Practical Trends in Anesthesia and Intensive Care 2018

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Editor

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Preface

The book is a useful guide to the management of the most-debated hot topics of practical interest in anesthesia and intensive care. It reviews the state of the art in issues related to both intensive care and anesthesia, such as the perioperative management of coagulation, pain, use of noninvasive ventilation, antifungal treatment for critically ill patients, and the diagnosis and treatment of septic shock and acute respiratory distress syndrome (ARDS).

Written by leading experts and including updated references, it provides a comprehensive, easy-to-understand update on anesthesia and intensive care. The book clearly explains complex topics offering practicing clinicians insights into the latest recommendations and evidence in the field while, at the same time, making it a valuable resource for students new to the study of anesthesia and intensive care.

Milan, Italy — Davide Chiumello

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Part I

Anesthesia and Pain

1 Perioperative Coagulation Management and Point-of-Care Monitoring in Anesthesia

Gianni Biancofiore

1.1 Introduction

Since the first report of a successful blood transfusion in 1667 by Jean-Baptiste Denys, blood transfusion has evolved considerably saving, undoubtedly, many lives. However, administration of blood products remains associated with numerous complications and side effects [1, 2]. This is of particular interest because the need for blood in hospitals continues to exceed the volume collected by the transfusion services with a substantial cost and a burden to the transfusion services [2]. Therefore, overuse of blood products and the resulting expenditure in a time when affordable health care is needed are receiving increasing attention by regulators and clinicians. This is in the forefront as more and more data suggest that many allogenic transfusions are either not needed or result in negative outcomes while lacking any demonstrable benefit to the patient. This is one of the reasons that led to an approach to transfusion medicine that challenges the traditional attitudes providing a strategy that will result in preemptive treatments so that allogeneic blood could be avoided or the patients' exposure to this therapy could be substantially reduced. Patient blood management (PBM) is currently defined by the Society for the Advancement of Blood Management as "the scientific use of safe and effective medical and surgical techniques designed to prevent anemia and decrease bleeding in an effort to improve patient outcome" [3]. This target is achieved by addressing the following issues: (1) prevention of present or potential coagulopathy; (2) detection, diagnosis, and proper treatment of anemia; (3) enforcement of all appropriate modalities of blood conservation; and (4) multimodal team approach including shared patient decision [4]. According to this matrix, one of the classic and simplest ways to reduce transfusion is to prevent

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blood loss. From this point of view, the most appropriate management of perioperative patient coagulation is of utmost importance [5]. In fact, perioperative coagulation management is a complex task that has a significant impact on the perioperative journey of patients. Anesthesia providers play a critical role in the decision-making on transfusion and/or hemostatic therapy in the surgical setting. Various tests are available in identifying coagulation abnormalities in the perioperative period. While the rapidly available bedside hemoglobin measurements can guide the transfusion of red blood cells, blood product administration is guided by many in vivo and in vitro tests. The introduction of newer anticoagulant medications and the implementation of the modified in vivo coagulation cascade have given a new dimension to the field of perioperative transfusion medicine. A proper understanding of the application and interpretation of the coagulation tests is vital for a good perioperative outcome.

The aim of this review is to report the basic principles of the current point-of-care (POC) coagulation analyzers, to outline their clinical use, and to evaluate their ability to monitor different pharmacological substances interacting with hemostasis in the perioperative setting.

1.2 Why POC Testing of Hemostasis Gained Interest in Recent Years?

Hemostasis is a combination of a number of events that occur in a sequence following the breach of vascular integrity. They include vasoconstriction, platelet aggregation, thrombus formation, recanalization, and healing. Conventionally, secondary hemostasis was described as intrinsic and extrinsic pathways merging at a final common pathway. This in vitro model ignores the link between primary and secondary hemostasis and is not applicable in vivo. The currently employed cell-based model of coagulation reflects the in vivo process, and it differs from the previous model in two key ways. First, the complex formed by the tissue factor and factor VII contributes in the activation of factor IX, demonstrating that the intrinsic and extrinsic coagulation pathways are interconnected almost from the beginning of the process. Second, the complete process requires three consecutive phases: an initial phase, an amplification phase, and the propagation phase. Platelets and thrombin are actively involved in the last two phases [6]. There is no universally accepted definition of hemostasis. The most simplistic definition is the "cessation of bleeding." An alternative view is the mechanistic concept that hemostasis represents the platelet and coagulation cascades involved in the cessation of bleeding. A more refined clinical definition of hemostasis is bleeding control without the induction of pathologic thrombotic events such as myocardial infarction, stroke, arterial thrombosis, or deep vein thrombosis. Hemostasis can thus be considered as control of bleeding within the finely tuned balance of procoagulant, anticoagulant, fibrinolytic, and antifibrinolytic activities [6]. A number of coagulation tests are available in the perioperative period to assist clinicians in identifying coagulation abnormalities. In recent years, incorporation of various forms of coagulation monitoring has provided valuable

information in the management of perioperative coagulopathies. The ideal laboratory test to evaluate hemostasis in the bleeding surgical or medical patient should reflect the dynamic status of bleeding and be accurate and available in real time to enable the physician to make treatment decisions rapidly. Testing should be specific for different physiologic mechanisms to target specific treatments to correct deficits in hemostasis. The test result should have meaningful clinical implications and closely reflect the patient's hemostatic status. Other characteristics of the ideal test include reproducibility, resistance to effect of pre-analytic variables, and ease of use in point-of-care settings such as the operating room, emergency department, and intensive care unit [6].

Perioperative management of coagulopathic bleeding requires timely hemostatic intervention using allogeneic blood products, administration of coagulation factor concentrates, or both. To guide these interventions, fast laboratory workup is essential. If it comes to the question which laboratory test should be performed to assess hemostasis, current guidelines usually refer to standard plasma coagulation tests (SLTs), that is, prothrombin time (PT)/international normalized ratio (INR) and activated partial thromboplastin time. Although the complete panel of standard coagulation testing almost always covers additional measurements of fibrinogen and platelet count, interpretation of SLTs is most frequently used to assess coagulopathy. Generally speaking, coagulopathy is presumed when SLTs are prolonged by more than 1.5-fold, although the evidence to support this degree of prolongation as diagnostic of coagulopathy is limited. However, there are major limitations to SLTs. In fact, these tests are time-consuming (with turnaround times sometimes longer than 60 min), and, as a consequence, they are often omitted in situations of severe bleeding, where prompt treatment must be ensured. Moreover, if the results of PT/aPTT are more than 1.5 times prolonged, the treatment options range from transfusion of fresh-frozen plasma (FFP) to administration of coagulation factor concentrates such as prothrombin complex concentrates (PCC) or activated recombinant factor VII. Remarkably, all these treatment options may be linked to serious side effects, and their administration should be rigorously justified. More importantly, we need to question what information we obtain from a PT or aPTT. In routine clinical practice, PT and aPTT are commonly used either for bleeding risk assessment before an invasive procedure or for the assessment of the hemostasis profile with respect to detection of underlying coagulopathy and guiding subsequent blood component therapy. In fact, PT/INR and aPTT are plasma-based coagulation tests that were basically designed to monitor vitamin *k* antagonists and heparin, respectively, and to assess coagulation factor deficiencies. However, it is important to outline that PT/INR and aPTT were not conceived or intended to monitor perioperative coagulation disorders, predict bleeding, or to guide bleeding therapy in the perioperative setting. All in all, there are significant shortcomings of SLTs in the perioperative and major bleeding management setting in terms of accuracy, evidence for their efficacy, valuable turnaround times in a clinical setting where a quick decision-making is mandatory [7]. Therefore, alternatives, such as the point-of-care coagulation tests (POCT), also termed as near-patient coagulation tests (NPT) that refer to measures of coagulation that can be performed at or near the patient and

provide results much more quickly with a more comprehensive overview of the whole coagulation process, became very attractive for clinicians.

1.2.1 Viscoelastic POC Testing of Hemostasis: Terminology

Thrombelastography was first described by Hartert in 1948 as a method to assess the global hemostatic function from a single blood sample. In the earlier literature, the terms "thrombelastography," "thrombelastograph," and "TEG" have been used generically. However, in 1996 the term "TEG®" became a registered trademark of the Haemoscope Corporation and from that time has been used to describe the assay performed using Haemoscope instrumentation. Alternative instrumentation marketed by Pentapharm GmbH uses the terminology thromboelastometry for the process of measurement and "ROTEM®" for the instrumentation and resultant graphical output. Thromboelastography and ROTEM are viscoelastic hemostatic assays [2–4] that provide a graphical evaluation of the kinetics of all stages of clot formation (initiation, propagation, strength, and dissolution) in whole blood. The descriptive data associated with both the described instruments is summarized in Table 1.1.

1.2.2 Viscoelastic POC Testing of Hemostasis: How it Works

The TEG/ROTEM® assesses the viscoelastic properties of blood samples under low shear conditions. The TEG® measures the clot's physical property by using a stationary cylindrical cup that holds the blood sample and oscillates through an angle

Table 1.1 Nomenclature used for TEG® and ROTEM®

Instrumentation	TEG®	ROTEM®
Measurement period	–	RT
Clot time (period to 2 mm amplitude)	*r*	CT
Period from 2 to 20 mm amplitude	*k*	CFT
Alpha angle	α (slope between *r* and *k*)	α (angle of tangent at 2 mm amplitude)
Maximum angle	–	CFR
Maximum strength	MA	MCF
Time to maximum strength	TMA	MCF-t
Amplitude (at set time)	*A* (A30, A60)	(A5, A10, …)
Clot elasticity	*G*	MCE
Maximum lysis	–	ML
Lysis at a fixed time	CL30, CL60	LY30, LY45, LY60
Time to lysis	TTL (2 mm drop from MA)	CLT (10% from MCF)
Maximum lysis	–	CLR (maximum tangent post-MCF)

of 4°45′ (Fig. 1.1a). Each rotation cycle lasts 10 s. A pin is suspended in the blood by a torsion wire and is monitored for motion (Fig. 1.2a). The torque of the rotation cup is transmitted to the immersed pin only after fibrin-platelet bonding has linked the cup and pin together. The strength of these fibrin-platelet bonds affects the magnitude of the pin motion. Thus, the output is directly related to the strength of the formed clot. As the clot retracts or lyses, these bonds are broken, and the transfer of cup motion is again diminished. The rotation movement of the pin is converted by a mechanical-electrical transducer to an electrical signal, finally being displayed as a tracing. The generated electric signal gets converted into a "bell- shaped" graphical display demonstrating the characteristic of shear elasticity against time. The shape of the graphical display aids in a quick qualitative assessment of different coagulation states (hypo, normal, hyper) representing specific abnormalities in clot formation and fibrinolysis.

The ROTEM® instrument (Fig. 1.1b) uses a modified technology: the signal of the pin suspended in the blood sample is transmitted via an optical detector system,

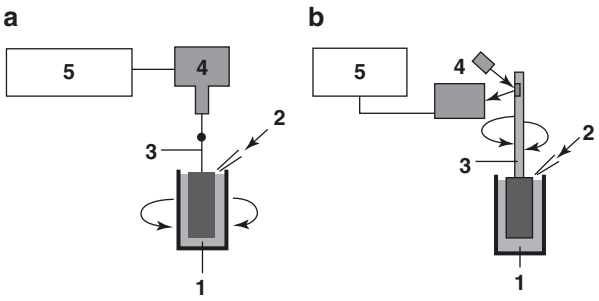

Fig. 1.1 Working principles of viscoelastic point-of-care coagulation devices. (**a**) TEG®: (1) rotating cup with blood sample, (2) coagulation activator, (3) pin and torsion wire, (4) electromechanical transducer, (5) data processing. (**b**) ROTEM®: (1) cuvette with blood, (2) activator, (3) pin and rotating axis, (4) electromechanical signal detection, (5) Print output

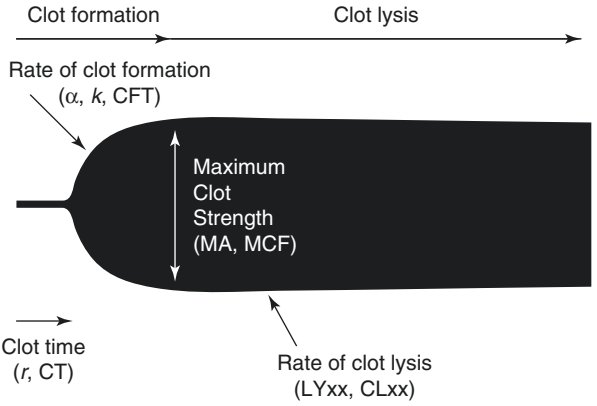

Fig. 1.2 Diagrammatic representation of a TEG®/ROTEM® trace indicating the commonly used variables

not a torsion wire, and the movement is initiated from the pin, not the cup. Both the instruments are now equipped with cartridges replacing cups, pins and electronic pipettes and look simpler and more user friendly.

TEG®/ROTEM® both measure and graphically display the changes in viscoelasticity at all stages of the developing and resolving clot, i.e., the time until initial fibrin formation (TEG®, reaction time; ROTEM®, clotting time [CT]), the kinetics of fibrin formation and clot development (TEG®, kinetics, α-angle; ROTEM®, clot formation time, α angle), the ultimate strength and stability of the fibrin clot (TEG®, maximum amplitude [MA]; ROTEM®, maximum clot firmness [MCF]), and clot lysis. Although TEG® and ROTEM® tracings look similar (Fig. 1.2), the nomenclature and reference ranges are different. The differences may be explained by different components, materials, and proprietary formulas of the coagulation activators (composition, concentrations) used.

1.2.3 Viscoelastic POC Testing of Hemostasis: Clinical Experience

There is emerging evidence that point-of-care tests based on "goal-directed" coagulation management can modify the transfusion strategy by providing better understanding of the underlying pathology and by the targeted use of not only FFP but also fibrinogen and prothrombin complex concentrates hence reducing the need for blood products, which enables the clinician to tailor hemostasis management according to the patient's needs. Although POC hemostasis testing may aid care of any critically ill surgical patient, it is likely to be particularly helpful in certain groups of patients who are more vulnerable to hemorrhagic complications. These include patients undergoing hepatic, cardiac, or vascular surgery and victims of polytrauma.

1.2.3.1 Liver Surgery

One of the first clinical applications of thrombelastography was in the hemostatic monitoring of liver transplantation. Problems associated with hepatic surgery and particularly orthotopic liver transplantation (OLT) stem from both surgery itself and preoperative coagulopathy from hepatic dysfunction. In particular, OLT was historically associated with major blood loss. However over the years, improvements in surgical and anesthetic management allowed significant improvements in the perioperative management of this class of patients with significant reduction in the transfusional needs. The same happened with liver surgery, particularly when performed in patients with liver disease. The coagulopathy of chronic liver disease is present preoperatively, and further disturbance of coagulation can occur intraoperatively, resulting in bleeding complications but also thrombotic events [8].

There is increasing evidence that the changes in coagulation factors and platelet count regularly observed in patients with liver cirrhosis cannot be interpreted as a reliable indicator of diffuse bleeding risk. Instead, a differentiated view on hemostasis has led to the concept of a rebalanced coagulation system. In fact, while it is

important to recognize that procoagulant factors are reduced in liver cirrhosis, it is also evident that synthesis of anticoagulant factors and fibrinolytic proteins produced in the liver is also diminished. Similarly, the decreased platelet count may be counterbalanced by increased platelet aggregability caused by highly active von Willebrand multimers. Although "rebalanced," hemostasis in cirrhotic patients is not as stable as in healthy subjects, and therefore, while under normal "unstressed" conditions, diffuse bleeding is rarely observed; both diffuse bleeding and thrombus formation may occur when compensation mechanisms are exhausted [9, 10].

