model of PM and further research and experiences are still needed. As more data will be available, a standardized "better care" package will be tailored. The challenge for the future national and local health systems lies in the ability to develop and innovate remaining within the current economic constraints.

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Perioperative Hypertension and Anesthesia

4

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4.1 Introduction

Blood pressure varies continuously, but a stable increase in pressure can cause stressful conditions, especially in the heart but also in other vital organs. Heart disease and stroke, important causes of death in Western countries, have a close correlation with hypertension [1, 2]. According to recent changes to the hypertension classification made in 2017 by the American Heart Association and the American College of Cardiology, a large portion of the population falls under the hypertensive classification. Among other things, just over half of these people have real blood pressure control. In addition to the number of deaths associated with failure to control blood pressure, this medical situation costs the NHS billions [1–3].

As you can imagine, a large percentage of surgical patients have pressure problems that must also be addressed by anesthesiologists. This chapter will provide a concurrent review of the definition, physiology, pharmacological management, and other concerns related to the management of hypertensive patient anesthesia.

The correct perioperative classification of the hypertensive patient will allow us to minimize perioperative hypertensive events and above all avoid suspension of operations because the patient is hypertensive. Poorly controlled hypertension causes marked fluctuations in blood pressure during anesthesia as a result of blood loss, pain, laryngoscopy, and intubation.

Except in cases where patients have a systolic blood pressure (SAP) > 180 mmHg and/or a diastolic blood pressure (DAP) > 110 mmHg, surgery should not be

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suspended. However in emergency situations, in the cases mentioned above, the surgery must be postponed after proper blood pressure control.

A management strategy during surgery that avoids large fluctuations in perioperative blood pressure can improve postoperative outcomes [4].

Maintaining blood pressure in a range between 100 mmHg (DAP) and 160 mmHg (SAP) allows for the reduction of complications as described in the literature. It must be emphasized that perioperative hypertension should not be treated excessively to avoid sudden drops in blood pressure following anesthesia drugs. For the perioperative control of blood pressure, the parenteral route and rapid onset and offset drugs should be chosen [5].

4.2 Classification and Guidelines

There are two types of hypertension: essential hypertension and secondary hypertension. Essential hypertension accounts for about 95% of cases and is apparently causeless. Many factors can contribute to essential hypertension such as obesity, insulin resistance, high alcohol consumption, high salt consumption, aging, sedentary lifestyle, stress, low intake of potassium, and low calcium intake, but the obvious relationships are not linear. Secondary hypertension has a clear etiology with many causes which can include kidney disease, hyperthyroidism, obstructive sleep apnea, hyperaldosteronism, and many others.

There are four blood pressure levels, as indicated by the American Heart Association/American College of Cardiology in the updated 2017 guidelines (see Table 4.1).

Considering the diagnosis of chronic hypertension, there is a distinctive difference between the ESC/ESH and ACC/AHA guidelines regarding the blood pressure level that defines hypertension that requires treatment. The European guidelines suggest treating patients with blood pressure > 140/90 mmHg, while the American guidelines recommend starting treatment with a blood pressure of 130/80 mmHg [6].

Currently, the optimal blood pressure is a systolic pressure below 120 mm Hg and a diastolic pressure below 80 mm Hg. The evaluation of the hypertensive patient must include the rise in diastolic pressure as a major discriminating factor for treatment.

Table 4.1 Classification of hypertension [1–3]

Class	Systolic pressure mmHg		Diastolic pressure mmHg
Optimal pressure	<120	and	<80
High	120–129	and	<80
Hypertension stage 1	130–139	or	80–89
Hypertension stage 2	≥140	or	≥90
Emergency/hypertensive crisis	>180	or	>120

4.3 Physiology of Blood Pressure Regulation

The physiology of blood pressure regulation consists in a delicate balance of the nervous system and hormonal control mechanisms to keep blood pressure at or near normal level. Average arterial pressure is the component that guarantees perfusion to vital organs and also optimizes cardiovascular work. Blood pressure regulation is due to a feedback mechanism consisting of pressure sensors and effector mechanisms. The most important mechanisms for blood pressure regulation are a fast, neuromediated baroreceptor mechanism and a slower, hormonally regulated aldosterone-regulated renin-angiotensin mechanism.

The sympathetic system also contributes to the maintenance of blood pressure, which by controlling the vasomotor tone stimulates vascular vasoconstriction and contractility to maintain normal blood pressure values.

But, the most important mechanism for blood pressure regulation turns out to be the baroreceptor reflex, initiated by the stretch receptors within the aortic arch and carotid bodies that transmit feedback signals to the central nervous system. The carotid receptors are more sensitive to a decrease in blood pressure, while the baroreceptors in the aortic arch are more sensitive to an increase in blood pressure. This control mechanism is extremely rapid.

The renin-angiotensin-aldosterone system (RAAS) is part of a powerful feedback system for long-term control of blood pressure and volume homeostasis. The RAAS is stimulated by reduced cardiac output, reduced renal perfusion, hypovolemia, and decreased sodium intake. Stimulation of the RAAS traditionally begins with angiotensinogen to form angiotensin I. Angiotensin I is further cleaved by the angiotensin-converting enzyme (ACE) to form the active hormone angiotensin II, which acts on a variety of sites for increasing blood pressure, mainly by binding to specialized receptors that induce vasoconstriction (AT type 1).

Vasopressin, also known as antidiuretic hormone, is the key humoral component of the vasopressinergic system, which has a profound effect on blood pressure control. Vasopressin is synthesized in the paraventricular and supraoptic nuclei of the hypothalamus, and the most potent stimuli for vasopressin release are hypertonic conditions, severe hypotension, and hypovolemia. The vasopressin receptors that are crucial in controlling blood pressure are the V1 receptors located on vascular smooth muscle and produce peripheral vasoconstriction, while the V2 receptors located in the collecting ducts of the kidneys promote water retention [7].

The atrial natriuretic peptide, which is released when the atrial stretch receptors are stimulated, also participates in pressure control with an increase in natriuresis and consequent decrease in blood volume. Furthermore, the chemoreceptors located in the carotid and aortic bodies are stimulated by low arterial oxygen concentrations and also play a role in regulating blood pressure. The chemoreceptor reflex, stimulated by changes in blood gases, is not a powerful regulator of blood pressure until the pressure drops below 80 mmHg.

4.4 Recommendations for Treatment

Hypertensive patients are first asked to change their lifestyle. Drug treatment in uncomplicated stage 1 hypertension is usually a thiazide-type diuretic, angiotensin-converting enzyme (ACEI) inhibitor, angiotensin receptor blocker (ARB), or calcium channel blocker. In stage 2 hypertension, treatment typically expands to a two-drug combination, which usually includes the introduction of β-adrenergic receptor blocking agents (β-blockers) associated with the stage 1 category.

The American Heart Association recommends that for most patients with hypertension, including patients with stable cardiovascular disease, chronic kidney disease, diabetes mellitus, and age-related problems, the target blood pressure to be achieved is <130/80 mmHg [1–3].

4.4.1 Common Antihypertensive Drugs and their Anesthetic Implications

The major classes of antihypertensive agents include diuretics, ACEIs, ARBs, direct renin inhibitors, calcium channel blockers, α-adrenergic blockers, β-adrenergic blockers, α2-adrenergic agonists, and vasodilators. It is important to remember the drugs that can interfere, worsening it, with treatment and therefore with pressure control.

4.4.2 Commonly Used Drugs

- Non-steroidal anti-inflammatory drugs
- Oral contraceptives
- Some antidepressants (e.g., tricyclic antidepressants, serotonin and norepinephrine reuptake inhibitor, bupropion, monoamine oxidase inhibitors)
- Sympathomimetics (e.g., nasal decongestants such as pseudoephedrine/ephedrine)
- Corticosteroids
- Voluptuous or abusive substances
- Alcohol
- Cocaine
- Amphetamines
- Chewing tobacco

4.4.3 Significant Predictors of Non-adherence to Antihypertensive Therapy

- Age < 50 years
- Male gender
- Hispanics or African Americans

- Low income
- Lack of health care
- No medical checks in the previous year

4.4.4 Diuretics

Diuretics increase the rate of urinary excretion and clinically act by decreasing renal tubular sodium reabsorption, causing natriuresis. There are many types of diuretics that mainly have a similar goal of inhibiting the tubular reabsorption of sodium but have different mechanisms of action at different points in the nephron. Some common diuretics and their mechanisms and sites of action are described in Table 4.2.

It is very important to know the electrolyte changes induced by the various diuretics, especially with regard to calcium and potassium. Loop diuretics, which increase distal calcium reabsorption, while causing lower degrees of hypokalemia, will induce potassium problems like thiazides.

Aldosterone antagonists act on the distal nephron by increasing the excretion of sodium and water with savings of potassium. Osmotic diuretics such as mannitol reduce water reabsorption by increasing the osmotic pressure of the tubular fluid and are mainly used in the operating room and in intensive care settings. Carbonic anhydrase inhibitors reduce the reabsorption of bicarbonate and therefore sodium, resulting in diuresis. Sodium channel blockers, such as recently underutilized triamterene, work by blocking the reabsorption of sodium to create their diuretic effects. Triamterene and spironolactone are called potassium-sparing diuretics and can be combined with thiazide diuretics to minimize hypokalemia.

Table 4.2 Classes of diuretics and their mechanism and site of action

Classes of diuretics	Mechanism of action	Action site
Thiazide diuretics (hydrochlorothiazide)	They inhibit the transport of Na and Cl	Proximal distal tubule
Loop diuretics (furosemide)	They inhibit the reabsorption of Na, K, and Cl	Loop of Henle
Aldosterone antagonists (spironolactone)	They inhibit the reabsorption of Na and the excretion of K	Collector tubules
Osmotic diuretics (mannitol)	They increase the osmotic pressure and inhibit the reabsorption of H2O and solutes	Proximal tubules, mainly
Carbonic anhydrase inhibitors (acetazolamide)	They inhibit carbonic anhydrase which reduces the reabsorption of Na through the inhibition of HCO3	Collector tubules
Sodium channel blockers (triamterene)	It directly inhibits the reabsorption of Na and the excretion of K	Collector tubules

4.4.4.1 Anesthetic Implications

It is important to monitor serum potassium levels after the administration of diuretics, both sparing and eliminating potassium, especially in patients with heart failure and renal insufficiency.

The depleting effect of diuretics leads to a reduction in circulating volume with an associated decrease in peripheral resistance. Thiazide diuretics can aggravate glucose control, especially in combination with beta-blockers. Furthermore, thiazide diuretics appear to prolong neuromuscular block with nondepolarizing neuromuscular blockers. Diuretics should be continued in the perioperative period but may be discontinued if there is reason to suspect volume depletion or hypokalemia. In addition, associated hyponatremia can cause volume displacement in the cells with a consequent hypovolemic state, typical of many long-term hypertensive patients. A careful increase in volume with a crystalloid solution prior to induction of anesthesia can help counteract masked hypovolemia.

4.4.5 ACEI

ACEIs block the conversion of angiotensin I to angiotensin II in the renin-angiotensin system. Blocking the formation of angiotensin II is fundamental in the control of pressure for the reduction of vasoconstriction operated by bradykinin which, by increasing capillary permeability, can cause angioedema (0.3–0.6%), with involvement of the glottic and laryngeal regions. The sensitization caused by bradykinin on the sensory nerves of the airways, together with an accumulation of kinins, substance P, and prostaglandins, can contribute to the pathogenesis of common and annoying cough with the use of ACEIs. This ACEI-related cough can occur in up to 10% of patients and is the most common side effect of ACEIs. The treatment of choice is to discontinue ACEI.

There are three classes of ACEIs which differ in potency, bioavailability, half-life, and route of elimination. Class I ACEIs, such as captopril, have the shortest half-life (6–12 h versus 24 h); class II ACEIs, such as enalapril, are prodrugs that are converted into active drugs by the liver; and lisinopril, the only class III ACEI, is not a prodrug and is excreted unchanged by the kidneys without hepatic metabolism.

4.4.5.1 Anesthetic Implications

Due to an increased risk of refractory hypotension, ACEIs are typically stopped on the day of surgery if general anesthesia or some type of deep sedation is planned, particularly during induction of general anesthesia [8]. If the patient has taken the usual dose of ACEI on the day of surgery, an intravenous bolus of 250 mL to 1 L of crystalloid solution can be administered before induction of general anesthesia to decrease the severity of hypotension, although it is advisable. The use of a vasopressor [9–11]. Sometimes vasopressin, epinephrine, and norepinephrine are used to treat hypotension. ACEIs can generally be continued during the perioperative period if moderate sedation is anticipated.

For the aforementioned reasons and due to hypotension that is sometimes refractory to treatment, it is recommended that these drugs be suspended 24 h before surgery unless they are prescribed for the treatment of heart failure.

Attention should be paid to angioedema and to the differential diagnosis with histamine-mediated edema. Although the incidence of ACEI angioedema is low, discontinuation of ACEI, maintenance of a patent airway, and supportive care are the mainstay of treatment. Corticosteroids and antihistamines are usually given to rule out histamine-mediated angioedema and are usually ineffective in bradykinin-mediated angioedema, as seen with ACEIs.

4.4.6 ARB

ARBs, otherwise known as angiotensin II receptor antagonists, prevent angiotensin II from binding to the angiotensin II receptor (AT type 1) on vascular smooth muscle cells. This block causes a decrease in peripheral vasoconstriction, thus reducing systemic vascular resistance and arterial blood pressure, increasing plasma levels of angiotensin II with normal bradykinin.

4.4.6.1 Anesthetic Implications

ARBs should also be suspended 24 h prior to surgery to avoid refractory hypotension during induction of general anesthesia. In addition to the refractory hypotension that can occur during induction, episodes of rebound hypertension have been described following discontinuation of ARBs. The risks and benefits of continuing or discontinuing ARBs should be considered during any adjustment of therapy in the perioperative period [8–11].

4.4.7 Direct Renin Inhibitors

The direct renin inhibitor Aliskiren binds to the S3bp binding site of renin and inhibits the RAAS by blocking the conversion of angiotensinogen to angiotensin I. It is a relatively new drug and as it does not significantly interfere with the cytochrome P450 system, it has been associated with few drug interactions.

4.4.7.1 Anesthetic Implications

It is well known that ACEIs and ARBs are associated with refractory hypotension during induction of general anesthesia and it can be assumed that direct renin inhibitors, which act first on the same pathway and produce similar if not more exaggerated downstream effects, would have similar anesthetic implications. Aliskiren has also been associated with an increased incidence of non-fatal stroke, renal complications, and hyperkalemia.

4.4.8 Calcium Channel Blockers

There are three main classes of CCB: (a) phenylalkylamines (verapamil) and (b) benzothiazepines (diltiazem), which inhibit atrioventricular node activity with a lesser degree of vasodilation than (c) dihydropyridines (e.g., amlodipine, clevidipine, nicardipine), which are selective for the arterial vascular bed (see Table 4.3). Calcium channel blockers (CCBs) inhibit the opening of L-type voltage-gated calcium channels and the contraction of smooth muscle cells in peripheral arterial blood vessels, thereby reducing blood pressure and afterload. Additionally, some CCBs reduce contractility, heart rate, and conduction speed. Some CCBs reduce both systemic vascular resistance and myocardial oxygen demand. The recent availability and advantageous pharmacological properties of clevidipine, compared to nicardipine, fast-acting, intravenously, rapidly metabolized by esterases and short-acting, have largely replaced the use of nitrodilators such as sodium nitroprusside. Clevidipine and nicardipine may be useful when used as an infusion for intentional hypotension, such as during orthognathic surgery, to decrease blood pressure without increasing depth of anesthesia and without using long-acting vasodilators or beta-blockers. Clevidipine is an appropriate drug for the management of acute perioperative hypertension. It has a short-acting effect, is easy to titrate due to a linear dose response, and exhibits a rapid "wash-out" after a half-life of approximately 1 min, which is an advantage over other calcium channel blockers [12]. Clevidipine has several advantages which make it an ideal option for perioperative use with a rapid onset, short duration of action pharmacokinetic profile; efficacy data showed limited excursions outside the desired blood pressure range and lack of renal and hepatic metabolism.

4.4.8.1 Anesthetic Implications

Inhaled agents reduce the availability of intracellular calcium, which in turn increases the negative inotropic, chronotropic, and dromotropic effects of CCBs. Phenylalkylamines and benzothiazepines differ in their cardiovascular selectivity with respect to dihydropyridines and exhibit cardiac depressive properties equal to vasodilatory properties. Physiological attenuation of expected reflex tachycardia is associated with reduced cardiac output determined by CCBs [12, 13]. Furthermore, CCBs can potentiate all neuromuscular blocking agents, potentially compromise hypoxic pulmonary vasoconstriction, and slightly increase intracranial pressure.

Table 4.3 Comparative properties of common calcium channel blockers (CCBs)

CCB	Inotropism	Cronotropism	Peripheral vasodilation	Coronaric vasodilation	Reflex tachycardia
Diltiazem	=/↓	↓	+	++	=
Verapamil	↓	↓	+	++	=
Nicardipine	=/↓	=	+++	+++	+
Nifedipine	↓	=	+++	+++	++
Clevidipine	=/↓	=	+++	+++	+

CCBs are contraindicated during the treatment of a malignant hyperthermia crisis due to an increased potential for cardiac collapse after concomitant administration of CCB and dantrolene. Except in cases where screening for malignant hyperthermia reveals susceptible patients, CCBs should generally be continued in the perioperative period.

The pharmacokinetic and pharmacodynamic properties of clevidipine recommend it as a drug for the treatment of perioperative hypertension and for perioperative hypertensive crises [14]. The handling of the drug and its safety profile make it an advantageous alternative to nitrodilators, especially for its selective action on arterial vessels (reduction of systemic vascular resistance), without action on venous capacity (lack of volume sequestration) [12, 13].

4.4.9 Antagonists of α-Adrenergic Receptors (α-Blockers)

A-blocking drugs act directly on α-adrenergic receptors and interfere with the ability of catecholamines or other sympathomimetics to provoke α responses in the peripheral vascular system and in the heart. These drugs include the non-selective α-adrenergic antagonists phentolamine, prazosin, and phenoxybenzamine. These drugs are rarely used as first-line therapies but are generally reserved for use in combination therapies. Their side effects, which include reflex tachycardia, marked orthostatic hypotension, and fluid retention, advise against their use for blood pressure control over highly selective drugs that have fewer adverse cardiovascular effects.

Phentolamine mesylate is used to manage a hypertensive crisis associated with pheochromocytoma, commonly in combination with a beta-blocking agent to attenuate the increased heart rate.

4.4.9.1 Anesthetic Implications

A-blocking drugs are not currently commonly used agents but must be continued prior to surgery.

4.4.10 Blocking Agents of β-Adrenergic Receptors (β-Blocking Agents)

Beta-blockers have a variety of pharmacological and physiological properties (see Table 4.4) and include an effective group of antihypertensive drugs used to treat not only hypertension but also tachyarrhythmias, ischemic heart disease, chronic congestive heart failure, and even migraine prophylaxis. By blocking the cardiac β-1 receptors, it is possible to decrease the inotropic, chronotropic, and dromotropic effects, as well as the renal effects and, in so doing, decrease the afterload and parietal stress, thus reducing the oxygen demand of the myocardium. In the case of non-selective β-blockers, β-2 receptors are also inhibited, which can have the undesirable physiological side effect of increased bronchial constriction.

Table 4.4 Comparative properties of beta-blockers

Beta-blockers	HR	MAP	Antagonism on the receptor	Onset	Duration
Esmolol	↓↓	↓	β-1	2 min	10–30 min
Labetalol	↓	↓↓	β-1, β-2, α-1	5–15 min	2–8 h
Metoprolol	↓	↓	β-1	1–5 min (peak 20 min)	5–8 h
Propranolol	↓	↓	β-1, β-2	2–10 min	6–10 h

Combined α- and β-blockers are a subclass of β-blockers which include drugs such as carvedilol, labetalol, and dilevalol, which non-selectively block all β-1 and β-2 receptors and selectively block α-1 receptors. The antihypertensive activity of these drugs is characterized by a decrease in peripheral vascular resistance without reflex tachycardia, following blockade of β-adrenoceptors. The α-1 adrenoceptor antagonist portion of these drugs accounts for most, if not all, of the vasodilator response produced by the drug. Labetalol deserves special attention due to its common use in anesthetic practice. The α-β-blocker ratio is 1:7 for intravenous labetalol and 1:3 for oral labetalol. The most common side effect of labetalol is orthostatic hypotension. Esmolol [15] and landiolol, short-acting β-1-selective beta-blockers, are currently the most widely used drugs for their manageability and rapid offset in the event of side effects (bradycardia and hypotension). The clinical effects begin after only 2 min (duration of action 10–30 min) which makes them extremely manageable drugs. Landiolol is more indicated for the control of tachyarrhythmias, having less antihypertensive efficacy.

4.4.10.1 Anesthetic Implications

Beta-blockers according to ESC guidelines in cardiac patients should be continued prior to anesthesia and surgery. Abrupt discontinuation of beta-blockers is associated with significant rebound hypertension and tachycardia, with cardiac consequences. These withdrawal symptoms are due to increased sympathetic activity due to upregulation of the β-adrenergic receptor causing hypersensitivity to circulating catecholamines. If the patient has forgotten to take their β-blocker on the day of surgery, it is reasonable to give the patient a long-acting β-blocker or a short-acting β-blocker i.v. A typical dose of esmolol for the immediate treatment of severe hypertension with tachycardia is 0.5 mg/kg over 60 s or by simply titrating in boluses starting with 5–10 mg intravenous esmolol followed by continuous infusion. In addition, beta-blockers can be used to reduce the use of opioids during the perioperative period, especially for hypertensive patients [15, 16].

Due to the possible bronchoconstrictive effects of β-2 receptor blocking with non-selective beta-blockers, there is of course an increased risk of bronchoconstriction during anesthesia when using these drugs. Therefore, non-selective beta-blockers should be used with caution in patients with clinically significant chronic obstructive pulmonary disease and asthma.

Adverse effects of β-blockers are bradycardia, orthostatic hypotension, atrioventricular conduction delays, and hypotension. Bronchospasm may occur, particularly with agents that block β-2 receptors. Furthermore, the warning signs of hypoglycemia (tachycardia and tremor) are masked by beta-blockers, and therefore it is prudent not to use them in patients with poorly controlled diabetes mellitus. In addition, β-blockade during the preoperative period can also attenuate the effects of surgical stimulation, which is advantageous for using fewer opioids, but can lead to the use of subanalgesic or subanesthetic doses of pain relievers and anesthetics.

One consideration regarding non-selective beta-blockers is their interaction with adrenaline. In the case of patients being treated with beta-blockers, it is preferable to consider the use of local anesthesia formulations not containing vasoconstrictors or formulations with a dose of less than 1:200,000 epinephrine.

4.4.11 α-2 Agonists: Adrenergics (α-2 Agonists)

The α-2 agonists include a class of drugs useful for their sedative, anxiolytic, and mild analgesic properties. These drugs act on α-2 receptors with various subtypes including the α-2A, α-2B, and α-2C subtypes. The α-2A and α-2C subtypes are found within the central nervous system and are thought to play a role in sedation, analgesia, and sympatholytic effects, while α-2B receptors are found peripherally on vascular smooth muscle and have been shown to mediate the effects of vasoconstrictors. Clonidine and dexmedetomidine are the main α-2-adrenergic agonists with a high selectivity for α-2 receptor activation (α-2: α-1 activity for clonidine 220:1 and for dexmedetomidine 1620:1).

4.4.11.1 Anesthetic Implications

It is important to consider that abrupt discontinuation of oral α-2 agonists, typically clonidine, may trigger a beta-blocker-like rebound hypertensive crisis which can be alleviated by administration of i.v. clonidine or labetalol. The onset of action of oral clonidine is 30–60 min, therefore, for severe episodes, acute treatment is with an intravenous beta-blocker such as labetalol. In contrast, intravenous dexmedetomidine has a faster onset of action and administered intravenously acts in approximately 30 seconds with a terminal elimination half-life of 2 h. At low doses, respiratory drive depression is minimal and not clinically significant with these drugs. In addition, α-2 agonists can reduce the anesthetic need for intravenous or inhalational agents during general anesthesia. Dexmedetomidine has been shown to be useful in minimizing opioid doses in obese or other patients with obstructive sleep apnea by providing adequate analgesia. The α-2 agonists have also been effective in relieving preoperative anxiety and delirium upon awakening from anesthesia, especially in children. The most common adverse effects are clinically significant hypotension and bradycardia, particularly in the case of continuous infusion for sedation or use in high doses.

4.4.12 Other Vasodilators

Vasodilators are used to control systemic hypertension; increase cardiac output by decreasing afterload, preload, or both; control pulmonary hypertension; and control cardiac shunt. Commonly used agents include nitroglycerin and hydralazine, with sodium nitroprusside less commonly used today. Nitroglycerin and sodium nitroprusside generate intracellular nitric oxide, which increases cGMP in vascular smooth muscle resulting in vasodilation. Sodium nitroprusside also interacts with oxyhemoglobin and forms methemoglobin while releasing cyanates (beware of prolonged use). Sodium nitroprusside primarily acts on the arterial vascular system, while nitroglycerin has its most prominent effect on venous capacitance vessels.

4.4.12.1 Anesthetic Implications

Sodium nitroprusside can cause cyanide and thiocyanate poisoning, especially in those with kidney failure or reduced renal perfusion. Hydralazine is an effective agent in reducing afterload, albeit unpredictable, because it relaxes the arterial smooth muscle more than it relaxes the venous tone. Due to this effect, hydralazine can cause reflex tachycardia, which can counterproductively increase cardiac oxygen demand. Furthermore, it is important to note a synergistic effect from the combination of phosphodiesterase inhibitors, such as sildenafil, and vasodilators that release nitric oxide, and use in combination for inadequate coronary perfusion should be avoided.

4.5 Hypertension and Non-steroid Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are postoperative pain medications commonly used in the perioperative period and may have some unwanted side effects in the hypertensive patient. They have powerful anti-inflammatory and analgesic properties through the cyclooxygenase pathway with subsequent reduction of inflammatory mediators such as prostaglandins (PG).

Circulating PGs maintain the balance between hypertensive and antihypertensive mechanisms, through thromboxane A2 and PGH2, both vasoconstrictor mediators, and through prostacyclin (PGI2) and PGE2, which are vasodilator mediators. NSAIDs can alter and disrupt this compensatory ability and can potentially lead to a predominance of vasoconstrictors and a consequent increase in blood pressure.

Combining NSAIDs with some antihypertensive drugs can also be problematic to varying degrees. The efficacy of diuretics and beta-blockers is usually moderately reduced by concomitant use of NSAIDs, whereas angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists are more affected by NSAID administration. These antihypertensive drugs have been implicated in the onset of acute renal failure especially when administered together with NSAIDs. CCBs do not depend on the action of PGs and therefore do not significantly interact with the use of NSAIDs.

It is therefore important to remember that the concomitant use of NSAIDs and antihypertensives can lead to a worsening of blood pressure control, especially in elderly patients with even serious cardiovascular consequences.

4.5.1 Anesthetic Implications

Since about one in three adults are hypertensive and only about 50% of these have their condition under control, a correct preoperative evaluation of the hypertensive patient is essential. Preoperative hypertension is often a hypertensive urgency, not an emergency, as it typically does not involve obvious end organ damage or acute symptoms. Elevated blood pressures (e.g., systolic ≥180 mm Hg, diastolic ≥110 mm Hg) have been associated with perioperative cardiac complications [16, 17]. If the antihypertensive drugs have been discontinued, it is possible to administer antihypertensive drugs intravenously or to reschedule the surgery [18] by instructing the patient to take the right antihypertensive therapy before surgery [16]. If significant hypertension is found in an untreated patient or in a patient who has taken their usual antihypertensive drugs, intravenous sedation may reduce anxiety-related sympathetic discharge. If this fails to control blood pressure, it is necessary to treat hypertension or reschedule surgery after medical follow-up.

Vascular disease and end organ function are important considerations in preoperative evaluation and, in a patient with more advanced hypertension, appropriate laboratory tests should include blood urea nitrogen, creatinine, serum potassium, and a recent electrocardiogram.

It is important to recognize that many chronically hypertensive patients have upward self-regulation of their tissue perfusion pressures due to an increase in their blood pressure. During anesthesia, the cardiac depressant effect of many general anesthetic drugs can cause a significant reduction in systemic vascular resistance and, especially when combined with the reduced baroreflex response, can lead to large swings in blood pressure. Hypertension causes an adequate shift in the physiological self-regulation curve, particularly for cerebral blood flow. Much caution is required as the risk of cerebral hypoperfusion and even ischemia can occur if perfusion pressures decrease during administration of anesthesia. In this setting, even an "optimal" blood pressure below 120/80 may be inadequate for critical organ perfusion.

Hemodynamic changes related to induction most likely reflect a reduced intravascular volume due to chronic hypertension combined with stiffening of the arterial vascular system. During direct laryngoscopy, there may be a strong sympathetic response that should be avoided with adequate analgesic drugs, beta-blockers, intravenous lidocaine, or other strategies. Intraoperative changes in blood pressure are common during surgery and the anesthetist must be aware of the fluctuations, especially with the chronically hypertensive patient. During anesthesia, the goal is to prevent extreme fluctuations in blood pressure, as hypertensive patients may exhibit exaggerated responses to anesthesia medications and surgical stimulation. These hemodynamic responses may be due to the cardiac depressive effect of many

general anesthetic drugs, which cause a large reduction in systemic vascular resistance along with a decrease in the baroreflex response. Therefore, it is important to avoid exaggerated changes in blood pressure during the induction and maintenance of anesthesia through a stability of sedation or general anesthesia [16]. Caution is warranted with the use of ketamine due to the increase in heart rate and blood pressure it can induce.