Because TEG®/ROTEM® are global tests providing a composite analysis that reflect function of plasma, blood cells, and platelets, they are increasingly viewed as an appropriate tool to investigate the coagulopathy of cirrhotic patients. In agreement with the concept of rebalanced hemostasis, patients with cirrhosis often maintain normal global hemostasis as assessed by TEG. In a cohort of 273 patients with stable cirrhosis, it was found that mean and median TEG® parameters were all within normal limits, although the MA decreased in proportion to the severity of thrombocytopenia and severity of liver disease [11]. Theoretical benefits of the use of TEG® or ROTEM® in the hepatic surgical setting include a rationalization of blood products, a reduction in transfusion-related side effects, and an improvement in patient outcomes including mortality with a reduction in costs. A typical example is fibrinogen. Fibrinogen is the first factor to reach critical levels when hemodilution or massive bleeding occurs. Fibrinogen concentration can easily be monitored by POC viscoelastic technologies, and substitution therapy based on guidance according to the clot firmness reduced the rate of red blood cells, fresh-frozen plasma, and platelet transfusion by more than 50%. Additionally the rate of transplantation without transfusion of the above blood-related products rose from 3.5% to 20% [12]. In a recent review on fibrinogen and fresh-frozen plasma in surgery, the authors concluded that fibrinogen level was generally associated with improved outcome measures, while fresh-frozen plasma failed to show evidence for effectivity and had severe side effects [13]. Besides fibrinogen, other coagulation factors may decrease during liver surgery and transplantation resulting in a reduction of thrombin generation and prolongation of clotting time. In these cases, prothrombin complex concentrate can correct coagulopathy. Theoretically, there are four-factor PCC and three-factor PCC. Four-factor PCC contain factors II, VII, IX, and X and the anticoagulant factors protein S and protein C. Infectious risk is reduced or eliminated by virus elimination, and thromboembolic complication occurs in only 0.9%. In liver transplantation, POC-guided substitution of blood products including prothrombin complex concentrate in liver transplantation did appear safe as they did not show to increase the occurrence of thrombosis, pulmonary, and ischemic events compared to patients who did not receive these concentrates [14].

TEG®/ROTEM® are not of exclusive use for OLT patients only but also for medical cirrhotic patients. A review was recently conducted using the following key words: "cirrhosis," "coagulation," "bleeding," "INR" (international normalized ratio), "aPTT" (activated partial thromboplastin time), and "thrombocytopenia." PubMed was used as the basic database. The authors showed that although pathological values of SLT and thrombocytopenia have traditionally been regarded

as indicators of a high risk for bleeding in all patients, and especially in those with cirrhosis, this approach has been challenged in recent years. The conventional approach in assessing a bleeding risk was based on pathological values of SLT. A 1.5-fold increase of INR or aPTT or platelets <50/nL is assumed as pathological. The traditional approach of reducing the risk of excessive bleeding during an invasive procedure was to transfuse FFP or PLT concentrates in order to improve hemostasis and to avoid bleeding complications. In the recent 20 years, several studies have provided us with a basis for questioning this approach. Their results indicated that SLT were not able to predict hypocoagulation and bleeding complications. Moreover, transfusion of various blood products has been associated with an increased risk for acute lung injury, transfusion-associated circulation overload, bacterial infections, and modulation of the immune system with increased numbers of nosocomial infections. Furthermore, a high-volume overload, which is required to correct a hemostasis disorder if FFP are being used in cirrhotic patients, may increase portal venous pressure. This might significantly increase bleeding in these subjects. However, some very recent studies demonstrated that the use of TEG/ROTEM for assessing the risk of bleeding avoids futile transfusion with a similar safety profile. The implementation of TEG®-/ROTEM®-based coagulation management and the use of coagulation factors (prothrombin complex, fibrinogen concentrate) have led to a highly significant reduction of FFP and red blood cell transfusions, without an increased incidence of thrombosis or bleeding [11]. In conclusion, also medical cirrhotic patients will benefit of a coagulation treatment based on TEG®/ROTEM®. Finally, a temporary hypercoagulable state is common after liver transplantation due to imbalance between the procoagulant and anticoagulant systems, as well as fibrinolytic shutdown. This may play a role in the early development of hepatic artery thrombosis. The use of TEG®/ROTEM® can accurately assess postoperative hypercoagulability and thrombosis. To this end, there is interesting evidence that this monitoring technique could demonstrate hypercoagulability in the majority of the subjects after living donor liver transplantation and general surgery and may, therefore, be used to guide antithrombotic treatment in the perioperative period [15, 16].

1.2.3.2 Cardiac Surgery

Postoperative bleeding is a common complication of cardiac surgery and a major cause of re-exploration. Coagulation management of patients undergoing cardiac surgery is complex because of a balance between anticoagulation for cardiopulmonary bypass (CPB) and hemostasis after CPB [17]. Furthermore, an increasing number of patients have impaired platelet function at baseline due to administration of antiplatelet drugs. During CPB, optimal anticoagulation dictates that coagulation is antagonized and platelets are prevented from activation so that clots do not form. After surgery, coagulation abnormalities, platelet dysfunction, and fibrinolysis can occur, creating a situation whereby hemostatic integrity must be restored. Heparin is used during cardiopulmonary bypass in open-heart surgery, and excessive postoperative bleeding has been attributed to the insufficient reversal of heparinization with protamine sulfate. This is partly due to the fact that conventional monitoring by

means of activated clotting time may fail to differentiate between the contributions from heparinization, dilution, and platelet dysfunction [17]. Johansson et al. reviewed over 3250 cardiac patients reported in 16 studies and demonstrated superiority of TEG®/ROTEM® over SLT in predicting bleeding and the need for reoperation. The total number of blood transfusions was reduced with TEG/ROTEM-guided transfusion compared with SLT-based practices. The degree of heparinization could be evaluated with assays that neutralize the heparin (heparinase in TEG and HEPTEM in ROTEM), so that non-heparin-related hemostatic problems could be detected [18]. These findings were corroborated in a recent Cochrane analysis [19].

In a recent meta-analysis of randomized controlled trials and observational trials retrieved from a literature search in PubMed, EMBASE, and Cochrane Library, trials comparing transfusion strategy guided by TEG®/ROTEM® with a standard-of-care control group undergoing cardiac surgery were included. The literature search retrieved a total of 17 trials (9 randomized controlled trial and 8 observational trials) involving 8332 cardiac surgery patients. POCT-guided transfusion management significantly decreased the odds for patients to receive allogeneic blood products (OR 0.63, 95% CI 0.56–0.71; $P < 0.00001$) and the re-exploration rate due to postoperative bleeding (OR 0.56, 95% CI 0.45–0.71; $P < 0.00001$). Furthermore, the incidence of postoperative AKI (OR 0.77, 95% CI 0.61–0.98; $P = 0.0278$) and thromboembolic events (OR 0.44, 95% CI 0.28–0.70; $P = 0.0006$) was significantly decreased in the TEG®/ROTEM® group. No statistical differences were found with regard to in-hospital mortality, cerebrovascular accident, or length of intensive care unit and hospital stay [20]. Furthermore, it has been shown that implementation of TEG®/ROTEM®-guided coagulation management is cost-effective and resulted in a significant reduction of transfusion blood products [21, 22]. Finally, the National Institute for Health and Care Excellence (NICE) has recently reviewed the available evidence for use of viscoelastic testing in cardiac surgery and concluded that viscoelastic testing improves the use of blood products and factor concentrates, reduces red cell transfusion, and is cost effective. It also concluded that the above was true for intra- and postoperative use; however, they did not recommend any particular transfusion algorithm. For ROTEM® and TEG®, the effect on mortality, length of ICU and hospital stay, and rate of re-sternotomy was not statistically significant across all studies [23].

There remains great controversy regarding the platelet transfusion threshold to be applied in cardiac surgery, due to the platelet function defect present in all patients after CPB [24]. Numeric platelet counts from the laboratory may not be accurate due to clumping, particularly if the patient is hypothermic or if the sample was taken during or immediately after CPB, which can lead to an artifactually low platelet count. The numerical analysis of platelets in the laboratory does not take into account a variable degree of platelet dysfunction induced by CPB and potentially exacerbated by preoperative treatment with platelet antagonists and/or uremia [17]. The monitoring of platelet blockade with impedance aggregometry (Multiplate®), platelet mapping (TEG®), or latex agglutination (Verify Now®; Accumetrics, San Diego, CA, USA) remains outside what is considered the standard of care, and the clinical utility of preserved patient platelet function in vitro

remains to be established. All in all, the best measure of platelet function postoperatively remains unresolved [17]. Currently, platelet function testing may be more important for preoperative risk stratification. Most measures of platelet function become invalid at platelet counts <50–100 × 10^9 in the test tube [25]. Enriching platelets in vitro to allow an assessment in this situation introduces significant delay, which is why platelet aggregometry, considered the gold standard of platelet function assessment, has never become standard in postoperative patients after cardiac surgery [26]. Finally, there has been a lot of interest in hyperfibrinolysis since the introduction of aprotinin. In current clinical practice, true hyperfibrinolysis apparent in vitro by TEG® is a rare occurrence. It would appear that a degree of fibrinolysis is to be expected after cardiac surgery, but the definition of systemically apparent hyperfibrinolysis is less clear [17].

Tranexamic acid (TXA), used almost ubiquitously in UK cardiac surgical practice, and epsilon aminocaproic acid (EACA) are synthetic lysine analogues that reversibly block the lysine-binding site of plasminogen which inhibits the lysis of polymerized fibrin. They have a plasma half-life of around 2 h and are excreted in the urine in high concentrations. The optimum dose of TXA is unknown despite its widespread international use, with 10 mg/kg bolus followed by 1 mg kg/h as a continuous infusion being the most commonly used regimen, with little evidence for higher doses. Both agents have been shown to reduce blood loss, when used prophylactically in cardiac surgery [17]. Tranexamic acid may be slightly more effective than EACA in reducing blood loss; however, there is little evidence to support the exceedingly high doses (up to 10 g) used in some centers [27].

1.2.3.3 Obstetrics

Globally, postpartum hemorrhage (PPH) is the leading cause of maternal morbidity and mortality. In the current treatment of severe PPH, first-line therapy includes transfusion of packed cells and fresh-frozen plasma in addition to uterotonic medical management and surgical interventions. In persistent PPH, tranexamic acid, fibrinogen, and coagulation factors are often administered. Secondary coagulopathy due to PPH or its treatment is often underestimated and therefore remains untreated, potentially causing progression to even more severe PPH. In most cases, medical and transfusion therapy is not based on the actual coagulation state because conventional laboratory test results are usually not available for 45–60 min. Therefore, TEG®/ROTEM® coagulation testing comes of interest. Data on thromboelastography and thromboelastometry in pregnant women are however limited, particularly during the peripartum period and in women with PPH, so more research in this field is truly needed [28]. However, the emergency nature of PPH makes randomized controlled trials logistically difficult. Therefore, population-based observational studies should be encouraged as they can usefully strengthen the evidence base, particularly for components of PPH treatment that are difficult or impossible to assess through RCT [29]. A recent observational cross-sectional/longitudinal study aimed at demonstrating changes in clot mechanics during pregnancy and to determine the effect that delivery has on immediate postpartum thromboelastography parameters. Thromboelastography was performed on whole blood aliquots obtained

from women carrying singleton pregnancies and was repeated 6 h after delivery among patients recruited in the third trimester or labor. Bleeding questionnaires were completed and routine clinical/demographic data obtained. Overall, 112 women were included. The thromboelastography parameters were significantly correlated with length of pregnancy. From the third trimester to the postpartum period, there was a significant decrease in time until fibrin formation ($P = 0.036$) and in time to reach a certain clot strength (amplitude of 20 mm; *k* value; 1.3 vs 1.1 min, $P = 0.007$). From established labor to after delivery, there was a significant increase in clot lysis at 60 min after the maximum amplitude of clot formation (LY60; 1.8% vs 3.1%, $P = 0.001$). The authors concluded that their study describes a novel finding regarding changes in clot mechanics in late pregnancy/puerperium and supports the concept of using thromboelastography as part of the routine assessments at delivery [30]. Another study aimed at comparing the use of thromboelastography and laboratory analyses to evaluate hemostasis during major obstetric hemorrhage. A secondary aim was to evaluate correlations between the results of thromboelastography, laboratory analyses, and estimated blood loss. Forty-five women with major obstetric hemorrhage and 49 women with blood loss <600 mL were included. The following thromboelastography analyses were performed: time to start of clotting (TEG-R), time to 20 mm of clot firmness (TEG-K), rate of clot growth (TEG-Angle), maximum amplitude of clot (TEG-MA), and lysis after 30 min (TEG-LY30). In addition, platelet count, activated partial thromboplastin time, prothrombin time, fibrinogen, antithrombin, and D-dimer were measured. Thromboelastography variables reflecting clot stability and fibrinolysis were decreased in women with massive obstetric hemorrhage compared to women with normal bleeding, while clot initiation was accelerated. Laboratory analyses also showed impaired hemostasis with the most pronounced differences in platelet count, fibrinogen concentration, and antithrombin activity. The strongest correlations existed between fibrinogen and TEG-MA and between estimated blood loss and TEG-MA, fibrinogen, and antithrombin, respectively. The authors conclude that impaired hemostasis, demonstrated by thromboelastography and laboratory analyses, was found after an estimated blood loss of 2000 mL. Thromboelastography provides faster results than standard laboratory testing which is advantageous in the setting of ongoing obstetric hemorrhage. However, laboratory analyses found greater differences in coagulation variables, which correlated better with estimated blood loss [31]. In a study of nonpregnant, healthy term pregnant women, and postpartum women, it was demonstrated that a hypercoagulable state exists during pregnancy and persists through the first 24 h postdelivery. Both native TEG and celite-activated TEG were used, and it was found that *r* and *k* were decreased, while alpha angle and MA were significantly increased in the pregnant and postpartum women compared with the normal group [32]. More recently, the hypercoagulability status of women with and without gynecologic malignancies was compared using TEG. Blood specimens from 25 women with newly diagnosed gynecologic malignancies and from 21 age-matched controls were analyzed. Hypercoagulability was defined by a short *r* value (min), a short *k* value (min), an elevated maximum amplitude (MA) value (mm), and a broad alpha angle (°). A two-tailed, two-sample *t*-test was used for statistical analysis. When

compared with specimens from age-matched controls, specimens from women with gynecologic malignancies demonstrated values consistent with hypercoagulability. The specific parameters are presented as a mean (±SD). Patients with gynecologic malignancies were found to have a short *r* value (7.1 ± 2.1 min vs. 11.8 ± 1.8 min; $P < 0.001$), a short *k* value (3.1 ± 0.9 min vs. 4.6 ± 0.9 min; $P < 0.001$), a prolonged MA value (64.7 ± 5.4 mm vs. 58.8 ± 6.1 mm; $P = 0.001$), and a greater alpha angle (70.6° ± 5.3° vs. 61.6° ± 4.9°; $P < 0.001$). The authors concluded that detection of hypercoagulability as measured by thromboelastography is statistically more common among women with gynecologic malignancies compared with age-matched controls [33]. In summary, goal-directed therapy using point-of-care testing has not been well studied in the obstetric setting but holds promise for individualizing resuscitation measures [34].

1.2.3.4 Trauma

Hemorrhagic shock is a leading cause of death in trauma patients. Surgical control of bleeding and fluid resuscitation with both crystalloid and blood products remain the mainstay of therapy for injured patients with bleeding. Current evidence suggests that hemodilution, hypothermia, acidemia, and the consumption of clotting factors all play roles in the pathogenesis of coagulopathy in trauma. In such a complicated panorama, there is an emerging understanding of the key role played by the management of coagulation in this particular clinical setting. In fact, restoration and subsequent maintenance of normal coagulation function is essential for survival of the severely injured bleeding patient. Furthermore, after initial stabilization, trauma patients paradoxically face the dangers of a hypercoagulable state, demanding accurate risk stratification and chemoprophylaxis for prevention of highly morbid thromboembolic events [35].

A systematic review found 55 studies of TEG®/ROTEM® examining the diagnosis of trauma coagulopathies, including hypocoagulation, hypercoagulation, platelet dysfunction, and fibrinolysis, guidance of blood product administration, and associations with mortality. To our knowledge, this review is the first to summarize the literature on the use of TEG® and ROTEM® in trauma [36]. The overall methodologic quality of included studies was moderate. No RCTs were reported; most cohort studies lacked clinically similar control groups managed without TEG®/ROTEM®, and standard measures of diagnostic accuracy were inconsistently reported. Observational data suggest that TEG® and ROTEM® may have adequate diagnostic properties for abnormalities identified by RSCTs and may identify additional coagulation disorders. However, the effect of these tests on the need for blood product transfusion and mortality is unclear. Studies also examined different patient populations, transfusion triggers, and transfusion protocols, limiting direct comparisons and generalizability. In summary, our systematic review demonstrated limited but rapidly growing observational evidence on the use of TEG® and ROTEM® in trauma. Both methods may be useful for diagnosis of early trauma coagulopathies, specifically hypocoagulability, hypercoagulability, hyperfibrinolysis, and platelet dysfunction. They may also be used to direct blood and blood product transfusion; effects on patient-important outcomes are uncertain. All in all, the existing literature helps clinicians to

appreciate the potential impact of these novel methods on transfusion guidance and outcomes in trauma. However, adequately powered and methodologically sound RCTs will be required to prove positive effects on blood product transfusion and patient-important outcomes [36].

Recently, the pan-European, multidisciplinary Task Force for Advanced Bleeding Care in Trauma, founded in 2004 and including representatives of six relevant European professional societies, used a structured, evidence-based consensus approach to address scientific queries that served as the basis for recommendations and supporting rationale. Expert opinion and current clinical practice were also considered, particularly in areas in which randomized clinical trials have not or cannot be performed. Existing recommendations were reconsidered and revised based on new scientific evidence and observed shifts in clinical practice; new recommendations were formulated to reflect current clinical concerns and areas in which new research data have been generated. This guideline represents the fourth edition of a document first published in 2007 and updated in 2010 and 2013 [37]. With regard to coagulation monitoring, this group of experts recommends that routine practice will include the early and repeated monitoring of coagulation, using either a traditional laboratory determination [prothrombin time (PT), activated partial thromboplastin time (APTT) platelet counts and fibrinogen] (Grade 1A), and/or a viscoelastic method (Grade 1C). The authors outline that despite the widespread use of viscoelastic methods, the usefulness has recently been questioned. In fact, In a recent systematic review Hunt et al. found no evidence of the accuracy of thrombelastography and very little evidence to support the accuracy of thromboelastometry and were therefore unable to offer any advice about the use of these methods [38]. In the above examined systematic review, Da Luz et al. concluded that only limited evidence from observational studies support the use of viscoelastic tests to diagnose early traumatic coagulopathy, but while these tests may predict blood product transfusion, mortality and other patient-important outcomes may be unaffected [36]. A number of other limitations to the use of viscoelastic methods have been described. Larsen et al. found that thrombelastography was unable to distinguish coagulopathies caused by dilution from thrombocytopenia, whereas thromboelastometry was indeed capable of distinguishing these two different types of coagulopathy and suggesting the correct treatment [39]. The use of thrombelastography may thus lead to unnecessary transfusion with platelets, whereas the application of thromboelastometry may result in goal-directed fibrinogen substitution. All in all, according to these findings, although use is rapidly increasing, controversy remains at present regarding the utility of viscoelastic methods for the detection of posttraumatic coagulopathy. Finally, according to the pan-European, multidisciplinary Task Force, the following are the leading key points regarding the use of TEG/ROTEM in trauma patients [37]:

1. The literature on TEG® and ROTEM® in trauma is limited by the lack of randomized controlled trials and the moderate quality of observational studies.
2. TEG® and ROTEM® may be superior to routine screening coagulation tests to promptly diagnose early trauma coagulopathy, including hypocoagulability, hyperfibrinolysis, hypercoagulability, and platelet dysfunction.

3. Many TEG® and ROTEM® abnormalities predict the need for massive transfusion and predict death, but predictive performance is not consistently superior to routine screening coagulation tests.
4. Limited evidence from one observational study suggests that a ROTEM®-based transfusion algorithm reduces the amount of blood and blood products transfused.
5. TEG® and ROTEM®-based resuscitation for bleeding trauma patients is not associated with lower mortality in most observational studies, but the question requires evaluation in randomized trials.

1.3 Shortcomings and Criticisms to TEG/ROTEM

Perioperative POC testing of hemostasis would be invaluable if it could identify patients at increased risk of postoperative hemorrhage. Nevertheless, it should always be considered that this technique is not without limitations. In fact, indeed the coagulation status is assessed in whole blood, allowing in vivo coagulation system interactions with platelets and red blood cells to provide useful information on the more appropriate clinical approach. However, a significant difference between in vitro and in vivo coagulation has to be considered: viscoelastic coagulation tests measure the coagulation status under static conditions (no flow) in an artificial situation (cuvette or cartridge and not an endothelialized blood vessel). Therefore, results obtained from these in vitro tests must be carefully interpreted after considering the clinical conditions (e.g., overt bleeding in the surgical site). As in any assay there are some blind spots in monitoring coagulation using the viscoelastic method. Platelet dysfunction either inherited or drug induced will not be detected. Another shortcoming is the insensitivity to detect the effects of von Willebrand factor, which is involved in the initiation of clot forming. Moreover, factor XIII, which is mainly responsible for stabilization of the fibrinogen network, is also not adequately displayed [40]. However, it must always bear in mind that thromboelastography is and remains a POC and not a traditional laboratory technology. More importantly, there are concerns about standardization of the assays [41, 42]. On an operational level, viscoelastic tests have been criticized for not having undergone the same evaluation process as conventional coagulation tests. There are wide technical variations in how TEG®/ROTEM® are performed, and the machine requires calibrations two to three times a day which causes significant inconvenience in daily point-of-care usage. While originally designed for fresh whole blood with no additional activators, subsequent modifications have included sample anticoagulation and the use of different activators to standardize the initiation of coagulation. Patients' gender, age, and alcohol drinking may also affect the result. Moreover, the normal reference ranges for viscoelastic tests were derived from hospitalized surgical patients in 1 study, and from a small sample of 12 healthy volunteers in another [43]. Hence, it is suggested that each center is recommended to generate its own reference range by specially trained personnel according to the guidelines from the Clinical Laboratory Improvement Amendments (the federal regulatory standards

that apply to all clinical laboratory testing performed on humans in the United States) [44]. All these necessitate an active and tightly controlled quality assurance program. Finally, there are conditions in which viscoelastic tests may fail to detect hemostatic dysfunction. The test setting is at 37 °C. Therefore, the effect of hypothermia, which has a well-recognized negative impact on coagulation, may not be recognized if not appropriately addressed. Lastly, the interchangeability of results between TEG® and ROTEM® has been questioned. Although they share the same fundamental principles, and similar parameters, hardware, and techniques, the results generated may not be directly comparable, possibly due to the use of different activators. Consistent correlations are limited to that between TEG-MA and ROTEM MCF measurements and that between TEG CL and ROTEM ML in diagnosing hyperfibrinolysis and predicting mortality [43].

1.4 Conclusions

Hemostatic function is a critical factor determining patient outcomes in emergency or elective procedures. Conventional coagulation tests have limitations in detecting hemostatic dysfunction in subgroups of patients and are largely ineffective in diagnosing hyperfibrinolysis. The viscoelastic tests are potentially useful point-of-care tools to provide information on clot formation, clot strength, and fibrinolysis, as well as to guide goal-directed transfusion and antifibrinolytic therapy. However, standardization of techniques and reference ranges is required before these tests can be widely used in different clinical settings. There is growing evidence that application of TEG®-/ROTEM®-guided transfusion strategies may reduce the need for blood products and improve morbidity in patients with bleeding. However, these results are primarily based on trials of elective cardiac surgery involving cardiopulmonary bypass, and the level of evidence remains low. Further evaluation of TEG®/ROTEM®-guided transfusion in acute settings and other patient categories in low risk of bias studies is needed.

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Complications Associated with Neuraxial Blockade

2

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2.1 Introduction

Greater benefits are attributed to regional anaesthesia (RA) compared to general anaesthesia, including reduced morbidity and mortality [1–5], best levels of postoperative analgesia [6–11] and, last but not least, cost reduction [12].

However, regional anaesthesia, despite providing excellent anaesthesia and analgesia in many surgical procedures, is not completely free of risks, which anaesthetists and patients must take into account, to make the best choice of anaesthetic technique, supported by a complete and correct information.

In the execution of the central blocks, the appearance of adverse events, even very serious ones, has been sporadically reported, among which the neurological damages are worthy of particular consideration, moreover of heterogeneous nature, with variable onset from the execution of the technique and often with dubious demonstration of the cause-effect relationship.

Rare case reports and retrospective studies highlight the possibility that central blocks can cause permanent neurological damage to the spinal cord and/or roots, whose causes often remain unclear.

Other types of neurological damages related directly or indirectly to a neuraxial block derive from infections (meningitis, abscesses) or, extremely rare, from intracerebral ischaemic-haemorrhagic accidents.

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Therefore, we can distinguish:

- Spinal cord or direct root trauma
- Spinal haematoma
- Intracranial haematoma
- Spinal cord ischaemia
- Infection

2.2 Epidemiology

Most of the studies in literature which investigated neurological complications after RA are dated and do not take into consideration either the current specificity of indication and application of AR, the progress in operators training and in technique execution, the availability of better and safer local anaesthetics and devices or the increasing prevalence of risk factors, such as diabetes, obesity and the use of anticoagulants and antiplatelet drugs.

If we consider the negative neurological sequelae related or associated with RA, excluding the local anaesthetic toxicity (characterized by epileptic seizures), the transitory neurological symptoms (characterized by strong, temporary, radicular-type back pain, after performing spinal anaesthesia) [13] and epidural haematoma and abscesses, we note that the nerve injury after RA is an extremely rare occurrence; therefore, a large number of patients must be recruited to define the true incidence of neurological complications; moreover, much of the available literature is limited to isolated clinical cases, retrospective studies and interviews with anaesthetists, in which an underestimation of the real incidence induced by omission of complication reports can be presumed.

One of the largest studies on the evaluation of neurological complications after central nervous block (CNB) was published by Moen et al. [14] in 2004; it considered a high CNB number (1,260,000 spinal and 450,000 epidural) over a long-period study (1990–1999), collecting data from multiple sources, including a survey of anaesthetists by mail and the Swedish database for mandatory reporting of adverse events.

Another important and extensive study was conducted by Aromaa et al. [15] in 1997. The authors collected all the reports presented by patients for insurance reimbursements of neurological complications associated with CNB in Finland between 1987 and 1993, compared with the total number of CNB, retrospectively estimated and performed in that country (550,000 spinals and 170,000 epidural) over the same period of time.

In the prospective study of Scott and Tunstail [16], 14,856 spinal and 108,133 epidural procedures in obstetrics were evaluated between 1990 and 1991 in 79 obstetrics units in the UK.

Finally, two large studies on neurological complications after CNB, performed by Auroy et al. [17, 18], examined hundreds of anaesthetic procedures in France—40,640 spinals and 30,413 epidurals performed in 1994 [18] and 41,079

spinals and 35,293 epidurals performed in the period 1998–1999 [17]—collecting the largest database available, in order to determine the frequency of major complications associated with all RA techniques.

According to Moen et al. [14], the overall frequency of major neurological complications after spinal anaesthesia is about 0.4:10,000, while Auroy et al. report an overall incidence of serious or major neurological complications significantly higher after spinal anaesthesia, in particular 11.8:10,000 in 1994 [18] and 3.7:10,000 in 1998–1999 [17]. One of the reasons for these differences is to be found in the definition given by the authors of "serious" and "major" neurological complications, as Auroy et al. [17, 18] include cases of radiculopathy and peripheral neuropathy in the casuistry of complications, while Moen et al. [14] don't. In relation to epidural anaesthesia, for Moen et al. [14] the frequency of "serious or major" neurological complications is about 1.6:10,000, while for Auroy et al. the overall incidence of these is 3.9:10,000 in 1994 [18] and 0.3:10,000 in 1998–1999 [17].

For all studies on CNB, the review of the overall data suggests that spinal anaesthesia carries a higher risk of radiculopathy or neuropathy (3.78:10,000) than epidural anaesthesia (2.19:10,000), with an incidence of permanent neurological damage of 0–4.2:10,000 and 0–7.6:10,000, after spinal and epidural anaesthesia, respectively.

2.3 Clinical Pictures

2.3.1 Radiculopathy

Radiculopathy usually occurs with hypoesthesia in the territory of the affected root and occasionally with impairment of the motor component resulting in weakness.

In the case of persistent paraesthesia, direct needle- or catheter-induced trauma is strongly suspected. On 19 radiculopathies reported by Auroy, in 12 cases a paraesthesia and in two cases a pain during injection were evoked.

On seven cases of persistent paraesthesia after epidural in obstetrics (two permanent, two longer than a month), evoked paraesthesia was constant at the introduction of the catheter, an event very frequent in practice, to which therefore cannot be attributed a univocal meaning such as "sentinel event". Certainly, the adoption of polyurethane catheters is associated with a reduced incidence in the evocation of paraesthesia when compared to other materials [19, 20], but there are no studies that confirm their protective role.

Paraesthesia can occur not only during the introduction of the catheter into the epidural space but also—even less frequently—during the execution of a spinal anaesthesia. In some cases, it may signal complications or particularly unusual situations (catheter node around the root [21], post-spinal myoclonus [22], root compression from the air following the use of air spindle [23] or pre-existing dorsal table [24]). Horlocker [25] reports 300 cases of paraesthesia during puncture on 4767 spinal anaesthesia (6.3%) and six cases of persistent paraesthesia on 4767 blocks (1.2%). Of the six patients with persistent paraesthesia, four had paraesthesia

to the puncture. Therefore, the incidence of persistent paraesthesia is 1:75 in the group with evoked paraesthesia at the puncture and 1:2200 in the group without paraesthesia.

Unlike the evocation of paraesthesia, the onset of acute pain at the introduction of the spinal needle or of the catheter (or its removal) should not be underestimated, as a signal of sometimes extremely serious events, such as the direct lesion of the spinal cord [26, 27].

2.3.2 The Cauda Equina Syndrome

The cauda equina syndrome (CE) is a dysfunction that involves the L2-S5 roots. The S2-S4 roots lesion causes bladder atony; the progression of the syndrome is characterized by weakness or paralysis of the muscles below the knee and saddle anaesthesia, which extends to the calves, in case of involvement of L5 and S1.

Aurory described five cases (1.2:10,000) caused by a combination of 5% lidocaine-CSE, therefore a local maldistribution toxicity is strongly suspected. Two similar cases were described by Kubina [28] in concurrence with the use of bupivacaine in CSE, and in one of them, spinal stenosis was present. Spinal stenosis L3-L4 is invoked as a cofactor in another case [29], while the use of intrathecal adrenaline in a vasculopathic patient [30] is implicated in another case of CE.

With the use of spinal micro-catheters, complications related to intrathecal access are associated with potential problems related to high concentrations of local anaesthetics, both due to the maldistribution within the liquor and to their intrinsic toxicity. Lidocaine and tetracaine in vitro have proved to be more toxic than bupivacaine [31–33].

Reports of CE [34, 35] associated with the use of spinal micro-catheters preceded the official communication of the FDA with regard to the increased risk of this kind of complication [36] in this specific technique.

2.3.3 Intracranial Haematoma

It is a very rare complication of central blocks; Scott [37] reports a frequency of 1:500,000. Intracranial haematomas (EI) are described following accidental puncture of the dura, usually under obstetric anaesthesia [38] but also in other specialties [39, 40], even after a simple spinal anaesthesia [41–44].

No particular risk factors are reported, except for a case [41] of difficult and repeated puncture and a second case in an alcoholic patient [42]. In the case reported by Cohen [45], a pre-existing cerebral atrophy was recognized as a contributory factor, whereas in the case [46] reported by Vaughan, the intracranial subdural haematoma, without accidental dural puncture, occurred in a obstetric patient in whom CT diagnosed a concomitant intracerebral vascular malformation.

The mechanism hypothesized for this type of complication would be the loss of liquor with traction of the vascular structures and their damage [47]. The persistent

headache in the days following the puncture is often confused with a simple PPDH, so that the blood patch is required, with possible diagnosis delay.

2.3.4 Anterior Spinal Artery Syndrome

The spinal cord is vascularized by the anterior spinal artery (in the anterior 2/3 of each segment) and by two posterior arteries (in the posterior 1/3 of each segment). These terminal arteries receive blood from three distinct aortic vessels (cervical, thoracic superior and thoracolumbar arteries), with poor anastomosis between lumbar and cervical tract. Small segmental arteries of variable calibre support the vascularization provided by the anterior spinal artery. The most important of these vessels is the Adamkiewicz artery, which originates from the left side and enters the spinal canal through the intervertebral foramen between T8 and L3 levels. A damage to this vessel can cause ischaemia of the entire lumbar spine due to lack of valid thoracolumbar collateral circulation.