While there is no evidence of what blood pressure to maintain during surgery, there is strong evidence that excessive intraoperative hypotension (systolic blood pressure < 70 mm Hg, mean blood pressure < 50 mm Hg, and diastolic blood pressure < 30 mm Hg) is associated with increased mortality [19]. This suggests that when normotensive blood pressure is difficult to maintain during the intraoperative period, it may be safer to keep the patient's blood pressure slightly higher than frankly hypotensive.

After surgery, many hypertensive patients will return to preoperative blood pressure levels. Some treat hypertension prophylactically immediately after awakening from anesthesia. If a more immediate antihypertensive drug is needed for recovery, an appropriate bridging drug could be an intravenous beta-blocking agent. A bridging drug capable of treating hypertensive crises or postoperative hypertension is clevidipine. When administering antihypertensive drugs during anesthesia, it is important to pay close attention to the pharmacokinetic profile of the drugs administered intravenously when resuming the patient's previously prescribed antihypertensive agents. Orthostatic hypotension must be avoided, especially when opioids are also used.

4.6 Conclusion

The goal of long-term antihypertensive treatment is to reduce the overall risk of cardiovascular disease and therefore its morbidity and mortality rates. Treatment is typically initiated with thiazide diuretics, aldosterone antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, or CCBs. When significant changes in blood pressure are required, a combination of the above medications is given and/or a β-blocker may be added. Fluctuations in blood pressure during surgery are common. Proper anesthetic management should be aimed at minimizing these pressure fluctuations, especially avoiding hypotension (MAP <65 mmHg).

Treatment of hypertension is highly variable, but common antihypertensive drugs should be well understood by anesthetists. The β- and α-blocking agents, the α-2 agonists, and the CCBs must be continued on the morning of the surgery for sedation or general anesthesia. Rebound hypertension is a concern when β- and/or α-blocker drugs and α-2 agonists are withdrawn. Angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and direct renin inhibitors should instead be discontinued before general anesthesia due to the risk of refractory hypotension during induction of anesthesia.

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Depth of Anesthesia Monitoring

5

Stefano Romagnoli, Lorenzo Fontanarosa, and Francesco Barbani

5.1 Introduction

The purpose of general anesthesia is to ensure the suppression of the patient's experience and to prevent explicit memory of the events taking place from induction to planned awakening. Even today, in many organizations, the effectiveness of our anesthesia is evaluated by observing physiological parameters (e.g., heart rate and arterial blood pressure) which can only indirectly guide us on the anesthetic level and which have proved unsuccessful in many clinical situations, exposing patients to the experience of intraoperative awakening with recall (awareness) (e.g., emergency surgery, hemodynamic instability due to cardiac tamponade, bleeding or hypertensive pneumothorax, obstetric anesthesia, and intervention by anesthetists in training who are still inexperienced) [1].

5.2 The Electroencephalogram Anesthesia Patterns

The brain is the target organ of our anesthesia drugs (i.e., gamma-amino-butyric acid receptor agonists, $GABA_A$, N-methyl-D-aspartate receptor agonists, NMDA, alpha-2 receptor agonists) and therefore benzodiazepines, propofol, halogenates-isoflurane, sevoflurane, desflurane, barbiturates, ketamine, nitrous oxide, and

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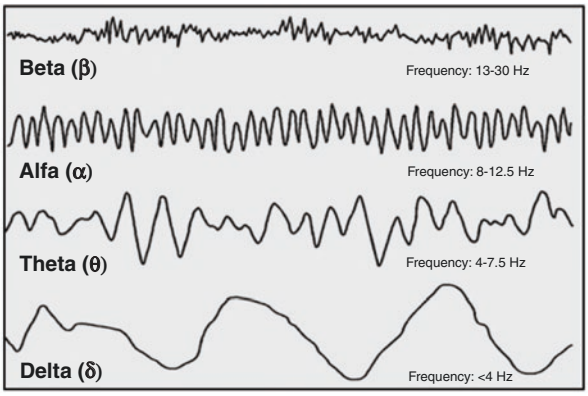

Fig. 5.1 Basic electroencephalographic waves

dexmedetomidine eventually cause changes in the electroencephalogram (EEG) determining patterns that the clinician can (quite) easily identify and interpret to recognize a specific level of anesthesia [2]. Drugs such as ketamine, nitrous oxide, and dexmedetomidine deserve some separate considerations [3].

The EEG can be analyzed in its raw traces where the component frequencies can be identified: beta, theta, alpha, and delta waves (Fig. 5.1). These waves combine with each other producing those patterns that characterize the depth levels (Fig. 5.2).

In order to facilitate the user in identifying the level of anesthesia, modern monitors (depth of anesthesia monitor, DoA), using a disposable sensor equipped with electrodes (with a variable number of channels; mono- or bi-lateral) process the trace (processing of the raw trace, hence the name processed EEG, pEEG) by applying complex proprietary algorithms that return a parameter whose name is linked to a particular brand of DoA.

What follows are some examples:

- Masimo SedLine® Root® (Masimo Corp, Irvine, CA) ➔ PSI (Patient State Index).
- BIS™ brain monitoring system (Medtronic, Boulder, CO) ➔ BIS.
- Conox® monitor (Fresenius Kabi AG, Bad Homburg, Germany) ➔ qCON.
- Entropy (GE Healthcare, Helsinki, Finland) ➔ SE (State Entropy).

These depth indicators represent dimensionless values ranging from 100 (awake patient) to 0 (complete suppression of brain activity, and, in addition to this indicator, they show other additional data useful to the clinician (e.g., BS, SEF, DSA, EMG – see later) (Figs. 5.2 and 5.3).

5.2.1 Density Spectral Array (DSA), Fig. 5.3

The DSA provides a series of information [2–4]: (1) The direct reading by the operator of the raw trace, in terms of amplitude and frequency, can be particularly complex because, unlike electrocardiography, the analysis must be extended to longer

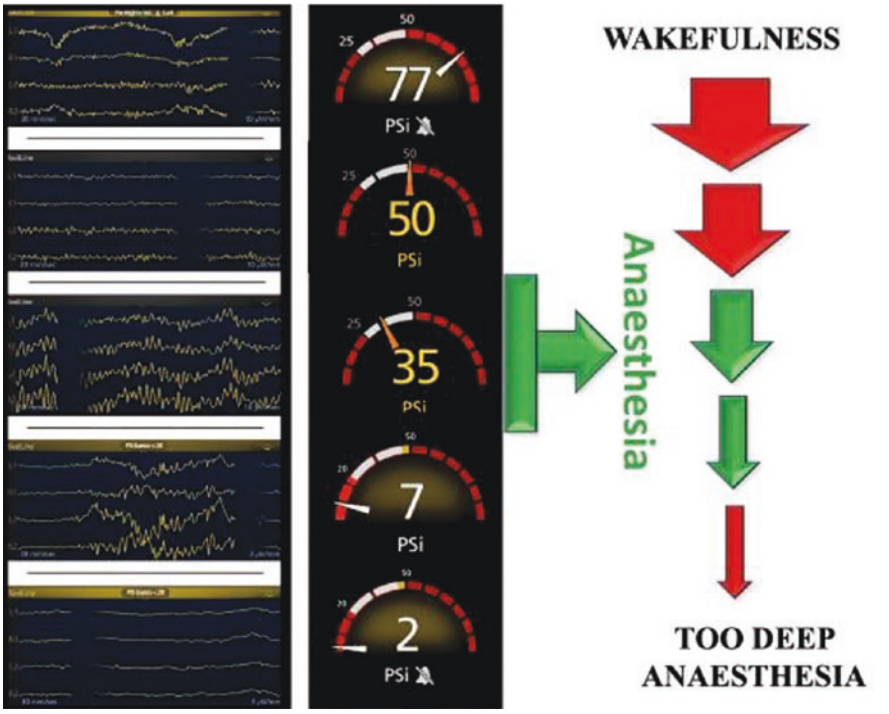

Fig. 5.2 Electroencephalographic patters representing the anesthesia depth levels

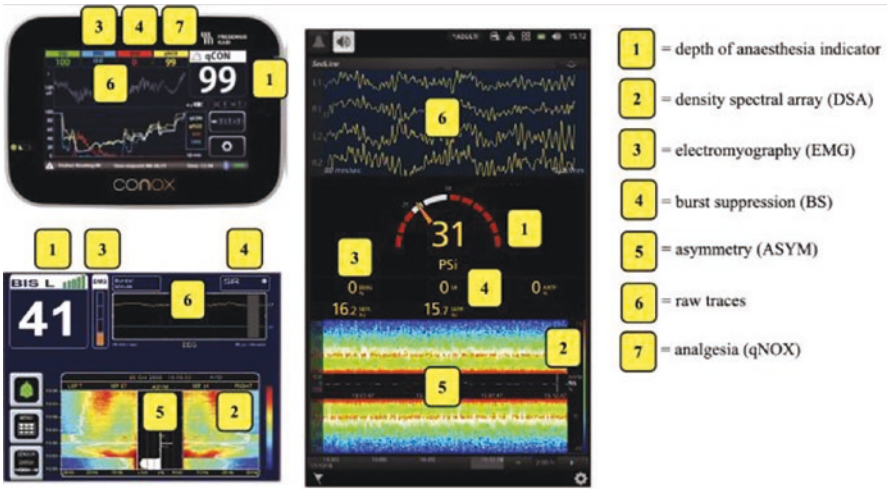

Fig. 5.3 Principal data delivered by processed EEG monitors

periods (epochs; generally, 1 epoch = 30 s). Many modern monitors (e.g., Masimo SedLine®, the BIS™, now also with the unilateral sensor, the Fresenius Conox®) scanning the frontal electrical activity mono- or bilaterally generate the DSA, a visualization of the rapidly interpreted brain electrical activity. Through the use of a color scale (from warm colors like red and orange to cold ones like blue and light blue, passing through green), the frequencies that make up the raw EEG traces are represented. In practice, through the application of the fast Fourier transform, a rough trace is decomposed into its sinusoidal components which are then reported on a graph where the "*x*" axis represents the frequencies while the "*y*" axis represents the amplitude. In other words, a Fourier analysis converts a complex waveform, which manifests itself in the time domain, into its sinusoidal components and generates a frequency spectrum, a series of amplitude histograms as a function of frequency (power spectral density, PSD). This intermediate step then leads to the creation of the DSA which, in turn, is nothing more than the colored representation of the distribution of frequencies in terms of power ("how much certain waves are present in the periods analyzed: a lot of ➔ red; little/no ➔ dark blue"). Black (vertical black stripes) often represents the phenomenon of burst suppression (BS) while white (vertical white stripes) the presence of clear electromyographic artifacts or activity. The DSA provides to the clinician some useful information: (1) visualization at a glance of the state of anesthesia; (2) observation of what happened in the preceding hours; (3) frequency of the trace (range 0–30/40 Hz); (4) the "power spectrum," y axis on the right - unit of measurement = decibel (dB) ➔ mathematical transformation of the EEG frequencies which, for practical reasons, allows the clinician to view very different frequencies in the same scale (−60 + 40 dB over a frequency range between 0 and 30 Hz; (5) SEF, spectral edge frequency (left, SEFL and right, SEFR), is a value between 0 and 30 Hz (also identified by a white trend line) below which 95% of the frequencies (SEF95) or 95% of the patient's total "power"; (6) the asymmetry graph, displays and quantifies the difference in brain activity between the left and right sides with an asymmetry measurement; and (7) BS, it is expressed as a fraction of the total recording time or "suppression ratio" (suppression ratio, SR) and represents the measure of the amount of electrical activity of the frontal and prefrontal cerebral cortex that is suppressed, expressed as a percentage of time.

Further useful information is represented by the electromyographic activity of the facial muscles (EMG: electromyography) and the presence of artifacts (Fig. 5.3).

➔ Important note: for depth indicator values at the upper limits, the systems detect a consistent influence of the β frequencies (characteristics of an incipient waking state). This involves a significant influence of the EMG activity, which is almost inevitably accompanied by an increase in the indicator, even in conditions of adequate sedation. This explains the "knockdown" effect of the indicator that has been observed in some past studies following the administration of muscle relaxants [5, 6].

Many systems have the option of using bilateral sensors. This allows for a comparison analysis between the cortical activities of the right and left frontal lobes.

Outside of carotid surgery, aortic arch, and all those conditions that for reasons of a vascular (vascular stenosis), traumatic, hemorrhagic, or ischemic nature (e.g., neuro-resuscitation) show interhemispheric asymmetries, the usefulness of the bilateral sensor must still find a precise place in literature. In the ICU setting, a bilateral analysis could help in understanding conditions of altered mental state (e.g., NCSE; non-convulsive status epilepticus) [7].

5.3 Artifacts and Factors Worth of Particular Attention

When using pEEGs in the operating room, a lot of attention must be paid to a whole series of factors: (1) **ketamine** (N-methyl-D-aspartate glutamate receptor antagonist [NMDA]) interrupts the inputs that reach inhibitory neurons with a non-competitive antagonism mechanism, allowing the neurons connected to them to be disinhibited and activated. The action of ketamine appears with dissociative anesthesia, which is accompanied by high-frequency oscillations in the order of beta frequencies generating patterns of "awake" patients even if they are unconscious/unresponsive, but with pEEG values that are tending to high (PSI > 50; BIS/IF>60; qCON>60). A piece of advice: avoid assuming that a high pEEG value is attributable to ketamine (e.g., use as an adjuvant analgesic) by accepting a trace "soiled" by the β components. This behavior exposes to awareness risks; (2) **nitrous oxide** increases the amplitude of the high EEG frequencies and reduces that of the low frequencies with minimal effects on the pEEG value; (3) the trace generated by the administration of **dexmedetomidine** assumes the characteristics of the typical trace of a patient in deep sedation (wide delta waves that are low in oscillations/alpha waves) without guaranteeing this condition from a clinical point of view [8]. Dexmedetomidine does NOT guarantee a low RASS (−4/−5). The use of a pEEG in patients undergoing sedation with dexmedetomidine can certainly be of great use but NOT in the operating room (where the drug has specific indications and limitations) especially in those who receive muscle relaxants.

Whenever an unexpected and unexplained increase in the indicator is observed, always check for the absence of **electromyographic** activity. This could explain the unexpected increase.

The electrical signal recorded on the surface of the scalp is approximately 100 times lower than that recorded by a common electrocardiograph. Consequently, any current that does not originate from the brain can have a great influence on the trace and on the analysis process (processing the raw trace). The most frequent of these currents is the EMG but other sources can also cause a disturbance (not always filtered by the system) [2]: (1) an ECG that runs along the neck; (2) electrooculography; (3) environmental electric currents (powerline signals); (4) instruments surrounding the patient (e.g., train-of-four, continuous or intermittent dialysis machines, infusion pumps, active heaters such as hot air blankets or an electric scalpel); and (5) zero-heat-flux thermometry.

5.4 Conclusions

In conclusion, DoA monitoring systems based on an EEG trace today represent fundamental tools for personalizing anesthesia. Their use has inviting, positive consequences that go beyond the reduction of the risk of intra-operative awakening (severe but rare), favoring a reduction of postoperative complications due to very deep anesthesia (e.g., hypotension, fluid overload, acute kidney injury, myocardial injury, neurocognitive decline, delirium). For the feeling of skepticism that still pervades the anesthetic environments to finally vanish completely, it is necessary to spread the knowledge of these tools by increasing the level of trust of the operators. It is not a case that the European Society of Anaesthesiology strongly suggests using these monitors in all the patients undergoing general anesthesia. Nevertheless, the skepticism is still creeping among too many colleagues.

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ERAS (Enhanced Recovery After Surgery) in Liver Surgery

6

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6.1 Introduction

By the term ERAS (Enhanced Recovery After Surgery), we intend a multimodal process implemented during the perioperative period to guarantee, after the surgical procedure, an optimal recovery and an early and safe return to daily activities.

Born in the 1990s and introduced by Kehlet [1] in the colorectal surgery, the concept is based on the implementation of different strategies and procedures aimed at reducing psychological and physiological stress related to the surgical procedure.

Then, ERAS has been extended to other disciplines such as urology, thoracic surgery, vascular surgery, and orthopedics [2–4].

The introduction of such processes has led, in these scenarios, to a considerable reduction of postoperative complications, a faster functional recovery, a shorter length-of-stay, and cost-cutting [5–7].

Liver surgery is a complex and demanding procedure, for the surgeon and the anesthetist as well as for the patient himself [8].

The major postoperative complications go from 17% related to surgery for benign pathologies to 27% related to malignancies, with a mortality up to 5% [7].

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In particular, respiratory complications can reach and exceed 30% of cases and also the thromboembolic risk is significantly increased [9, 10].

The perioperative stress, particularly in major liver surgery, is increased and therefore all the measures that reduce the metabolic and inflammatory response could reduce medical complications [5].

At the moment, it is not yet completely sorted out if all the elements of ERAS procedures in colorectal surgery can be extrapolated and applied to all liver surgery.

In fact, most of the studies which include the use of ERAS protocols in liver surgery have been conducted on patients with normal hepatic parenchyma, while there is few evidence in cirrhotic patients and patients with deteriorated hepatic function.

On the contrary, there is more and more evidence for a real advantage in applying ERAS procedures in patients undergoing liver surgery; a recent meta-analysis and a randomized study have shown a reduction of postoperative complications and of length-of-stay [11, 12].

The ERAS society, in 2016, has published specific guidelines for liver surgery based on a systematic review of the literature [8].

In this document, we have analyzed 23 ERAS elements validated in colorectal surgery and related to preoperative, intraoperative, and postoperative period; among these, 16 have been studied specifically in the context of liver surgery.

All kind of liver resection according to Brisbane [13] classification have been included and patients undergoing choledochal jejunostomy and vascular reconstruction have been examined too.

Transplantations and combined procedures have been excluded from this analysis and so they cannot be strictly included in ERAS protocol.

6.2 Preoperative Evaluation

Globally, the preoperative evaluation of a patient proposed to liver surgery includes a careful medical history and physical examination.

Laboratory tests (including specific markers of hepatic function and necrosis), ECG, and chest X-rays are performed.

Particular attentions is needed for cardiovascular evaluation, which is conducted following guidelines for the evaluation of a cardiopathic patient undergoing non-cardiac surgery [14], using the NSQIP model and the RCRI calculator for the stratification of perioperative cardiologic risk.

In cirrhotic patients, in patients undergoing major resection surgery and in patients candidated to minor resections but with METs < 4, the execution of an echocardiogram has to be considered.

Liver function is evaluated especially in the cases of major hepatic resection, when liver volumetry is assessed and liver function is investigated with indocyanine green.

In cirrhotic patients, CHILD and MELD score have to be calculated; the evaluation of cirrhosis degree plays an important role in terms of hemodynamic, metabolic, and coagulative impact that can arise.

The altered renal function leads the patient to a major risk of AKI, thus the hemodynamic management and the “restrictive” fluid therapy have to be even more careful in these patients.

In the case of anemia, a preoperative optimization is needed according to the recommendations for a correct patient blood management [15].

The management of medical therapies with metformin, ACE-inhibitors, antiplatelets, and/or anticoagulants follows SIAARTI recommendations and international guidelines.

As far as the specific items of preoperative period considered by ERAS society, the actual evidences take into account the preoperative consultation/counseling, the nutritional optimization, the preoperative fasting, and the bowel preparation.

6.3 Preoperative Consultation/Counseling

There are no studies that evaluate the therapeutic effect of consultation/counseling and of education/information of the patient regarding the elements of perioperative process in liver surgery.

On the contrary, in major abdominal surgery, it is evident that patient involvement in the care process and the adoption of informative explicative materials at the time of pre-hospitalization improve the adherence to nutritional programs, mobilization, and respiratory physiotherapy with consequent reduction of complications [2, 16].

Thus it is strongly recommended to routinely envisage these strategies even in patients undergoing liver surgery.

6.4 Perioperative Nutrition

Malnutrition is an important and modifiable risk factor for the development of complications in the field of abdominal surgery, and the nutrition evaluation should be mandatory for all patients undergoing major surgery.

Different screening scores can be used, whose validity has been fully demonstrated: among the most used, the Nutritional Risk Score (NRS), the Malnutrition Universal Screening Tool (MUST), and the Subjective Global Assessment (SGA) [17–20].

Patients at risk (loss of weight > 10–15% in 6 months, BMI < 18.5 kg/m^2, albuminemia <3 g/dL without hepatic and renal disease) should receive a nutritional enteral supplement for a week before surgery.

6.5 Preoperative Fasting and Carbohydrates Load

Preoperative fasting should not exceed 6 h for solids and 2 h for clear liquids, and there is a strong recommendation in adopting this management.

A recent review has demonstrated how the preoperative assumption of carbohydrates, an element regularly listed in colorectal ERAS, reduce the perioperative insulin resistance and the occurrence of sickness, hunger, thirst, nausea, and anxiety [21].

Maltodextrin load, thus, is advisable the evening before surgery procedure and even up to 2 h before the induction.

6.6 Bowel Preparation

Despite the absence of specific studies in liver surgery, bowel preparation by mouth, which can alter fluid and electrolyte balance, is not indicated.

6.7 Surgery

One of the cornerstone of the ERAS approach is the reduction of invasiveness of surgical procedure. Thus, even in liver surgery, the development of laparoscopic techniques is more and more important, not only for minor resections of anterior segments, but also for major resections or posterolateral segments where there is evidence of an improvement in patient outcome [22–24].

The advantages related to a laparoscopic approach in this surgery are well-known and have been pointed out in the occasion of the Southampton Consensus Conference in 2017 [25], verifying a reduction in intraoperative blood loss, length-of-stay, and complications.

Moreover, already in 2014 the second International Consensus Conference on laparoscopic liver surgery had assessed that the mini-invasive technique was to consider as the gold standard for minor resections [26].

Even if the advantages are not questionable, we have to remember that, especially for major resections and posterolateral segment resections, this is a surgery that has to be performed by skilled surgeons with a significant learning curve.

Thus, the indications of ERAS society underline, as a strong recommendation, that the laparoscopic liver surgery is performed by hepatobiliary surgeons, experienced in this technique, with special regard to lateral left segment resections and isolated lesions of anterior segments resections [8].

In case of open surgery, the choice of incision is left to the surgeon and it depends on the anatomic abdominal characteristics of each patient and on the lesion localization; however, it is strongly advised against the Mercedes incision because of the risk of incisional hernia related to this approach [27, 28].

6.8 Nasogastric Tube

Two recent Cochrane reviews have shown that the prophylactic use of nasogastric tube in abdominal surgery must be abandoned and reserved to particular situations only. Its routine positioning, in fact, increases postoperative respiratory complications and time needed to return to a normal bowel function [29].

A RCT has confirmed these results in patients undergoing hepatectomy [30], and, therefore, the ERAS society strongly recommends not to use the prophylactic nasogastric tube in this surgery field.

6.9 Prophylactic Abdominal Drainage

As far as the item, the major evidence about the non-use of abdominal drainage after major abdominal surgery comes from a meta-analysis of 2004 where liver resection is taken into account only marginally.

Therefore, at the moment, there are not recommendations about the use or not of the post-hepatectomy abdominal drainage.

6.10 Anesthesia

Liver resection is considered a major surgery procedure, independently from the quantity of removed parenchyma; the principal indications to the procedure are hepatocellular carcinoma and metastasis from colorectal carcinoma, especially in Western countries.

Anatomically, liver is divided into eight functional segments which can be partially or totally removed according to disease extension; more precisely, when three or more segments are removed, we are talking about major liver resection.

The intrinsic liver characteristics and its complex vascularization make hemorrhage in resection surgery a very common event, nearly unavoidable; the control of such phenomenon significantly reduces postoperative complications and patients mortality, minimizing blood components transfusion needs and related risks too.

Fundamental in this sense, besides specific techniques implemented by the surgeon (such as Pringle and ultrasonic knife), is the intraoperative anesthesia management, with particular attention to hemodynamics management and that is going to be specifically examined later.

Liver resection procedures are conducted in general anesthesia, combining a locoregional technique to guarantee an adequate postoperative analgesia.

6.11 Premedication

A recent Cochrane review [31] and the ERAS society [8] strongly recommend to avoid long half-life anxiolytic drugs as premedication for liver surgery.

Short half-life drugs can be used (such as midazolam), especially during the execution of anesthesia/loco-regional anesthesia procedures.

6.12 Antibiotics Prophylaxis and Steroids

Liver surgery is classified as clean-contaminated due to the transection of biliary ducts. Thus antibiotics prophylaxis is recommended and has to be administered within 1 h from the incision; a first-generation cephalosporin is usually used or, in case of allergy, clindamycin.

There is no evidence that supports the use of postoperative antibiotics; thus this practice is not recommended.

There is a modern evidence and a weak recommendation as far as preoperative administration of steroids; in some cases, methylprednisolone administered within 1 h from the incision at the dose of 500 mg has shown efficacy in the prevention of ischemia/reperfusion damage to the liver parenchyma [32].

In other studies, a reduction of bilirubin and IL-6 levels has been demonstrated in the first postoperative day and a reduction of postoperative complications [33, 34].

Because of the increased difficulty in glycemic control after liver surgery, steroids administration should be avoided in diabetic patients.

6.13 Monitoring and Maintenance of Anesthesia

The monitoring for a patient proposed to liver resection in the context of the ERAS protocol should include:

- ECG, SpO_2
- Invasive BP
- Internal temperature (esophageal or bladder)
- Hour diuresis
- TOF and PTC

The arterial catheter allows the punctual evaluation of hemodynamics conditions, the monitoring of dynamic indexes of fluid responsiveness, of cardiac output through the use of dedicated systems and of derived indexes.

In case of severe cardio(myo)pathy or in the presence of difficult venous accesses (such as obesity, venous frailty due to chemotherapy), the positioning of CVC is indicated; the latter is discussed with the surgeon even in the case of minor resection in order to use it in the surgical ward for the evaluation of volume state.

At the moment, there is no evidence that the use of CVC interferes with the ERAS protocol of a patient undergoing liver surgery.

Therefore, $ScvO_2$ measure and the possible derivation of DO_2 and VO_2 allow an accurate and deep monitoring of organ perfusion which remains the main objective in the hemodynamic management of a patient proposed to this surgery.

Equally important is the maintenance of body temperature at normal levels to preserve acid-base equilibrium and hemostatic-coagulative process at the optimal state.

Warming systems are thus indicated, such as hot fluids and thermic blankets.

The maintenance of general anesthesia usually happens through the delivery of halogenated gases (desflurane or sevoflurane) keeping MAC 0.6–1 and/or BIS 40–60.

The intraoperative analgesia is guaranteed by short half-life and independent from organ function opioids, such as remifentanil, whose dosage is adjusted to the hemodynamic response and the progressive opioid-sparing effect of intrathecal morphine, if it has been administered as a part of the multimodal analgesic strategy.

In laparoscopic resections, during all the hepatic transection, and especially during the phase of dissection in the retro-hepatic region, on the caval plan and in the preparation of suprahepatic axis, it is important to maintain a deep neuromuscular block with the use of TOF/PTC monitoring (TOF 0 and PTC <2). This allows not only a reduction of insufflation pressures of pneumoperitoneum, but also a reduction in pulmonary transmural pressures that could be responsible for a reduction in venous return and in blood reflux of suprahepatic veins, with their congestion.

At the end of the procedure, we proceed to the reversal of titrated neuromuscular blockade with TOFr, leading to the patient extubation for values >0.9.

The most indicated drug is sugammadex, direct antagonist of aminosteroid neuromuscular blockades, rocuronio and vecuronio; in fact in liver surgery, residual liver function treated with portal clamps is not predictable with a possible redistribution of neuromuscular agent and risk of postoperative residual curarization (PORC).

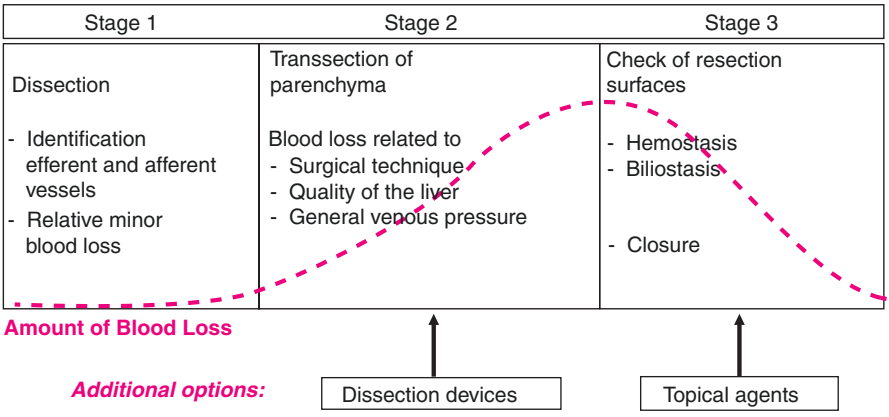
6.14 Hemodynamic Management

As already said, hemorrhage in liver resection surgery is a very common event and nearly unavoidable given the complex vascular liver anatomy.

Hepatectomy includes three surgical phases: dissection, parenchyma transection, and hemostasis/cholestasis.

During transection, especially in its second part, the major blood losses occur; hemorrhage and blood transfusions are associated to increased perioperative morbidity and mortality [35, 36].

We have also to remember and highlight that patients with abdominal adherences and/or significant portal hypertension have a general increased bias to hemorrhage.