The anterior region of the spinal cord, where the pyramidal and anterolateral spino-thalamic ways run, is particularly vulnerable to ischaemia, especially when arteriosclerosis, intraoperative hypotension and the use of vasoconstrictors are associated with local anaesthetics. The ischaemic lesion of this region causes below the lesion level flaccid paralysis, loss of sensibility and preservation of the proprioceptive sensitivity.

Kane [48] reports four cases of ischaemia of the spinal cord following prolonged intraoperative hypotension. Similar cases are also reported in the course of general anaesthesia without CNB [49], where other factors can be invoked such as posture, caval compression and administration of adrenaline [50–52].

In some case reports with CNB, basal vasculopathies [53, 54], use of adrenaline in association with LA [53], a possible direct damage of the radicular artery [55] and operative hypotension [54, 56] are described. Despite being very rare, needle- or catheter-induced damage of the anterior spinal artery, where it enters the intervertebral foramen, is suspected to be a cause of transient ischaemic syndrome [57].

A separate discussion is reserved for the description of the bleeding complications during a CNB; the most fearful one of these is represented by the spinal haematoma, which requires a rapid diagnosis in order to prevent the permanent neurological sequelae; its occurrence has been the object of numerous studies, considering the wide diffusion of the use of pharmacological principles with anticoagulant and/or antiplatelet action with both prophylactic and therapeutic purposes.

2.3.5 Spinal Epidural Haematoma

Spinal haematoma, defined as a symptomatic bleeding within the neuraxis, is a rare and severe complication of the CNB. The actual incidence of this complication is unknown. The probable incidence of haemorrhage after performing a CNB without specific risk factors has been calculated to be about 1:220,000 for spinal anaesthesia

and less than 1:150,000 for epidural anaesthesia. The highest risk of bleeding is related to the placement and removal of an epidural catheter, the lowest one to a single-shot spinal puncture, while another variable is related to the needle gauge used [58, 59].

Approximately 60–80% of all the most severe cases of bleeding are associated with haemocoagulation disorders or bleeding from the needle [60].

Performing neuraxial anaesthesia in patients treated with antithrombotic drugs is controversial due to the increased risk of haematoma. Numerous studies carried out on a large number of patients have shown the relative safety in performing central blocks during antiplatelet therapy, but the total number of patients enrolled has been relatively low [61]. Three spinal haematomas during ticlopidine or clopidogrel therapy have been described [62–64].

NSAIDs, widely used in pain treatment, are not anticoagulant drugs but, similar to aspirin, interfere with platelet aggregation mechanisms. Administration of NSAIDs alone does not increase the risk of bleeding, but it has been shown that association with other anticoagulants increases the frequency of spontaneous bleeding.

Because of the rarity of this complication, the recommendations on CNB in the case of concomitant thromboprophylaxis are not based on prospective randomized studies but rather on case reports and expert opinions. The latter ones are mainly based on the knowledge of the pharmacokinetics of the single drugs involved. A practical rule adopted by most scientific societies sets the time interval between withdrawal of the drug and CNB execution to twice the elimination half-life of the drug.

An extensive review of the main anticoagulant drugs used in therapy describes its most important properties, with particular reference to the mechanisms of action and the duration of their activity. At the same time, the guidelines published by the most important scientific societies were analysed, comparing the recommendations provided for the correct use of drugs and the relative levels of evidence. In particular we have examined and compared the main guidelines developed by the main study groups and scientific associations in various American and European countries. At this time these guidelines represent the reference point for anaesthesiological activities in the various countries, even if they contain indications that are often not supported by clear evidence or even, significantly different indications which often confuse the operators.

We classified the level of recommendations and the level of evidence using the definitions of the Committee for Practice Guidelines of the ESC (Table 2.1) [65].

2.3.6 LMWH

With the release of LMWH for general use in the USA in May 1993, labelled indications included thromboprophylaxis at a scheduled dose of 30 mg every 12 h, with the first dose administered as soon as possible after surgery. An alarming number of spinal epidural haematomas, some with permanent paraplegia, were reported [66], triggering a warning from the US Food and Drug Administration (FDA). The

Table 2.1 Classes of recommendations and levels of evidence

Classes of recommendations
Class I Evidence and/or general agreement that a given treatment or procedure is beneficial
Class II Conflicting evidence and/or divergence of opinion about the usefulness/efficacy of the treatment or procedure
Class IIa Weight of evidence/opinion in favour of usefulness/efficacy
Class IIb Usefulness/efficacy is less well established by evidence/opinion
Class III Evidence or general agreement that the treatment or procedure is not useful or effective and in some cases may be harmful
Level of evidence
Level A Data derived from multiple randomized clinical trials or meta-analyses
Level B Data derived from a single randomized clinical trial or large non-randomized studies
Level C Consensus of opinion of the experts and/or small studies, retrospective studies and registries

marked increase in the frequency of spinal haematoma in patients anticoagulated with LMWH prompted a re-evaluation of the relative risks and benefits of neuraxial blockade [67, 68]. Collation of these cases in the USA allowed the risk of spinal epidural haematoma during concurrent administration of low-molecular-weight heparins (LMWHs) to be calculated at 1:40,800 for spinal anaesthesia, 1:6600 for single-shot epidural anaesthesia and 1:3100 for epidural catheter anaesthesia [66]. What seems to be a relatively high incidence of bleeding was attributed to the daily administration of LMWH twice a day and the lack of recommendations at that time regarding time intervals between neuraxial puncture or catheter removal and thromboprophylaxis. The response in the USA has been to introduce recommendations that are stricter than those in place in Europe, proposing avoidance of LMWH during the entire time epidural catheters are in place [67]. Particularly, ASRA guidelines have consistently recommended against the administration of twice-daily LMWH in a patient with an indwelling epidural catheter [67, 68]. Although once-daily LMWH dosing in the presence of an epidural catheter is safe, caution was advised if the patient received an additional haemostasis-altering medications, including antiplatelet therapy.

Anaesthetic management of the patient receiving LMWH by anaesthesiologists in North America provides the following points:

- In patients on preoperative LMWH thromboprophylaxis, we recommend that needle placement should occur at least 10–12 h after the LMWH dose.
- In patients receiving higher (treatment) doses of LMWH, it is recommended a delay of at least 24 h to ensure normal haemostasis at the time of needle insertion.
- In case of postoperative LMWH, patients with postoperative LMWH thromboprophylaxis may safely undergo single-injection and continuous catheter techniques.
- In case of twice-daily dosing, the first dose of LMWH should be administered no earlier than 24 h postoperatively. Indwelling catheters should be removed before

initiation of LMWH thromboprophylaxis. If a continuous technique is selected, the epidural catheter may be left indwelling overnight but must be removed before the first dose of LMWH. Administration of LMWH should be delayed for 2 h after catheter removal.

– In case of single-daily dosing, the first postoperative LMWH dose should be administered 6–8 h postoperatively. The second postoperative dose should occur no sooner than 24 h after the first dose. Indwelling neuraxial catheters may be safely maintained. However, the catheter should be removed a minimum of 10–12 h after the last dose of LMWH. Subsequent LMWH dosing should occur a minimum of 2 h after catheter removal. No additional haemostasis-altering medications should be administered due to the additive effects [69].

In Europe, the widespread adoption of a single-daily dose of enoxaparin 40 mg produced a lower incidence of complications. A retrospective analysis in Sweden found that the risk was 1:156,000 after spinal anaesthesia and 1:18,000 after epidural anaesthesia, with bleeding occurring more rarely in obstetrics (1:200,000) than in female orthopaedic patients undergoing knee arthroplasty (1:3600) [14]. Risk factors for spinal haematoma after neuraxial regional anaesthesia were identified as lack of guidelines, administration of antithrombotic agents, female sex and difficult punctures. Subsequent reports from various countries indicate that spinal epidural haematoma after neuraxial blockade occurs in 1:2700 to 1:19,505 patients [70–73], with one report indicating that haematoma may be more common after lumbar (1:1341) compared to thoracic epidural anaesthesia (1:10,199) [72].

According to European guidelines, to avoid bleeding complications, there should be a time interval of at least 12 h between subcutaneous administration of LMWH at prophylactic doses and neuraxial blockade or removal of an epidural catheter [60, 74] (Class IIa, level C). If thromboprophylaxis with LMWH is prescribed in a twice-daily schedule, compared to a once-daily regimen, the risk of epidural haematoma may be increased because the trough levels of anti-Xa activity are higher [75]. In this situation, one dose of LMWH should be omitted creating a 24-h time interval before catheter removal and the subsequent dose (Class IIb, level C). Similarly, when therapeutic doses of LMWH are being administered once or twice daily, catheter placement or removal should also be delayed for at least 24 h after the last dose (Class IIa, level B).

A meta-analysis of preoperative versus postoperative studies shows that LMWH given 12 h preoperatively does not reduce the risk of VTE compared to a postoperative regimen [76]. As antithrombotic drugs increase the risk of spinal epidural haematoma after neuraxial blockade, a postoperative start may be advantageous, especially in patients also receiving aspirin (Class IIb, level B).

Spinal epidural haematoma is not restricted to LMWH and similar drugs but can occur with any agent that interferes with haemostasis. New antithrombotic drugs are continually under development. The administration of these medications in combination with neuraxial anaesthesia must be carefully considered, and we can apply lessons learned from the LMWH experience to develop initial management recommendations [77] (Table 2.2).

Table 2.2 Recommended time intervals before and after neuraxial puncture or catheter removal

	Time before puncture/catheter manipulation or removal[a]	Time after puncture/catheter manipulation or removal[a]	Laboratory tests
Unfractionated heparins (for prophylaxis, ≤15,000 IU per day)	4–6 h	1 h	Platelets during treatment for more than 5 days
Unfractionated heparins (for treatment)	i.v. 4–6 h s.c. 8–12 h	1 h 1 h	aPTT, ACT, platelets
Low molecular weight heparins (for prophylaxisb)	12 h	4 h	Platelets during treatment for more than 5 days
Low molecular weight heparins (for treatment)	24 h	4 h	Platelets during treatment for more than 5 days
Fondaparinux (for prophylaxis, 2.5 mg per day)	36–42 h	6–12 h	(Anti-Xa, standardized for specific agent)
Rivaroxaban (for prophylaxis, 10 mg q.d.)	22–26 h	4–6 h	(PT, standardized for specific agent)
Apixaban (for prophylaxis, 2.5 mg b.i.d.)	26–30 h	4–6 h	?
Dabigatran (for prophylaxis, 150–220 mg)	Contraindicated according to the manufacturer	6 h	?
Coumarins	INR ≤ 1.4	After catheter removal	INR
Hirudins (lepirudin, desirudin)	8–10 h	2–4 h	aPTT, ECT
Argatroban	4 h	2 h	aPTT, ECT, ACT
Acetylsalicylic acid	None	None	
Clopidogrel	7 days	After catheter removal	
Ticlopidine	10 days	After catheter removal	
Prasugrel	7–10 days	6 h after catheter removal	
Ticagrelor	5 days	6 h after catheter removal	
Cilostazol	42 h	5 h after catheter removal	
NSAIDs	None	None	

ACT, activated clotting time; aPTT, activated partial thromboplastin time; b.i.d., twice daily; ECT, eparin clotting time; INR, international normalised ratio; IU, international unit; i.v., intravenously; NSAIDs, non-steroidal anti-inflammatory drugs; s.c., subcutaneously; q.d., daily

[a]All time intervals refer to patients with normal renal function

2.3.6.1 Fondaparinux

Fondaparinux, an injectable synthetic pentasaccharide, produces its antithrombotic effect through factor Xa inhibition [78]. The "expert study" with a total of 5387 patients included 1428 undergoing regional anaesthesia procedures: a single dose of fondaparinux was omitted the evening before catheter removal [79], and this provided a time interval of 36 h before catheter removal and 12 h (6 h according AAS guidelines) [80] between catheter removal and the next dose of fondaparinux. Neuraxial regional anaesthesia should not be performed when therapeutic doses of fondaparinux (5–10 mg per day) are employed due to the substantial risk of accumulation (Class III, level C) [77].

2.3.6.2 NOACs

The new oral anticoagulants (NOACs) currently include thrombin inhibitor dabigatran and factor Xa inhibitors (rivaroxaban, apixaban, edoxaban).

The ASRA guidelines on regional anaesthesia did not make recommendations, probably because of the lack of studies, whereas the European and the Scandinavian guidelines based their recommendations on the half-life of the drugs. The European and Scandinavian guidelines adopted a 2 half-life interval between discontinuation of the drugs and neuraxial injection.

Current recommendations for neuraxial blocks with new oral anticoagulants are different when they are used for postoperative thromboprophylaxis after hip or knee replacement or for prevention of thromboembolic disease in patients with non-valvular atrial fibrillation (AFIB), because in the first case, much lower doses are given compared with patients with AFIB [81] (Table 2.3).

Dabigatran is an oral reversible monovalent thrombin inhibitor. The oral prodrug dabigatran etexilate is metabolized by plasma esterases into dabigatran [82]. Currently it is licenced to be given once daily 220 mg starting with 110 mg within 1–4 h after surgery for 10 days after knee replacement surgery and for 28–35 days

Table 2.3 Simplified scheme of suggested times when neuraxial blocks are planned during NOAC administration

	Drug used for postoperative thromboprophylaxis (low doses)		Drug used in high doses for AFIB
NOAC	Time before puncture/ catheter manipulation or removal	Time after puncture/ catheter manipulation or removal	Drug withdrawal if neuraxial blocks are performed for surgery
Dabigatran	1–1.5 days	2–12 h	3.5–4 days
Rivaroxaban	22–26 h (Eur. guidelines) 18 h (Scand. guidelines)	4–6 h (Eur. guidelines) 6 h (Scand. guidelines)	2–3 days
Apixaban	26–30 h No data	4–6 h 6 h	3–4 days
Edoxaban	12 h	2 h	2 days

NOAC new oral anticoagulant, *AFIB* non-valvular atrial fibrillation

after hip replacement surgery while is typically given 2 × 150 mg daily in AFIB patients.

The long (12–17 h) half-life of dabigatran in healthy patients suggests a time interval of 34 h (from 1 to 1.5 days) between the last dose of dabigatran and catheter manipulation or withdrawal. However, the manufacturer advises against the use of dabigatran in the presence of neuraxial blockade (Class III, level C) [77, 83, 84]. Analysing licencing studies involving 4212 neuraxial blocks, the first dose of dabigatran was given at least 2 h after epidural catheter removal. Other suggestions for next dose range from 2 to 12 h [80, 84, 85].

When used in patients with AFIB, if a neuraxial block for surgery is planned, the suggested withdrawal time is 3.5–4 days [83, 86].

Rivaroxaban is a potent selective and reversible oral activated factor Xa inhibitor. When used for thromboprophylaxis, rivaroxaban is generally administered once daily 10 mg within 6–10 h after surgery for 5 weeks after hip replacement surgery and 2 weeks after knee replacement surgery.

A minimum of 18 h between the last dose of rivaroxaban (10 mg) and removal of an indwelling catheter and a minimum of 6 h before resumption of the drug have been recommended by the Scandinavian Society guidelines [27]. The European Society guidelines recommend an interval of 22–26 h between the last dose of rivaroxaban and removal of an indwelling catheter (Class IIa, level C) and an interval of 4–6 h between epidural catheter removal and the next dose of rivaroxaban (Class IIb, level C). These two recommendations represent a 2-half-life interval between rivaroxaban discontinuation and epidural catheter placement or removal. Extreme caution is recommended when using rivaroxaban in the presence of neuraxial blockade (Class IIb, level C) [77].

Rivaroxaban is given 1 × 20 mg for deep venous thrombosis treatment or stroke prevention inpatients with non-valvular AFIB. Experts recommend rivaroxaban discontinuation for 2–3 days [84, 87, 88] before neuraxial puncture. Expert opinions concerning resumption after catheter removal range from 5 to 24 h [84, 87].

Apixaban is an oral, reversible, direct factor Xa inhibitor related to rivaroxaban [82]. It is given twice daily 2.5 mg within 12–24 h after hip or knee replacement surgery for 32–38 days and 10–14 days, respectively [81]. Although the Scandinavian guidelines did not make recommendation on the interval between cessation of apixaban and neuraxial injection because of lack of available data, the European guidelines suggest a time interval of 26–30 h between the last dose of apixaban (2.5 mg) and catheter withdrawal and that at least one dose should be omitted (Class IIb, level C). After catheter withdrawal, the next dose of apixaban may be given 4–6 h later (Class IIb, level C) [77]. The Scandinavian guidelines recommend 6 h after a neuraxial injection or catheter removal before resumption of the drug [80]. Extreme caution is recommended when using neuraxial blockade in the presence of apixaban (Class IIb, level C).