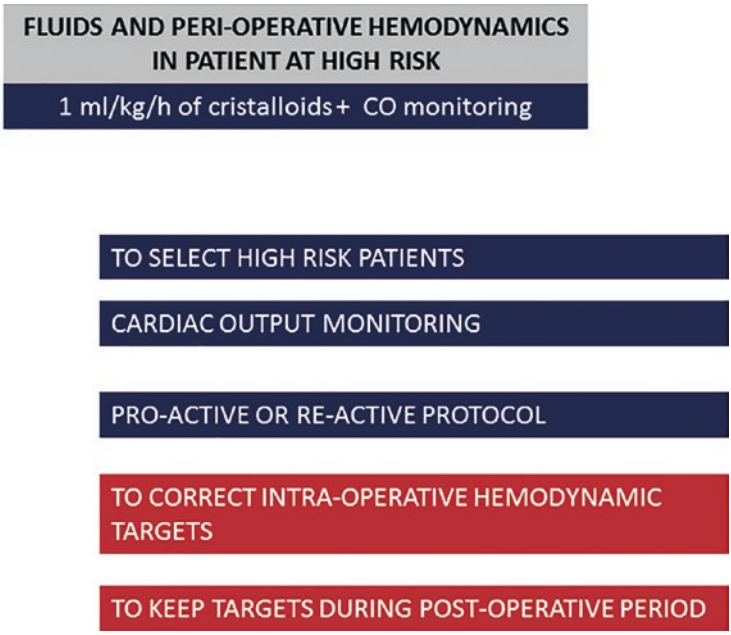
Therefore it is crucial to limit hemorrhage as much as possible, reducing hepatic vein congestion; preload reduction (usually identified in literature as PVC < 5 mmHg) and maintenance of controlled hypovolemic state are necessary during parenchymal resection.

A Cochrane review of 2009 and a meta-analysis of 2015 have shown that the maintenance of a low central venous pressure is associated with less intraoperative blood loss and less need in blood transfusion [37, 38].

The optimization of tissue perfusion and oxygen delivery (DO_2) to residual liver and other organs, avoiding fluid overload and excessive hypovolemia, represents the fundamental part of a right hemodynamic management in liver surgery, especially in major resections.

The guidelines of European Society of Anesthesiology and SIAARTI recommendations suggest to follow the principles of goal-directed therapy as intraoperative infusion strategy [39].

A recent study has therefore shown as the application of goal-directed therapy at the end of hepatic transection and in the first 6 postoperative hours allows a faster recovery of circulating volume with a reduction of complications [40].



The actual indications of ERAS society for liver surgery do not clearly point out it but the use of monitoring systems for cardiac output and DO_2 as goals directing fluid therapy is highly advisable.

Some recent studies [36, 41] show as the dynamic indexes such as pulse pressure variation (PPV) or stroke volume variation (SVV), available through calibrated or non-calibrated systems, can be an alternative to PVC.

Probably, especially in major resections, standard hemodynamic monitoring should include continuous monitoring of PVC as well as of dynamic indexes.

In fact, even if PVC does not seem to have predictive value in response to fluid challenge, there is evidence that its value could contribute to the evaluation of organ

perfusion pressure, among whose determinants there is the difference between mean arterial pressure (PAM) and PVC.

PPV and SVV, which measure the respiratory variation of pulse pressure and of cardiac output in mechanical ventilation, are already considered extremely reliable indexes of fluid responsiveness.

Schematically, therefore, taking into account the comments about the need of relative hypovolemia, hemodynamic management can be summarized as follows:

Dissection
- Normotension
- Infusion 2–4 ml/kg/h of warm fluid, administering balanced crystalloids solutions and avoiding salt solution or colloids
- Maintaining a normovolemic or slightly hypovolemic patient
- CI > 2.2 L/min/m^2
- SVRI in range

Transection
- To tolerate slight hypotension, maintaining however PAM 60–65 mmHg and PAS > 90 mmHg eventually with vasoactive drugs or fluid challenge
- Target PPV/SVV > 15% (however <20%) and PVC < 5 cmH_2O
- CI > 2.2 L/min/m^2
- SVRI in range
- Maintaining diuresis 0.5 ml/kg/h
- Slight Trendelenburg (about 10°) to promote the discharge of suprahepatic veins
- To consider with attention furosemide 10 mg

Hemostasis/Cholestasis
- Fluid optimization according to PPV/SVV with target <12%
- MAP recovery at basal levels
- Diuresis recovery

In case of excessive hypovolemia with PPV and/or SVV > 20% and MAP <60 mmHg during the phase of transection, a bolus of 250 ml of crystalloids is administered in 5–10 min, repeatable, in order to optimize hemodynamic targets.

The use of an inotrope or an inodilator can be required for CI values less than predicted targets.

In cirrhotic patients, with a hyper-dynamic state characterized by a stronger peripheral vasodilation, the more advanced the disease, the myocardial-depressive and vasodilating effect of general anesthetics are such as to nearly always bring to the use of vasopressors to maintain adequate peripheral perfusion and oxygen delivery.

In all patients and in all procedure phases, DO_2 indexed should be kept at optimal levels, considering a value of 600 ml O_2/min/m^2 as reference target [42].

The adequacy of peripheral perfusion has to be monitored also following lactate curve during the different procedure phases, considering that its serum concentration increases proportionally to the procedure duration, the cumulative time of Pringle maneuver, and blood loss [43].

Moreover, the non-cirrhotic patient is the most exposed to the risk of intraoperative hyperlactacidemia.

6.15 Intraoperative Ventilation

The ventilatory strategy does not differ from the standard management carried out during laparotomic or laparoscopic abdominal surgery.

During the transection phase, it is indicated to maintain low intrathoracic pressure with a tidal volume 6–8 ml/kg and a low or null PEEP (between 5 cmH_2O and ZEEP).

This reduces trans-mural pressure and lead to less suprahepatic vein congestion improving surgical field and reducing hemorrhage.

There are not specific indications about respiratory rate that has to be regulated according to $EtCO_2$.

6.16 Analgesia

American Pain Society guidelines of 2016 recommend multimodal analgesia for the treatment of postoperative pain, administering different drugs acting at various levels of the transmission of pain signaling and combining multiple analgesic techniques [44].

Procedures of liver resection are performed in general anesthesia, combining where possible a loco-regional technique.

In consideration of the potential postoperative alteration of coagulation parameters that, especially in major resection, can persist for the first 72–96 h, the positioning of epidural catheter is to carefully evaluate and to consider case to case [8].

A recent randomized study has demonstrated that epidural analgesics in laparotomic liver surgery can be a risk factor for the development of renal insufficiency because of the hypotensive effect secondary to this technique [45].

Thus, the ERAS society does not recommend the routine use of this item in open resection in liver surgery.

The administration of intrathecal opioids, associated with a multimodal analgesia, represents a good alternative.

Different studies and recommendations [46, 47] suggest to administer 150–200 mcg of morphine at lumbar level (L2–L3 or L3–L4) before the induction of general anesthesia; these doses are reduced to less than 150 mcg in case of a patient >75 years old, cognitive/motor decline, or moderate/severe cirrhosis.

The use of adjuvants has to be considered. The intraoperative ketamine is administered with a bolus of 0.15–0.5 mg/kg followed by an infusion of 4–5 mcg/kg/min

up to 30–45 min before the end of the procedure; its use can be particularly indicated in major surgery and in "addicted" patients that is with great tolerance to opioids.

Lidocaine continuous infusion at 100 mg/h (1.5 mg/kg/h) in abdominal laparoscopic surgery is associated to a reduction in postoperative pain, especially in the immediate period, to a more precocious gastrointestinal recovery, to a reduction in PONV, and to a reduction in opioids need and so it is also to consider into the multimodal analgesic strategy [48].

In all kind of resections (major open, minor open, LPS) about 30–40 min before the awakening, we have to administer a bolus of paracetamol 1 g and, if no contraindications, of ketorolac 30 mg.

Paracetamol will be then continued in postoperative time at the dose of 1 g × 3, associated to ketorolac 30 mg as rescue, at most three times per day carefully monitoring renal function and hemostasis.

Another option studied in the field of multimodal analgesia is the continuous postoperative infusion of local anesthetics at the level of laparotomic wound (if this kind of surgical approach is needed).

A meta-analysis of four studies has shown a reduction in length-of-stay, a reduction in postoperative complications, and a satisfying pain control in patients treated with infusional catheter [49].

In alternative, we ask the surgeon to infiltrate the laparotomic wound with ropivacaine 0.5%, up to 30 ml in major wounds.

If it is not possible to perform the central block, TAP block with ropivacaine 0.375% has to be considered, using the standard lateral technique (20–25 ml per side) or the technique of four points (subcostal + lateral) injecting 15 ml of anesthetics per site.

If VNR is still >4, we combine morphine iv in continuous infusion or in PCA strategy if available, at a dose between 10 and 20 mg/die.

A possible solution is scheduled below:

Minor LPT	Minor LPT	Laparoscopy	Laparoscopy
Intra-operative analgesia	1) Spinal analgesia 2) Adjuvant 3) Paracetamol 1 gr 4) Ketorolac 30 mg 5) Wound infiltration	1) Spinal analgesia 2) Adjuvant 3) Paracetamol 1 gr 4) Ketorolac 30 mg 5) Wound infiltration	1) Spinal analgesia +/- TAP block 2) Paracetamol 1 gr
Post-operative analgesia (Up to POD 1)	Paracetamol 1 gr x 3	Paracetamol 1 gr x 3	Paracetamol 1 gr x 3
Rescue (Up to POD 1)	Ketorolac 30 mg (max 90 mg/die) Morphine (10-20 mg/die)	Ketorolac 30 mg (max 90 mg/die) Morphine (10-20 mg/die)	Ketorolac 30 mg (max 90 mg/die) Tramadol 100 mg (max 300 mg/die)

6.17 Postoperative Period

Among elements of ERAS protocol related to postoperative period, actual evidences particularly recommend adherence to the re-introduction of feeding from the first postoperative day and to the prevention of nausea and vomiting (PONV).

Some essential items for colorectal surgery, among which early removal of vesical catheter and the already mentioned positioning of surgical drainage, are not actually to recommend at the moment since there is no real confidence about their efficacy in patients undergoing liver surgery [50].

6.18 Postoperative Feeding and Early Nutrition

Hendry et al. [51] have shown the benefit of early nutrition combined with oral assumption of laxatives in patients undergone hepatectomy and treated according to ERAS protocol.

Moreover, postoperative feeding improves the immune system function and reduce the rate of infectious complications [52].

Postoperative enteral or parenteral feeding is to reserve to malnourished patients only or in case of complicated postoperative progress (ileus, gastro-paresis) such as to prelude early refeeding.

ERAS society strongly advices against postoperative routine artificial nutrition.

6.19 Postoperative Nausea and Vomiting (PONV)

Postoperative nausea and vomiting are common after major surgery, but the application of a multimodal strategy to control and reduce this phenomenon—together with other interventions of ERAS protocol—allows patients to start eating during the first postoperative day [40].

Risk factors to develop PONV are previous development thereof, female gender, high-dose opioids, young age, no smoking, and exposure to anesthetic gases (Apfel score) [53]. The international consensus about PONV [54] as well as ERAS society [22] recommend preventive administration of two antiemetic drugs.

The serotoninergic 5HT3 receptor antagonist (ondansetron 4–8 mg 40 min before procedure end) usually represent first-line treatment, typically associated with low-dose dexamethasone (0.15 mg/kg), administered soon after preoperative period.

Anti-histamines, phenothiazines, and butyrophenones represent second-line treatment for PONV prevention.

Lastly, early mobilization after hepatectomy should be encouraged from the morning after surgical procedure to the moment of hospital discharge.

6.20 Conclusions

ERAS protocol—applied to liver resection surgery—is feasible and safe and leads to a reduction of length-of-stay and of postoperative complications with a subsequent cost-cutting [55].

Combination of mini-invasive approach, if possible, and implementation of protocols aimed at fast patient recovery can improve outcome even in case of technically complex procedures; the advantage of adhering to fast-track program is evident even in open resections [22].

However evidence levels are not high for all items traditionally used; ERAS society for liver surgery recommends them only for some patients.

Some of the studies taken into consideration in different reviews and meta-analysis are in fact of mean-low quality, with non-sufficiently wide and inhomogeneous samples.

Recommendation grade is nonetheless strong for the majority of them since it is therefore evident and considerable the clinical advantage subsequent to their use.

The actual reasonable advantage, that different ERAS clinical measures result in, still has to be confirmed by future studies of quality, in order to get a greater procedure standardization as well as it is now consolidated in colorectal surgery.

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Part II

Critical Care Medicine

The Microbiome in Critically Ill Patients

7

Giorgio Tulli and Zuanetti Gabriele Maria

7.1 The Forgotten Organ and the Critical Care Medicine

Common conditions of critical illness, including sepsis and septic shock, acute respiratory distress syndrome (ARDS), and multi-organ dysfunction/failure, cause high global mortality and a vast and ever-increasing economic burden [1]. Although some specialties such as oncology and rheumatology have been revolutionized by the discoveries of molecular medicine, decades of research on diseases that cause critical pathological situations have unfortunately not produced targeted therapies.

Intensive care remains synonymous with supportive therapy for organs and their metabolisms.

There are several possible reasons why molecular therapies have not been developed for these common and fatal diseases. A credible explanation is that the main focus of the studies, host inflammation and cell damage in the host's organs, are the downstream consequences of a neglected upstream source: the diverse ecosystems of microbes on the human body and in the human body.

The interest in the microbiota/microbiome has exploded only in the last decade thanks to the discovery of culture-independent methods for identifying microbes [2, 3]. Although a wide range of clinical and experimental evidence now suggests that the microbiome is central to the pathogenesis of critical pathological situations, the common diseases that eventually lead to critical pathological situations have been included in very few microbiome studies. In turn, the review articles and clinical guidelines on critical pathological conditions largely ignore the microbiome, neglecting what is, in effect, a 1 kg organ containing more DNA than all the host's

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organs: the forgotten organ. We now know that critical illnesses and intensive care interventions substantially alter the microbiome. In turn, the microbiome predicts patients' susceptibility to disease, and manipulation of the microbiome can prevent or modulate critical disease in both animal models and clinical trials. A description of the altered ecosystem of the microbiome in critically ill patients should focus primarily on the gut and lungs and should describe the role of the microbiome in sepsis, ARDS, pneumonia, and exacerbations of chronic lung disease, placing important questions, still unanswered to date, which from today can perhaps be resolved with the techniques of modern clinical microbiology.

7.2 Critical Disease and the Ecosystem of the Human Microbiota

The observation that critical illness alters the body's microbiota ecosystem was first made in a landmark study by Johanson and colleagues [4]. In 1969, decades before the dawn of high-throughput sequencing. Host exposure to a hospital setting has minimal effect on upper respiratory tract bacterial communities: the oropharynx of healthy hospital workers and only mildly ill patients staying in the hospital is no more frequently colonized by Gram-negative bacteria than to those in people without hospital exposure. However, in patients who remain in hospital, the change in the microbiota depends on the severity of their disease rather than in which hospital setting they are admitted.

Critical illness substantially alters the physiology of the host, which in turn alters the environmental conditions and community structures of the resident microbes. This clinical observation illustrates an often quoted principle in microbial ecology, "Everything is everywhere, but the environment selects" [5].

Decades after this first observation, we have a still incomplete but, indeed, growing understanding of how the internal environment of critically ill patients creates selective pressure on the relative growth of its microbiota. The composition of each microbial community is determined by the balance of three ecological factors: immigration into the community, elimination of members from the community, and relative reproduction rates of community members. Any change in the microbiome, whether acute or chronic, must be attributable to a combination of these three forces. These three factors are significantly altered in the intestinal and pulmonary ecosystems of critically ill patients due to the pathophysiological effects of the critical illness itself and the therapeutic and supportive interventions of intensive care (Tables 7.1, 7.2, 7.3, and 7.4).

Table 7.1 Ecological effects of critical illness on the gastrointestinal microbiome pathophysiological processes

ECOLOGICAL EFFECTS OF CRITICAL ILLNESS ON THE GASTROINTESTINAL MICROBIOME

PATHOPHYSIOLOGICAL PROCESSES	Microbial immigration	Microbial elimination	Environmental growth conditions
Decreased oral intake	Decreased immigration of food associated microbiota	No direct effect	Shift to stress conditions of nutrient scarcity and altered nutritional substrate
Altered oropharyngeal microbiota	Increased immigration of Proteobacteria and potential pathogens	No direct effect	No direct effect
Intestinal dysmobility	No direct effect	Decreased elimination, increased upper-gastrointestinal community burden	No direct effect
Systemic hyperglycaemia and electrolyte disturbances	No direct effect	Decreased elimination (intestinal dysmobility	No direct effect
Gut hypoperfusion, reperfusion injury, impaired mucosal integrity	No direct effect	Increased elimination via translocation to mesenteric lymphatics	Increased mucosal inflammation, increased free radical concentrations and nitrate availability, shift from commensal anaerobes to Proteobacteria and select Firmicutes
Decreased bile salt production	No direct effect	Decreased elimination of bile sensitive species (eg. *Enterococcus* spp)	Selective overgrowth of bile sensitive species (eg *Enterococcus* spp)
Endogenous opioid production	No direct effect	Decreased elimination (intestinal dysmobility)	Selective increase in virulence of opioid-responsive species (eg. *Pseudomonas aeruginosa*) disruption of stabilising commensal relationships
Endogenous cathecolamine and inflammatory cytokine production	No direct effect	Decreased elimination (intestinal dysmobility)	Selective promotion of growth and virulence of potential pathogens (eg *Pseudomonas aeruginosa*) increased mucosal inflammation (via splanchnic hypoperfusion), decreased oxygen tension and pH
Disruption of intestinal mucus layer	No direct effect	Increased elimination via translocation to mesenteric lymphatics	Altered nutrient supply, altered oxygen gradients, loss of mucus reservoir of antibacterial peptides
Impaired mucosal immunity, decreased IgA and defensin production	No direct effect	Decreased elimination of potential pathogens. Increased elimination via translocation to mesenteric lymphatics	Loss of growth inhibition for potential pathogens, decreased abundance of commensal Bacteroidetes

Table 7.2 Ecological effects of critical illness on the gastrointestinal microbiome. Clinical interventions

Ecological effects of critical illness on the gastrointestinalmicrobiome

CLINICAL INTERVENTIONS	Microbial immigration	Microbial elimination	Environmental growth conditions
Supine positioning	No direct effect	Decreased elimination from upper gastrointestinal tract (intestinal dysmotility)	No direct effect
Gastric acid suppression	No direct effect	Decreased elimination from upper gastrontestinal tract (neutralised pH)	Selective growth promotion of acid-intolerant bacteria
Enteral feeding	No direct effect	Increased elimination due to antimicrobial actions of luminal bile salts. Decreased elimination via translocation to mesenteric lymphatics	Altered nutritional substrate. Shift away from stress conditions of nutrient scarcity
Parenteral feeding	No direct effect	Increased elimination vis translocation to mesenteric lymphatics	Loss of growth inhibition for potential pathogens via impaired mucosal immunity (eg. decreased IgA secretion)
Sedatives, opiates and neuromuscolar blockade	No direct effect	Decreased elimination (intestinal dysmotility)	Selective increase in virulence of opioid-responsive species (eg. Pseudomonas aeruginosa) disruption of stabilising commensal relationships
Systemic cathecholamines	No direct effect	Decreased elimination (intestinal dysmotility)	Selective promotion of growth and virulence of potential pathogens (eg. Pseudomonas aeruginosa) increased mucosal inflattion (via splanchnic hypoperfusion) decreased oxygen tension and pH
Oral decontamination	Diecreased immingration of oropharyngeal microbiota	No direct effect	No direct effect
Selective decontamination of the digestive tract	Decreased immingration of oropharyngeal microbiota	Increased elimination of select bacteria (eg Enterobacteriales spp)	Selective growth suppression of select bacteria (eg. Enterobacteriales spp)
Systemic antibiotics	No direct effect	Increased elimination of select bacteria (depending on antibiotic regimen)	Selective growth suppression of bacteria (depending on antibiotic regimen)

Table 7.3 Ecological effects of critical illness on the respiratory microbiome. Pathophysiological processes

Ecological effects of critical illness on the respiratory microbiome

PATHOPHYSIOLOGICAL PROCESSES	Microbial immigration	Microbial elimination	Environmental growth conditions
Altered oropharyngeal microbioma	Increased immigration of Proteobacteria and potential pathogens	No diret effect	No direct effect
Depressed level of cosciousness	Increased immigration via aspiration of oropharyngeal and gastric contents	Decreased elimination (impaired cough reflex)	No direct effect
Aspiration of gastric contents	Increased immigration of gastric microbiota	No direct effect	No direct effect
Impaired mucociliary clearance	No direct effect	Decreased elimination (impaired mucociliary escalator)	No direct effect
Increased bronchial mucus production	No direct effect	No direct effect	Increased nutrient substrate, altered gradients of oxygen and temperature
Endogenous cathecolamine and inflammatory cyto kine production	No direct effect	Increased elimination via innate and adaptive immune response	Selective promotion of growth and virulence of potential pathogens (eg. Pseudomonas aeruginosa)
Recruitment and activation of neutophils	No direct effect	Increased elimination of select community members	Selective suppression of bacterial growth , increased free radical concentrations and nitrate availability, altered temperature gradients
Alveolar oedema	No direct effect	No direct effect	Increased and altered nutrient substrate , altered oxygen gradient
Inactivation of alveolar surfactant	No direct effect	Decreased elimination of surfactant.sensitive bacteria	Loss of growth inhibition for selective potential pathogens

Table 7.4 Ecological effects of critical illness on the respiratory microbiome. Clinical interventions

Ecological effects of critical illness on the respiratory microbiome

CLINICAL INTERVENTIONS	Microbial immigration	Microbial elimination	Environmental growth conditions
Supine positioning	Increased immigration via aspirationof oropharyngeal and gastric microbiota	No direct effect	No direct effect
Head of bed raised	Decreased immigration via aspiration of oropharyngeal and gastric microbiota	Decreased elimination (gravitationally limited mucus clearance)	No direct effect
Endotracheal intubation	Increased immigration via aspiration of oropharlyngeal microbiota	Diecreased elimination (impaired cough and mucociliary escalator)	Altered airway temperature and humidity
Mechanical ventilation	No direct effect	No direct effect	Increased alveolar oedema , increased neutrophil, cytokine and catecholamine concentrations
Subglottic suctioning	Decreased immigration of oropharyngeal microbiota	No direct effect	No direct effect
Gastric-acid suppression	Increased immigration of gastric microbiota	No direct effect	No direct effect
Sedatives, opiates and neuromuscolar blockade	No direct effect	Decreased elimination via impaired cough reflex and mucociliary clearance	No direct effect
Systemic catecholamines	No direct effect	No direct effect	Selective promotion of growth and virulence of potential pathogens (eg. Pseudomonas aeruginosa)
Oral decontamination	Decreased immigration of oropharyngeal microbiota	No direct effect	No direct effect
Selective decontamination of digestive tract	Decreased immigration of oropharyngeal microbiota	Increased elimination of select bacteria (eg. Enterobacteriales spp)	No direct effect
Systemic antibiotics	No direct effect	Increased elimination of select bacteria (depending on antibiotic regimen)	Selective growth suppression of bacteria (depending on antibiotic regimen)

7.3 Microbiota and Microbiome

About 40 trillion microorganisms reside in the gut [6]. Under basal conditions, the microbiota is not simply an innocent bystander, living peacefully alongside its human host. Rather, commensal microbes promote health and play a number of different roles in maintaining human well-being. The human microbiota is the set of microorganisms that reside in our body.

The human microbiome has been defined as the collective genome of millions of bacteria, viruses, and fungi that exist on every human host. The microbiome plays an elegant mutualistic relationship with the human host from birth [7].

The human gastrointestinal tract contains, as mentioned, trillions of bacteria that make up a complex ecosystem known precisely as the intestinal microbiota which has significant implications for human health and diseases, especially when we are in the hospital [8]. The microbiota residing in the human body can compete with pathogens for space, metabolites, and nutrients and can inhibit pathogens by calibrating the host's immune response.

The microbiome is severely altered in multiple disease states by converting the health-inducing microbiome into a disease-promoting microbiome, also known as a pathobiome [9].

These perturbations are particularly pronounced in intensive care, where the gut has long been hypothesized to be the very "engine" of critical illness [10, 11]. The intestinal microbiota is made up of three life domains: bacteria, archaea, and eucaria.

The human gut microbiota has a great variety of bacterial species: about 200 dominant species and 1000 non-predominant species—and they vary from individual to individual. The diversity within an individual's microbiota is known as alpha diversity, while the different composition between individuals is called beta diversity. Four phyla represent the majority of the members of the microbiota: *Bacteroidetes*, *Firmicutes*, *Actinobacteria*, and *Proteobacteria*, the former and the latter representing more than 90% of the bacterial population of the colon. The *Bacteroidetes* phylum is composed of rod-shaped Gram-negative bacteria that digest complex polysaccharides with the release of volatile short-chain fatty acids (SCFA) that regulate cell growth of the intestinal epithelium and differentiation and stimulation of the immune system. The *Firmicutes* phylum is mainly composed of Gram-positive bacteria that can form endospores (Clostridia class). These bacteria release butyrate, promoting intestinal epithelial health and inducing colic regulatory T cells. However, these phyla also contain clinically relevant members such as *Bacteroides fragilis*, *Clostridium perfringens*, *Clostridium difficile*, *Enterococcus* spp., and *Streptococcus* spp. which can cause sepsis and fatal outcome during intestinal dysbiosis [8].

Since the composition of the gut microbiota is specific to each person, dysbiosis can be interpreted as a relative change in the composition of an individual's commensal microbiota relative to others in the community, which can be interpreted as a loss of beneficial microbiota, an increase in pathogenic microbiota, or a reduced microbiotic variety.

Disruption of these mechanisms is a common starting point for infection, with antibiotic therapy representing the most common cause of microbiome dysregulation [12]. The interaction between sepsis (understood according to the latest definition SEPSIS-3: a life-threatening organ failure caused by a dysregulated response of the host to an infection) and the microbiome has been defined as a "non-bi-directional relationship fully understood."

Some scientific evidence has been able to demonstrate that a varied and balanced intestinal microbiota is able to improve the host's immunity against both enteric and systemic pathogens and that disturbance of this balance can potentially lead to an increase in susceptibility to sepsis.

The largest microbiome study in critical illness to date compared stool samples from 115 adult ICU patients admitted to 4 health centers within 48 h of admission and at discharge or on the 10th day of ICU admission to 1242 healthy patients [13]. Critically ill patients experienced a rapid reduction in health-promoting bacteria and an overgrowth of known pathogens. In particular, when examining the taxonomy at the phylum level, the common Gram-positive *Firmicutes* and Gram-negative *Bacteroidetes* were both decreased, as was *Faecalibacterium*, an anti-inflammatory organism. Conversely, potential pathogens such as *Enterobacter* and *Staphylococcus* were increased and there was also a relative increase in *Proteobacteria*. Phylogenetic diversity was also significantly reduced at discharge compared to ICU entry. This study used 16S rRNA amplicon sequencing, which does not provide sufficient genomic resolution to identify bacterial species, but instead identifies genera. This notation is important because genera are unable to distinguish between pathogenic and non-pathogenic species (*Staphylococcus aureus* versus other non-pathogenic staphylococci, for example). On the other hand, other studies have shown that the composition of the gut microbiota is severely altered by sepsis and its treatments, but the clinical consequences of these disorders need to be further investigated. Similarly, a prospective observational study of 34 ICU patients (both septic and non-septic) and 15 healthy controls demonstrated a marked change in fecal bacterial composition in critically ill patients with disappearance of genera of bacteria with key functions in the metabolism of host [14]. In particular, extreme individual differences were noted in 13 critically ill patients with a single bacterial genus constituting over 50% of the gut microbiota. However, no association was identified between microbial diversity, *Firmicutes*/*Bacteroidetes* ratio or Gram-positive/Gram-negative ratio, and survival or complications.

This notable loss of diversity is similar to that of a study of 14 ICU patients who reported the emergence of communities of very low diversity in 35% of patients, communities containing only one to four bacterial *taxa* [15]. At the phylum level, communities commonly contained *Enterococcus*, *Staphylococcus*, and *Enterobacter*. In particular, the cultured stool samples correlated with the analysis of 16S rRNA but revealed the appearance of *Candida albicans* and *Candida glabrata* in 75% of patients.

To better understand the mechanisms of dysbiosis, it is necessary to return to the ecological effects of critical illness: immigration, elimination, and reproduction.

The main route *of immigration of microbes into the gut microbiome is through the oropharynx*, which in turn changes surprisingly in critical diseases. In some *studies* [4, 16], it was noted that, in critically ill patients, the healthy oral microbiota is displaced by Gram-negative aerobes, including the most important members of the *Proteobacteria* phylum. The catabolic state caused by fasting in critical illness causes a decrease in the immigration of food-associated bacteria and a reduction in the nutritional intake for commensal *microbes* [17]. Well-researched preventive interventions, such as topical oral decontamination, reduce the bacterial load of the oropharynx and decrease immigration from the community of origin [18]. In healthy subjects, the primary means of microbial elimination from the gut microbiome is transit through and from the gastrointestinal tract, which is normally rapid. Through defecation, a healthy adult excretes approximately 1014 bacterial cells per day [19]. In critically ill patients, transit time is substantially slowed by various pathophysiological factors (glucose and electrolyte disturbances [20] and endogenous opioid production) and therapeutics (sedatives, opiates, and systemic catecholamines [21]). In the stomach, which is normally fast in emptying and extremely acidic, transit time slows [22] and the pH is neutralized by the use of agents to suppress gastric acid *production* [23]. Other mechanisms of microbial elimination are compromised in critical illnesses: bile salt production decreases [24], IgA production is impaired [25], and the dense mucous barrier of secreted antimicrobial peptides is lost [26–28]. The net effect is a reduction in the elimination of bacteria, especially in the upper gastrointestinal tract, which transforms into a pH-neutral reservoir that is rapidly invaded by Gram-negative bacteria [29]. The environmental growth conditions of the gut turn into critical diseases and affect the relative reproduction *rates of community* members. Hypoperfusion and reperfusion of the intestinal wall cause intense inflammation of the mucosa, which leads to a cascade of environmental changes. Increased nitrate concentrations [30] *and an oxygen gradient altered mucosal* [31] favor the growth of microbes in the *Proteobacteria* phylum, which contains many clinically familiar Gram-negative bacteria, such as *Pseudomonas aeruginosa* and *Escherichia coli*, and some members of the phylum *Firmicutes*, such as *Staphylococcus aureus* and *Enterococcus* spp. [32–34]. Importantly, in many critically ill patients, the thick layer of intestinal mucus is thinned, interrupted, or absent [26, 27]. This crucial anatomical component of gut anatomy houses its own protective microbiota and provides a physical barrier between the gut ecosystem and the host.

Almost every clinical intervention commonly used in ICU (e.g., enteral feeding [35] *proton pump inhibitors* [36, 37], *systemic catecholamines* [36, 37], and *systemic antibiotics* [38, 39]) changes the environmental growth conditions of bacteria intestinal (Fig. 7.1).

The net effect of these alterations in ecology is an unstable and often collapsed community with catastrophically low diversity.

The stomach and proximal small intestine, which are usually sparsely populated, become invaded by a small number of species, such as *E. coli*, *P. aeruginosa*, and *Enterococcus* spp. [40, 41].

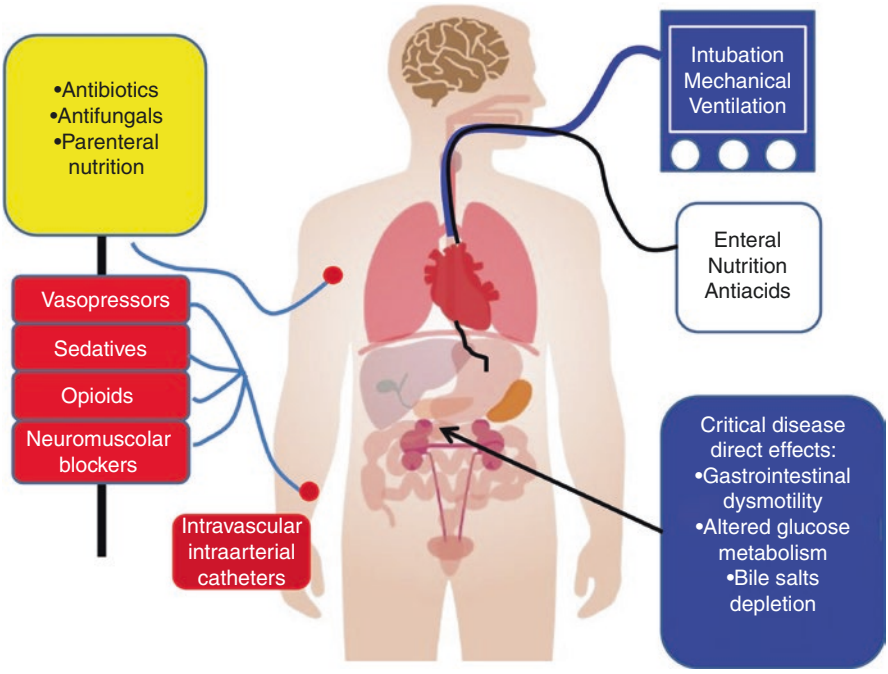

Fig. 7.1 Potential alterations of the microbiota in the critically ill patient. Schematic vision of factors leading to a dysbiosis in the critically ill patient

The upper gastrointestinal tract becomes a stagnant reservoir of potential pathogens, the presence of which is predictive of extra-abdominal infections and multiorgan failure [29, 40]. The lower gastrointestinal tract, which in healthy people contains hundreds of distinct bacterial species, loses diversity, and the community is invaded by some (in some cases only one) bacterial species [15, 42, 43].

Dominant species include *S. aureus*, *Enterococcus* spp., and members of the Enterobacteriaceae family (including *E. coli* and *Klebsiella* spp.). *P. aeruginosa*, which is normally low in terms of abundance, instead grows in evidence [15, 42]. Furthermore, normally rare fungi, such as *Candida* spp., flourish and thrive [15]; culture-based detection of candidemia is an indicator of disease severity and predictive of an unfavorable outcome [44].

Viruses, archaea, and eukaryotes represent less than 10% of the gut community in healthy subjects [45] and the effects of critical diseases on the abundance and behavior of these organisms are unknown. This catastrophic decline in bacterial diversity, compared to the relatively subtle differences observed in chronic disease states, is striking.

In critical diseases, the gut microbiome resembles an infection rather than a bacterial community.

The absence of specific bacteria in the gut is just as important as the presence of other bacteria. Resident microbes of the lower gastrointestinal tract normally

perform essential metabolic and immunomodulatory functions. Even slight differences in the abundance of healthy gut bacteria have been implicated in several systemic diseases [46]. The lower gastrointestinal tract in critically ill patients becomes an inhospitable wasteland for these resident stabilizing microbes. For example, *butyrate* is the primary energy source for the epithelial cells that line the colon. Without butyrate, these cells are starved, wilt, and degrade [47]. Butyrate also dampens the intestinal and systemic immune response by stimulating the development of regulatory T cells [48].

In gut microbiome studies in critically ill patients, butyrate-producing bacteria are rare or absent [15, 42, 43], butyrate production is at a minimum [45], and the effects of critical diseases on the abundance and behavior of these organisms are unknown. This catastrophic decline in bacterial diversity, compared to the relatively subtle differences observed in chronic disease states, is striking [42].

The pathophysiological consequences of this condition are predictable (epithelial cell death and dysregulated inflammation), but the clinical consequences are unfortunately unknown.

The ecological effects of critical illness are also extreme in the respiratory tract.

Although even healthy lungs are subject to constant immigration from oropharyngeal microbes through microaspiration [49–51], this immigration is accelerated due to depressed consciousness from *hypnotics and/or sedatives and endotracheal intubation*.

The dynamics of the aerodigestive tract are reversed during critical illness: while in health the oropharynx is the main source of origin for the lungs and stomach [52], the microbial reservoir of the overgrown stomach and small intestine becomes the main community of origin for the mouth and lungs [29, 40]. The oropharynx is usually populated by benign *Prevotella* spp. and *Veillonella* spp. [2, 49, 50] but is invaded by potentially pathogenic bacteria, including prominent *Proteobacteria*, such as *P. aeruginosa* and *K. pneumoniae* [4, 16, 53].

Although the elimination of microbes from the respiratory tract is accelerated in critical diseases in part by the activation of the immune defenses, most pathophysiological and clinical factors reduce the rate of microbial elimination. *Depressed consciousness and sedation attenuate the cough reflex* [54], and intubation endotracheal and acute diseases impair the ciliary mucus sliding scale [55]. *Elevating the head of the bed reduces the immigration rate of the gastric microbiota* [56] but also prevents microbial elimination, which is predominantly gravity-dependent when cough and mucociliary clearance are impaired [57]. *Inactivation of the alveolar surfactant decreases the elimination of bacteria sensitive to the surfactant* [58, 59].

Acute critical illness therefore substantially modifies the environmental growth conditions of the lungs. The normally nutrient-poor environment of the alveolus is flooded with nutrient-rich edema, which creates oxygen pockets and heterogeneous temperature *gradients* [60, 61] and host stress response signaling molecules selectively promote the growth of potential pathogens [37, 62, 63].

The ubiquitous use of systemic antibiotics further alters the relative reproduction rates of community members. The expected effect of these ecological forces in the

lungs, therefore, is a state of increased immigration, reduced elimination, and favorable growth conditions for potential pathogens [64–67].

Understanding of these ecological forces will be best obtained from longitudinal, culture-independent investigations of microbial communities in the upper and lower respiratory tract in critically ill patients.

7.4 Mechanisms of Dysbiosis in Sepsis

As noted above, in recent years, the resident gut microbial flora has been better identified as a key factor in a wide range of functions, such as *food digestion*, *hormone production*, and *immune system development*. Furthermore, it has been shown that a disturbed condition of the gut microbiota, also called "dysbiosis," can certainly influence the susceptibility of the host to infections.

Several mechanisms, which arise during intestinal barrier dysfunction, can be considered both a result and a cause of development of sepsis: *increased permeability of the intestinal mucosa, tissue edema, reduced perfusion, dysregulation of coagulation in the tissues, displacement in the intestinal microbiome, apoptotic damage* to the mucosal epithelium, and *bacterial translocation*. Intestinal mucosal perfusion is reduced during sepsis, causing destruction of the barrier mucosa and increased permeability [68].

The transmigration of bacteria and endotoxin can induce relevant systemic effects, generating in turn an immune response in the gut-associated lymphoid tissue (GALT-gut-associated lymphoid tissue), which in turn activates the toll-like receptor (TLR) 4 and priming of neutrophils, causing remote lung lesions, thus explaining the appearance of acute respiratory distress syndrome (ARDS) during sepsis [69].

Dysregulation between different bacterial populations residing in the gut can lead to a "pathobiome" that ultimately disrupts the entire immune system [42]. In critically ill patients, hypoxic lesion, impaired epithelial permeability, impaired intestinal motility, and treatment with vasopressors, parenteral nutrition, and opioids facilitate the expansion of pathobionts, including multiple antibiotic resistance (MDR) bacteria [70].

It is very important to note that the composition of the microbiome is not static but evolves rapidly over time during ICU admission and with the severity of the disease. As mentioned, it was reported nearly 50 years ago that the prevalence of Gram-negative oropharyngeal bacteria is low in physiologically normal subjects despite hospital exposure but increases significantly in sick patients, and this higher prevalence is closely related to disease severity [4].

More recently, a pilot study of 12 adult ICU patients examined stool samples from mechanically ventilated patients on days 1–2, 2–4, 5–8, and 7–10 [71].

Bacteria belonging to the phyla *Firmicutes* and *Bacteroidetes* were predominant in all the samples, but the percentages then changed markedly over time. In particular, a *Bacteroidetes/Firmicutes* ratio > 10 was observed in four of the six non-survivors, while a ratio <0.1 was observed in one non-survivor. No survivors had a

ratio > 10 or <0.1. Unfortunately, this small study is not yet able to draw conclusions regarding the relationship between this relationship and mortality.

The gut microbiome of septic ICU patients demonstrates a loss of microbial richness and diversity, single taxon dominance (often a potential pathogen), and loss of site specificity with isolation of the same organism at multiple sites [71].

The duration of dysbiosis in intensive care, the clinical impact of dysbiosis, and phenotypes of critically ill patients more prone to developing it are all aspects that still need to be fully clarified.

The microbiome is also altered in critically ill children.

A comparison of 37 pediatric ICU patients with a mean age of approximately 3 years versus both pediatric and adult reference datasets demonstrated that pediatric ICU patients had reduced gender-enriched diversity of *Enterococcus* and *Staphylococcus* in multiple body sites with depletion of commensals such as *Faecalibacterium* and *Ruminococcus* from the intestine [72].

In particular, both alpha and beta diversity were unstable over time in patients followed longitudinally.

The microbiome is not limited to the gut, and multiple sites in the body contain microbes that have been implicated in critical diseases. For example, a study comparing 15 patients requiring mechanical ventilation on healthy subjects with lower respiratory tract sampling by bronchoscopy showed that upper and lower respiratory tract microbiota diversity decreased within 24 h of intubation and further decreased over time [73].

In a study of patients admitted to the ICU after severe blunt trauma, being a smoker before admission was significantly associated with microbial composition both at ICU admission and after 48 h, and this was also associated with the development of the acute respiratory distress syndrome [74].

In a study of lipopolysaccharide-induced acute lung injury in mice, the lung microbiota was shown to change [75].

7.5 Dysbiosis Is a Potential Risk Factor for Sepsis

It is generally assumed that the mortality from sepsis is due to an immunological disorder, where the pathogen causing the infection is considered irrelevant once the dysregulated immune response has begun [9, 76].

Since a healthy gut microbiota has protective effects on the host and can prevent colonization with MDR bacteria, several researchers have hypothesized that changes in the composition of the microbiota may predispose patients to a state of immunosuppression and therefore increase the risk of sepsis. Increasingly emerging evidence suggests that gut-derived bacteria travel to other sites in the body in critical illness. Using culture-independent tests in a mouse model of sepsis, lung communities were dominated by gut-associated bacteria, and ecological analysis revealed the lower gastrointestinal tract as a likely source of post-sepsis lung bacteria (rather than the upper respiratory tract). Furthermore, specific gut bacteria were abundant in patients with acute respiratory distress syndrome [69].

Similarly, gut-associated bacteria increased in the brains of mice 5 days after abdominal sepsis, and this was associated with the severity of neuroinflammation [77].

The etiology underlying microbiome modifications in critical diseases is almost certainly multifactorial. Plausible causes include critical state-induced changes and unintended side effects of critical disease treatments (e.g., antimicrobial therapy, opioids, proton pump inhibitors, and enteral and parenteral feeding). It is often difficult to decouple the effects of critical illness from the impact of antibiotics on the microbiome in the ICU, as most ICU patients receive antimicrobial therapy at some point during hospitalization. Furthermore, since the microbiome acts as an important modulator of innate immunity, it is theoretically possible for antibiotics to alter the immune response by altering the microbiome (distinct from their expected antimicrobial action). In an attempt to build a model, a proof of principle study randomized 16 healthy men to receive broad-spectrum antibiotics or no treatment for 7 days, followed by a single dose of endotoxin, designed to mimic a transient septic-like state [78].

As expected, microbial diversity was significantly reduced by antibiotic treatment. After endotoxemia, however, no differences were observed in neutrophil influx, cytokine production, coagulation activation, endothelial activation, or leukocyte response to multiple toll-like receptor ligands or clinically relevant bacteria ex vivo. This study is reassuring on some levels; however, the relevance of these findings for septic patients with ongoing infection, antimicrobial therapy, physiological disruption, and organ failure is unclear. It should be noted, however, that a study of 15 critically ill patients without antibiotic exposure reported significant changes in their microbiome within 6 h of arriving at the emergency room compared to healthy volunteers [79].

Unfortunately, the concept of "good" bacteria and "bad" bacteria is overly simplistic as bacteria can alter their virulence depending on host factors, so identical bacterial species can be adaptive or maladaptive depending on the clinical situation. In basal conditions, bacteria rarely express virulence genes. However, in host stress contexts when resources are limited, bacteria can develop both ancestral genes and newly acquired resistance genes. This could lead to bacterial invasion and, in turn, drive a maladjusted host response [10].

Specifically, the time scale at which bacteria can shift their evolutionary trajectories is much shorter (hours) than that of the human host (days or weeks). Therefore, within us the internal microbial world has the ability to adapt to changes more quickly than the critically ill patient, which can potentially be devastating if the microbial response is to aggressively attack its host. An elegant preclinical example of the implications of this has been published by Alverdy's group [80].

Both healthy mice and mice undergoing a 30% non-lethal hepatectomy were injected with *Pseudomonas aeruginosa* in the cecum. The bacteria were then picked up and injected into the peritoneum of operated mice. All animals that received bacteria from healthy mice survived, but all animals that have received bacteria from mice with 30% hepatectomy died. The underlying mechanism is that bacteria injected into mice with a hepatectomy detected host stress and, in turn, induced

virulence factors which subsequently killed the unoperated mouse. Since identical bacteria were used in this experiment, this highlights the importance of the host environment in impacting the microbial community, which in turn directly affects the health of the host.

In an animal model of mice fed an obesogenic Western diet, a diet high in fat and sucrose and low in fiber, it was recently shown that mice become susceptible to lethal sepsis with multiple organ damage after exposure to antibiotics and an otherwise recoverable sterile surgical lesion. The analysis of the intestinal microbiota in this model showed that the Western diet alone led to the loss of *Bacteroidetes*, the increase of *Proteobacteria*, and the development of antibiotic resistance even before antibiotic administration. In this elegant work, it was clearly shown how dietary selective pressure, antibiotic exposure, and surgical lesions can converge on the microbiome, resulting in lethal sepsis and organ damage even without the introduction of an exogenous pathogen [81].

A recent similar study while confirming the effect of the Western diet on disease status and outcomes of a lipopolysaccharide (LPS) sepsis model found that this relationship was independent of the microbiome. Indeed, it showed that mice fed the Western diet had higher basal inflammation and signs of immunoparalysis with associated sepsis than mice fed a standard high-fiber soup. Western diet mice also had an increased percentage of neutrophils, some with an "aged" phenotype, in their blood during sepsis compared to mice fed the standard high-fiber diet. Importantly, the increased severity of sepsis and diet-dependent mortality was independent of the microbiome, suggesting that the diet can directly regulate the innate immune system through a mechanism unknown to date [82].

This preclinical observation has been confirmed by some limited clinical studies in which patients who developed sepsis exhibited an altered microbiota pattern. In a recent study, differences in gut microbiota and plasma LPS level were evaluated in 32 patients undergoing splenectomy and 42 healthy subjects. The splenectomy group was divided into three subgroups based on the length of their postoperative time. Significant differences were observed in the composition of the gut microbiota measured by sequencing the 16s rRNA gene with regard to the relative bacterial abundance of 2 phyla, 7 families, and 15 genera. The LPS level was significantly higher in the splenectomy group than in healthy controls and was negatively associated with five low-abundance bacterial families in the splenectomy group. The degree of gut microbiota alteration increased with length of postoperative time [83].

Similarly, a study showed that allogeneic bone marrow transplant patients who developed antibiotic-induced dysbiosis had a five- to ninefold increased risk of bloodstream infection and sepsis [84].

These observations were confirmed by a retrospective cohort study comprising over 10,000 elderly patients in the United States which showed that dysbiosis was associated with a more than tripled incidence of subsequent hospitalization for sepsis [85].

Recently another study showed that exposure to longer durations of antibiotics, additional classes of antibiotics, and broad-spectrum antibiotics during hospitalization were each associated with dose-dependent increases in sepsis risk. This

association was not found for other causes of hospital admissions, suggesting that the association between antibiotic exposure and sepsis is related to microbiome depletion, not disease severity [86].

The accumulated evidence therefore indicates that alteration of the intestinal microbiota can increase the risk of sepsis; future innovations focused on restoring or protecting the gut microbiota from its alteration could become a possible approach for the prevention of sepsis, especially in fragile populations.

7.6 Can the Intestinal Microbiota Predict the Clinical Outcome of Sepsis?

The transition of a microbiome into a pathobiome is thought to be a driver of severe outcome and mortality from sepsis, at least in part due to the ability of invading bacteria to act as antigens and thus modulate the host's immune response. In animal models, the effect of the gut microbiome on the outcome of sepsis has been clearly demonstrated by several studies. In a recent study, the evolution of sepsis was analyzed in a genetically identical way, based on the age and sex of mice obtained from different suppliers and subjected to cecal ligation and puncture (CLP), the most used sepsis model [11].

Microbiome beta diversity measured from mouse feces from two different labs demonstrated significant differences, and, more importantly, the first lab mice had significantly higher mortality following CLP, compared to mice from the second lab (90% vs. 53%). Differences in immune phenotypes were also found in splenic lymphocytes or Peyer's plaque lymphocytes. To test whether the differences in the microbiome were responsible for the different results, the mice were put to live together for 3 weeks, after which they assumed a similar composition of the microbiota. Mice housed together had similar survival regardless of their supplier of origin and differences in immune phenotype disappeared.

This elegant experiment clearly shows that the microbiome plays a crucial role in the survival and immune response of the host to sepsis, representing a potential target for therapeutic intervention.

Clinical studies have also confirmed the observation that the outcome of sepsis could be influenced by the alteration of the gut microbiota. In the ICU setting, changes in the gut microbiota in patients with systemic inflammatory response syndrome (SIRS) were measured quantitatively. These patients had 100–10,000 times fewer total anaerobes including *Bifidobacterium* and *Lactobacillus* and 100 times more bacteria such as *Staphylococcus* than healthy volunteers. An important finding from this study was that the dominant factors associated with mortality and septic complications were the total number of obligate anaerobes [42].

To evaluate the effect of gut microbiome dynamics, a prospective single-center study analyzed 12 critically ill patients and demonstrated that changes in the microbiota could be associated with patient prognosis. The percentages of *Bacteroidetes* and *Firmicutes* significantly changed during ICU admission and "extreme changes" in the *Bacteroidetes*/*Firmicutes* ratio were observed in nearly all patients with poor

prognosis, suggesting a correlation between the altered gut microbiome composition and the outcome in sepsis [71].

It has long been thought that the intestine was the engine of MOD (multi-organ dysfunction) [87].

Indeed, evidence from murine sepsis models and from patients with ARDS has shown that the lung microbiota is enriched with bacteria that move from the intestine. It is important to underline that the presence of these bacteria, such as *Bacteroides* spp., is associated with the degree of local and systemic inflammation [69]. Preliminary studies in mice and patients dying of sepsis suggest that microbial translocation from the gut may be related to neuroinflammation in sepsis [77].

All of these observations provide evidence that the dysbiosis seen during sepsis could potentially contribute to the worsening of inflammation and consequently to a serious clinical outcome. However, more human clinical trials are still needed because our current knowledge of the consequences of ICU-related dysbiosis in clinical practice is still limited.

7.7 Can Sepsis Originate from the Intestine?

The suspicion that the gut microbiome may be aimed at the host is as old as the germ theory. In 1868, at the same time as Pasteur, Hermann Senator hypothesized that "self-infection" within the gastrointestinal tract could release systemic factors that cause fever, tachycardia, and dullness [88].

In 1952, a decade after the introduction of penicillin [89]. Fine and colleagues reported that pretreatment of the intestine with enteric antibiotics significantly reduced the risk of death in an animal model of hemorrhagic shock [90]. In 1972, 5 years after the first description of ARDS [91], Cuevas and colleague [92] showed that the disease could be prevented in animal models of shock by pretreatment with enteric antibiotics.

During severe systemic disease, such as sepsis or hemorrhagic shock, the bacterial content of the intestine determines the severity of the systemic injury. When the bacterial load of the intestine is minimized, both with pretreatment with enteric antibiotics and with the use of germ-free animals, inflammation and injury to distal organs in shock decrease. This relationship has been consistently reported across species (mice [93, 94], rats [95], rabbits [92], and dogs [90]), types of shock (hemorrhage [90], sepsis [92], and ischemia-reperfusion [93]), and decades of rigorous investigation.

The microbiome, therefore, is of clear relevance to any discussion of precision medicine in the ICU: the treatment groups in these studies differed not in genetics or exposure history but rather only in their microbiota.

This connection between patients' microbiota and their susceptibility to critical illness has been strengthened by an even larger study. When more than 10,000 hospitalized patients were stratified by estimated degrees of intestinal dysbiosis, a strong and consistent dose-response relationship was discovered between the microbiome disturbance and subsequent development of severe sepsis [85]. This

association between the microbiome and susceptibility to critical illness has been shown at all levels of investigation: laboratory bench, clinical studies, meta-analyses, and population studies. However, despite the clarity of this biological signal, the underlying mechanisms remain controversial and not fully understood. The oldest and most intuitive explanation for the so-called gut-derived sepsis is that in the states of critical illnesses, bacteria and bacterial products escape from the intestine and travel through the bloodstream to the distal organs, where they cause inflammation and injury. The intestinal wall of critically ill patients is permeable and the degree of permeability correlates with subsequent risk of organ injury and death [96]. In a study of trauma patients at high risk of multi-organ failure [97], serial blood cultures taken from the portal vein using catheters showed minimal evidence of bacterial translocation and no association between portal venous bacteremia and subsequent disease. The explanation of bacteria translocating, at least by blood, has therefore waned in popularity. The explanation was later refined after considering the intestinal anatomy [98]. The lower gastrointestinal tract drains not only into the portal circulation but also in the mesenteric lymph nodes. These lymph nodes drain into the thoracic duct, which in turn empties to the left into the subclavian vein. Therefore, the lungs are the first capillary bed to filter 1–4 L kilo per day which is emptied into the blood through the thoracic duct. These anatomical considerations gave rise to the so-called gut-lymphatic hypothesis [99]. Robust clinical and experimental evidence supports the gut-lymphatic hypothesis. In clinical studies of high-risk surgical patients in critical condition and animal studies of shock, bacteria were grown from mesenteric lymph nodes [98, 100]. Detection of bacteria in mesenteric lymph predicts subsequent sepsis and infectious complications [101].

In animal studies with shock, mesenteric duct ligation protects against lung injury [100] and mesenteric lymph collected from critically ill animals can cause lung injury in otherwise healthy animals [102]. The toxicity of this lymph is not dependent on the presence of endotoxin or detectable bacteria, which suggests that other factors of bacterial or tissue damage are important mediators of damage. A final explanation for sepsis derived from the gut suggests that translocation of microbes and microbials is unnecessary for the microbiome to cause systemic inflammation and damage [36, 103, 104].

Just as the community composition of the gut microbiome is changed by the intestinal environment in critically ill patients, the behavior and virulence of individual community members have also changed [36]. A normally inert and invisible to the host's immune system can be transformed by critical illness conditions and get virulence that ignites systemic inflammation and sepsis. The virulence of pathogens very familiar in ICU is promoted by conditions of nutrient scarcity, competition from members of the neighboring community, disruption of stabilizing commensal relationships [15], and exposure to mediators of the host response to stress (e.g., catecholamines, inflammatory cytokines and endogenous opioids) [55, 60, 105].

In all likelihood, the pathogenesis of gut-derived sepsis, like most processes in critical illness conditions, is multifactorial, full of biological redundancy [104, 106].

All three hypotheses (systemic translocation, gut-lymph translocation, and virulence in situ) probably explain complementary features of a complex pathogenesis of multi-organ failure, and all three will be better explained by the culture-independent microbiology revolution. The detection and identification of translocated bacteria and the characterization of collapsing communities are no longer limited by culture-based insensitive techniques, which are unable to detect most intestinal bacteria [107]. Modern techniques allow us to understand how clinical interventions contribute to these parallel processes. Many daily therapies and intensive care interventions increase intestinal permeability (e.g., non-steroidal anti-inflammatory drugs [20, 108] and parenteral nutrition [58, 65]), bacterial translocation (e.g., antibiotics [38], corticosteroids [109], and opiates [110]), and bacterial virulence (e.g., opiates [111] and catecholamines [36, 63]). With modern techniques, the mechanisms underlying the role of the microbiome in the progression from acute injury to systemic inflammation to death can be explained.

7.8 The Altered Ecology of the Damaged Alveolus

Even in healthy subjects, the lungs are subject to constant bombardment by bacteria from the upper respiratory tract [49–51]. Unlike the intestine, however, the alveolar space is an environmentally unfavorable environment for most bacteria, and reproduction is minimal [49, 112]. An important reason for low reproduction is the lack of nutrient substrate for the metabolism of bacteria. While the intestinal lumen offers an abundance of energy from protein and carbohydrate sources, the alveolus is empty except for the thin bactericidal layer of lipid-rich surfactant which lines the epithelium.

7.8.1 From a Bacterial Point of View, Healthy Alveoli Are Inhospitable

In states of alveolar damage, however, such as in ARDS or pneumonia, the environmental conditions change abruptly. The previously empty alveoli are flooded with protein-rich fluid that provide a new source of abundant energy for the reproduction of microbes.

The bactericidal surfactant layer is inactivated [58, 59] and microbial elimination is slowed by impaired mucociliary clearance [55]. Ecologically, the damaged alveoli begin to resemble the intestine more than the healthy lungs, and, therefore, it is not surprising that most of the pathogens that appear in critical diseases are of enteric origin. The microbiome and the alveolar lesion can push each other in a dysregulated feedback loop that spans the host-microbiome relationship [58, 113].

Important features of the relationship between alveolar damage and lung microbiota were validated by animal studies [75]. Direct sterile lung in mice leads to increases in the bacterial content of the lungs, indicating increased reproduction. Pulmonary community members shift toward overgrowth of specific community

members who were present in small numbers prior to injury. Flush from damaged lungs contains specific nutrients that are metabolized by newly enriched species, as predicted by the hypothesis that lung injury alters the microbiome through changes in nutrient availability. When bacterial communities from injured lungs are introduced into the lungs of otherwise healthy mice, they cause more inflammation and injury than bacteria acquired from undamaged lungs. These new findings reveal numerous new goals for clinical intervention. Virtually all preventive and therapeutic strategies for ARDS have been aimed at dampening host inflammation and damage. This model suggests that the dynamic interface between the host and its disordered lung communities is a mature and unexplored target for intervention. This model of pathogenesis can be applied to ARDS and pneumonia and could explain why there is such a large clinical overlap between the two disorders. Pneumonia is the most common cause of ARDS [114], and approximately half of the patients with established ARDS developed pneumonia during hospitalization in the ICU [115].

In the most compelling study to date to test the preventive value of protective lung ventilation in patients without ARDS, the intraoperative use of larger tidal volumes (inducing alveolar injury and leakage [116]) increased the rate of postoperative pneumonia fivefold (from 1.5% to 8.0%) [117].

Nutrient delivery is not the only way the ecology of the socket changes in critically ill patients. The influx of edema creates strong oxygen gradients, which reshape the structure of the bacterial community [31, 60]; the surfactant is inactivated, which disinhibits the growth of susceptible bacteria [58, 59]; mucociliary clearance is impaired [55]; and innate immunity cells (macrophages and neutrophils) increase in number and activation, causing the alveolar concentration of molecules related to the host stress response to increase [118].

These molecular stress signals, increased concentrations of catecholamines and inflammatory cytokines, alter lung bacteria [119, 120]. In vitro, the growth of *P. aeruginosa* is enhanced by the presence of catecholamine [63] in human bronchoalveolar lavage samples, increased concentrations of alveolar catecholamine strongly correlate with collapse of the lung microbiome around a dominant species (most frequently *P. aeruginosa* [62]. Therefore any source of alveolar damage and inflammation, whether direct ventilator-induced lung injury or aspiration [116] or indirect (e.g., sepsis or shock), can trigger an inflammatory cascade that leads to an increase in intra-alveolar catecholamine concentrations [121] which in turn promote the growth and virulence of selected members of the bacterial community and a disordered bacterial community that perpetuates alveolar inflammation. The promotion of bacterial growth by host stress molecules is not exclusive to *P. aeruginosa* and is also unique to *Streptococcus pneumoniae* [122], *S. aureus* [123], and *Klebsiella pneumoniae* [124].

In addition to catecholamines, growth promotion of TNFα; interleukins 1, 6, and 8 [1, 17, 20]; and glucocorticoids [37, 125–127] is observed.