Apixaban is given 2 × 5 mg daily for the prevention of stroke and systemic embolic disease in adult patients with non-valvular AFIB. Expert opinions defining

the time from apixaban discontinuation to neuraxial block placement range from 3 to 4 days [84, 87].

Edoxaban, a new Xa inhibitor, has currently been approved in the USA and Japan for the reduction in the risk of stroke and systemic embolic disease in patients with non-valvular AFIB with a dose of 60 mg once daily. Indwelling epidural or intrathecal catheters should not be removed earlier than 12 h after the last administration of edoxaban, and the next dose of edoxaban should not be administered earlier than 2 h after the removal of the catheter. However, in analogy to expert reasoning with rivaroxaban and apixaban, edoxaban should be stopped 2 days before a neuraxial puncture or epidural catheter manipulation [81].

2.3.6.3 Antiplatelet Drugs

Antiplatelet medications, including NSAIDs, thienopyridine derivatives (ticlopidine and clopidogrel) and platelet GP IIb/IIIa antagonists (abciximab, eptifibatide, tirofiban), exert diverse effects on platelet function.

Low-dose aspirin, when used for secondary prophylaxis, has been shown to reduce the risk of stroke and myocardial infarction in the range of 25–30% [89, 90]. Furthermore, the discontinuation of aspirin for secondary prophylaxis is associated with significant risk [91], and a platelet rebound phenomenon may occur, resulting in a prothrombotic state [92]. When aspirin is used for primary prophylaxis, its value in preventing cardiovascular events is unclear. [93, 94]

Nonaspirin NSAIDs bind reversibly and competitively inhibit the active site of the COX enzyme.

The degrees of reversible inhibition of COX-1, after single doses of frequently used NSAIDs (diclofenac, ibuprofen, indomethacin, naproxen and piroxicam), are dependent on the selected NSAID and measured timeframe in the first 24 h [95].

NSAIDs that selectively inhibit the enzyme COX-2 do not alter platelet function [96].

The ASRA and European guidelines recommend that central neuraxial blocks may be performed in individuals using aspirin or NSAIDs [69, 77]. On the basis of the available data, NSAIDS, including aspirin, when given in isolation, do not increase the risk of spinal epidural haematoma and are not a contraindication to neuraxial block (Class IIb, level C). Spinal anaesthesia has better support than epidural (Class IIb, level C).

To avoid any negative effect of NSAIDS on platelet function and neuraxial block, it is sufficient to miss a dose the evening before a planned procedure or catheter removal.

The Scandinavian guidelines for the performance of central neuraxial blocks in individuals using aspirin based their recommendations on the indication for aspirin use and the daily dose. In individuals taking aspirin for secondary prevention, a shorter discontinuation time of 12 h was recommended. For individuals not using aspirin for secondary prevention, the discontinuation time is 3 days unless the dose is greater than 1 g per day for which the discontinuation time is extended to 1 week [80].

For NSAIDs, the Scandinavian guideline recommendations are guided by the specific half-life for each drug [80].

Although the administration of aspirin alone does not appear to increase haematoma formation, a higher rate of complications has been observed in both surgical and medical patients when heparins were administered concurrently [97]. Because preoperative, versus postoperative, thromboprophylaxis is not proven to be beneficial [98], a cautionary approach in the presence of aspirin would be to start VTE prophylaxis postoperatively (Class I, level B).

In patients receiving NSAIDS, we recommend against the performance of neuraxial techniques if the concurrent use of other medications affecting clotting mechanisms, such as oral anticoagulants, UFH and LMWH, is anticipated in the early postoperative period because of the increased risk of bleeding complications [69].

The thienopyridines block the ADP receptor, P2Y12 subtype.

Ticlopidine has a long elimination half-life and causes an irreversible inhibition of platelet function [99]. European guidelines [77] suggest a time interval between discontinuation of this thienopyridine therapy and neuraxial blockade of 10 days, American guidelines of 14 days [69].

Clopidogrel is a prodrug [100]. Neuraxial anaesthesia should only be performed at least 7 days after the last intake (Class IIa, level C) [69, 77], whereas the Scandinavian guidelines noted that 5 days interruption is probably adequate [80].

Prasugrel, a novel thienopyridine, is a prodrug [100, 101], has a rapid onset, is ten times greater than that of clopidogrel [102] and is a particularly potent antiplatelet agent. In view of this properties, neuraxial anaesthesia should be strongly discouraged during prasugrel treatment, unless a time interval of 7–10 days can be observed (Class III, level C) [24], whereas the Scandinavian guidelines states that 5-day stoppage may be sufficient [80].

Ticagrelor acts directly on the P2Y12 receptor. Like prasugrel, it provides much faster, greater and more consistent P2Y12 inhibition than clopidogrel [102]. However, neuraxial anaesthesia should be discouraged during treatment with ticagrelor, unless at least 5 days have lapsed since the last dose (Class III, level C) [77]. For resumption of the antiplatelet drug after a neuraxial procedure or catheter removal, the Scandinavian guidelines recommended that the drug be started after catheter removal, whereas the European guidelines recommended 6 h after catheter removal before prasugrel and ticagrelor can be started [77].

Blocking the glycoprotein IIb/IIIa receptor, the final common pathway of platelet aggregation, represents the most potent form of platelet inhibition. It is reversible. After administration, the time to normal platelet aggregation is 24–48 h for abciximab and 4–8 h for eptifibatide and tirofiban [103, 104]. As glycoprotein IIb/IIIa inhibitors are used only in acute coronary syndromes, in combination with anticoagulants and aspirin and as cardiac surgery procedures are usually conducted as emergencies with continuing anticoagulation, neuraxial blockade is contraindicated (Class III, level C). If a catheter has to be removed after their administration, most guidelines recommend waiting at least 48 h after abciximab and 8–10 h after tirofiban or eptifibatide [105].

Neuraxial techniques should be avoided until platelet function has recovered.

The increasing spread of RA practices both in Europe [106] and in North America [107] requires the concomitant operators' knowledge of the risks of neurological injuries associated with the most common RA techniques. Historically, nerve injury after CNB is rare. Numerous large-scale studies published in the 1950s and 1960s on neurological complications after CNB emphasized the safety of spinal and epidural anaesthesia [108–116]. In a prospective study for examining the complications of spinal anaesthesia, Vandam and Dripps [112] documented 71 cases of transient neurological deficits after 10,098 spinal anaesthesias. Of these cases, only one permanent nerve injury was subsequently considered to be foreign to spinal anaesthesia [109]. A review of neurological complications after 32,718 epidural anaesthesia published by Dawkins [113] showed that the frequency of transient and permanent nerve lesions is 0.1% and 0.02%, respectively.

It is interesting to note that the incidence of the permanent neurological deficit after CNB reported by Dahlgren and Tornebrandt [117] is significantly higher than the one reported in most other studies in the literature. A reason for this discrepancy may be that the authors considered all the neurological complications (including very light sensitive deficits too) suffered by patients in all age groups (including children) and in both sexes, subjected to a wide range of operations, often followed by a continuous infusion by epidural catheter [117].

In contrast, most of the other examined studies included, in whole [16, 118, 119] or in part [14, 17, 120], young healthy women undergoing spinal or epidural obstetric anaesthesia. In fact, Moen et al. [14] calculated that the frequency of serious neurological complications after epidural anaesthesia is 2.8:10,000 when the obstetric population is excluded, while it falls to 0.4:10,000 in obstetric epidural anaesthesia. Similarly, Auroy et al. [17] reported an overall incidence of the main neurological complications related to the CNB of 3.4:10,000 compared to a 0.6:10,000 specific for the obstetric population.

Another reason for the relatively large number of neurological complications reported by Dahlgren and Tornebrandt [117] may be the questionable causal association between the CNB and the subsequent neurological symptoms described in at least one of the three cases after spinal anaesthesia and in all seven cases after epidural anaesthesia that could be attributed to surgery, patient position or intercurrent diseases [117].

A comparison between various guidelines reveals similarities in the management of patients receiving thrombolytics, UFH and antiplatelet therapy. The ASRA guidelines for LMWH are much more conservative than the corresponding European statements owing to the large number of haematomas in North America. It is notable that an indwelling epidural catheter during single-daily dosing of LMWH is still considered safe in Europe. However, if the patient is receiving antiplatelet therapy, LMWH will not be administered 24 before needle placement and/or catheter removal. An additional major difference is the management of the patient receiving fondaparinux. The German guideline [121] allows maintenance of an indwelling epidural catheter, although it is recommended against in both the Belgian [122] and the ASRA statements. Finally, European guidelines support neuraxial techniques (including continuous epidural analgesia) in the presence of

direct thrombin inhibitors. However, this is relatively contraindicated by the ASRA guidelines.

The comparison between the guidelines of the main societies shows, for the majority of considered anticoagulants, very strong differences, particularly concerning the time intervals to be respected in carrying out regional anaesthesia procedure. Furthermore, the evidences for prescriptions to be taken are weak. Therefore, the decision for or against regional anaesthesia always requires a careful risk-benefit analysis, noting any history of bleeding, followed by a physical examination looking for signs of increased bleeding tendency, for example, petechiae or haematoma (Class I, level A) [123]. Several conditions may be associated with altered coagulation. These include the perioperative use of various anticoagulant drugs, low platelet count, renal and/or hepatic failure, chronic alcoholism, chronic steroid therapy and perioperative infusion of dextrans. Laboratory tests, if indicated at all, should be appropriate to the individual (Class I, level A).

The perioperative cessation of anticoagulant drugs in order to improve the safety of neuraxial block needs to be critically evaluated. An alternative anaesthetic technique should be used if it is judged that the administration of the anticoagulant must not be interrupted (Class IIa, level C) [77].

Therefore, if neuraxial blockade is felt to be beneficial to a given patient, a spinal anaesthetic technique may be a valuable alternative as current data from the literature suggest that spinal puncture may be associated with less risk of spinal haematoma than epidural anaesthesia.

Finally, the guidelines are not meant to bypass clinical judgement. When the anaesthesiologist decides not to comply with these guidelines, the reasons should be noted in the patient's chart.

In summary, the rate of neurological complications after CNB results to be <4:10,000 (<0.04%), and the permanent neurological damage after RA is extremely rare in the current anaesthetic practice, even considering that the rate of neurological complications reported in the literature could be underestimated, because much of the data originates from self-reporting by operators rather than controlled prospective studies.

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3 Cardiac Patients and Noncardiac Surgery: Pathophysiological Basis for Clinical Management

G. Frasacco and L. Tritapepe

3.1 Ischemic Heart Disease

In developed countries about 5–10% of patients eligible for surgical procedures have some degree of ischemic heart disease. They have an increased risk of perioperative acute myocardial infarction (AMI) and 30% of hospital mortality [1].

Usually it is a consequence of a "silent" myocardial ischemia (ischemia without typical symptoms of angina).

The strong association between postoperative silent ischemia and other cardiac adverse events defines the crucial role of anesthesia techniques used to minimize ischemia onset.

Ischemic heart disease is characterized by atherosclerosis plaques of the coronary arteries, resulting in narrowing of vessels and decreased coronary blood flow. Imbalance between myocardial oxygen supply and demand may occur during exercise, leading to precordial pain due to stress-related stable angina.

Unstable angina (pain at rest), silent ischemia, and myocardial infarction are due to plaque rupture, ulceration, or erosion with thrombus and coronary spasm [2].

Several factors in the perioperative period can result in perioperative myocardial infarction (PMI):

- High level of circulating epinephrine and other catecholamine after surgery, with tachycardia, coronary constriction, and increased platelet viscosity [3]
- High blood coagulation with increased risk of coronary thrombosis [1]

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The risk of perioperative complications depends on predictive factors (patient's condition before surgery, comorbidities, etc.), functional capacity, and surgical risk [4].

Recent myocardial infarction, unstable angina, untreated heart failure, severe arrhythmias, and severe valvular disease are predictors of high perioperative risk.

Intermediate-risk values are stable angina, history of AMI, heart failure under treatment, and diabetes. Low-risk predictors are old age, ECG abnormalities, cerebral ischemic stroke, and uncontrolled hypertension.

Determination of functional capacity is a pivotal step in preoperative cardiac risk assessment, and it should be performed with cardiopulmonary test. Without testing, functional capacity is estimated in metabolic equivalents (METs). One MET is metabolic demand at rest. High-risk patients have poor functional capacity (e.g., inability to climb two flights of stairs or run a short distance, <4 METs) and increased incidence of postoperative cardiac events [4].

The Lee index score [5] predicts the risk of postoperative myocardial infarction and mortality, according to six variables (type of surgery, history of IHD, history of heart failure, history of cerebrovascular disease, preoperative treatment with insulin, and preoperative creatinine >2 mg/dL).

Surgical factors that influence cardiac risk are related to the urgency, invasiveness, type, and duration of the procedure. With regard to cardiac risk, surgical interventions (open or endovascular procedures) can be broadly divided into low-risk, intermediate-risk, and high-risk groups, with estimated 30-day cardiac event rates (cardiac death and myocardial infarction) of <1%, 1–5%, and >5%, respectively.

3.1.1 Anesthetic Management

Anesthetic challenge is to guarantee an adequate balance between oxygen delivery and demand to myocardial tissue. Increased heart rate, afterload, or preload with a consequent increasing in cardiac work is associated with high myocardial oxygen consumption, and it must be avoided [6] (Table 3.1). Several factors can reduce oxygen delivery, low hematocrit value, preoperative anemia, low oxygen saturation, coronary thrombosis, and vasoconstriction. Every surgical operation elicits a stress

Table 3.1 Factors determining the oxygen supply/demand

Oxygen supply	Oxygen demand
Heart rate – *Diastolic period*	Heart rate
Coronary perfusion pressure – *Arterial diastolic aortic pressure* – *End-diastolic ventricular pressure*	Transmural ventricular pressure – *Preload* – *Afterload*
Arterial oxygen content – *Partial arterial pressure of oxygen* – *Hemoglobin concentration*	Contractility

response and may cause an oxygen mismatch, with myocardial ischemia, even without severe coronary lesions. Fluid shift, acute anemia, changes in preload and afterload and heart rate, and activation of neuroendocrine and inflammatory systems caused by surgical stress increase oxygen consumption [6]. In this setting it's crucial to gain an adequate level of anesthesia, avoiding hemodynamic instability or low systemic arterial pressure (which will lead to low coronary perfusion pressure). Anyway, the majority of ischemic events during surgical operation are not related to hemodynamic variations. Other causes are vasoconstriction and coronary thrombosis.

In high-risk patients, intra- and postoperative hemodynamic monitoring is necessary, with increasing level of invasiveness (transesophageal echocardiography (TEE) or Swan-Ganz catheter) [7].

There is conflicting evidence, over whether a specific anesthetic technique is superior to another one, in reducing perioperative mortality in patients with cardiac disease.

Clinical trials comparing outcomes among regional and general anesthetic techniques have shown some evidence of improved outcome and reduced postoperative morbidity with regional anesthesia. Benefits of regional anesthesia are best neuroendocrine stress response control, reduced incidence of postoperative thromboembolic events, and cardiac (coronary thrombosis) and pulmonary complications (respiratory failure).

Other clinical trials have shown that neuroaxial and regional techniques reduce sympathetic tone, leading to reduction in afterload (reduced myocardial oxygen consumption) and in venous return due to increased compliance of the venous system, vasodilatation, and finally decrease in blood pressure (reduced coronary perfusion). So in patients with ischemic heart disease and good left ventricular function, performing regional or neuroaxial anesthesia may have benefic effects [6].

Patients with left ventricular dysfunction may not tolerate hemodynamic changes due to sympathetic blockade, and they may be advantaged by general anesthesia with selected drugs (less impact with cardiac function). Balanced anesthesia with opioids seems to be the best choice in these patients. Volatile agents used for general anesthesia have myocardial protective effects, and they may prevent perioperative myocardial infarction.

According to guidelines, perioperative continuation of beta-blockers is recommended, and preoperative initiation of beta-blockers may be considered in selected patients [4].

3.2 Valvular Heart Disease

Patients with valvular heart disease (VHD) are increasing in number, considering the aging population with more than 13% of mild/severe valvulopathies in elderly [8].