The network of interactions between the lungs, the microbiome, and alveolar inflammation are complex, dynamic, and bidirectional.

7.9 Are Exacerbations of Chronic Respiratory Diseases Acute Infections?

Not all respiratory failure in the ICU is attributable to alveolar lesions. A common presentation is the clinical exacerbation of chronic airway diseases, such as asthma, chronic obstructive pulmonary disease (COPD), bronchiectasis, and cystic fibrosis. These exacerbations are associated with an increased and persistent inflammation of the airways and lead to the result of severe morbidity and death and high costs related to intensive care [2].

Although viral infections play a unequivocal role as a common precipitating factor of exacerbations, the role of bacteria in the pathogenesis of exacerbations has been controversial for decade [2].

The theory that exacerbations represent acute bacterial infections varies from those universally assumed (cystic fibrosis [128] and bronchiectasis [129]) to highly controversial ones (COPD [130]) or widely rejected ones (asthma).

The confusion and debate on this problem derives from the low sensitivity of classical culture-based approaches in the characterization of lung communities [2].

Culture-independent techniques have helped to clarify this long-debated relationship between bacteria, infections, and exacerbations.

Ecologically, infections are characterized by an increase in microbial load and a decrease in community diversity, coupled with an increase in host inflammation and tissue injury. Bacterial pneumonia, a true lung infection, exemplifies these characteristics: it is characterized by increased bacterial burden and low community diversity (generally a dominant pathogen) [66, 131, 132].

These characteristics are closely related to multiple indices of host inflammation including alveolar neutrophilia [94] and high alveolar concentrations of catecholamines [62] and TNF-α [133].

Conversely, exacerbations do not exhibit these ecological characteristics of the infection.

Culture-independent studies compared bacterial communities at baseline and during airway exacerbations of *COPD* patients [134, 135] with cystic fibrosis [136–140] or with bronchiectasis [141]. Consistently, all studies report no increase in bacterial burden and no reduction in community diversity during exacerbations. By any conventional or modern definition, then, exacerbations are not acute bacterial respiratory infections.

Nor do exacerbations behave clinically like true acute respiratory infections, such as pneumonia. Whereas in vitro bacterial sensitivity to antibiotics is crucial in management of pneumonia, there is no detectable relationship between organisms' susceptibility to antibiotics in culture and clinical response to therapy in exacerbations, including cystic fibrosis [141–143]. Antibiotics are undoubtedly useful in the treatment of pneumonia, but in respiratory exacerbations, opinions on their use range from controversial (COPD) to useless (asthma).

Also, while pneumonia is the most common cause of sepsis, exacerbations rarely occur or never cause a septic response.

Although the exacerbations are not bacterial infections, the microbiome is clearly involved in the pathogenesis of exacerbations. Baseline differences in airway microbiota predict subsequent frequency of exacerbation [144].

The intervention that has most consistently been shown to reduce the frequency of exacerbations (in COPD [145], in cystic fibrosis [146], and in bronchiectasis [147]) is azithromycin, a macrolide antibiotic. In states of exacerbation, members of the lung bacterial community often move toward enrichment of the *Proteobacteria* phylum [135, 148] which contains clinically relevant Gram-negative bacilli rods, such as *Pseudomonas* spp. and *Haemophilus* spp.

Unlike infections, therefore, exacerbations are more precisely described as respiratory dysbiosis: disturbance of the respiratory ecosystem associated with a dysregulated host immune response. Airway inflammation leads to conditions of impaired microbial growth, and the resulting disordered bacterial community leads to airway inflammation [2]. This self-sustaining positive feedback could explain why clinical exacerbations can last weeks longer than the presence of their triggers and why macrolides (which have antimicrobial and immunomodulatory effects [149]) have consistently demonstrated preventive benefits in all of these diseases [145–147].

7.10 Clinical Lessons to Undertake Further Studies

With virtually every treatment used in the ICU, the patient's microbiota is knowingly or unknowingly manipulated. In view of the clear relevance of the microbiome on outcomes in critically ill patients, the ecological effects of interventions need to be rigorously studied. Where the effects are known, they should be taken seriously. For example, proton pump inhibitors reduce the elimination of gastric microbiota and increase the immigration of bacteria into the lungs, with increased risk of pneumonia [150].

In an exasperated way, however, proton pump inhibitors are commonly included in treatment protocols for the prevention of ventilator-associated pneumonia and prescribed indiscriminately in critically ill patients.

Other common interventions need to be reconsidered from an ecological perspective.

Elevating the patient's bedhead reduces gastric microbiota immigration to the gastric microbiota lungs compared to supine positioning [151] but even this good practice compromises microbial elimination from the lungs, which is gravitationally dependent in critically ill patients [57]. Lowering the headboard could be more protective than lifting it [57], but this practice has not been studied in clinical trials. Historically, the composition of enteral nutrition has been adapted to meet the host's perceived metabolic needs, without taking into account its effects on the microbiome. This approach, however, may overlook the more direct ways of modeling environmental growth conditions within the gut microbiome [152]. Observational human studies alone cannot untangle the effects of critical illness from effects of its treatment (e.g., antibiotics). Therefore, future study of the role of the microbiome in critical diseases will require the use of prospective and controlled animal studies and clinical trials in critically ill patients.

7.11 Modulation of the Microbiota as a Potential Therapeutic Immunonutrition

There are currently a number of therapeutic strategies for manipulating the microbiome in the ICU. These include *probiotics, prebiotics, synbiotics, fecal microbial transplantation (FMT), and selective digestive tract decontamination (SDD)* (Fig. 7.2).

Evidence of therapeutic manipulation of the microbiome in critical diseases is promising [104]. Each of these manipulations has shown some promising results, but each also represents a significant challenge both from the point of view of how to implement it and how to think about it.

Probiotics are selective exogenous bacteria administered to the host.

Meta-analyses and various studies have indicated that probiotics are effective, for example, in reducing ventilator-associated pneumonia (VAP) [153–155], but they do not alter the length of stay in the ICU or mortality. A clear limitation in the published work on probiotics is the significant heterogeneity of the studies with respect to dose, study length, and the bacteria administered. In addition, most of the probiotic studies were conducted before the current understanding of the microbiome, which implies that a better designed project could be more effective.

Probiotics are considered living microorganisms, which, in adequate quantities, can induce health benefits to the human host. Among these, the genera *Lactobacillus*

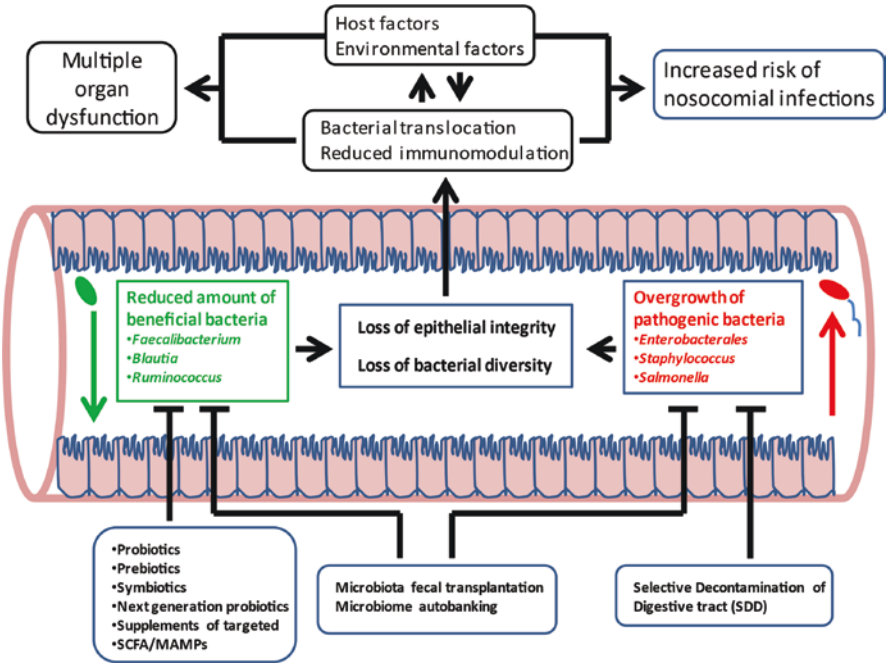

Fig. 7.2 Targeted therapies on the microbiota in the critically ill patient

and *Bifidobacterium* are the most used. Probiotics have been increasingly applied and studied in different clinical situations. Probiotics have been hypothesized to reduce the risk of disease by competing with pathogens for the binding locus and for nutrients, producing bacteriocins to kill pathogens, synthesizing IgA to support the immune system, and thus reducing inflammation.

In the context of sepsis models and critically ill patients, probiotics were studied and evaluated in terms of the evolution of sepsis and subsequent outcome. A study by Chen and co-authors reported that the prophylactic administration of a probiotic bacterial species in a septic mouse model effectively reduced mortality. More recently, a study in a septic mouse model showed that after the onset of sepsis, there was an appearance of opportunistic intestinal pathogens such as *Staphylococcaceae* and *Enterococcaceae* and disappearance of beneficial *Prevotellaceae* [156, 157]. A relative abundance of potentially pathogenic commensal bacteria is associated with more severe immune responses during sepsis, demonstrated by higher peripheral levels of pro-inflammatory cytokines, apoptosis of intestinal epithelial cells, and disruption of tight junctions. Interestingly, in animals pretreated with *Lactobacillus rhamnosus GG*, opportunistic pathogens decreased or even disappeared, while beneficial bacteria, such as Verrucomicrobiacee, increased and promoted the inhibition of intestinal epithelial cell apoptosis and promoted the formation of tight junctions. Furthermore, in a novel in vitro intestinal model to study the pathogenicity of *Candida*, the introduction of an antagonistic lactobacillus microbiota emerged as a significant factor for protection from necrotic damage by *C. albicans*, with time, dose, and species dependent and as a protective effect of probiotics against *C. albicans*-induced cytotoxicity [158]. Early intensive care studies on probiotics suggest a reduction in the risk of pneumonia and a decrease in the length of stay in the intensive care unit for mechanically ventilated patients [159] and a reduction in systemic infections in high-risk postoperative patients [160]. Improved survival has been reported in a mouse model of sepsis [161]. Unfortunately these generic and too broad interventions, with a cocktail of antibiotics and "one size fit all" probiotics, represent the opposite of precision therapy. With the advent of culture-independent microbiology, the means are finally available to identify the specific characteristics of the microbiome that promote or disrupt homeostasis in critically ill patients. At the current pace of development, community point-of-care sequencing and pathogen identification will be available and affordable within years rather than decades [131, 146]. It is urgent to have a better understanding of what constitutes a healthy microbiome in this population so that rational therapies can be developed to restore and maintain it.

Prebiotics are non-digestible nutrients that stimulate commensal bacterial growth.

Synbiotics are a combination of probiotics and prebiotics.

Prebiotics are defined as non-digestible food ingredients that act in a beneficial way on the host by stimulating the growth and/or activity of a limited number of bacterial species in the intestine.

Prebiotics directly regulate host mucosal signals to modify the response to bacterial infection; however, the clinical data are still preliminary [162, 163].

Synbiotics are composed of probiotics and prebiotics.

The use of prebiotics/probiotics/synbiotics in intensive care has been evaluated in many small studies on very different populations: *(1) to prevent infections, in the postoperative setting and in mechanically ventilated patients; (2) to improve the outcome of sepsis; and (3) to restore intestinal commensals after sepsis and reduce late infections and subsequent mortality*.

Administration of probiotics and synbiotics appears to reduce infectious complications, and meta-analyses suggest that probiotics are safe and effective in preventing infection in both postoperative and mechanically ventilated patients [164, 165]. But various concerns have been raised regarding the type and optimal dose of probiotic therapy, as well as the small size of the individual studies. Morrow et al. in a more rigorous study, reported that the incidence of ventilator-associated pneumonia (VAP) in patients treated with *L. rhamnosus GG* was significantly lower than in controls (19.1% vs. 40.0%) in 138 ICU patients. Furthermore, probiotic administration significantly reduced oropharyngeal and gastric colonization by pathogenic species [166]. However, other clinical reports have shown no significant difference results in the onset of VAP in ICU [167]. In a recent randomized controlled trial, the effect of prophylactic symbiotics on the gut microbiota and the incidence of infectious complications including enteritis, VAP, and bacteremia were evaluated in mechanically ventilated patients with sepsis. Seventy-two patients completed the trial, of which 35 patients received synbiotics and 37 patients did not. In the synbiotic group, the incidence of enteritis and the incidence of VAP were significantly lower than in controls. The incidence of bacteremia and mortality, however, did not differ significantly between the two groups [168]. Results of a large randomized controlled trial are currently pending [169] aimed at determining the effect of *L. rhamnosus GG* on the incidence of VAP and other important clinical outcomes (infection with *C. difficile*, secondary infections, diarrhea) in critically ill mechanically ventilated patients (Clinicaltrials.gov: NCT02462590). Several studies have evaluated the role of probiotics in other populations, such as preterm and underweight infants, finding no differences in the incidence of sepsis and mortality, indicating that the potential effects of microbiota recovery are not uniformly conserved across populations and various settings [170, 171]. It is interesting that in a recent randomized and double-blind placebo-controlled trial that tested a symbiotic oral preparation (*Lactobacillus plantarum* plus a fructo-oligosaccharide) in healthy full-term infants in India was discontinued early due to a 40% reduction in mortality and sepsis in the treatment arm [172]. The final frontier in the context of immunonutrition is the development of next-generation probiotics capable of selectively inhibiting specific pathogens, such as *C. difficile* and MDR bacteria, in order to govern a target population which would support colonization resistance and prevent infections and sepsis [173].

Fecal microbial transplant (FMT) instead of administering selective bacteria transfers an entire microbiome from a healthy patient to a sick one, with the aim of restoring a normal microenvironment. The microbiome can be manipulated therapeutically, as has been shown by the success of fecal microbiota transplantation in the treatment of refractory *Clostridium difficile* infection. Fecal microbial transplantation has been shown to be remarkably successful in recurrent *Clostridium difficile*

colitis, where a recent meta-analysis of 37 studies shows 92% resolution and 0.23 relative risk compared to oral vancomycin similar to the reference study FMT original showing a healing rate of 93.8% [174, 175]. However, the evaluation of the use of FMT in ICU is currently restricted to a limited number of clinical cases [176]. It must be said that most patients in intensive care receive antibiotics that should immediately alter the transplanted microbial community. Furthermore, the long-term impact of FMT administration in the ICU is not known. Fecal microbiota transplantation (FMT) consists of administering fecal material from a healthy donor into the intestinal tract of a patient with an altered gut microbiota to restore its functions. Physician interest in this treatment increased in 2013 with the publication, as already mentioned, of the results of a randomized controlled trial showing the substantial superiority of FMT over standard care in the treatment of recurrent *C. difficile* infections [177]. Based on the absolute number of introduced bacteria, it is thought that the FMT is the most powerful immunomodulatory tool. In animal models, FMT alone is capable of restoring bacterial communities in the cecal crypts, which act as a reservoir for commensal bacteria to restore the intestinal epithelium. Crypts are also crucial in intestinal protection of intestinal stem cells and in the preservation of immunological pathways by enhancing the expression of nod-like receptors and toll-like receptors. The depletion of commensal organisms in the crypts strengthens the proliferation of pathogens, which can result in severe inflammation and disruption of homeostasis.

Another potential advantage of FMT is that, together with the transfer of bacterial communities, other products (short-chain fatty acids, bile acids, eukaryotes, and prokaryotic viruses) are introduced into the intestinal ecosystem, leading to a complete restoration of homeostasis [178]. The rationale for the use of FMT in critical illness is fascinating and promising. However, its application in clinical practice among ICU patients has not been explored. FMT is thought to have a potential role in critically ill patients in two directions: *(1) restoration of dysbiosis associated with ICU admission and (2) implementation of intestinal decolonization by MDR organisms*. Indeed, introducing a high load of commensal bacteria can reverse the dominance of resistant pathobionts and even decrease the antibiotic resistance genes present in the microbiome (resistome) [179]. However, only five cases have been described in which FMT has been used to treat the alteration of the microbiota in intensive care. All of these cases demonstrated that FMT treatment led to a successful reversal of dysbiosis, resulting in improved outcomes. Furthermore, in some cases, a sharp decline in inflammatory mediators and normalized Th1/Th2 and Th1/Th17 ratios has been observed following FMT. Apart from the difficulties with extrapolating the data derived from these clinical cases to the general ICU population, we are far from being able to obtain conclusive evidence that the restoration of dysbiosis by FMT in critical illnesses is beneficial. However, given the promising FMT results learned from *C. difficile* treatment experience, clinical trials are needed to improve the microbiota-targeted approach.

Colonization with MDR bacteria is a major cause of complications of sepsis, especially among vulnerable ICU patients [180]. The use of FMT for this purpose has been evaluated in several case series, with retrospective and prospective studies,

highlighting that this approach may be feasible, safe, and effective [181]. The results cannot be easily analyzed due to the high risk of bias in small studies, but in a recent review that considered only studies with low and moderate risk of bias, an eradication rate between 37.5% and 87.5% was described [182]. The results of several studies may not be conclusive because of different patient populations (with the presence of more commonly isolated pre-FMT organisms such as carbapenem-resistant *Enterobacteriaceae* (CRE), vancomycin-resistant enterococci (VRE), and ESBL-producing bacteria extended spectrum β-lactamases (ESBLs) and also *Pseudomonas*, *S. aureus* (MRSA) resistant to methicillin, and *Acinetobacter*) and differences in route of administration, choice of donors, and duration of the completed follow-up [181]. A randomized controlled trial was recently completed which demonstrated that patients who received non-resorbable oral antibiotics followed by FMT had a slight decrease in ESBL and CRE colonization compared to control patients, without reaching statistical significance. The unfavorable results are potentially due to study design (two different FMT pathways in the intervention group and concurrent administration of antibiotics may have influenced transport in the interventional group) and early trial termination [183]. However, it is important to note that none of the published studies so far have been conducted in ICU patients. So far, only one pilot study is underway among ICU patients with an expected enrollment of ten mechanically ventilated patients with MDR colonization (Clinicaltrials. Identifier gov: NCT03350178).

Various specific concerns have been raised for ICU patients in addition to other unanswered questions regarding the FMT itself (e.g., pathogen transmission, dose, path, and long-term safety), as well as several practical aspects that still need to be studied. First of all, we do not know which is the best candidate population of septic patients and what the correct timing of FMT administration is in relation to the use of antibiotics due to the risk of cancel the effects of the transplant. A microbiota suspension such as fecal filtrate transfer (FFT) appears to maintain the ability to stimulate host responses via PRR pattern recognition receptors which make it possible for ecological niches to be modified with the growth of existing beneficial bacteria and for until successful new colonization [184].

This feature, together with the possibility of using a capsule, can increase the chance of successful FMT application even during antibiotic treatment, also reducing the potential risk of instillation of large bacterial loads in immunocompromised patients. Furthermore, even more experience is essential to evaluate which is the best route of administration (colonoscopy or enema vs nasogastric tract) and use of autologous versus heterologous transplantation. Colonoscopy or enema are the most commonly used methods of stool administration. A randomized study found that FMT using the nasogastric tract was less effective than colonoscopy [185]. Expert opinion tends to favor colonoscopy because of its ability to visualize the entire colon and deliver large amounts of stool near the affected pathological segment of the intestine [186]. Furthermore, it has been demonstrated in one randomized study the non-inferiority of capsule use compared to colonoscopy [187].

Finally, the use of autologous vs heterologous FMT needs to be clarified because autologous FMT may have potentially higher application in ICU among solid or

hematopoietic transplant patients in an attempt to prevent infections after a period of dysbiosis.

In conclusion, it can be believed that the potential benefits of FMT (regarding the control of MDR bacteria and *C. difficile* infection) may justify the study of this promising approach in critically ill patients admitted to ICU.

7.12 Selective Decontamination of the Digestive Tract

In the 1980s, some experimental observations led to the implementation of clinical studies on the suppression of intestinal bacteria in critically ill patients or patients at risk of critical illness with a view to preventing secondary infections related to care and sepsis.

Selective digestive tract decontamination (SDD) is achieved by prophylactic administration of tailored antibiotics to minimize the overgrowth of potential pathogens in the gut. From the first randomized controlled trial in 1987 (which was also the first positive) [188], SDD has been tested in over 65 randomized controlled trials that have studied more than 15,000 patients [189]. The results are not ambiguous: patients receiving SDD are less likely to develop multi-organ failure [190] or to die [189] compared to patients who do not. However, the clinical use of SDD remains little widespread, especially in North America, due to the perceived risk of antimicrobial resistance, although this concern is not supported by large clinical trials and meta-analyses [191]. Although the ecological effects of SDD on antibiotic-resistant pathogens at the ICU level remain controversial [192], the reality of patient-level benefits is beyond question.

Selective decontamination of the digestive tract represents an opposite approach to probiotics or FMT. Instead of increasing healthy bacteria or stimulating bacterial growth, SDD seeks to reduce pathogenic bacteria. Selective decontamination of the digestive tract is somewhat improper as patients are given systemic antibiotics in addition to topical antibiotics. Regardless, this approach has proven to be very effective with a meta-analysis of nearly 30 high-quality studies showing a reduction in mortality with a relative risk of 0.73 [193]. However, each of the studies in the review was conducted in countries with low antimicrobial resistance. Although there is little real-world evidence that SDD induces antimicrobial resistance, its use is currently limited to a few countries due to the theoretical concern that SDD may induce antibiotic resistance. SDD is the most thoroughly studied intervention in ICU research and has unequivocal benefits in the prevention of infections, multiple organ failure, and death [189, 190].

The microbiome is central to the biology of critical illness and, therefore, should be included in any discussion of ICU disease phenotyping.

Most studies and reviews of precision medicine in critical illness, however, focus on host genetics, immune responses, and exposures to therapies and diets [194–196].

None of these hold in debt in account for differences in results attributable solely to differences in the patients' microbiota. Before tailored therapy can be provided to patients, it must be understood how the microbiota informs prognosis and response

to treatment needs. All critical disease clinical trials must consider assessing the microbiome, gut, and lungs, as an important secondary outcome, both as mediator of the disease and modifier of therapy. Newborns represent an important and discrete population as they are highly vulnerable to alterations in the developing microbiome and to life-threatening critical diseases. Premature infants are subject to innumerable microbiome-altering exposures (e.g., antibiotics and formula feeding) and lack mature innate and adaptive immune responses. In multiple studies, the composition of the early gut microbiome was predictive of neonatal sepsis [43, 197, 198] which can plausibly be explained either by enteric harboring of potential pathogens or from systemic immune disorders caused by intestinal dysbiosis.

Experimental data suggest that early exposure to a different gut microbiome is essential for the development of an intact immune response: newborn mice with antibiotic suppression of the microbiota have an increased susceptibility to lung infections [199] and bacterial sepsis [200].

Necrotizing enterocolitis, a devastating and idiopathic disease of newborns, has been linked intestinal dysbiosis in animal studies [201] and on humans [202] and randomized controlled trials support a protective role of probiotics [203, 204].

The acute and chronic consequences of dysbiosis in infants are worthy of immediate clinical and experimental study.

Finally, even if we focus on the causes and consequences of acute microbiome disruptions in critical illness, the search for ICU outcomes over the past decade has convincingly shown that the sequelae of critical illness persist long after patients are extubated and discharged. Survivors of ARDS and sepsis have chronic illness with impaired cognitive function and functional status and are at high risk of hospital readmission in the months following discharge [205] disproportionately due to infection-related events. The mechanisms behind this so-called post-intensive care syndrome are still poorly understood, but the contribution of a persistently altered microbiome should still be explored. Disorders of the microbiome persist for weeks and months even after a short course of antibiotics [39]. And how quickly or completely the microbiome recovers after the insults and disruptions of critical illness is not yet known. Research is needed to define the natural history of microbiome recovery after critical illness, to determine whether recovery can be accelerated (e.g., via probiotics or fecal microbiota transplantation) and whether this recovery improves in the long term. In patients recovering from multiple organ failure, the microbiome may be the last organ to be recovered.

7.13 Future Perspectives

Despite the impressive milestone in microbiome knowledge, there is still a huge gap on microorganisms residing outside the gut and the interactions of bacteria with viruses, archaea, helminths, fungi, and protozoa, what influence does the one with the other and in turn adjust the guest. In the context of critically ill septic patients, we need a large number of human cohort studies documenting the composition of the microbiota, before, during, and after a sepsis episode in order to identify

protective commensals and the potentially associated microbiota with greater susceptibility and worse outcome.

At the same time, new treatment opportunities need to gain space in clinical practice, including adding a probiotic or customizing microbiome therapy and selecting a replacement for specific diners that could target a specific infectious disease. In this context, human studies and randomized clinical trials are challenging but still fundamental for translating basic research into innovative paradigms.

Although the importance of the microbiome in critical diseases has been established for many years now, the revolution in culture-independent microbiology has finally produced tools capable of determining its contribution to the pathogenesis of sepsis, ARDS, and multi-organ failure.

Ongoing clinical and experimental studies will explore how the microbiome is altered in critical illness and, in turn, how its ailment perpetuates organ injury.

The microbiome represents a key therapeutic target for the prevention and treatment of critical illnesses and should be included in any discussion of precision medicine in the intensive care unit.

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Coagulation Abnormalities in Patients with COVID-19

8

Fabrizio Racca, Christian Zanza, and Yaroslava Longhitano

8.1 Introduction

A novel coronavirus was identified in late 2019 that rapidly reached pandemic proportions. The World Health Organization has designated the disease caused by the virus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) as coronavirus disease 2019 (COVID-19). Bilateral pneumonia, acute respiratory failure (ARF), systemic inflammation, endothelial dysfunction, and coagulation activation has been described as key features of severe COVID-19 [1–6]. An increased risk of venous thromboembolism (VTE) in patients with COVID-19 pneumonia admitted to intensive care unit (ICU) [7–11] and in non-ICU wards has been reported despite adequate thromboprophylaxis. Thus, several authors [7, 8] suggested that higher anticoagulation targets than in usual critically ill patients should probably be taken into consideration for patients with COVID-19 pneumonia.

This review provides practical information for evaluation and management of coagulation abnormalities in individuals with COVID-19.

8.2 SARS-CoV-2 Clinical Feature

SARS-CoV-2 outcome seems to be determined by the extent of the host immune system imbalance. The primary immune response usually leads to viral clearance. However, for unclear reasons, the secondary immune response may be exaggerated and, in some cases, may lead to multiple organ failure, acute respiratory

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distress syndrome (ARDS), and death [12]. This exaggerated response is known as cytokine release syndrome (CRS), and it has an important role in the activation of coagulation.

The spectrum of symptomatic COVID-19 infection ranges from mild to critical; most infections are not severe. Specifically, in a report from the Chinese Center for Disease Control and Prevention, that included approximately 44,500 confirmed infections, an estimation of disease severity was described [13]. Mild disease (or mild pneumonia) was reported in 81%. Severe disease (e.g., with dyspnea, hypoxia, or >50% lung involvement on imaging within 24–48 h) was described in 14%. Critical disease (e.g., with respiratory failure, shock, or multiorgan dysfunction) was identified in 5%. The overall case fatality rate was 2.3%; no deaths were reported among noncritical cases. Among hospitalized patients, the proportion of critical or fatal disease is higher. In a study that included 2741 patients who were hospitalized for COVID-19 in a New York City health care system, 665 patients (24%) died or were discharged to hospice [14]. Of the 749 patients who received intensive care (27% of the total hospitalized cohort), 647 received invasive mechanical ventilation; of those patients, 60% died and 13% were still ventilated. In Italy, 12% of all detected COVID-19 cases and 16% of all hospitalized patients were admitted to the ICU; the estimated case fatality rate was 7.2% [15, 16].

Individuals of any age can acquire SARS-CoV-2 infection, although adults of middle age and older are most commonly affected, and older adults are more likely to have severe disease. Symptomatic infection in children and adolescents appears to be relatively uncommon; when it occurs, it is usually mild, although a small proportion (e.g., <2%) experience severe and even fatal disease. Severe illness can occur in otherwise healthy individuals, but it predominantly occurs in adults with underlying medical comorbidities. Comorbidities and other conditions that have been associated with severe illness and mortality include cardiovascular disease, diabetes mellitus, hypertension, chronic lung disease, cancer (in particular hematologic malignancies, lung cancer, and metastatic disease), chronic kidney disease, obesity, and smoking. In a report of 355 patients who died with COVID-19 in Italy, the mean number of pre-existing comorbidities was 2.7, and only three patients had no underlying condition [16].

Asymptomatic infections have also been well documented [17]. The proportion of infections that are asymptomatic has not been systematically and prospectively studied. One literature review estimated that it is as high as 30 to 40%, based on data from two large cohorts that identified cases through population-based testing [17, 18].

The incubation period for COVID-19 is generally within 14 days following exposure, with most cases occurring approximately 4–5 days after exposure.

Pneumonia appears to be the most frequent serious manifestation of infection, characterized primarily by fever, cough, dyspnea, and bilateral infiltrates on chest imaging [3]. However, other features, including upper respiratory tract symptoms, myalgias, diarrhea, and smell or taste disorders, are also common. Although some clinical features (in particular smell or taste disorders) are more common with COVID-19 than with other viral respiratory infections, there are no specific

Table 8.1 Laboratory features associated with severe COVID-19

	Possible threshold
↑ D-dimer	>1000 ng/mL (normal range: <500 ng/mL)
↑ CRP	>100 mg/L (normal range: <8.0 mg/L)
↑ LDH	>245 units/L (normal range: 110 to 210 units/L)
↑ ferritin	>500 mcg/L (normal range: females 10 to 200 mcg/L; males 30 to 300 mcg/L)
↑troponin	>2× the upper limit of normal
↑CPK	>2× the upper limit of normal
↓ absolute lymphocyte count	<800/microL (normal range for age ≥ 21 years: 1800 to 7700/microL)

Possible threshold are extrapolated from published cohort data and individualized to the reference values used at our laboratory. However, the specific thresholds are not well established
COVID-19, coronavirus disease 2019, *CRP* C-reactive protein, *LDH*, lactate dehydrogenase, *CPK*, creatine phosphokinase

symptoms or signs that can reliably distinguish COVID-19. Some patients with initially nonsevere symptoms may progress over the course of a week [19].

Common laboratory findings among hospitalized patients with COVID-19 include lymphopenia, elevated aminotransaminase levels, elevated lactate dehydrogenase levels, elevated inflammatory markers (e.g., ferritin, C-reactive protein, and erythrocyte sedimentation rate), and abnormalities in D-dimer levels (see Table 8.1). Several laboratory features, including high D-dimer levels and more severe lymphopenia, have been associated with critical illness or mortality [4].

Common abnormal radiograph findings in patients with COVID-19 most were consolidation and ground-glass opacities, with bilateral, peripheral, and lower lung zone distributions. Chest CT commonly demonstrates ground-glass opacification with or without consolidative abnormalities. Chest CT abnormalities are often bilateral, have a peripheral distribution, and involve the lower lobes. Among patients who clinically improve, resolution of radiographic abnormalities may lag behind improvements in fever and hypoxia.

Several complications of COVID-19 have been described. ARDS is the major complication in patients with severe disease. Other complications have included arrhythmias, acute cardiac injury, and shock. Thromboembolic complications, including pulmonary embolism and acute stroke, have also been reported. Other inflammatory complications and auto-antibody-mediated manifestations have been described. Guillain-Barré syndrome may occur, with onset 5–10 days after initial symptoms. A multisystem inflammatory syndrome with clinical features similar to those of Kawasaki disease and toxic shock syndrome has also been described in children with COVID-19.

The proportion of patients with COVID-19 who are diagnosed with ARDS on the basis of oxygenation criteria ranges between 20% and 67% in patients admitted to hospital and is 100% in mechanically ventilated patients [20, 21]. Grasselli et al. recently published a systematic analysis of clinical and laboratory features in patients with COVID-19-associated ARDS in 301 consecutive patients

prospectively enrolled in 7 Italian hospitals [15]. They compared the pathophysiology of COVID-19-related ARDS with classical ARDS using two large historical datasets, showing that patients with COVID-19-associated ARDS have a form of injury that is similar to that of classical ARDS characterized by decreased compliance and increased lung weight. In many patients, this injury was complicated by increased dead space, which was probably related to diffuse microthrombi or emboli of the pulmonary vascular bed. In this study, patients with COVID-19-related ARDS had a median static compliance of the respiratory system 28% higher in patients with COVID-19 (n = 297; 41 mL/cm H_2O [IQR 33–52]) than in those with classical ARDS (n = 960; 32 mL/cm H_2O [22–40], $p < 0{\cdot}0001$). Moreover, they found that most of the patients had markedly increased D-dimer concentrations (median 1880 ng/mL [IQR 820–6243]). In this study, 28-day mortality was 36% (93 of 261 patients). In particular, when an easily identified phenotype of increased parenchymal damage (low static compliance) and increased D-dimer concentrations occurs together, mortality is extremely high.

Secondary infections including respiratory infections and bacteremia do not appear to be common complications of COVID-19 overall, although data are limited [41]. Several reports have described presumptive invasive aspergillosis among immunocompetent patients with ARDS from COVID-19, although the frequency of this complication is uncertain [42].

Recovery time appears to be around 2 weeks for mild infections and 3–6 weeks for severe disease based on early data from China. However, the recovery course is variable and depends on age and pre-existing comorbidities in addition to illness severity.

Systematic evaluation of the long-term sequelae of COVID-19 is lacking, but emerging data [43] suggest the potential for ongoing respiratory impairment. Moreover, cardiac imaging studies have suggested the potential for cardiac sequelae after COVID-19 [22].

8.3 Coagulation Abnormalities in Patients with COVID-19

SARS-CoV-2 may predispose patients to thrombotic disease, both in the venous and arterial circulation, due to excessive inflammation, platelet activation, and endothelial dysfunction [23–25]. The predominant coagulation abnormalities in patients with COVID-19 are summarized in Table 8.2. Bleeding does not appear to be a major manifestation of COVID-19. However, patients may have bleeding for other reasons, including trauma and/or treatment with anticoagulation. If it occurs, treatment is similar to non-COVID-19 patients and may include transfusions, anticoagulant reversal or discontinuation, or specific products for underlying bleeding disorders.

Laboratory findings in COVID-19 are the following: prothrombin time (PT) and activated partial thromboplastin time (aPTT) normal or slightly prolonged, platelet counts normal or increased, fibrinogen increased, D-dimer increased, factor VIII activity increased, von Willebrand factor (VWF) antigen greatly increased, and

Table 8.2 The hypercoagulable state in patients with COVID-19 [26]

Predominant coagulation abnormalities
• D-dimer increased
• Fibrinogen increased
• Prothrombin time (PT) and aPTT[a] normal or slightly prolonged
• Platelet counts normal or increased
• Factor VIII activity increased
• VWF antigen greatly increased
• Small decreases in antithrombin and small increase in protein C

PT prothrombin time, *aPTT* activated partial thromboplastin time, *VWF antigen* von Willebrand factor antigen, *LA* lupus anticoagulant

[a]The presence of a LA is common in individuals with a prolonged aPTT

minor changes in natural anticoagulants (i.e., small decreases in antithrombin and small increase in protein C) [26]. The presence of a lupus anticoagulant (LA) is common in individuals with a prolonged aPTT. Very elevated levels of D-dimer have been observed that correlate with illness severity, especially if levels are increased several-fold [27].

This state appears to be distinct from disseminated intravascular coagulation (DIC), even if some critical patients with COVID-19 have met criteria for probable DIC. Clinical findings of acute DIC include bleeding, thrombocytopenia, prolonged PT and aPTT, low plasma fibrinogen, elevated plasma D-dimer, and microangiopathic changes on peripheral blood smear. DIC is a clinical and laboratory diagnosis. The International Society on Thrombosis and Haemostasis (ISTH) has developed in 2009 a scoring system to be applied to individuals with an underlying disorder associated with DIC, which incorporates laboratory features including the PT, platelet count, fibrinogen level, and D-dimer [28]. The ISTH scoring system (see Table 8.3) is reported to have a sensitivity of 91% and a specificity of 97%, but is not widely used. COVID-19 has some similar laboratory findings to DIC, including a marked increase in D-dimer and in some cases, mild thrombocytopenia. However, other coagulation parameters in COVID-19 are distinct from DIC. In particular, the typical findings of high fibrinogen and high factor VIII activity suggest that major consumption of coagulation factors is not occurring [26]. As a matter of fact, in one of the largest series that reported thromboembolic events in subjects with COVID-19, none of the patients developed overt DIC [8].

The pathogenesis of hypercoagulability in COVID-19 is incompletely understood. However, we know that cytokine release syndrome (CRS) is thought to play an important role in disease severity [29]. CRS is associated with increased levels of inflammatory cytokines and activation of T lymphocytes, macrophages, and endothelial cells. In particular, interleukin 6 and tumor necrosis factor seems to hold a key role leading to vascular leakage and to activation of complement, tissue factor, and coagulation cascade [30, 31]. Moreover, all three of the major contributions of Virchow's triad to clot formation (i.e., endothelial injury, stasis, and hypercoagulable state) apply to severe COVID-19 infection. There is evidence of direct invasion of endothelial cells by the SARS-CoV-2 virus, potentially leading to endothelial injury [32]. Other sources

Table 8.3 The International Society on Thrombosis and Haemostasis (ISTH) scoring system [28]

A ISTH score of 5 or more points suggests DIC is probable
• **Thrombocytopenia**
– 1 point for platelet count 50,000 to 100,000/microL
– 2 points for platelet count r < 50,000/microL
• **Prolonged PT**
– 1 point for 3–6 s of prolongation
– 2 points for more than 6 s of prolongation
• **Low fibrinogen:** 1 point for <100 mg/dL
• **Increased D-dimer**
– 2 points for moderate increase
– 3 points for "strong" increase

PT prothrombin time, *DIC* disseminated intravascular coagulation

of endothelial injury include intravascular catheters and mediators of the acute systemic inflammatory response such as cytokines (e.g., interleukin 6) and other acute phase reactants [33]. The contribution of complement-mediated endothelial injury has also been suggested [34]. Immobilization can cause stasis of blood flow in all hospitalized and critically ill patients, regardless of whether they have COVID-19. Finally, a number of changes in circulating prothrombotic factors have been found in patients with severe COVID-19: elevated factor VIII, elevated fibrinogen, neutrophil extracellular traps (NETs), and hyperviscosity [26, 35].

These coagulation abnormalities in the direction of an underlying hypercoagulable state raise questions about appropriate evaluations and interventions to prevent or treat thrombosis.

8.4 Venous Thromboembolism in Critically Ill Patients

Critically ill patients have an increased risk of VTE of the upper and lower extremities. The risk factors include immobility associated with serious illness such as sepsis and trauma and invasive procedures such as central venous lines [36]. The most serious manifestation of VTE is pulmonary embolism (PE). Of all PEs, 90% are estimated to originate from deep venous thrombosis (DVT) of the lower limbs [37]. DVT and PE share common risk factors [38].

The main clinical importance of DVT lies in its association with potentially life-threatening PE. In critically ill patients with impaired cardiopulmonary reserve, a small PE might have severe or fatal sequelae. In addition, evaluation for VTE in critical ill patients may be challenging. Thus, some mechanically ventilated patients with sudden episodes of hypotension, tachycardia, or hypoxia may have undetected PE [39].

PE is stratified into massive, sub-massive, and low risk based upon the presence or absence of hypotension and right ventricular dysfunction or dilation. This stratification is associated with mortality risk [40].

The prevalence of VTE in non-COVID-19 ICU patients ranged from 2 to 8% [7, 44, 45]. In a retrospective observational cohort study in 12 adult ICUs, including

12.338 medical-surgical critically ill patients, VTE appears to be an apparently infrequent problem, occurring also among patients receiving prophylaxis [44]. Indeed, only 1–2% of patients developed VTE. Across these 12 ICUs, the incidence of definite DVT or PE ranged from 0.1% to 2.6% and 0.2% to 2.4%, respectively. In particular, 252 (2.0%) patients had confirmed VTE (166 DVT events and 122 PE events). Most incident events occurred within 2 weeks of ICU admission. Two thirds of patients required mechanical ventilation and one third required vasopressors or inotropes at some point during their ICU stay. The proportion of patients with VTE who received thromboprophylaxis for 80% or more of their ICU stay was 65.8%. Thus, most VTE events were due to prophylaxis failure rather than failure to provide prophylaxis.

8.5 Venous Thromboembolism in Hospitalized Patients with COVID-19 Pneumonia

Among hospitalized COVID-19 patients, an increased risk of VTE has been reported despite adequate thromboprophylaxis [7–11, 46]. In particular, higher prevalence of VTE was found compared to non-COVID-19 ICU patients [7–45]. Case series of ICU patients including more than 600 patients reported high rates of VTE (range 20 to 43%), mostly PE [8, 47–49]. Data regarding VTE rate outside the ICU are more limited but also suggest a possibly increased rate (range 3% to 6%) [24, 49]. Other studies focused on COVID-19 patients also show a higher rate of DVT (65–69% in ICU patients [50, 51] and 11.9–21% in general ward patients [11, 52, 53]).

In a retrospective study, 11 diagnoses of PE were described in a population of 62 patients with ARDS related to COVID-19 [9]. In all these patients, main pulmonary arteries were involved (Fig. 8.1).

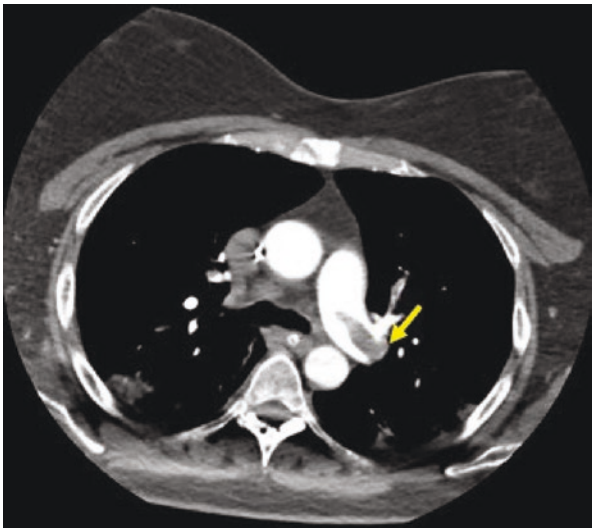

Fig. 8.1 Computed tomography scan imaging of ARDS associated to COVID-19 and pulmonary emboli. Pulmonary embolus across the bifurcation of pulmonary trunk is noted, as indicated by the arrow

Autopsy studies in small series of patients who have died from COVID-19 have also demonstrated microvascular thrombosis in the lungs [34, 54]. The universality and clinical implications of these observations require further research.

Several factors contribute to the increase in VTE risk in ICU patients. Recognized risk factors for DVT are related to one or more elements of Virchow's triad: flow stasis, vessel injury, and hypercoagulability. Flow stasis, due to prolonged immobility, mechanical ventilation, use of sedatives, and neuromuscular block, plays a major role in ICU patients [55–57]. In addition, in this population vessel injury may be due to catheter insertion in central veins, and hypercoagulability may be induced by sepsis or dehydration [55, 56].

Evaluation for DVT or PE in these patients may be challenging because symptoms of PE overlap with COVID-19, and imaging studies may not be feasible in all cases [9]. The threshold for evaluation or diagnosis of DVT or PE should be low given the high frequency of these events and the presence of additional VTE risk factors in many individuals. In patients with suspected PE due to unexplained hypotension, tachycardia, worsening respiratory status, or other risk factors for thrombosis, computed tomography with pulmonary angiography is the preferred test to confirm or exclude the diagnosis. On the other hand, bilateral complete duplex ultrasound (CDUS) is the suggested test to screen for DVT.

Heparin resistance (requirement for very high doses of heparin to achieve a therapeutic aPTT or anti-factor Xa activity) might be another concern in acutely ill patients with COVID-19. In a French study, 43% of patients reported VTE despite thromboprophylaxis, and thrombotic complications occurred despite prophylactic or therapeutic anticoagulation, respectively, in 70% and 30% of patients [7]. In another series, among 74 patients, VTE was reported in 29 patients [49]. All of them were receiving anticoagulation, both at prophylactic and therapeutic levels. In addition, a series of 15 individuals in the ICU anticoagulated for VTE noted a very high requirement for unfractionated heparin or low molecular weight heparin. In particular, five patients receiving dalteparin had anti-factor Xa peak below expected (<0.6 international units/mL for twice daily dosing or <1 international units/mL for once daily dosing]) [58]. The reason for heparin resistance is not understood; the authors stated that heparin is negatively charged and can interact with a variety of positively charged plasma proteins, some of which behave like acute phase reactants and will compete for heparin binding. Furthermore, the suboptimal efficacy of higher anticoagulation dose could also be explained by the underlying pathophysiological mechanism which explains the presence of thrombotic material in pulmonary circulation [59, 60]. In the context of COVID-19, pulmonary thrombosis may develop via a distinctive mechanism and therefore may not respond adequately to intensified anticoagulation.

Based on these reports, many physicians are advocating the empiric use of therapeutic anticoagulation even in patients who do not have a documented diagnosis of VTE [7, 61, 62]. On the other hand, the current position of the majority of medical societies still recommend using standard prophylactic doses of anticoagulation for hospitalized COVID-19 patients, similar to what is recommended for other acutely ill medical patients [63].

A small randomized trial (HESACOVID) randomly assigned 20 individuals with severe COVID-19 to receive therapeutic-dose anticoagulation (enoxaparin, 1 mg/kg twice daily) or prophylactic-dose anticoagulation (enoxaparin, 40 mg once daily or unfractionated heparin, 5000 units three times daily); adjustments were made for age, weight, and kidney function as appropriate [64]. Half the patients in the prophylactic group received unfractionated heparin and half enoxaparin. Compared with prophylactic dosing, therapeutic dosing led to fewer days on the ventilator and significant reductions in D-dimer levels. However, confidence in the results is hampered by the open-label design and small size of this study. Besides, in our general ICU, a high prevalence of PE was registered among the first 62 patients (19.3% cases) affected by COVID-19-related ARF, admitted from 1 March to 31 March 2020, despite a regular antithrombotic prophylaxis [9]. Thus, a protocol with increased doses of thromboprophylaxis was introduced in our hospital for these patients. Subsequently, we performed a prospective, observational study to assess thrombotic risk in COVID-19 pneumonia patients and to compare populations treated with three different antithrombotic prophylaxis protocols (Fig. 8.2) [10]. Seventy-four patients were enrolled (44 men and 30 women, average age 68.6). Diagnosis of venous thromboembolism was made in 21 cases (28.4%). Forty-seven out of 74 patients (63.5%) received intermediate or therapeutic dose of anticoagulation, while 27 patients (34.5%) received standard antithrombotic prophylaxis. Our analysis showed that an intermediate or therapeutic dose of anticoagulation did not

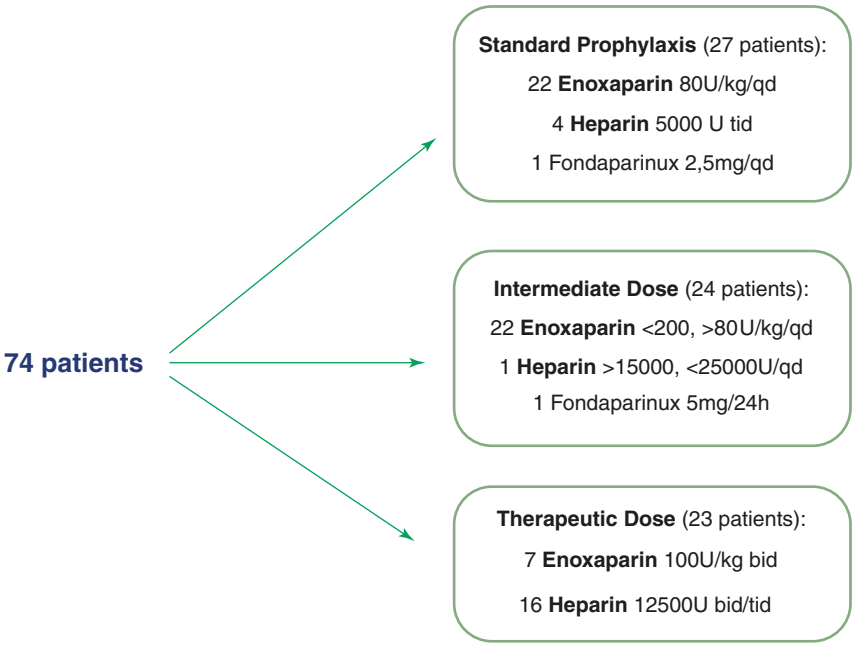

Fig. 8.2 Antithrombotic prophylaxis in Longhitano study [10]. Antithrombotic prophylaxis: molecules and doses

decrease the prevalence of thrombotic events. On the other hand, six patients reported severe hemorrhagic complications (two cases with standard antithrombotic prophylaxis group and four cases with increased antithrombotic dose), with a hemorrhagic shock in three cases. In addition, mortality among patients receiving a higher dose of antithrombotic prophylaxis was three times higher than in subjects treated with standard prophylaxis. More recently, a randomized trial was stopped when the prespecified criterion for futility was met for therapeutic-dose anticoagulation after the inclusion of 1098 critical ill patients with COVID-19 [65]. The authors of this study concluded that in critically ill patients with COVID-19, an initial strategy of therapeutic-dose anticoagulation with heparin did not result in a greater probability of survival to hospital discharge or a greater number of days free of cardiovascular or respiratory organ support than did usual-care pharmacologic thromboprophylaxis.

To date, VTE prophylaxis using at least prophylactic dosing is appropriate in all hospitalized medical, surgical, and obstetric patients with COVID-19, unless there is a contraindication to anticoagulation (e.g., active bleeding or serious bleeding in the prior 24–48 h) [66, 67]. American Society of Hematology 2021 guidelines on the use of anticoagulation for thromboprophylaxis in hospitalized patients with COVID-19 suggested prophylactic dosing rather than more intensive (intermediate or therapeutic) dosing [68].

Low molecular weight (LMW) heparin is preferred for thromboprophylaxis, but unfractionated heparin can be used if LMW heparin is unavailable or if kidney function is severely impaired. In case of history of heparin-induced thrombocytopenia (HIT), an alternative agent such as fondaparinux may be used. The presence of a prolonged aPTT due to the lupus anticoagulant (LA) phenomenon does not reflect decreased risk of thromboembolic complications (in some individuals, it reflects increased risk) and is not a reason to avoid anticoagulation.

Therapeutic-dose (full-dose) anticoagulation for at least 3 months is always appropriate to treat DVT or PE, and tissue plasminogen activator (tPA) is appropriate for massive PE, unless there is a contraindication.

8.6 Arterial Thrombosis

Arterial thrombotic events such as stroke, myocardial infarction, and limb ischemia are also increased, but to a lesser extent than venous thrombosis.

The largest study, which included 3334 individuals (829 ICU and 2505 non-ICU), reported stroke in 1.6% and myocardial infarction in 8.9% [69]. Risk factors for arterial thrombosis included older age, male sex, Hispanic ethnicity, history of coronary artery disease, and D-dimer >230 ng/mL on presentation. Arterial thrombotic events were associated with increased mortality.

A report described 20 patients with COVID-19 who developed acute limb ischemia at a single institution over a 3-month period [70]. This represented a significant increase in limb ischemia over the previous year (16%, versus 2% in early 2019). Most were male, and the average age was 75 years. Surgical

revascularization procedures were performed in 17, of which 12 (71%) were successful, a lower-than-expected success rate. Individuals who received postoperative heparin did not require reintervention, although the benefits of postoperative heparin did not reach statistical significance.

8.7 Conclusion

COVID-19 is characterized with a hypercoagulable state associated with acute inflammatory changes and laboratory findings that are distinct from DIC, safe for some patients with very severe disease. The risk for VTE is markedly increased, especially in patients in the ICU, often despite prophylactic-dose anticoagulation. Pulmonary microvascular thrombosis and arterial thrombotic events such as stroke, myocardial infarction, and limb ischemia are also increased, but to a lesser extent than venous thrombosis. Bleeding is less common than thrombosis but can occur.

The threshold for evaluation or diagnosis of DVT or PE should be low given the high frequency of these events and the presence of additional VTE risk factors in many individuals. In patients with suspected PE, computed tomography with pulmonary angiography is the preferred test to confirm or exclude the diagnosis. CDUS is the suggested test to screen for DVT.

All inpatients should receive thromboprophylaxis unless contraindicated. In hospitalized patients with COVID-19, prophylactic dosing rather than more intensive (intermediate or therapeutic) dosing is suggested. Therapeutic dose of anticoagulation is always appropriate to treat DVT or PE, unless contraindicated.

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Vascular Failure and Sepsis in Pediatrics

9

Giovanna Chidini and Giada Donà

9.1 Introduction

Sepsis in children and infants is one of the main causes of morbidity, mortality, and the need for intensive care in pediatrics. The incidence of pediatric and neonatal sepsis is estimated at 1.2 million cases per year [1]. More than 4% of all the hospital admissions for patients under the age of 18 and about 8% of all children admitted to pediatric intensive care in industrialized countries present sepsis/septic shock [2–6]. Mortality ranges from 4% to 50% depending on severity at presentation, risk factors, and where the patient is [2, 3, 7–9].

Most pediatric deaths are due to refractory septic shock and/or multiple organ failure. Mortality occurs mainly in the first 48–72 h of admission [10–12]. It is therefore fundamental to identify patients with suspected sepsis promptly and start the appropriate treatment rapidly, in order to ensure a favorable outcome, and reduce mortality.

This review looks at pediatric sepsis in relation to the guidelines issued by the major international societies, bearing in mind that on several topics there is still no reliable evidence from randomized clinical trials, and many of the guidelines rely on panels of acknowledged experts [13–15].

The recommendations set out in the guidelines are based on current evidence but can never replace the clinician's decisions, as this is the person increasingly required to draw up the medical plan for each individual patient. In addition, the guidelines generally establish diagnostic and treatment methods that take account of the diagnostic and care facilities in industrialized countries, where a large part of the population is assured of access to specialist intensive care. These guidelines are often not

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applicable in all countries, especially those with limited capacity for intensive care for their population.

The FEAST trial provides an example of this asymmetry. It shows that applying the protocol for the treatment of sepsis with high crystalloid loads in the first hours results in an excess of mortality in countries where patients have limited access to intensive care units that can ensure adequate treatment for dealing with the consequences of these high loads [16].

9.2 Sepsis in Pediatrics: Definition and Diagnosis

Sepsis in children is defined as an unregulated immune response to an infectious stimulus—bacterial or viral—that can cause organ failure, with risk for survival. In children it is essential to diagnose sepsis/septic shock promptly so as to reduce short-term mortality. Like in adults, sepsis in children too must be identified and treated in the shortest time possible—the "golden hour." Unlike in adults, however, in children the signs of sepsis or septic shock are extremely vague and hard to recognize, particularly when defining organ failure (Table 9.1).

The first difficulty is classifying vital parameters and organ failures as percentages in relation to age. Matics in 2017 in JAMA adapted and validated the SOFA score for children (PSOFA) taking account of how the parameters varied in relation to age. For PSOFA the original SOFA was adapted to take account of this age-related variability in cardiovascular and renal parameters, applying validated cut-offs from the PELOD2; then the respiratory score was extended to include SpO_2/FIO_2 as indicators of pulmonary damage, when arterial blood gas was not available (Fig. 9.1). PSOFA performs well for monitoring the clinical course in intensive care but is hard to apply for prompt diagnosis in an emergency setting.

Generally repeated clinical examination is essential to identify a child with sepsis and make a prompt diagnosis, as hypotension is a very late sign (Table 9.2).

Early clinical signs that help in diagnosing sepsis and organ failure include tachycardia, scant peripheral perfusion, capillary refill >2″, cold extremities, marbling of the flesh, scant diuresis (<1 mL/kg/h), neurological manifestations (agitation, drowsiness), tachypnea, skin rash, and hyper- or hypothermia. In breast-fed infants, however, the clinical signs of sepsis often overlap the signs and symptoms of dehydration, which may be due to other causes (Table 9.3).

Various clinical scales have been drafted to facilitate the interpretation of vital parameters and specifically in this pathology, aimed at prompt identification of the

Table 9.1 Different approaches for adults and children

Adult	Child
Univocal indicators of sepsis (quick SOFA, SOFA)	Clinical and laboratory findings are age-related. Non-univocal indicators of sepsis
Univocal definition of organ failure	Organ dysfunction delayed and vague
Hypotension is an early sign	Hypotension is a late sign

Variable	score[a]				
	0	1	2	3	4
Respiratory					
PaO2:FiO_2[b] or SpO2:FiO_2[c]	≥ 400	300-399	200-299	100-199 with respiratory support	< 100 with Respiratory support
	≥ 292	264-291	221-264	148-200 with respiratory support	< 148 with respiratory support
Coagulation					
Platelet count, x 10^3/μL	≥ 150	100-149	50-99	20-49	< 20
Hepatic					
Birilubin, mg/dL	< 1.2	1.2-1.9	2.0-5.9	6.0-11.9	> 12.0
Cardiovascular					
MAP by age group or vasoactive infusion, mmHgor μg/kg/min[d]					
< 1 mo	≥ 46	< 46	Dopamine hydrochloride ≤ 5 or dobutamine hydrochloride	Dopamine hydrochloride > 5 or epinephrine ≤ 0.1 or noreepinephrine bitartrate ≤ 0.1	Dopamine hydrochloride > 15 or epinephrine > 0.1 or noreepinephrine bitartrate > 0.1
1-11 mo	≥ 55	< 55			
12-23 mo	≥ 60	< 60			
24-59	≥ 65	< 65			
60-143 mo	≥ 67	< 67			
144-216 mo	≥ 70	< 70			
> 216 mo[e]					
Neurologic					
Glasgow Coma Score[f]	15	13-14	10-12	6-9	< 6
Renal					
Creatinine by age Group, mg/dL					
< 1 mo	< 0.8	0.8-0.9	1.0-1.1	1.2-1.5	≥ 1.6
1-11 mo	< 0.3	0.3-0.4	0.5-0.7	0.8-1.1	≥ 1.2
12-23 mo	< 0.4	0.4-0.5	0.6-1.0	1.1-1.4	≥ 1.5
24-59	< 0.6	0.6-0.8	0.9-1.5	1.6-2.2	≥ 2.3
60-143 mo	< 0.7	0.7-1.0	1.1-1.7	1.8-2.5	≥ 2.6
144-216 mo	< 1.0	1.0-1.6	1.7-2.8	2.9-4.1	≥ 4.2
> 216 mo[e]	< 1.2	1.2-1.9	2.0-3.4	3.5-4.9	≥ 5

Fig. 9.1 Pediatric Sequential Organ Failure Assessment Score (pSOFA)

Table 9.2 Pediatric physiological parameters

Pediatric physiological parameters			
Glasgow Coma Scale	≤ 8 or loss of 2 points		
Respiratory rate, breath/min	< 20	>70	(0–5 month of age)
	< 16	> 60	(6 month–2 years of age)
		> 50	(2 years–6 years of age)
		> 40	(≥ 7 years of age)
Oxygen saturation, %	≤ 90% at room airs		
Heart rate, beat/min	< 80	> 200	(0–5 month of age)
	< 65	> 180	(6 month–2 years of age)
	< 50	> 160	(2 years–6 years of age)
	< 50	> 150	(≥ 7 years of age)
Blood pressure, mmHg Severe hypertension	SBP	> 97	(0–1 month of age)
	DBP	> 71	
	SBP	>110	(1 month–2 month of age)
	DBP	> 72	
	SBP	> 115	(1 year–5 years of age)
	DBP	> 75	
	SBP	> 124	(6 years–10 years of age)
	DBP	> 85	
	SBP	> 136	(10 years of age)
	DBP	> 90	
Blood pressure, mmHg Severe hypotension	SBP	< 60	(0–1 month of age)
	SBP	< 70	(1–12 month of age)
	SBP	< 76	(1 year–5 years of age)
	SBP	< 86	(6 years–10 years of age)
	SBP	< 90	(10 years of age)

SBP systolic blood pressure, *DBP* diastolic blood pressure

Table 9.3 Signs and symptoms of dehydration in infants in relation to loss of body fluid

% Weight loss	Signs and symptoms	% loss of fluids ml/kg (breast-fed)	% loss of fluids (child)
Light 1–5%	Vomiting-diarrhea Dry mucosa Oliguria (<1 mL/kg/h)	50 (5%)	30 (3%)
Moderate 6–10%	Skin folds Rings around eyes Fontanel depressed Oliguria Lethargy	100 (10%)	60 (6%)
Severe 11–15%	Metabolic acidosis Lactate >2 mmol/L Myocardial depression Oliguria Lethargy	150 (15%)	90 (9%)
>15%	Coma, death		

		Color CODE	SCORE
Assessment of the general conditions in the febrile child		**White**	>16
		Yellow	10-16
		Green	9-7
		Red	< 7
	1= Normal	**2= moderate impairment**	**3= severe impairment**
Quality of cry	Strong with normal tone or content and not crying	Whimpering or sobbing	Weak or moaning or High pitched
Reaction to parent stimulation	Cries briefly then stops or content and not crying	Cries off and on	Continual cry or hardly responds
Neurological status	If awake, stays awake or if asleep and stimulated, wakes up quickly	Eyes close briefly awake or awakes with prolonged stimulation	Falls to sleep or will not rouse
Skin color	pink	Pale extremities or cyanosis	Pale or cyanotic or mottled or ashen
Hydration	Normal skin and mucous membrane moist	Normal skin and mouth slightly dry	Skin doughy or tented and dry mucous membrane or sunken eyes
Response (talk, smile) to social	Smile or alert	Brief smile or alerts briefly	No smile or face anxious, dull, no expressions or no alerting

Fig. 9.2 PEWS scoring system

septic child. Rapid diagnosis of sepsis using these scoring systems is essential for identifying the patient at risk, and they should be part of every hospital quality improvement program [17–19]. However, there are still no data from randomized clinical trials to prove the superiority of one system over another [20–22].