Hemodynamic instability is common in these patients, and hemodynamic management is crucial and really complex (Table 3.2).

Table 3.2 Management of hemodynamics in valvulopathies

	MVS	MVI	AVS	AVR
Preload	↑↓	↑	↑↓	↑
Afterload	=	↓	=	↓
HR	60–70 bpm	90–100 bpm	60–70 bpm	90 bpm
SVR	Keep	Reduce	Keep	Reduce
PVR	Reduce	Reduce	=	=
Rhythm	Sinus, absolutely	AF tolerated	Sinus, absolutely	AF tolerated
Inotropes	Inodilators	Inodilators	Norepinephrine	Inodilators

MVS mitral valve stenosis, *MVI* mitral valve insufficiency, *AVS* aortic valve stenosis, *AVR* aortic valve insufficiency, *HR* heart rate, *SVR* systemic vascular resistance, *PVR* pulmonary vascular resistance

Beyond general indications to guarantee a hemodynamic stability, it is essential to understand the pathophysiology of every single valvular disease and to consider that different valvular dysfunction may be present in the same patient.

Echocardiography should be performed on any patient with known or suspected VHD scheduled for noncardiac surgery, in order to assess the severity of the valvular defect and its hemodynamic consequences, during preoperative evaluation.

3.2.1 Aortic Valve Stenosis

Aortic valve stenosis (AVS) is the most common VHD in Europe. Acquired aortic stenosis is due to an idiopathic calcific degeneration of the aortic valve. The major risk factors are atherosclerosis complicated by inflammatory phenomena. The incidence of AVS increases with age, due to mechanical stress factor and other comorbidities like hypertension, diabetes, smoke, and hypercholesterolemia.

The incidence is 2–4% in the older population (>65 age) but is probably underestimated [9].

Bicuspid aortic valve is the most common congenital cardiac abnormality, affecting approximately 1–2% of the general population. Patients are asymptomatic till the valve opening guarantees an adequate blood flow; subsequently the continuous and repeated abnormal opening and closing of the aortic cusps leads to valve degeneration and leaflets calcification. So elderly patients may present with valve stenosis and or insufficiency (aortic valve regurgitation or AVR) [10].

In developing countries especially in the last decades, as a consequence of migration phenomenon, also in Europe, there are new cases of rheumatic valve degeneration which cause AVS and AVR.

Severe aortic stenosis constitutes a well-established risk factor for sudden irreversible death despite cardiopulmonary resuscitation.

The suspicion of aortic stenosis from symptoms and physical examination, has to be confirmed by echocardiography evaluation.

Aortic valve stenosis signs and symptoms generally develop when narrowing of the valve is severe. Some patients with aortic valve stenosis may not experience

symptoms for many years. Signs and symptoms of aortic valve stenosis may include heart murmur (systolic murmur extended to the neck vessels), angina, and tightness or shortness of breath, especially during activity. The heart-weakening effects of aortic valve stenosis may lead to heart failure and syncope. Echocardiography evaluation is crucial for diagnosis and stenosis quantification. It allows to measure the valve area (normal value 3–4 cm^2) [11]. Severe aortic stenosis is defined according to an integrative approach taking into account valve area (<1.0 cm^2 or 0.6 cm^2/m^2 body surface area, except in obese patients) and flow-dependent indices (maximum jet velocity 4 m/s and mean aortic pressure gradient ≥40 mmHg). Pathophysiology of aortic stenosis is characterized by left systolic ventricular flow obstruction with increased wall stress, which chronically leads to pressure overload and concentric ventricular hypertrophy. Left ventricle produces a high-pressure peak for the increased transvalvular gradient, with a reduction in wall stress thanks to the myocardial concentric hypertrophy. Naturally it leads to a diastolic dysfunction with a consequent increasing in ventricular end-diastolic pressure, which is the preamble for a subendocardial ischemia. Reduction in ejection fraction is due to reduction in myocardial contractility. Myocardial dysfunction and loss of myocardial contractility determine a reduction of ejection fraction, which implies a complex estimation of the severity of aortic stenosis (reduction in valve flow gradient named "low-gradient aortic stenosis").

3.2.1.1 Anesthetic Management

Complications after noncardiac surgery depend on patient-related risk factors (degree of stenosis, ischemic heart failure, etc.), on the type of surgery, and on the circumstances under which it takes place. Moreover, cardiopulmonary resuscitation may not provide an adequate cardiac output in patients with severe aortic stenosis. Aortic stenosis implies for anesthetists a complex management and an accurate patient monitoring to avoid hemodynamic instability or variation in volume status, heart rate, and vascular tone, despite the anesthetic technique [12].

For clinical assessment it is crucial to avoid arrhythmias and to guarantee heart sinus rhythm. In patients with diastolic dysfunction, atrial stroke is essential in maintaining cardiac output. In fact atrial fibrillation leads to the loss of atrial systole with consequent severe hypotension (low cardiac output). In this situation with low cardiac output and hemodynamic instability, clinicians have to quickly perform an electrical cardioversion, also in the preoperative time, to get a hemodynamic stability.

Heart rate variations have to be avoided, also in sinus rhythm. Bradycardia can cause collapse in cardiac output (loss of stroke volume). On the other hand, tachycardia can lead to an increased cardiac stress and work, especially in a hypertrophic heart (as a consequence of stenosis) where discrepancies between oxygen delivery and demand may worsen coronary blood flow. Optimization of fluid load is mandatory. Preload must be increased because of the diastolic dysfunction [13].

Peripheral vascular tone and afterload have to be high, avoiding hypotension and vasodilatation. In case of low arterial pressure and low coronary perfusion pressure,

vasopressors as norepinephrine may help in maintaining vascular tone and cardiac contractility.

Anesthetic management is aimed at ensuring the best compromise between depth of sedation or type of locoregional blockade (avoiding bradycardia or tachycardia) and the management of vascular tone and fluid load to avoid vasoplegia and reduction in preload.

Neuroaxial anesthesia may be contraindicated unless constant maintenance of an adequate afterload is performed [13].

In this setting hemodynamic monitoring is mandatory: heart rate, ECG, oxygen saturation, and invasive blood pressure. In high-risk surgery, continuous central venous pressure (CVP) monitoring or semi-invasive/invasive cardiac output monitoring system may help in the volemic status and cardiac assessment. Intraoperative echocardiography [11], when available, is the most comprehensive monitoring system, which allows to evaluate cardiac contractility and output, heart filling volume, diastolic and systolic function, and volemic status.

In symptomatic patients, aortic valve replacement should be considered before elective surgery. In patients at high risk or with contraindication for aortic valve replacement, balloon aortic valvuloplasty, or, preferably, transcatheter aortic valve implantation (TAVI) may be a reasonable therapeutic option before surgery. Neuroaxial anesthesia (spinal or epidural anesthesia) can be tolerated in the moderate aortic stenosis (especially in asymptomatic patients), but it's not recommended in severe AS, because of the reduction in preload and afterload due to sympathectomy which could lead to a severe hypotension and reduction in coronary perfusion.

3.2.2 Aortic Valve Regurgitation

Aortic valve regurgitation (AVR) depends on an incomplete closure of valve cusps with a regurgitation of an amount of blood in the left ventricle during diastole [12].

Aortic regurgitation can be divided into severe and acute forms due to endocarditis or aortic dissection and chronic regurgitation ones, with a better prognosis. In this last form, regurgitation is due to incompetence of the aortic valve or any defect of the valvular apparatus (leaflets, annulus) for congenital causes, connective degeneration, inflammatory or rheumatic diseases, and annular dilatation (due to aging and hypertension). Coaptation defect allows blood regurgitation to increase the left ventricular end-diastolic pressure [14]. Chronic volume overload leads to a ventricular remodeling with eccentric hypertrophy and dilatation. For this reason, patients may be asymptomatic for many years, till severe regurgitation causes heart failure with fatigue, dyspnea, orthopnea, and nocturnal paroxysms. Reduced diastolic pressure causes angina also without coronary lesions. Stroke volume is increased from low peripheral vascular resistances, so EF% is normal. With the worsening of the ventricular dilatation and the ventricular remodeling, cardiac output fails, with hypotension, increased sympathetic tone, and severity of regurgitation [14].

Echocardiography is the key examination in the diagnosis and quantification of AVR severity, using color Doppler and pulsed-wave Doppler. Echocardiography is also important to evaluate regurgitation mechanisms, describe valve anatomy, and determine the feasibility of valve repair [15].

AR may be mild (regurgitation volume <20%), moderate (volume 20–39%), and severe (volume 40–60%). Entity of regurgitation is due to diastole duration too.

3.2.2.1 Anesthetic Management

In the anesthetic management, the aim is to gain a heart rate of about 90 bpm to shorten the diastolic time and the consequent regurgitation fraction [6]. Mild tachycardia in fact allows to increase diastolic arterial pressure and to reduce end-diastolic left ventricle pressure, with optimization of myocardial perfusion. Drugs reducing heart rate have to be avoided. Sinus rhythm is desirable, but unlike the aortic stenosis, tachyarrhythmia is well tolerated. Preload has to be increased and adequate to the dilated ventricular chamber; reduction in afterload is crucial to allow the antegrade flow through the valve and to avoid regurgitation [6]. Myocardial contractility must be preserved, optimizing the vasodilatation and avoiding the reduction in preload.

Vasoconstrictor drugs increase the afterload with consequent worsening in valve regurgitation and ventricular dilatation. In case of the necessity of inotropic drugs, it's better to choose an inodilator as levosimendan or milrinone, instead of dobutamine. Locoregional anesthesia (subarachnoid or epidural) can certainly represent technique of choice, provided that adequate intravascular volume is maintained.

3.2.3 Mitral Valve Stenosis

Rheumatic fever is the predominant etiology of mitral valve stenosis (MVS), and it has greatly decreased in Europe in the last decades; nevertheless, migration has led to new rheumatic disease cases.

Mitral valve area is about 4–5 cm^2. Moderate reduction in area (<2.5 cm^2) causes symptoms as dyspnea getting worse with exercise, anemia, pregnancy, and fever (need to increase the cardiac output) [16].

The severity of the mitral stenosis is defined by the valve area: mild (valve area 2.5–1.5 cm^2), moderate (1.5–1 cm^2), and severe (<1.0 cm^2).

The diagnosis is usually established by echocardiography and cardiac catheterization. Valve area should be measured using planimetry and the pressure half-time method, which are complementary. Echocardiography also evaluates pulmonary artery pressures, concomitant valve disease, and left atrium (LA) size. In fact the obstruction of the mitral flow determines an increase in left atrial pressure with enlargement of the atrium, risk of atrial fibrillation, and auricular thrombus.

In case of atrial fibrillation, patients need anticoagulation therapy with vitamin K antagonists (VKAs) or non-VKA direct oral anticoagulants (NOACs) or heparin

and rhythm control medications or cardioversion (in rapid-onset fibrillation and hemodynamic instability). Transesophageal echocardiography (TEE) should be performed to exclude LA auricular thrombus before cardioversion or after an embolic episode.

High atrial pressure causes increase in pulmonary pressure with vessels remodeling and postcapillary pulmonary hypertension, consequent enlargement, and hypertrophy of the right ventricle [17].

Slowing in diastolic ventricular filling determines low pressure and low end-diastolic ventricular volume (with reduction in stroke volume). Stroke volume is reduced, especially in case of increased heart rate. Contractility can be maintained, but it is often depressed due to structural alterations of the ventricle and the subvalvular apparatus with a reduction in the compliance of the left ventricle and subsequent diastolic dysfunction. The septal shift for enlargement of the right ventricle also contributes to diastolic dysfunction.

3.2.3.1 Anesthetic Management

The pathophysiology of the SVM involves the control of cardiac rhythm, preload, left ventricular contractile function, and pulmonary hypertension. It is essential to avoid tachycardia (tachyarrhythmia in many cases) because, reducing the diastolic time irreversibly, it compromises ventricular filling. The acute increase in the transvalvular gradient should also be avoided, avoiding the increase of sympathetic tone [5, 6]. Where possible sinus rhythm should be preserved and maintained, favoring the atrial contribution to the determinism of cardiac output. In the case of atrial fibrillation, rhythm control (digital, beta-blockers, even short-acting amiodarone) must be absolutely guaranteed.

An adequate preload must be guaranteed to maintain the trans-stenotic flow; therefore, it must pay attention to the vasodilatation due to anesthetics. However, optimizing the preload involves the risk of further increase in left atrial pressure and the development of pulmonary edema. The excessive reduction of the afterload is not particularly advantageous anyway. Despite normal peripheral vascular resistances and contractility in most patients, it is possible that the empty/unloaded left ventricle develops systolic and diastolic dysfunction. In these patients, it is crucial to monitor pulmonary hypertension, hypoxemia, acidosis, hypercapnia, and the use of nitrous oxide must be avoided [17]. It is also necessary to predict the increase in bleeding linked to anticoagulation. Avoid excessive premedication that compromise ventilation: even mild hypercapnia precipitates hemodynamic stability. Patient with SVM requires monitoring of invasive blood pressure, CVP, and intraoperative echocardiographic monitoring. In high-risk surgeries, monitoring of cardiac output and pulmonary arterial pressure with the Swan-Ganz catheter is recommended, given the simultaneous presence of right ventricular dysfunction. It is essential to avoid hypoxemia and hypercapnia, to maintain optimal acid-base balance, and to reduce pulmonary hypertension with vasodilators, inodilators, and nitric oxide. Locoregional techniques can be poorly tolerated for their effects on systemic vascular resistance; epidural anesthesia is preferable to the subarachnoid one for the most gradual appearances of the sympathetic block.

3.2.4 Mitral Valve Insufficiency

Mitral valve insufficiency (MVI) is a very common valvular disease. It is determined both by changes in the valve and in the subvalvular apparatus including the anomalous remodeling of the left ventricle which leads to pathological valvular coaptation. Mitral valve abnormalities include prolapse, myxomatosis degeneration, rheumatism insufficiency, mitral cleft, and infiltrative/degenerative processes. Functional MVI accounts for about 10–20% of patients with ishemic heart disease [18]. In these patients, morphology of the mitral valve is normal. In conclusion, there are two categories of patients with MVI: those with myxomatous valve degeneration (cordial rupture, cord lengthening, prolapse, flail) and those with ischemic MI (from myocardial ischemia). Valvular regurgitation depends on the regurgitation orifice, the ventricle-atrial pressure gradient, and the duration of the systolic time [18]. Symptoms of chronic MVI range from fatigue and palpitations to heart failure. Echocardiography is essential for the diagnosis and stratification of the degree of mitral insufficiency, but diagnosis, as well as clinical presentation, can also be performed by cardiac catheterization. MVI is defined by the percentage of regurgitation compared to stroke volume as mild (<30%), moderate (30–39%), and severe (40–60%) [8]. The Doppler mode on pulmonary veins helps in quantifying the severity of the MVI. Systolic regurgitation increases pressure and volume of the left atrium, but increase of the pressure is gradual and limited in relation to chronic dilation of the left atrium. Left atrium enlargement determines atrial fibrillation that further alters atrium compliance and leads to pulmonary hypertension [19]. As with MVS, a slower pressure balance is achieved in the small circle with pulmonary hypertension and consequent right ventricular dysfunction. The pathophysiology of MVI is linked to the pressure and volume increase of the atrium and left ventricle. This causes a chronic dilatation of the left ventricle with mild eccentric hypertrophy without increase in ventricular thickness. Stroke volume is guaranteed for a long time, thanks to the reduction of afterload determined by the MVI. Stroke volume begins to decrease as a consequence of the degree of regurgitation which increases the dilatation of the left ventricle itself. The percentage of ejection fraction (EF%) may also be normal considering the amount of regurgitation, but the reduction of EF% significantly compromises hemodynamic status and it requires cardiac surgery.

In patient undergoing high-risk surgery, in selected cases, percutaneous palliation procedure (MitraClip) can be used to reduce the degree of MVI.

Acute MVI from myocardial infarction (rupture of chordae or papillary muscle) or from endocarditis determines a condition of hemodynamics emergency due to the impossibility of atrial adaptation and acute development of pulmonary edema. Usually these patients can be in cardiogenic shock requiring treatment with inotropes, NIV, IABP, and often urgent cardiac surgery.