Among the various scales for prompt recognition of the clinical risk the Pediatric Early Warning Score (PEWS) (Figs. 9.2 and 9.3) is generally considered the easiest to apply. PEWS can predict the need for specialized medical attention in 96% of cases, and only 17% of these need intensive care after being dealt with by the first team. This illustrates the efficacy of early detection of clinical instability in different clinical settings [23].

The PEWS is applied in medical and emergency units, any time a child is identified as at risk of sepsis. Some children can be classified as at risk of sepsis even though their clinical and laboratory findings do not suggest it (congenital immunodeficiency, syndromic patients, patients repeatedly hospitalized).

Pediatric Early Warning Score					
	0	1	2	3	Score
Cardiovascular	Pink or capillary refill 1-2 seconds	Pale or capillary refill 3 seconds	Grey or capillary refill 4 seconds tachycardia of 20 above normal rate	Grey and mottled or capillary refill ≥ 5seconds tachycardia of 30 above normal rate	
Respiratory	Within established baseline No retractions Room air	≥10 above established baseline Mild contractions Up to 2L/min or 30%	≥ 20 above established baseline Moderate contraction Up to 4L/min or 40%	≥ 30 above established baseline Severe Contractions Grunting Up to 5L/min or 50%	
Behavior	Playing appropriate or Sleeping	Irritable, but consolable	Irritable and Inconsolable	Lethargic or confused Reduced response to voice or pain	
Score an additional 2pts nebulizer use, suctioning, or persistent vomiting after surgery					
Final score					

Retraction severity

Mild	Moderate	Severe
Subcostal or substernal	Intercostal or supraclavicular	Suprasternal or sternal

Fig. 9.3 Pediatric early warning score

9.3 Sepsis and Septic Shock in Children: Physiopathology

The physiological transition of the fetal to the neonatal circulation and its adaptations during the first 2 years of life greatly affect the hemodynamic response of a child with sepsis. Briefly, the passage from fetal to neonatal circulation involves closure of the fetal shunts (venous duct, foramen ovale, and Botalli duct) and the shift from pulmonary circulation with high pulmonary vascular resistance (PVR) to the low-pressure resistance circulation.

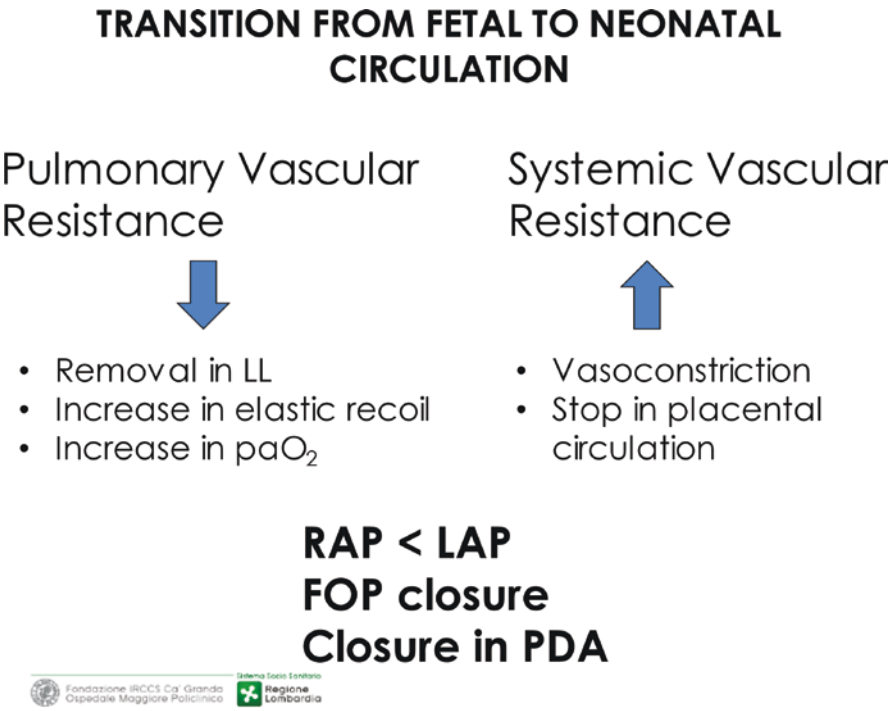


Fig. 9.4 Transition from the fetal to the neonatal circulation, septic shock hemodynamics in neonates and children

The reduction of the PVR permits alveolar expansion and increased pulmonary elastic recoil. In this transition, the systemic vascular resistances (SVR) increase as the placental circulation is gradually excluded. It is the increase in SVR, together with pulmonary recruitment and reduction of the PVR, that cause the physiological closure of neonatal shunts in the first 48–72 h of life.

In the newborn, all the conditions that induce acidosis and hypoxia—many linked to sepsis—act as powerful stimuli for the increase in PVR and re-opening of the fetal shunts. This results in overload of the right heart, right decompensation, and pulmonary hypertension (Fig. 9.4). Inodilators like milrinone and nitric oxide may be indicated in a newborn with septic shock as an inotropic support, together with vasopressors such as adrenaline. In these conditions, volume replacement must be checked by monitoring cardiac output (usually by echocardiography).

Septic shock in the infant and child up to about 2 years causes a circulatory situation where signs of shock predominate with high peripheral resistances (sometimes referred to as "cold shock" though this term is no longer used in recent guidelines), marked reduction of the volemia, and consequently of cardiac output.

9.4 Identification and Treatment of Pediatric Sepsis in a Non-intensive Setting: Pediatric Sepsis 6 Algorithm

This algorithm, used in various emergency departments in the English-speaking world, specifies three levels of intervention:

1. Early identification of the septic child and activation of the reanimation specialist.
2. Six clinical steps to be completed in the first hour after admission.
3. Transfer to the pediatric intensive care unit (PICU).

Early Identification of the Septic Child

Table 9.3 lists the vital parameters by age. Any child presenting with suspected or proven infection, and two of the following, is to be considered at risk of sepsis.

(a) Core temperature < 36 °C or > 38.5 °C (38.0 °C if immunodepressed)
(b) Tachycardia (see the PEWS Table)
(c) Altered mental state (stato mentale)
(d) Capillary refill >2”

Or

One of the following (Red Alert):

(a) Hypotension (see PEWS table)
(b) Lactate >2 mmol/L
(c) Tachycardia/tachypnea
(d) SPO2 in air <92%, irregular respiratory pattern, bradypnea/apnea
(e) Skin cold, marbled

Even only one of the red alerts indicates septic shock and calls for an emergency/urgency consultation with a pediatrician or reanimation specialist.

Within an hour of the diagnosis, therefore, the following items must be completed:

1. Ventilatory support
2. Establishment of a vascular access—IV or IO—and sampling for blood culture, blood gas analysis, lactate, and glycemia
3. Volemic replacement
4. Inotropes/vasopressor drugs
5. Empirical antibiotic therapy
6. Transfer to PICU

9.4.1 Ventilatory Support

A patient with sepsis but not needing inotropic or vasopressor drugs, and with no signs of acute respiratory failure, should be given oxygen therapy with a high- or

low-flow system, to maintain adequate peripheral oxygenation (SPO2 > 94%). For patients with signs of moderate pARDS (P/F 200–300) induced by sepsis, but with no clear indications to intubation and mechanical ventilation, and relatively stable hemodynamics (not requiring inotropic drugs, or refractory septic shock), a reasonable first step is to establish non-invasive respiratory support, with CPAP or Bilevel [24–31]. For a child with septic shock, requiring inotropes or vasopressors, but not presenting respiratory failure, it is clinical practice to consider intubation and mechanical respiration so as to reduce the respiratory work arising from the metabolic load of the sepsis. This holds true even though there are no randomized clinical trials indicating a clear advantage of starting intubation and mechanical ventilation early—bearing in mind the hemodynamic complications of anesthetic drugs, and the shift to positive pressure ventilation [32, 33].

9.4.2 Establishing Vascular Access (IV, IO) and Sampling for Blood Culture, Blood Gas Analysis and Lactate, and Glycemia

Vascular access is often one of the main difficulties in a child in a critical situation, especially if there is acute circulatory failure (septic shock, hemorrhagic, hypovolemic). The PALS and EPLS guidelines insist that vascular access should be established as soon as possible and intraosseous access should be evaluated promptly. This route permits the infusion of drugs, fluid, inotropes, and vasopressors. It should be replaced as soon as possible with central venous access.

The preferred venous entry sites—under ultrasound guidance—in an emergency are the right and left anonymous veins, subclavian, interior jugular, and femoral. The diameter and length of the catheters should be related to the diameter of the vein, keeping the diameter of the catheter less than 30% of that of the vein (to reduce the risk of vascular thrombosis).

As soon as access is stable, samples should be taken for blood gas analysis, lactate, glycemia and calcemia, and blood culture. Lactate higher than 2 mmol/L in blood taken without a tie, from a central or peripheral access, should be considered pathological. The blood gas analysis should be completed, particularly as regards monitoring the glycemia. If there is severe hypoglycemia (<60 mg/dL), it should be corrected with a 10% glucose bolus, 2 mL/kg (glycemia target 60 to 180 mg/dL).

9.4.3 Volemic Filling

Volemic top-up with balanced electrolytic solution (Ringer's lactate) is the first main step in the treatment of pediatric septic shock. The volume and timing of this strategy, however, are still debated. An approach involving the rapid administration of large amounts of crystalloids (40–60 mL/kg) in the first hours, necessary to restore the circulation, can trigger respiratory and circulatory collapse, making intubation and mechanical ventilation necessary. A more conservative approach, with

fluids and 5% albumin, gave less mortality in countries with limited intensive care facilities (FEAST trial). It therefore seems reasonable to establish the replacement volume in relation to the local setting where the clinician is working: for instance, is there a PICU where the patient can be managed? Is transport feasible, and is the child hypotensive? In a center with a PICU, for example, it is reasonable to administer 40–60 mL/kg of balanced crystalloid solution, in doses of 10–20 mL/kg, with hemodynamic monitoring of cardiac output (echocardiography) [34–39]. Non-invasive hemodynamic monitoring is based on measurements of cardiac output, respiratory effort with pulmonary edema, and hepatomegaly.

During volemic filling with large amounts of crystalloids, complications linked to electrolytic and glycemic imbalance may arise. Large doses of Ringer lactate in particular can expose the patient to a risk of hyponatremia and hypoglycemia. Sodium and blood sugar levels must therefore be monitored and corrected as necessary.

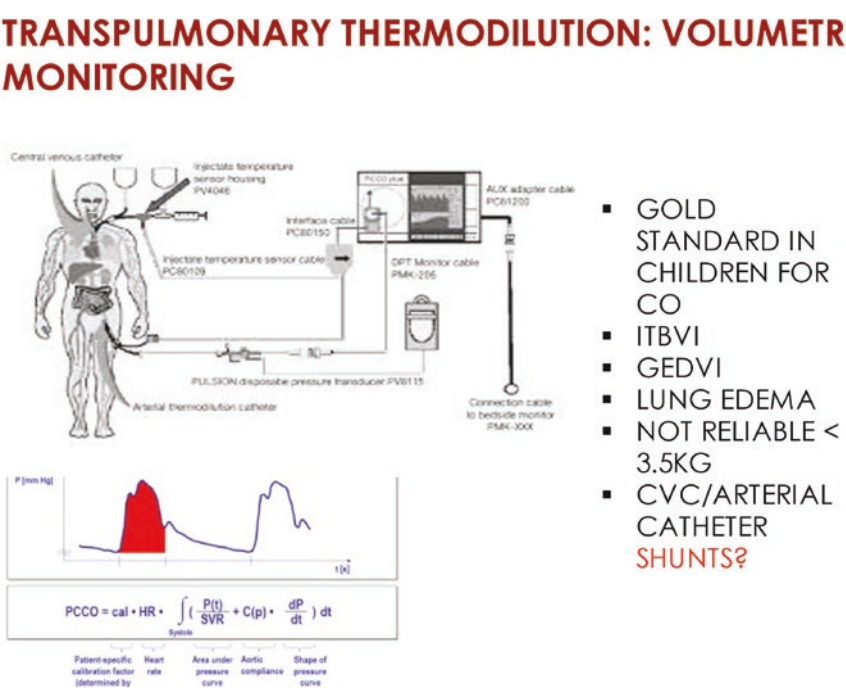
9.4.4 Inotropic and Vasopressor Agents and Hemodynamic Monitoring

ESPNIC 2021 recommends keeping mean arterial pressure (MAP) between the 5th and 50th percentiles established for each age bracket. Some authors accept lower MAP if organ perfusion is adequate. Invasive hemodynamic monitoring is recommended, to include measurements of cardiac output, vascular resistances, and venous saturation in the superior vena cava.

CI, cardiac index	
CI = cardiac output/body surface area	(3.5–5.5 L/min/m^2)
SI = CI/heart rate	(30–60 mL/m^2)
SVRI = 80 × (MAP-PVC)/CI	(800–1600 dyne-s/cm^5)

The gold standard for invasive hemodynamic monitoring is the cold bolus thermodilution method (PiCCO, pulse index contour cardiac output). The PULSION PiCCO is a continuous cardiovascular monitoring system, particularly for cardiac output, based on the pulse contour and arterial thermodilution. Analysis of the pulse contour requires an arterial catheter for continuous measurement of arterial pressure. Arterial thermodilution requires a temperature sensor in the bolus injection line and a second sensor to take the blood temperature. Thermodilution is counterindicated, however, in the following specific situations:

- Intracardiac shunt: left-right shunt CO, overestimation; right-left shunt – CO severe aortic stenosis and severe aortic insufficiency
- Pulmonary thromboembolism



Inotropes/vasopressors are indicated in patients with septic shock refractory to fluids, a reasonable time after receiving 40–60 mL/kg of crystalloids. There are still no clinical trials reporting any clear indication of superiority for adrenaline or noradrenaline in the early stages of fluid-refractory septic shock. In general adrenaline is reserved for cases of cold septic shock with low cardiac output, and noradrenaline is always the first-line drug for hot septic shock. Both these drugs can be injected intraosseously, or in a dilute solution to a peripheral vein if no other vascular access is available, especially in an emergency [40–45] (Table 9.4).

9.5 Identification of the Source of Infection and Empirical Antibiotic Therapy

Antibiotics are the main weapon in the treatment of pediatric sepsis and septic shock. From studies in adults, and the limited evidence in the pediatric literature, the ESPNIC panel of experts agree on recommending antibiotics within an hour of presentation to a child with clinical evidence of septic shock [46–50]. For children with suspected sepsis but no hemodynamic impairment, this time window can be enlarged to the first 3 h from admission, in order to exclude doubtful cases of sepsis or febrile infants without sepsis.

Table 9.4 Preparation and use of vasoactive drugs

Pediatric schedule			
Drug	Preparation	Concentration	Continuous perfusion
Epinephrine	1 mg to 50 ml DW5%	0.02 mg = 20 mcg/mL	0.02–1 mcg/kg/min
Norepinephrine	2 mg to 50 ml DW5%	0.04 mg = 40 mcg/mL	0.02–1 mcg/kg/min
Dobutamine	62.5 mg to 50 ml DW5%	1.5 mg = 1500 mcg/mL	2–20 mcg/kg/min
Dopamine	50 mg to 50 ml DW5%	1 mg = 1000 mcg/mL	2–20 mcg/kg/min
Milrinone	10 mg to 50 ml DW5%	0.2 mg = 200 mcg/mL	0.25–0.75 mcg/kg/min
Nitroglycerine	5 mg to 50 ml DW5%	0.1 mg = 100 mcg/mL	0.2–1 mcg/kg/min
Sodium nitroprussiate	25 mg to 50 ml DW5%	0.5 mg = 500 mcg/mL	0.3–1 mcg/kg/min

The ESPNIC recommendations for antibiotics in pediatric septic shock indicate several steps: (1) First of all, an empirical approach with a broad-spectrum antibiotic, or more than one drug, for septic shock or organ failure, continuing treatment for at least 10 days; (2) narrowing the spectrum and de-escalation of the antibiotic therapy when a diagnosis has been made and an antibiogram done; and (3) when there is no microbiological diagnosis, suspend or de-escalate the therapy in line with the clinical and laboratory signs, in consultation with the infectious diseases specialist [46].

Identifying the source of the infection is important for orienting the antibiotic therapy. Several hypothesis must be taken into consideration to guide treatment in the very first hours, in relation the clinical suspicion and the patient's age: (a) unknown source; (b) meningitis/encephalitis; (c) pneumonia; (d) abdominal infection; (e) surgical site infection; (f) infection in the vascular line; (g) ventriculoperitoneal shunt infection; and (h) febrile neutropenia. For immune-depressed patients or those at risk of infection with multiresistant bacteria, a multidrug empirical strategy is advisable, bearing in mind the possibility of fungal sepsis or opportunistic pathogens [51, 52].

The concept of early source control plays an important part in pediatrics, especially in children with necrotizing fasciitis, bacterial or fungal infections from a vascular catheter or ventriculoperitoneal shunt, and drain for empyema or abscess [53–55].

Below are some schedules used in our unit for empirical antibiotic therapy in children (Sanford Guide Antimicrobial Therapy 2021, 57).

9.5.1 Sepsis/Septic Shock, Source Not Identified, Age up to 28 Days

Early-Onset Neonatal Sepsis

Etiologies. *Streptococcus agalactiae*, *E. coli*, *Klebsiella* spp., *Enterobacter*, *Enterococcus* spp., *Staph aureus*, *Listeria*

Age less than 7 days: Ampicillin iv 150 mg/kg/day IV div q8h + cefotaxime iv 100 mg/kg/day div q12h, +/− gentamycin iv 5 mg/kg/day q24 or 2.5 mg/kg q8h IV

Age more than 7 days: Ampicillin iv 200–300 mg/kg/day IV q6h + cefotaxime 150 mg/Kg/day, div q8h +/− gentamycin IV 5 mg/kg/day

Late-Onset Sepsis

Etiologies As above, plus *Haemophilus I* and *Staph epidermidis* in patients with central venous catheter:

Ampicillin iv 200 mg/kg/day IV div q6h, plus ceftriaxone IV 75–100 mg/kg q24h dose

Or

Ampicillin iv 200–300 mg/kg/day IV q6h +/− gentamycin IV 5 mg/kg/day

If MRSA is a concern: Vancomycin IV 15 mg/kg/day, q12h two doses. Monitor plasma vancomycin levels (10–15 mcg/mL).

9.5.2 Sepsis/Septic Shock, Source Not Identified, Age 28 Days or More

Etiologies: *Streptococcus pneumoniae*, *Streptococcus pyogenes* group A, *Staph aureus* MSSA and MRSA, *Enterococci*

Cefotaxime 50–74 mg/kg/day IV q8h or ceftriaxone 100 mg/kg/day q24h+/− vancomycin 60 mg/kg/day divided q6h or continuous infusion (target blood level 10–15 mcg/mL)

Or

Piperacillin/tazobactam IV 75 mg/Kg/day IV q6h + vancomycin IV 60 mg/kg/day divided q6h or continuous infusion (target blood level 10–15 mcg/mL)

Or

Meropenem 40 mg/kg IV q8h, ± vancomycin 60 mg/kg/day divided q6h or continuous infusion (target blood level 10–15 mcg/mL).

Carbapenems should be considered for a patient with suspected or previous ESBL+ bacteria, neutropenia, or immune-depression (congenital immune deficiency, oncology, transplant). Swabs for these patients should be submitted as soon as possible to test for multidrug resistance (MDR); blood culture should be done and tests for fungal infection.

Recommended duration of therapy 7–10 days if clinical course and laboratory findings are favorable, with no microbiological isolation.

Table 9.5 Epidemiology

Bacteria	Age group			
	Birth to 1 month	1–3 months	3 months to 5 years	5–18 years
Streptococcus pneumoniae	+	+++	++++	+++
Haemophilus influenzae[a]	+	+	+	±
Streptococcus pyogenes		+	+	+
Staphylococcus aureus	++	++	+	+
Streptococcus agalactiae	+++	+		
Escherichia coli	++	+		
Mycoplasma pneumoniae		+	++	++++
Chlamydophila pneumoniae		+	+	++
Chlamydia trachomatis	+	++		
Bordetella pertussis	±	++	+	+

++++ indicates very common; +++, common; ++, relatively un common; +, rare; ±, rare; −, absent
(Adapted from: Esposito SDo We Know When, What and For How Long to Treat? The Pediatric Infectious Disease Journal: 10.1097/INF.0b013e318255dc5b58)

9.5.3 **Pneumonia** (Table 9.5)

Up to 3 months:

Cefotaxime 200 mg/kg/day, three doses, or ceftriaxone 75–100 IV mg/kg/day, q24h; azithromycin 10 mg/kg q24h for 3 days if *Bordetella* is suspected (hyperleukocytosis, PARDS, pulmonary hypertension, cardiogenic shock).

Over 3 months:

Cefotaxime 200 mg/kg/day, three doses, or ceftriaxone 75–100 IV mg/kg/day, q24h; azithromycin 10 mg/kg q24h for 3 days if *Bordetella* is suspected (hyperleukocytosis, PARDS, pulmonary hypertension, cardiogenic shock). Oseltamivir if influenza A is suspected.

Duration of treatment 10–14 days

9.5.4 Meningitis

In the neonate, the prevalent central nervous system infections are caused by *Streptococcus agalactiae*, *E. coli*, *Listeria monocytogenes*, and *Klebsiella pneumoniae*. Among children younger than 2 years, the most frequent pathogens are *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus I*, and *Streptococcus agalactiae*; among patients over 2 years and up to 50 years, the prevalent pathogens are *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus I*. Patients older than 50 years mainly present *Streptococcus pneumoniae*, *Neisseria meningitidis*, and, again, *Listeria monocytogenes*.

Duration of treatment 10–14 days

Age 1 month to 50 years

Cefotaxime 300 mg/kg/day IV divided q6-8h or ceftriaxone 100 mg/kg/day divided 12 h +/− vancomycin 60 mg/kg/day divided q6h or continuous infusion (see below).

+/− Dexamethasone 0.15 mg/kg IV q6h x 2–4 days administered with or just before first dose of antibiotic for *Haemophilus I*. No data exist actually to support the use of steroids for *Streptococcus pneumoniae* meningitis.

Or

Meropenem 40 mg/kg IV q8h, ± vancomycin 60 mg/kg/day divided q6h or continuous infusion (target blood level 10–15 mcg/mL).

For a patient with brain injury, recent surgery, cochlear implant, or infection from ventriculoperitoneal shunt:

Cefotaxime 300 mg/kg/day IV divided q6-8h + vancomycin 60 mg/kg/day divided q6h or continuous infusion (target blood level 10–15 mcg/mL).

Alternatively

Meropenem 40 mg/kg IV q8h, ± vancomycin 60 mg/kg/day divided q6h or continuous infusion (target blood level 10–15 mcg/mL).

For *Listeria monocytogenes*: Ampicillin 300–400 mg/kg IV divided q6h + gentamycin 2.5 mg/kg every 8 h.

Duration of treatment 10–14 days

9.6 Corticosteroids

There is as yet no published evidence to back the use of corticosteroids in pediatric sepsis. Cortisone can be employed if hypotension persists despite volemic replacement and vasopressors.

9.7 Glycemia

The ESPNIC guidelines are against a policy of tight glycemic control of glycemia <140 mg/dL [56–58]. However, 180 mg/dL is commonly accepted as the limit above which insulin in children is virtually risk-free.

9.8 Nutrition

When possible, enteral nutrition is recommended within 48 hours from admission to all patients with septic shock or sepsis who present no specific contraindications to enteral treatment.

9.9 Transfusions

The guidelines do not recommend any transfusion threshold for the unstable patient. For a stable patient, they recommend blood derivatives with more than 7 g/dL of hemoglobin.

9.10 Substitution therapies, immunoglobulin

There are no strong recommendations for these methods in pediatric sepsis or multiorgan failure (MOF). They may be indicated in selected cases.

9.11 Conclusions

Pediatric sepsis or septic shock raises certain diagnostic difficulties that call for an extremely prudent approach, considering any febrile infant or child with organ dysfunction at risk of sepsis. In particular, the physiopathology of septic shock in neonates or children implies the need for close attention to the incidence of myocardial dysfunction and its prompt diagnosis.

There are several main key points in this condition: (1) prompt diagnosis; (2) rapid access to the patient and activation of the sepsis bundle in use in each center; (3) rapid assessment of volemia, electrolytic status, and glycemia (blood gas analysis, echocardiography, caval US); (4) correction of volemia with balanced solutions; (5) prompt injection – even early—in a peripheral vein of dilute solutions of vasopressors/inotropes; (6) antibiotics in the first 3 h; (7) surgical, infectology consultations.

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Ventilatory Management of the Patient with Severe Obesity

10

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10.1 Introduction

Obesity (defined by a body mass index (BMI) ≥ 30 kg/m^2) is a disease caused by an excessive or abnormal distribution of adipose tissue resulting in chronic diseases related to chronic inflammation and metabolic dysfunction [1, 2]. The prevalence of obesity, which has now become a global epidemic, is increasing in both developed and developing countries. The United States occupies the first place in 2020 (36%) followed by Australasia (30%), with an expected prevalence in the United States increasing by up to 50% by 2030 [3], while European countries have a prevalence between 20 and 30%. The proportion of patients with obesity in intensive care is expected to increase concomitantly or even to a greater extent, as obesity increases the risk of a more serious course of the disease with a greater need for intensive care and mechanical ventilation [4] as shown in trauma [5], in patients with traumatic brain injury [6], in the out of hospital cardiac arrest [7], during the H1N1 pandemic [8], and, recently, also in patients suffering from coronavirus disease 2019 (COVID-19) [9–12]. Obesity, in particular abdominal obesity (android fat

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distribution) and severe obesity [13], causes alterations in anatomy and respiratory physiology and, therefore, complicated management of the airways and ventilator settings during mechanical ventilation. Obesity also appears to be associated with an increased risk of acute respiratory distress syndrome (ARDS) [14] and infections, mainly pneumonia [15], probably correlated to an unbalanced production of adipochines [16].

In ventilated patients, obesity increases the duration of ICU length of stay and the duration of mechanical ventilation [17]. The phenomenon where obesity increases the morbidity but seems to protect against mortality in selected critical patients, known as the "obesity paradox," has been evoked in patients with ARDS [14] and in those under mechanical ventilation [17], although it remains much debated.

10.2 Respiratory Pathophysiology

Obesity causes alterations in respiratory pathophysiology in patients suffering from this disease. One of the trigger factors is a reduced pulmonary volume, caused by the displacement of the diaphragm in a cranio-caudal direction due to an increase in abdominal tissue mass, and an increase in the tissue of the thoracic wall. The reduction in resting pulmonary volume after normal exhalation, functional residual capacity (FRC), is 5–15% for each 5 kg/m^2 increase in BMI [18]. The patient with obesity is therefore characterized by an increased respiratory workload and altered gas exchanges. Both alterations reduce physical capacity and functional reserve if the patient is exposed to respiratory stress. The consequence of increasing tissue mass will be greater in supine position than in an upright position, due to a greater cranial displacement of the diaphragm. In addition, a further decrease in FRC can be observed during anesthesia due to the loss of respiratory muscle tone and, most likely, in intensive care for the use of sedatives and relaxing muscles. The reduction of the FRC promotes the closure of the airways and the formation of atelectasis, as it will be discussed later.

There are several causes of increased respiratory work in the patient with obesity. One is the increased resistance of the airways due to the reduced caliber of the airways and an increase in the incidence of asthma. Another is the increased displacement of tissue, both in the abdomen and in the lung and chest wall. Finally, increased tissue resistance is added to respiratory work [19]. The patient with obesity can easily develop respiratory fatigue during exercise and, in severe cases, already at rest. It is often assumed that the elastance of thoracic wall or its inverse, the compliance of the thoracic wall, is affected by obesity. However, the increase in the weight of the abdomen and chest wall requires work while moving the tissue, but when the movement is finished, no additional pressure is required [19]. End-inspiratory and end-expiratory pauses should be long enough when measuring chest wall compliance. Pulmonary compliance, on the other hand, is reduced in the obese patient [20]. The decreased lung volume may require additional pressure during inhalation to open closed units, and this can be translated into a reduction in compliance.

The airways can close in dependent lung regions during expiration, an age-dependent physiological phenomenon. Although this concept has been known for many years, greater or even complete airway closures have been shown in recent years in obese anesthetized patients [21] or patients in ICU with obesity on mechanical ventilation. This means that a certain airway pressure is necessary to start lung inflation and is not caused by a time-dependent positive end-expiratory pressure (PEEP). It is not clear where the complete closure occurs, but it could take place in the most central airways and not in the peripheral ones. In the latter case, the simultaneous closure of thousands of airways would be needed, as discussed recently [22].

A consequence of the classic closure of the airways is an obstacle to ventilation where closure takes place and the decrease in ventilation will be higher the longer the closure during the respiratory cycle. If the airways are continuously closed, as can be seen during anesthesia and most likely in intensive care, the distal alveoli at closure will collapse due to gas absorption [23]. The higher the concentration of oxygen in the inhaled gas, the faster the collapse. With pure oxygen, it can take a few minutes and with air, a couple of hours. The complete closure, on the other hand, will delay the beginning of inspiration without affecting the distribution itself.

The irregular distribution of ventilation caused by airway closures will occur mainly in dependent lung regions. Regions that are little but still ventilated will cause a ventilation-perfusion mismatch and regions that collapse due to the continuous closure of the airways will cause shunt [23].

Both phenomena alter oxygenation [24] and a high shunt can even alter the elimination of carbon dioxide (CO_2). With a very high shunt, oxygenation responds little or no to the increase in oxygen in the inhaled gas. Finally, in patients with obesity, there is significant heterogeneity in both resistance and compliance; therefore, inflation or uneven deflation of the lungs can cause dynamic differences in pressure between lung regions and lead to inter-regional air flows known as the pendelluft effect.

However, patients with obesity are not an homogeneous group with regard to physiological changes, since the level of obesity and the distribution of fat (gynoid versus android) are confusing factors that should be taken into account.

10.3 Management of the Obese Patient with Acute Respiratory Failure

Although acute hypoxemic respiratory failure (ARF) is not the leading cause of ARF in patients with obesity [25, 26], hypoxemia is frequent as it is favored by increased oxygen consumption or work of breathing and the formation of atelectasis, especially in patients with pathological obesity and during ARF [27]. Noninvasive strategies should first optimize the position of the patient with a reverse Trendelenburg position, “beach chair position” or sitting position, which improve respiratory compliance and gas exchange in patients with pathological obesity [28, 29].

In patients with postoperative hypoxemia or ARF, noninvasive ventilation (NIV) is recommended with moderate evidence, justified by a decreased need for intubation, mortality, and morbidity with respect to standard oxygen [30, 31]. An observational study of 72 patients with ARF after abdominal surgery showed that NIV avoided intubation in 67% of cases [32].

In a post hoc analysis of a large study of 830 chest postoperative patients [33], it has been shown that among the 272 patients with obesity (average BMI of 34 kg/m^2), NIV was not superior to oxygen therapy with high-flow nasal cannulas (HFNC), with treatment failure occurring in 15% and 13%, respectively, in the NIV and HFNC groups.

Therefore, NIV could be considered first-line therapy in obese patients with postoperative ARF [34], but further studies are needed to confirm the role of CPAP (continuous positive airway pressure) and/or HFNC in this context [35, 36].

Data on the management of hypoxemic ARF with noninvasive ventilation/oxygen therapy strategies are scarce, especially in patients with obesity. Recent international guidelines failed to provide a recommendation on the use of NIV in hypoxemic ARF [30]. A large trial compared NIV with standard oxygen and HFNC in 310 patients with hypoxemic ARF [37]. The results showed lower mortality rates with HFNC than NIV, thus suggesting the negative effects of NIV. Similarly, an observational study involved 76 patients with BMI > 40 kg/m^2 showed that hypoxemic ARF caused by pneumonia was associated with NIV failure [38].

However, given the possibility of physiological abnormalities in patients with obesity, NIV could play a role, especially in patients with pathological obesity, thanks to PEEP which could improve oxygenation and lung volume or alveolar recruitment [39]. Finally, the possible use of NIV or HFNC as an alternative to standard oxygen in patients with obesity and hypoxemic ARF has not been determined yet, and further trials are needed.

Hypercapnic ARF in patients with obesity may not only be part of the clinical course of cardiogenic pulmonary edema, pneumonia, asthma, and exacerbation of chronic lung disease but may also be due to exacerbation of obesity hypoventilation syndrome (OHS) [40]. Positive airway pressure, such as CPAP or NIV, is the recommended outpatient treatment for patients with OHS [40]. Similarly, NIV is the usual treatment used in OHS exacerbations, but no study has assessed its advantage over other oxygen therapy strategies. NIV combines potentially beneficial physiological effects, including PEEP which preserves the patency of the upper airways and the pressure support to control central hypoventilation. However, an observational study of 33 patients with pathological obesity reported a lower BMI (47 kg/m^2) in patients where NIV was effective compared to BMI of 62 kg/m^2 in those where NIV failed [26]. In this context, NIV may be an appropriate treatment, but HFNC interspersed with NIV trials should be considered.

10.4 Airway Management

Patients with obesity are also characterized by morphological alterations potentially associated with difficulty during masked ventilation and during airway management: reduced neck mobility, limited opening of the mouth, increased size of the pharynx,

soft tissues and of the tongue, unfavorable conformation and position from the larynx, increased neck circumference, and reduced thyromental distance [41]. In addition, patients with obesity have a high incidence of obstructive sleep apnea [42], which is directly related to complications occurring during the airway management of this subpopulation of critical patients [43]. Obesity contributes to airway compression due to increased airway fat deposits [44]. Obesity, in particular severe obesity (BMI $\geq$ 40 kg/m^2) with an android fat distribution, is an important risk factor for major complications, morbidity, and mortality related to intubation procedure in ICU [45].

Most of the existing literature on airway management of patients with obesity is related to management in the operating room [46]. In this case several strategies are often recommended, including the adoption of the "ramped position" using specific devices or pillows/blankets under the patient's head and shoulders, pre-oxygenation with positive pressure ventilation [39], and the use of videolaryngoscopes [47].

However, compared to elective surgery in patients with obesity, the intubation of the critical patient has profound differences in terms of indications, timing, and coexisting conditions. In ICU, the incidence of difficult intubation is twice as high as in the operating room and the occurrence of serious complications is considerably higher [46].

The patient's pre-procedural preparation is the key to successful intubation. An ideal preparation aims to prolong the desaturation time, which in patients with obesity is mainly related to the rapid loss of FRC after sedation. As for positioning, a randomized controlled study questioned the usefulness of ramped position applied in critical patients [48]; however, the study included a large percentage of patients without obesity.

Therefore, the positioning of the patient must be individualized on the patient's anatomy and based on the experience of the intensivist. A semi-sitting position during pre-oxygenation could help reduce positional flow limitation and air trapping [43]. Conventional masked ventilation can cause rapid desaturation in patients with pathological obesity. Several studies have confirmed that pre-oxygenation with CPAP or NIV improves oxygenation and allows a longer time window for intubation [39, 49].

For these reasons, positive pressure pre-oxygenation should be considered the reference technique in critical patients with obesity, considering that obesity leads to an intrinsic increase in the risk of difficult masked ventilation. HFNC could also play a role [50], especially in rapid sequence intubation in non-severe hypoxemic patients, where avoiding balloon ventilation may be desirable but is associated with an increased incidence of severe desaturation [51].

However, the role of HFNC in patients with obesity needs to be clarified and cannot replace pre-oxygenation by positive pressure [52]. The intubation maneuver should always be considered as potentially difficult in patients with obesity [46], with advanced age, higher BMI, high Mallampati score, and reduced neck mobility being independent risk factors for both difficult mask ventilation and difficult intubation. A meta-analysis in surgical patients with obesity suggests an advantage of videolaryngoscopes over direct laryngoscopy [47]. In patients with obesity in intensive care, it seems reasonable to consider the use of videolaryngoscopes by properly trained intensivists, especially in patients with multiple risk factors.

10.5 Mechanical Ventilation in Non-ARDS Patients

Obesity is associated with abdominal and thoracic tissue mass, which transmit additional hydrostatic pressure through the chest wall and diaphragm to the pleural space and, thus, the alveoli. If pleural pressure is higher than intra-alveolar pressure, the alveoli will collapse, and compression atelectasis will occur predominantly in dependent lung areas, where hydrostatic pressure is highest. For example, functional residual capacity is impaired by up to 21% in non-ventilated subjects with obesity in the supine position [53] and total lung and vital capacity are reduced as well. Induction of anesthesia with muscle relaxation following pre-oxygenation with 100% O_2 further reduces end-expiratory lung volume (EELV) by about 50%, if a positive end-expiratory pressure (PEEP) of 5 cmH_2O is used after initiation of mechanical ventilation (Fig. 10.1) [53]. The main mechanism of gas exchange impairment is, therefore, shunt (atelectasis) in patients with obesity [24].

10.6 Recruitment Maneuver

Because the opening pressure of alveoli is higher than the pressure needed to keep them open, application of an initial recruitment maneuver (RM) followed by adequate PEEP after intubation or disconnection of the patient from the ventilatory circuit seems intuitive. Due to the high pleural pressure in patients with obesity, opening pressures up to 50 cmH_2O applied during a RM in patients with obesity without lung injury may not result in full lung recruitment [54]. Potential side effects of applying such high airway pressures include a decrease in venous return and, thus, cardiac preload with a drop in cardiac output and systemic blood pressure. In addition, barotrauma such as pneumothorax or pneumomediastinum especially in patients with pre-existing structural lung damage such as emphysema, and a mechanically triggered boost of pre-existing lung inflammation may occur. Thus, RM is not generally recommended, and their use remains a decision based on individual risk/benefit considerations.

10.7 PEEP

In mechanically ventilated patients, PEEP is used to keep alveolar pressure above the closing pressure of alveoli, thereby maintaining end-expiratory lung volume (EELV) and arterial oxygenation. In another words, PEEP does not strictly induce alveolar recruitment but PEEP avoids alveolar derecruitment by maintaining open alveoli. Thus, protective ventilation strategies may improve clinical outcomes even in patients without ARDS [55]. Due to the superimposed pressure transmitted by adipose tissue on the pleural space, closing pressures in patients with obesity are higher and lungs of these patients are more prone to such complications (Fig. 10.1). Despite these considerations, routinely used PEEP levels applied for ventilation of patients with obesity are often not higher than in normal weight patients [56]. In

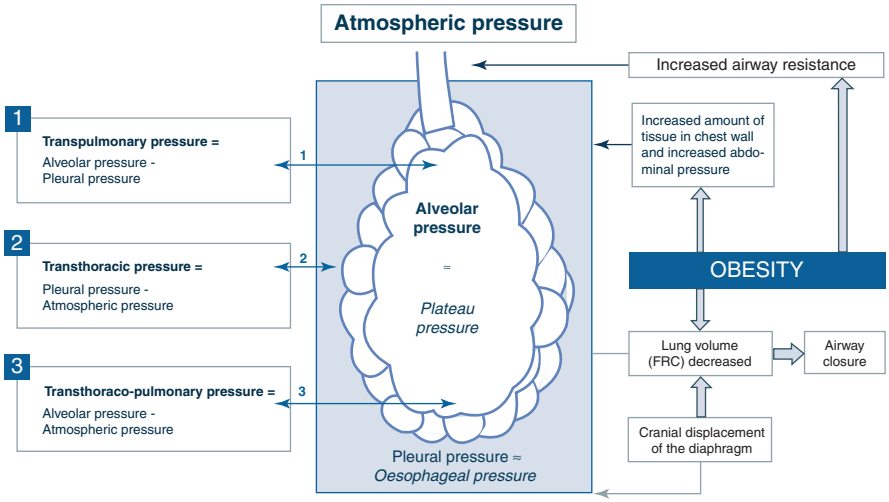

Fig. 10.1 Effect of obesity in main pressures of the respiratory system. The respiratory system includes the lung and the chest wall, and the airway pressure is related to both transpulmonary and transthoracic pressures, which differ in the patient with obesity compared to the patient without obesity. The relative part of pressure due to transthoracic pressure is often higher in the patient with obesity than in the patient without obesity (elevated pleural pressure, which can be estimated by esophageal pressure). The plateau pressure represents the pressure used to distend the chest wall plus lungs. In patients with obesity, elevated plateau pressure may be related to an elevated transthoracic pressure, and not an increase in transpulmonary pressure with lung overdistension. FRC functional residual capacity. (Figure taken from the review by De Jong et al. [1])

previous studies, different methods to find the individualized "best" PEEP in patients with obesity have been used. These approaches targeted improvements in oxygenation, lung mechanics, and regional ventilation distribution. In patients undergoing bariatric surgery, individualized PEEP resulted in a range of PEEP levels between 10 and 26 cmH_2O with a median of 18 cmH2O [53] and restored EELV to the same level before intubation and initiation of mechanical ventilation. Other studies regularly found PEEP levels >15 cmH_2O [57, 58].

However, a large trial of ventilation in patients with obesity during anesthesia did not demonstrate a difference in postoperative pulmonary complications for constant PEEP levels of 4 versus 12 cmH_2O [59]. The PEEP levels in this pragmatic study, however, were not aiming at and resulting in full lung recruitment. As mentioned above, use of higher airway pressures is often associated with hemodynamic depression and higher requirements for fluids and vasopressors [59]. At least in the perioperative setting, evidence from meta-analysis and clinical trials are somewhat conflicting regarding improved clinical outcomes [55, 60].

10.8 Tidal Volume

Limiting tidal volume (VT) has been shown to reduce ventilation-associated lung injury and inflammation in non-selected patients with and without ARDS. The idea of normalizing VT for predicted body weight (PBW) is based on the expected lung volume (dependent on patient's height and sex) and aims to limit the VT/EELV ratio, i.e., mechanical lung strain. As mentioned above, EELV is regularly below the values in a normal weight population. Thus, referencing VT to PBW per se can result in higher strain than in normal weight patients. If PBW is not formally calculated but just estimated, there is a tendency to overestimate PBW and, thus, VT in patients with obesity [56]. Positioning patients with obesity in ramped or sitting positions and even early mobilization may facilitate unloading the diaphragm from increased abdominal pressure and may thereby improve aeration of dependent lung areas. Early implementation of spontaneous breathing activity can preserve diaphragmatic tension, redistribute ventilation to dependent lung areas [60], may avoid diaphragmatic muscle atrophy caused by muscle relaxation [60], and reduce duration of mechanical ventilation [61].

10.9 Mechanical Ventilation in ARDS Patients

Anzueto et al. [62] and Karla et al. [63] showed that ARDS patients with obesity were ventilated with higher VT (per kg of PBW) compared to ARDS patients without obesity. It is tempting to speculate that the amount of atelectasis was different between patients with and without obesity and that the higher VT was chosen by the clinicians to maintain an adequate alveolar ventilation. A study by Grasso et al. [64] tempted to confirm this hypothesis by reporting a decrease in the use of extracorporeal membrane oxygenation (ECMO) in patients with abdominal hypertension by increasing the airway pressure—often above 30 cmH_2O—based on a transpulmonary pressure target. Interestingly, in the study by Karla et al. [63], the airway plateau pressure and driving pressure were similar between patients with and without obesity. Of note, in both studies, the outcome was similar between the two groups. Similarly, De Jong et al. [65], in ARDS patients with obesity, did not find any difference in driving pressure between survivors and non-survivors [66]. When 21 ARDS patients with obesity were compared to 44 patients with ARDS but with a normal BMI, it was found that the two groups had similar recruitability and changes in oxygenation when PEEP was increased from 5 to 15 cmH_2O [67]. In these two groups, abdominal pressure and chest wall elastance were also similar. In contrast, Fumagalli et al. [68] found an impressive improvement in oxygenation and lung elastance using higher PEEP (22 cmH_2O) compared to lower PEEP (13 cmH_2O). The higher PEEP was selected according to transpulmonary pressure, while the lower PEEP was selected according to a PEEP/FiO_2 table. Once again, the abdominal pressure was not measured (or reported). The same authors in a retrospective study of patients with severe ARDS found better gas exchange, respiratory mechanics,

and survival in 50 patients treated according to a personalized approach (based on transpulmonary pressure) compared to 70 patients treated with a standard protocol [69]. The personalized approach resulted in much higher PEEP levels of 20 cmH_2O compared to 9 cmH_2O used in the standard approach. A retrospective analysis of the ALVEOLI trial showed improved outcome using PEEP 12 cmH_2O compared to 9 cmH_2O [70]. In this trial, however, patients with a weight > 1 kg/cm of height and BMI usually >50 kg/m^2 were not included. We may wonder why the reported effect of different levels of PEEP differs among studies. We have to note that the BMI of the population of the different studies was 31 kg/m^2, as in the study of Chiumello et al. [67] and likely in the ALVEOLI study [70], versus a BMI higher than 50 kg/m^2 in the study by Fumagalli et al. [68]. Given such a different BMI, it is likely that the abdominal pressure and mechanical impairment were different in the different populations. The normalized mechanical power, which has been shown being strongly associated with mortality [71], was not monitored. Moreover, RM was not consistently used, and their use and timing remain a matter of debate in ARDS patients with and without obesity [72]. A PEEP decremental trial preceded by a RM may decrease lung overdistension and collapse in ARDS obese patients [73]. In 21 ARDS patients with severe obesity (BMI = 57 ± 12 kg/ m^2) [73], RM was performed during pressure controlled ventilation with delta pressure of 10 cmH_2O, and PEEP was increased until a plateau pressure of 50 cmH_2O for 1 min. After, the ventilator mode was switched to volume controlled ventilation (5 ml/kg of PBW), and the PEEP dropped by 2 cmH^2O every 30 s. The optimal PEEP was determined by the PEEP value with the best compliance of the respiratory system plus 2 cmH_2O.

Finally, a second lung RM was performed and the selected optimal PEEP was set. Required PEEP was increased to 8 [8, 11] cmH_2O above traditional ARDSnet settings with improvement of lung function, oxygenation, and ventilation/perfusion matching, without impairment of hemodynamics or right heart function. Moreover, in a retrospective study [69], the same authors also reported that patients treated with RM and with higher PEEP were weaned from vasopressors agents faster (and improved survival) than patients who were treated with low ARDSnet PEEP table. Future investigations would be beneficial to clarify the lung-heart interaction when high airway pressure is used in the settings of high pleural pressure. Given that the setting of mechanical ventilation (VT, PEEP) and the indicators of ventilator-induced lung injury (mechanical power, driving pressure) are crucially dependent on chest wall elastance, it is our opinion that it is difficult to propose any treatment if key variables such as transpulmonary pressure and intra-abdominal pressure are not measured or ignored (Fig. 10.1).

Prone position [74] also deserves attention in patients with ARDS and obesity. The safety and efficiency of this therapeutic were similar between patients with and without obesity, and the ratio of alveolar pressure in oxygen over fraction of inspired oxygen (PaO_2/FiO_2) was significantly more increased after prone position in patients with obesity compared to patients without obesity [75]. Prone position is a therapeutic choice in patients with severe ARDS and obesity, and the mechanisms of action, caution, and clinical effects are detailed in Fig. 10.2. In case of severe ARDS

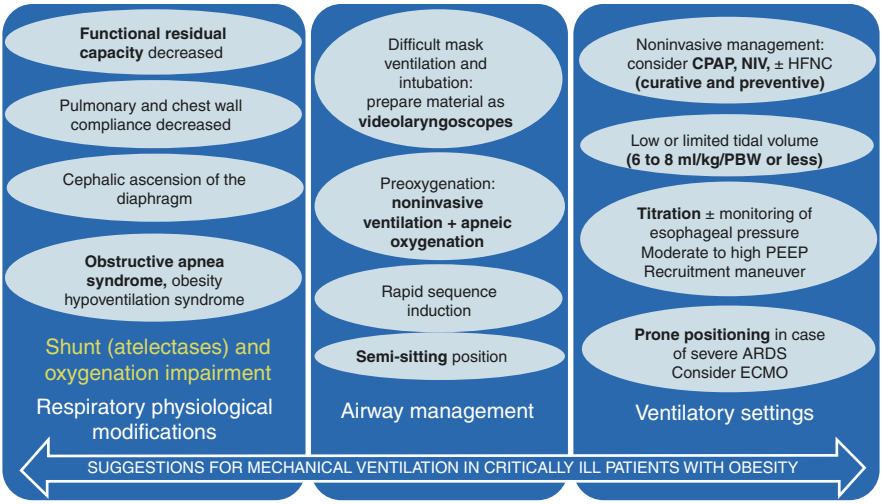

Fig. 10.2 4 main respiratory physiological modifications and suggestions for mechanical ventilation in critically ill patients with obesity. The main respiratory physiological modifications (functional residual capacity decreased, abdominal pressure often increased, pulmonary and chest wall compliance often decreased, cephalic ascension of diaphragm, oxygen consumption and work of breathing increased) lead to shunt via atelectasis and gas exchange impairment. Comorbidities are often associated with obesity: obstructive apnea syndrome and obesity hypoventilation syndrome. Consequences on airway management, potentially difficult, include the preparation of adequate material for difficult intubation as videolaryngoscopes, pre-oxygenation with noninvasive ventilation in a semi-sitting position, considering adding apneic oxygenation (OPTINIV method), rapid sequence induction, and recruitment maneuver following intubation after hemodynamic stabilization. Ventilatory settings include low or limited tidal volume (6–8 ml/kg/PBW or less), moderate to high PEEP (7–20 cmH2O) if hemodynamically well tolerated, recruitment maneuver (if hemodynamically well tolerated, in selected patients), monitoring of esophageal pressure if possible, use of prone positioning in a trained team in case of severe ARDS, and without contraindicating ECMO. After extubation, CPAP or NIV should be considered early, as implementation of positive pressure therapies at home after evaluation. PBW predicted body weight, PEEP positive end-expiratory pressure, ARDS acute respiratory distress syndrome, ECMO extracorporeal membrane oxygenation, CPAP continuous positive airway pressure, NIV noninvasive ventilation, and HFNC high-flow nasal cannula oxygen (figure taken from the review by De Jong et al. [1]).

after failure or inability to use prone positioning and neuromuscular blockers, veno-venous extracorporeal membrane oxygenation (ECMO) can also be safely used in ARDS obese patients [76, 77].

10.10 Weaning and Extubation

The specificities of weaning and extubation in intensive care patients with obesity are summarized in Table 10.1.

The spontaneous breathing trial should be clearly separated from the level of pressure support and PEEP set before extubation and the respiratory support

Table 10.1 Characteristics of weaning in obese patients

• Prolonged release of drugs: stop sedation as soon as possible (as in patients without obesity)
• Higher PEEP levels
• Personalized monitoring
• More effective pronation than obesity-free patients
• Spontaneous breathing test: prefer T-tube or pressure support with 0 pressure support and 0 PEEP
• Extubation as soon as possible
• Preventive/curative NIV and HFNC could help

PEEP positive end-expiratory pressure, *NIV* noninvasive ventilation, *HFNC* high-flow nasal cannula oxygen

following extubation. A physiological study specifically assessed the inspiratory effort during weaning of mechanical ventilation in critically ill patients with morbid obesity [78]. The main result of this study was that for patients with obesity, T-piece and pressure support ventilation 0 + PEEP 0 cmH_2O were the weaning tests predicting post-extubation inspiratory effort and work of breathing the most accurately [78]. If the work of breathing is closely the same between T-tube and after extubation [78], the patient with obesity remains prone to atelectasis, and therefore, atelectasis should be avoided as much as possible. That is why after a T-tube, the obese patient should be reconnected to mechanical ventilation, as already demonstrated in patients without obesity [79] and put again under pressure support with sufficient PEEP and pressure support. Similarly, following extubation, as detailed below, preventing atelectasis has to start as soon as possible, using CPAP or NIV. Moreover, to perform extubation as soon as possible, sedation should be stopped as early as possible and benzodiazepines avoided, even more than in patients without obesity due to prolonged release of drugs in patients with obesity [80]. Prophylactic NIV after extubation decreases the risk of ARF by 16% and length of ICU stay [81]. In hypercapnic ICU patients with obesity, using NIV after extubation is associated with decreased mortality [81]. A randomized controlled trial performed in patients with morbid obesity undergoing bariatric surgery found an improvement of ventilatory function when CPAP was implemented immediately after extubation as compared to CPAP started 30 min after extubation [82]. In case of positive pressure therapy already used at home, it should be reintroduced as early as possible in the ICU as soon as higher levels of assistance requiring the use of an ICU ventilator are no longer needed. Home positive pressure therapy could also be introduced in ICU for selected patients with obesity. CPAP is indicated for use in patients with severe obstructive sleep apnea syndrome, as first-line therapy in these indications. In the case of combined obstructive apnea syndrome and moderate hypercapnia between 45 and 55 mmHg, a CPAP device will be offered as first-line therapy, and a NIV device, allowing ventilation at two pressure levels, will be offered in case of failure. If there is a history of respiratory decompensation with acute hypercapnic respiratory failure, hypercapnia greater than 55 mmHg, and/or no associated obstructive sleep apnea

syndrome, a NIV device will be offered [83]. HFNC was not found to be superior to standard oxygen to prevent extubation failure in 155 post-cardiac surgery patients with obesity [84]. Among cardiothoracic surgery subjects with obesity with or without respiratory failure, the use of continuous HFNC compared to NIV did not result in a worse rate of treatment failure [33]. Similarly, in the study by Hernandez et al. [85] including 20% of patients with obesity, among high-risk adults who have undergone extubation, preventive HFNC was not inferior to preventive NIV for reducing reintubation rate and post-extubation respiratory failure. In a randomized controlled trial of the same team comparing HFNC to standard oxygen [86] in high-risk non-hypercapnic patients including 22% of patients with obesity, the study was stopped due to low recruitment after 155 patients, without any difference in extubation failure rate found between the two groups. A summary of the main respiratory physiological modifications and some suggestions for mechanical ventilation in critically ill patients with obesity are proposed in Fig. 10.2.

10.11 The Obesity Paradox

In the general population, obesity is one of the top 10 risk factors of chronic diseases and a risk factor for death. Consistent with this trend in the general population, the number of obese patients admitted to the ICU is rapidly increasing [87]. Obesity decreases life expectancy in the population, and obesity in childhood is now a healthcare crisis for our next generation with unknown consequences. There are overwhelming scientific data on overall mortality/morbidity, the healthcare system shortcomings to deliver adequate care, and the social discrimination and injustice that individuals with obesity are subject on daily basis. However, in ICU, patients with obesity may be more likely to develop ARDS, but their survival sometimes appeared to be better, a phenomenon called the “obesity paradox” [88]. Patients with obesity have immunological and pulmonary mechanics differences compared to patients without obesity. These differences are increased for patients with higher level of obesity. Furthermore, clinicians may overestimate the lung size of patients with obesity, by considering real instead of PBW, and use higher VT during mechanical ventilation, risking ventilator-induced lung injury. The mentioned patient factors may also cause respiratory muscle fatigue and difficult weaning. Indeed, 2 meta-analyses show that in close to 200,000 ARDS patients, obesity is linked to a higher risk of developing ARDS and patients with obesity need mechanical ventilation for a longer period, compared to critically ill patients without obesity [14, 17]. Consequently, ICU length of stay is also prolonged in patients with obesity, while hospital length of stay is not [14, 17]. While patients with obesity are on mechanical ventilation for a longer period, these meta-analyses also demonstrate a survival advantage for patients with obesity. This observation has coined the “obesity paradox” as a survival benefit may appear counterintuitive in view of the detrimental alterations in respiratory function as described above. Several reasons to explain the obesity paradox in ARDS patients with obesity have been put forward. Apart from

the described immunological differences, patients with obesity have more metabolic reserve and may, therefore, tolerate the catabolic stress of critical illness during ARDS better, because of energy stores in the form of adipose tissue. It is important to also address the possibility that patients with obesity may have a lower threshold for ICU admission, e.g., because of the need of more nursing staff not available on the ward or monitoring purposes. This would mean that patients with obesity admitted to the ICU are less sick and therefore may show a better survival because of selection bias, not representing a real phenomenon. As in the meta-analysis, adjustments for covariates like disease severity were not possible; this may appear plausible. In a large study in over 150,000 ICU patients, however, the obesity paradox remained present even when adjusted for several covariates including disease severity [89]. Also, patients with obesity may have been misclassified as ARDS if atelectasis is interpreted as bilateral infiltrates. Using a causal inference approach to reduce residual confounding bias due to missing data, it was found that the survival of patients without obesity would not have been improved if they had obesity [90], findings which question the obesity paradox.

10.12 Conclusions

In summary, patients with obesity are more likely to develop respiratory complications, including ARF and ARDS. Considering some physiological studies, for non-invasive management, using NIV has to be considered both for preventing and treating ARF, even if the level of proof is low, especially in comparison with HFNC. Airway management in critically ill patients with obesity poses specific challenges, and adequate patient evaluation, pre-oxygenation, and choice of intubation devices might improve outcomes. After intubation procedure for invasive mechanical ventilation, patients with obesity being more prone to lung collapse require higher PEEP to avoid it. Low VT according to PBW should be used both in non-ARDS and ARDS patients. RM is not systematically recommended, and their use remains a decision based on individual risk/benefit considerations. Prone positioning should be used in severe ARDS patients with obesity.

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