3.2.4.1 Anesthetic Management

Management of patients with MVI requires maintenance of anterograde stroke volume, with a heart rate between 80 and 100 bpm, which reduces the time of systole

and the amount of regurgitation. Bradycardia can be deleterious because it increases the duration of systole and therefore the regurgitation but also the diastolic time and therefore the overload of the left ventricle. Sinus rhythm should be maintained, but atrial fibrillation is tolerated [3]. Less tolerated are the alterations in preload and afterload due to the effect of anesthesia that can lead to an aggravation of the MVI. As an indication, the slight reduction of the afterload associated with an increase of the preload determines an optimization of the hemodynamics. So an adequate anesthesia depth, a moderate vasodilation, even with inodilators, determines an increase in cardiac output. It is fundamental to avoid hypertension and hypertensive crises which may get MVI worsen [6]. Usually cardiac contractility is maintained, but contractility does not correlate with FE% for the regurgitation quota. In case of hypotension, heart rate (increased) and preload should be improved, absolutely avoiding vasoconstrictor drugs. In case of low EF% and reduced cardiac output, inodilators and inotropes such as dobutamine should be used. Increases in pulmonary arterial pressure should also be avoided. Locoregional techniques are well tolerated, if heart rate control is always monitored.

3.2.5 Antibiotic Prophylaxis of Bacterial Endocarditis

Recommendation for antibiotic prophylaxis in patients with valvular heart disease is complex. Recent guidelines classify different conditions of heart disease by referring to the probability of contracting endocarditis as a secondary effect in high-, moderate-, and low-risk patient groups. Subjects with congenital heart disease, acquired valvulopathies, hypertrophic cardiomyopathy, and mitral prolapse with a regurgitation murmur are included in the moderate-risk group, and they require perioperative antibiotic therapy based on the type, location, and severity of the surgical intervention. In general, antibiotic prophylaxis against *Streptococcus viridans* is necessary for dental, oral, and respiratory tract surgery, while antibiotic prophylaxis toward *Enterococcus faecalis* is indicated for genitourinary and gastrointestinal surgery. Adequate antibiotic therapy must be started before the beginning of surgery.

3.3 Heart Failure

Heart failure is the inability of the heart to pump enough blood to satisfy tissue requests. It occurs in a high percentage of the population, with an increase of 10% in the group over 75 years old, and it is associated with an increase in mortality after anesthesia. Ischemic heart disease is the most common cause. Other causes include hypertension, valvular heart disease, and cardiomyopathies. One third of surgical patients with an ejection fraction of less than 30% die within a year [7].

Cardiac output is lower in heart failure because the systolic output decreases for the same end-diastolic volume of the left ventricle compared to a normal heart.

Because of the decompensated heart has a limited ability to increase the systolic volume, the only response to increased preload is an increase in heart rate, which can cause ischemia. Furthermore, high end-diastolic ventricular pressure hinders blood flow to the endocardium.

In decompensated heart, cardiac output is reduced, and it collapses if the ventricular end-diastolic volume rises to high levels, as in the overload status of heart failure [6].

The goal is to evaluate the severity of the disease and the myocardial contractility. Limited exercise tolerance, orthopnea, and paroxysmal nocturnal dyspnea are indicators of severity. Pharmacological treatments may include ACE inhibitors, diuretics, and nitrates. In some patients with mild or moderate heart failure, cardioselective beta-blockers can be used in an attempt to control heart rate, but the risk is that they can depress sympathetic nerve activity that guarantees myocardial contractility in the decompensated heart. Useful instrumental investigations are ECG (to search ischemia sign), chest radiography, and especially echocardiogram to evaluate the ejection fraction. EF is the percentage of the end-diastolic blood volume ejected from the left ventricle during systole, and values below 30% are index of severe heart failure.

3.3.1 Anesthetic Management

"Safe" anesthesia for patient with heart failure does not exist, but in any case, an optimal conduct is to optimize ventricular filling, keeping in mind that preload can be reduced by the use of diuretics and nitrates. Arterial and central venous blood pressure should be monitored, and sometimes pulmonary arterial pressure should also be monitored. It is advisable to monitor the cardiac output to highlight silent periods of low flow and consequent occult tissue hypoxia. If available, transesophageal echocardiography is a useful tool for visualizing and monitoring overall cardiac performance.

Heart rhythm should be maintained as arrhythmic changes may compromise cardiac output (systolic and diastolic dysfunctions). Especially in advanced diastolic dysfunction (restrictive form), loss of sinus rhythm can lead to fatal episodes, and immediate electrical cardioversion should be performed. Many patients already have an implantable defibrillator and biventricular pacing that needs to be optimized before surgery. However, the heart rate should be maintained in the 80–90 bpm range, as the cardiac output may solely depend on the heart rate.

Proper cardiac contractility must be maintained; in particular, the use of inotropes may be necessary to counteract the cardio-depressive action of anesthetic agents. Reduction of the afterload due to vasodilatation, for example, as a secondary effect of spinal or epidural anesthesia, can have positive effects, as it does not only reduce myocardial work but also help to maintain the cardiac output [6]. However, the benefit of such actions can be limited by falls in blood pressure which can compromise the blood flow to vital organs such as the brain and kidney.

Particular attention should be paid to preoperative therapy with ACE inhibitors, which may result in a massive vasodilation induced by severe vasoplegic action of the anesthetic drugs, difficult to treat [20].

Patients with heart failure should follow a protocol of hemodynamic optimization (optimization of DO_2) intraoperatively and especially in the postoperative time in intensive care where, in addition to arrhythmias monitoring, hemodynamic monitoring and optimization must be continued to ensure better outcomes.

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Postoperative Pain Management

4

Franco Cavaliere and Carlo Cavaliere

4.1 Postoperative Pain

Pain is the first of the consequences of the surgical intervention the patient feels. If not effectively controlled, pain influences the postoperative course of the patient, is remembered as a very negative experience, and can become chronic, causing algic syndromes, which may last for years. The importance of the theme is evidenced by the numerous guidelines on the subject published by prestigious scientific societies [1–3].

Postoperative pain originates from different mechanisms [4, 5]. The component caused directly by the surgical procedure is the result of multiple factors: the incision of the skin and the section of the tissues, the traction and compression exerted by the retractors, and the traumatisms suffered by myofascial structures, muscles, bones, tendons, joints, and ligaments. Not only the nerve section, but also the stretching due to the nearby sutures plays a particularly important role as a cause of neuropathic pain. Tissue inflammation that develops after the surgical trauma is a source of algogenic stimuli through the release of a series of mediators, including potassium and leukotrienes from damaged cells, serotonin from platelets, and bradykinin from endothelial cells. Then, there is the irritation of tissues and nerve structures due to compression or suction related to drainages and the presence of fluids and in particular blood in the pleural and peritoneal cavities. A final, important factor is the mixing of somatic and visceral pain and the involvement of the autonomic nervous system.

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4.1.1 The Importance of Treating Postoperative Pain Adequately

Inadequate analgesia can lead to a long series of negative events. Pain is often accompanied by intense emotional and psychological components that condition the patient's degree of satisfaction and his judgment on the structure to which he has entrusted. Pain activates the autonomic nervous system and is responsible for a series of cardiocirculatory responses (tachycardia, hypertension) and respiratory responses (tachypnea, current volume reduction) that engage the functional reserves of the patient. The endocrine response includes the secretion of ACTH, cortisol, catecholamines, glucagon, thyroxine, and the activation of the renin-angiotensin system, while insulin secretion is inhibited. In general, catabolic reactions are stimulated and anabolic ones are inhibited [6].

Pain involves functional limitations to the movement that hinder the early mobilization of the patient and facilitate the establishment of deep vein thrombosis. In thoracic and abdominal interventions, the presence of pain limits the expansion of the thorax and the activity of the diaphragm, favoring the onset of pulmonary atelectasis, bronchopneumonia outbreaks, and hypoxemia refractory to oxygen therapy. The persistence of pain can delay the discharge of the patient, increasing the length of hospital stay and related costs. Finally, several evidences suggest that inadequate analgesia could facilitate pain chronicization.

Among the potential effects of postoperative antalgic treatment, a depression of the immune system, attributed mainly to opioids, has been reported, which may increase the risk of relapse in neoplastic patients [7, 8]. However, conclusive evidence on this point is still missing.

4.1.2 Chronic Pain as a Consequence of Surgical Procedures

Postoperative pain is defined as chronic when it is still present 3–6 months after surgery [4]. It is generally a neuropathic pain, which originates from nerve structures assigned to the transmission of painful stimuli, rather than from the persistence of algogenic stimuli. This type of pain often manifests itself with a burning sensation, which can be associated with a lack of sensitivity or hyperesthesia. Frequently, there are also hyperalgesia (increased perception of painful stimuli) and allodynia (painful perceptions caused by stimuli other than noxious). The pathogenesis is complex because central and peripheral nervous sensitization can coexist; often, there is an interaction between the immune and nervous systems. At the level of the posterior horns of the spinal cord, sensitization takes place due to the prolonged stimulation of the nerve fibers C, with release of molecules that amplifies the transmission of the painful stimuli that travel through fibers A [5]. These substances include substance P, the calcitonin gene-related peptide (CGRP), and the excitatory amino acid glutamate and aspartate. Sensitization also involves a general activation of pain transmission pathways and a depression of the descending inhibitory pathways.

The incidence of chronic postsurgical pain is probably still underestimated and is variable in relation to age, sex, genetic predisposition, and the presence of pain in the preoperative period. The type of surgical procedure is naturally the main factor. The incidence is low after minor interventions, increases in the most invasive ones, and reaches very high values in some interventions as limb amputation (around 50–80%), mastectomy (20–40%), and thoracotomy (30–50%) [9]. Numerous data suggest that adequate analgesic treatment can prevent chronic postoperative pain [10]. In addition, it should be borne in mind that some drugs are particularly effective against neuropathic pain and perform a fundamental action for multimodal analgesia. Among these substances, we find magnesium, ketamine, clonidine, gabapentinoids, and antidepressants [11]. The effectiveness in preventing chronic pain of local analgesia (wound infiltration) or regional techniques with respect to systemic analgesia with opioids and analgesics has been the subject of a recent review by Cochrane [12]. The conclusions pointed out that, generally-speaking, the data collected so far are not yet sufficient to draw definitive conclusions because of the differences between the studies about surgical procedures taken into account and modalities of pain therapies used. However, available literature suggests that local or regional analgesia could avoid chronic postoperative pain in one patient out of every four after thoracotomy or mastectomy.

4.1.3 Pain Evaluation

The intensity of postoperative pain reported by different patients after the same surgical procedure is variable. In fact, the sensitivity to pain stimuli changes from individual to individual, is greater in young subjects than in the elderly, and increases in the presence of anxiety and strong emotional involvement. Pain intensity is greater when it overlaps with a painful symptomatology already present before the intervention, especially if it is a chronic pain in pharmacological treatment. Finally, the same intervention may involve different degrees of tissue trauma.

Pain is one of the vital parameters, and its entity must always be monitored, evaluating both the intensity at rest and during movement. In the postoperative period, adequate analgesia cannot be performed based solely on the type of surgery performed. The intensity of the pain varies from subject to subject and changes over time; therefore, analgesic administration should be titrated on the intensity of pain perceived by the patient and measured at regular intervals. For this purpose, the numerical scale (NRS, numeric rating scale), the visual scale (VAS, visual analogical scale), and the verbal scale (VRS, verbal rating scale) are easy-to-use and well-reproducible tools recommended by guidelines [1]. In patients unable to communicate, the Bieri scale can be used, in which levels of pain are expressed by six faces with different facial expressions [1]. Other scales, such as the Multidimensional Affect and Pain Survey (MAPS), the McGill Pain Questionnaire (MPQ), and the Karnofsky Performance Status (KPS), are multidimensional; they ensure a more complete assessment of perceived pain at the price of a longer and more laborious application.

In Italy, the obligation to perform periodic pain assessments and to report the results in the medical record is enshrined in law [13]. Furthermore, the assessment of the patient's satisfaction level can be easily performed with the administration of a special questionnaire at the time of discharge. This practice prevents inadequate analgesic treatment from going unnoticed and helps to improve internal protocols.

4.2 Postoperative Analgesia

4.2.1 A Multimodal Approach

Each drug and analgesic technique currently available has limitations, and usually only the association of some of them allows obtaining adequate analgesia. In addition, each drug has side effects, often dose-dependent, such as the respiratory depression and increased incidence of postoperative vomiting and nausea (PONV) associated with the use of opioids. For this reason, a polypharmacological approach has undoubted advantages in terms of reducing the doses of individual analgesics and consequently their undesirable effects. This approach, called multimodal analgesia, is defined as the use, with the same route of administration or with different routes, of two or more analgesic drugs acting with different mechanisms [14].

Currently, therefore, postoperative analgesia is generally a multimodal analgesia, which combines multiple techniques (systemic and locoregional) and multiple drugs (opioids, NSAIDs, anti-COX2, paracetamol, local anesthetics, adjuvants) to achieve better results with less incidence of side effects. This approach not only reduces the doses and therefore the side effects of the drugs, but also allows to individualize the treatment based on the characteristics of the patient, the type of surgery, the degree of tissue inflammation, and the nature of pain (usually a mix of somatic, visceral, and neuropathic components). The use of regional anesthesia techniques allows, for example, the early mobilization of the patient at risk of respiratory complications. Applying the pyramidal scheme proposed by some authors, in mild pain we could foresee the use of NSAIDs, paracetamol, and anti-COX2, in association with local techniques such as wound infiltration; the addition of an opioid administered at regular intervals is suggested in moderate pain and the administration of an opioid by continuous infusion (by elastomers or patient-controlled analgesia) together with the use of nerve blocks, in intense pain [15].

4.2.2 Preemptive Vs Preventive Analgesia

The term preemptive analgesia means the administration of analgesic drugs already in the preoperative phase that precedes the surgical incision [16, 17]. For preventive analgesia, we mean instead the administration of analgesics before the end of general anesthesia, when anesthetic drugs are still active. Both of these techniques assume that sensitization of pain transmission circuits in response to algogenic

stimuli occurs already in the intraoperative phase and can be prevented by administering analgesics by systemic route or by using local-regional anesthesia techniques. The administration of analgesics prior to surgical incision is particularly important in patients suffering from pain already before surgery.

In practice, techniques used to perform preventive analgesia include intravenous opioid and NSAID administration, epidural analgesia with local opioids and analgesics, nerve blocks, and infiltration of the surgical site with local anesthetics. Of particular interest is the administration of drugs effective against peripheral and central sensitization to pain, such as the inhibitors of NMDA receptors (ketamine, clonidine, and dextromethorphan), local anesthetics by intravenous infusion, and epidural prostigmine. The studies available in the literature did not point out significant differences about the efficacy of preemptive vs preventive analgesia and even of preventive vs postoperative analgesia. Pending further study, it should however be noted that the theoretical considerations underlying these techniques are absolutely reasonable and that their implementation does not involve any special risk for patients.

4.3 Systemic Analgesia

4.3.1 Opioids

Opioids are natural or synthetic molecules that share the property of binding to some receptors that modulate the transmission of pain. These receptors are divided into the three classes (mu, delta, and kappa), which differ from each other for the distribution in the different areas of the brain and spinal cord and for their functions, which are partly common. The activation of these receptors inhibits the excitation of neurons, through a reduction of the adenylyl cyclase activity and therefore of the levels of cyclic AMP.

The antalgic effect of opioids is complex and manifests itself both with an increase in the pain threshold and with a marked reduction in the emotionality associated with pain. The increase of threshold occurs partly due to the inhibition of the activity of the second-order projection neurons to which C fibers connect in the spinal cord. Further action is carried out on supraspinal GABAergic neurons, which exert the activity of inhibiting the descendant inhibitory serotoninergic neurons of the brainstem which, in turn, hinders the transmission of painful stimuli. By binding supraspinal GABAergic neurons, opioids inhibit them and allow the inhibitory action of serotonergic neurons on pain transmission to take place. The effects of opioids on the emotional component of pain are equally important and derive from the action on the limbic system.

Current-use opioid drugs include morphine, fentanyl, sufentanil, codeine, tramadol, methadone, buprenorphine, and hydromorphone. These drugs differ in their pharmacodynamic and pharmacokinetic aspects. Pharmacodynamics partly reflects the different affinity for the three classes of receptors. For example, morphine and fentanyl are strong agonists of mu receptors and weak agonists of delta and kappa

receptors, while buprenorphine is a partial agonist of mu receptors on which, however, it also exerts an antagonist action. Tramadol and methadone are mu-receptor agonists but have other side effects that enhance the analgesic effect, represented, for example, by the inhibition of neuronal reuptake of norepinephrine and serotonin. Among the pharmacokinetic differences, particular importance has the degree of liposolubility that affects the speed with which the drug crosses the blood-brain barrier to reach the effector sites located inside the spinal cord and the brain. Morphine is characterized by relatively low liposolubility and therefore has a fairly long latency of action; the analgesic effect appears about 5 min after intravenous administration and reaches its maximum effect after about 30–60 min. Fentanyl, on the other hand, has greater liposolubility; after intravenous administration, the analgesic effect appears after approximately one minute. However, the short latency typical of more liposoluble opioids may increase the risk of complications. Indeed, the rapid passage through the blood-brain barrier leads to the achievement of higher peaks at the effector sites, which may favor the onset of severe respiratory depression.

The side effects of opioids are numerous. Respiratory depression is dose-dependent and related to mu receptors; it is characterized by a reduction in the respiratory rate up to apnea, whereas a reduction in the current volume occurs at higher dosages. Sedation and dysphoria are other side effects of opioids together with an increased incidence of postoperative nausea and vomiting (PONV). The paralytic ileus is a consequence of the stimulation of the mu and kappa receptors in the intestinal nerve plexus, which determines an increase in the basal tone of the intestinal musculature and of the sphincters. The slowing of recovery of intestinal function is one of the main reasons for which opioids are not recommended by the enhanced recovery after surgery (ERAS) protocols [18]. Another possible side effect is pruritus.

Morphine can be administered in 2 mg intravenous boluses to be repeated every 5–10 min until an adequate analgesic effect is achieved (VAS of three or less on a scale of one to ten), followed by a continuous infusion with elastomer or, better, by patient-controlled analgesia (PCA), programmed to deliver only boluses, without continuous infusion. A continuous infusion should be performed in a protected environment due to the risk of drug accumulation and consequent respiratory failure. On this regard, elderly people and patients with renal insufficiency are particularly at risk because the former has a greater sensitivity to morphine and the latter a greater risk of accumulation of morphine-6-glucuronide and morphine-3-glucuronide metabolites, which may cause respiratory depression.

Compared to morphine, *fentanyl* has 100 times higher potency, is much more liposoluble, and has short duration of action and no active metabolites. It is used intravenously and intrathecally.

Sufentanil is ten times more potent than fentanyl and can be used both intravenously, in protected environments, and by epidural route, in association with local anesthetics.

Codeine or *methylmorphine* is an opioid ten times less potent than morphine, often marketed in association with other nonnarcotic analgesics. Codeine is

metabolized by the hepatic CYP2D6 enzyme to morphine; the rate of the reaction varies according to different phenotypes present in the population. Pain relief may be inadequate in poor metabolizers, because the blood levels of morphine remain too low. On the other hand, in so-called ultrarapid metabolizers, the rate is so high that blood levels of morphine may increase enough to cause side effects, in particular respiratory failure. The prevalence of ultrarapid metabolizers varies in different ethnic groups and is particularly high in African populations, where it can reach about 30%; in those individuals, codeine should not be used, but morphine and NSAIDs are safe [19].

4.3.2 Paracetamol

Paracetamol or acetaminophen is an analgesic, antipyretic, and weak anti-inflammatory drug [20]. Its mechanism of action has not yet been fully clarified and could be manifold. The sites of action are in the central nervous system, where this drug penetrates quickly, overcoming the blood-brain barrier due to its high liposolubility and low protein binding. Among the various pharmacological actions highlighted in vivo and in vitro, there is the inhibition of the enzyme cyclooxygenase (COX) with a higher affinity for COX-2, the stimulation of serotonergic descending pathways that inhibit the transmission of algogenic stimuli, and the increase in concentrations of endogenous cannabinoids. Paracetamol can be administered orally, rectally, and intravenously. Its precursor proparacetamol, which is rapidly metabolized to paracetamol, can also be given intravenously. The intravenous route offers the advantage of a lower latency (about 30 min less) and of a greater effectiveness due to the immediate absorption and the absence of the first-pass effect. The metabolism of paracetamol is hepatic and occurs through reactions of sulfation, glucuronidation, and oxidation. In the oxidative pathway, the main one, the drug is converted into the metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI), which is in turn transformed into some inactive metabolites that are eliminated with the urine after conjugation with intracellular glutathione. The accumulation of NAPQI can result in a toxic damage to the liver, even very serious, if the availability of glutathione is not adequate. This condition can occur both because of toxic dosage or because the intracellular glutathione deposits are depleted, as in the case of acute or chronic alcohol abuse. The dosage of intravenous paracetamol is 1 g every 4–6 h with a maximum of 4 g/day. In children over 2 years of age, adolescents, and adults weighing less than 50 kg, a dosage of 15 mg/kg every 4–6 h is suggested. In children younger than 2 years, dosage should not exceed 10 mg/kg every 4–6 h. The duration of the analgesic effect is about 4–6 h but may be longer in young children and in patients with renal insufficiency. Paracetamol administration is effective in reducing postoperative pain, opioid use, and the incidence of PONV. Apart from the risk of hepatotoxicity associated with the use of high dosages (over 4 g/day) in small subjects (body weight less than 50 kg), the side effects of paracetamol are quite rare and include arterial hypotension, thrombocytopenia, hypersensitivity reactions, and elevated plasma concentrations of liver enzymes.

4.3.3 NSAIDs

Nonsteroidal anti-inflammatory drugs (NSAIDs) have analgesic and anti-inflammatory properties. They act by inhibiting the cyclooxygenase enzyme (COX) and then the production of prostaglandins, prostacyclins, and thromboxanes, compounds that all intervene in the pathogenesis of inflammation and in the generation of algogenic stimuli. NSAIDs are the most prescribed category of analgesic drugs; they are effective on moderate pain and, in association with opioid analgesics, on the control of severe pain. The NSAIDs most frequently used in the postoperative period are diclofenac, ketorolac, ibuprofen, indomethacin, piroxicam, tenoxicam, and lysine acetylsalicylate. The most frequent complications caused by their use is the alteration of platelet function with a consequent increase in the risk of postoperative hemorrhages and gastrointestinal bleeding; in addition, NSAIDs can cause acute renal failure and exacerbations of bronchial asthma, especially in atopic patients. These drugs inhibit COX isoforms 1 and 2. Therapeutic effects are mainly attributable to the inhibition of COX-2, the inducible isoform implicated in pathological processes such as inflammation and various cancer types, while toxicity is related to the inhibition of COX-1, the constitutive form. It is therefore possible to evaluate the safety level of each NSAID based on the relationship between the activity on COX-1 and COX-2, considering that drugs with a ratio lower than 1 carry a lower risk of side effects than those with a ratio above 1 [21].

4.3.4 Selective COX-2 Inhibitors

Selective COX-2 inhibitors include celecoxib, rofecoxib, valdecoxib, and parecoxib. The cyclooxygenase enzyme is present in the human body in two forms, the most widespread COX-1 and the COX-2, whose synthesis is activated by numerous pathological conditions, including inflammation. NSAIDs inhibit both forms of COX, and their side effects, in particular gastrointestinal bleeding, are partly caused by COX-1 inhibition. Selective anti-COX-2 drugs allow obtaining the analgesic and anti-inflammatory effect with a lower risk of gastrointestinal bleeding. Unfortunately, the reduction of side effects related to COX-2 inhibition alone is balanced by an increased risk of myocardial ischemic diseases, initially reported only in patients who were chronically taking these drugs. Currently, therefore, the use is contraindicated in patients with ischemic heart disease, cerebrovascular disease, congestive heart failure, and postoperative coronary artery bypass surgery. Besides, particular caution should be used in the treatment of hypertensive, diabetic, or hyperlipidemic subjects.

4.3.5 Adjuvants

Ketamine has antalgic properties but is also effective to prevent the occurrence of hyperalgesia following the administration of opioids [22]. This last action takes

place through binding to N-methyl-D-aspartate (NMDA) receptors and requires minor concentrations compared to those necessary to use the drug as an anesthetic. Dosages are lower than 1.2 mg/kg/h and are usually preceded by a bolus of 1 mg/kg. The majority of studies evaluating the effects of low-dose ketamine in the perioperative period agree on three points: the use of this drug leads to a significant reduction in opioid use, has a dubious or modest effect on the intensity of postoperative pain, and is characterized by substantial safety, even as regards the hallucinatory effects of the drug. Some studies suggest that ketamine could also reduce the risk of chronic postoperative pain.

Gabapentin and its derivative *pregabalin* are drugs effective on neuropathic pain [23]. Their use in the perioperative period has been proposed in order to prevent the painful component due to the traumatism of peripheral nerve endings and the consequent risk of central sensitization. The results of some studies suggest that, in addition to preventing the onset of chronic postoperative pain, these drugs could reduce preoperative anxiety, the hemodynamic response to laryngoscopy and tracheal intubation, the opioid requirement, the frequency of postoperative nausea and vomiting, and the incidence of postoperative delirium. Gabapentin and pregabalin are usually administered before the start of the operation; respective dosages are 75 and 1200 mg/day.

4.3.6 Drug Administration

Systemic analgesia can be administered in various ways. In particular, recurrent or continuous administration can be used, and the latter can take place according to the indications of the patient or can be directly managed by him or her, on the basis of the intensity of the perceived pain, within predefined limits. Interval administration is usually performed by intramuscular or subcutaneous injections. It has the advantage that a severe overdose is unlikely to occur, because the patient's condition is evaluated before each new administration of the analgesic. On the other hand, it is easier for the pain to be treated inadequately, especially in the final phase of the interval between two doses. Continuous administration usually takes place intravenously. The use of infusion devices (elastomers) provides a constant infusion rate, scheduled over 24 or 48 h. This type of infusion prevents the risk of inadequate analgesia prior to the next dose of the analgesic, as occurs in intermittent administration, but can promote the accumulation of the drug. This is particularly important in the case of drugs with a long and context-sensitive (i.e., dependent on the duration of the infusion) half-life, such as morphine or fentanyl, or with pharmacologically active metabolites, such as morphine-6-glucuronide that originates from morphine metabolism.

Patient controlled anesthesia (PCA) is a technique of intravenous (but also regional) administration by means of a sophisticated infusion pump that allows to set up or not an initial bolus and a constant rate of analgesic infusion and, characterizing aspect, allows the patient to get a bolus of analgesic by pressing a button. The doctor can program the volume of the delivered bolus, the maximum number of

boluses in a given time frame, and the minimum time interval between two administrations. Data reported in the literature show that, compared to traditional intramuscular or intravenous administration, opioid infusion using PCA allows better control of pain and a higher degree of patient satisfaction, but does not affect the amount of opioids administered, the incidence of side effects, and the length of hospital stay [24, 25].

4.3.7 Individual Response to Drugs

The results of some studies indicate that both the intensity of postoperative pain sensation and the response to drugs and in particular to opioids are influenced by patients' genetic variability. The genetic variants of the μ receptor 115 G, which involves the substitution of an asparagine with an aspartate molecule, is particularly interesting on this regard. A recent meta-analysis on the postoperative pain in patients who carry this variant did not highlight significant influences on the level of perceived pain but a lower sensitivity to opioids, which results in a greater postoperative consumption and fewer side effects, in particular nausea and vomiting [26]. It is interesting to note that the distribution of this genetic variant has a geographical component, being present in 16% of Europeans and North Americans and 46.5% of Asians.

Individual genetic variations can influence the effects of analgesic drugs also by modifying their pharmacokinetics. In this case, most of the available data regards opioids and in particular the variants that affect the enzymes that are part of the cytochrome P450 group, responsible for the metabolism of many drugs and among these of the opioids. The most interesting data concern a functional protein, CYP2D6, the genetic variants of which make it possible to distinguish four types of individuals based on the rate of opioid metabolization. Poor (PM), intermediate (IM), extensive (EM) and ultrarapid (UM) metabolizers have been identified. As reported previously, in the case of codeine, a weak opioid that is metabolized to morphine by cytochrome P450, the analgesic efficacy of the drug is poor in PM subjects and high in EM subjects [27]. In the latter, the drug is most effective at the price of an accentuation of the side effects of morphine and in particular of the risk of respiratory depression. Similarly, tramadol, a weak opioid whose main metabolite *O*-desmethyltramadol is a more potent opioid than the original molecule, may be more effective in EM subjects and less in PM subjects.

4.4 Locoregional Analgesia

Locoregional analgesia plays a particularly important role in multimodal analgesia. During the operative phase, it can be used as the main analgesic technique or as an accessory one, also in the framework of preemptive analgesia. Some data reported in the literature suggest that, compared to general anesthesia, locoregional analgesia could provide advantages such as a marked reduction in systemic opioid demand; a

lower incidence of delirium and a better and faster postoperative recovery have been reported, but at the moment there is no conclusive evidence [27, 28]. Finally, the results of some studies suggest that epidural analgesia could help prevent the chronicization of pain after thoracotomy and breast surgery in one out of four/five cases treated [12].

Neuraxial administration occurs by spinal or epidural route. The association of opioids and local anesthetics at low dosage allows preserving tactile and proprioceptive sensibility and muscle control, which are of great importance to early mobilization (e.g., by allowing the patient to ambulate). With respect to spinal administration, the epidural route requires larger doses (about ten times) because the drugs must reach the receptors located in the spinal cord, at the level of the gelatinous substance of Rolando by diffusion through the meninges. Furthermore, part of the injected drugs is absorbed into the bloodstream through the abundant venous plexuses present in the epidural space. Epidural administration is also characterized by a higher latency of the analgesic effect, which can be abbreviated with the use or addition of a fat-soluble opioid, such as fentanyl, or of local anesthetics such as bupivacaine. The addition of alpha-2-agonists such as clonidine or dexmedetomidine increases the intensity and extent of analgesia and prolongs its duration. Among the possible complications of the neuraxial techniques, there are respiratory depression, spinal and epidural hematomas, and infection. Respiratory depression that occurs shortly after the administration of the drug is usually caused by the spread of the drug into the blood and the attainment of toxic concentrations; later, the depression is generally due to the diffusion of the drug in the cerebrospinal fluid to the brainstem. Epidural hematomas can lead to irreversible damage to the spinal cord if not treated within a few hours from their formation. It is therefore necessary to check the mobility and sensitivity of the lower limbs periodically and, in suspicion, to perform a CT scan or a rachis MRI, followed by surgical decompression by laminectomy in the event that the clinical suspicion is confirmed.

The paravertebral block consists injecting a local anesthetic into the paravertebral space to block the roots of the spinal nerves after they exit the intervertebral foramen. It can be carried out with a single injection, but more frequently with repeated administration through a catheter positioned percutaneously under ultrasound guidance. It is used in thoracic, upper abdomen, and breast surgery and in rib fractures.

Intrapleural analgesia consists in the administration of local anesthetics in the pleural cavity in a single administration or repeatedly through a catheter. It is effective against pain associated with thoracotomy, thoracic drainage positioning, and surgery of the upper quadrants of the abdomen. It lasts for several hours and is contraindicated in the presence of hemothorax or pleural effusion, phlogosis, or fibrosis.

The transverse abdominis plane (TAP) block is the injection of a local anesthetic between the internal and transverse oblique muscles of the abdominal wall and is generally performed under ultrasound guidance. Indications include procedures of abdominal surgery, urology, and gynecology. Numerous studies have shown a significant saving in the dosage of opioids administered systemically with consequent

reduction of their side effects. This type of blockade is contraindicated in the presence of abdominal wall infections.

Continuous nerve blocks are performed with ultrasound- or electrostimulation-guided techniques and ensure a degree of analgesia comparable to that of neuraxial blocks but with a more limited extent. They also significantly reduce the need for systemic analgesics.

Intra-articular anesthesia is performed by injecting a local anesthetic or an opioid such as morphine into the joint cavity of the shoulder or knee.

The infiltration of the wound with long-acting local anesthetics can be performed by the surgeon at the time of closure and is effective in prolonging the time interval between the end of surgery and the first analgesic request. By placing a catheter, infiltration analgesia can be repeated several times; however, this second modality may have a limited effectiveness in reducing the further need for systemic analgesics.

4.5 Organizational Aspects

An efficient organizational structure is at the basis of a correct postoperative pain treatment [1–3]. The use of shared protocols is of fundamental importance. Theoretical instruction and practical training of the medical and nursing staff increase the knowledge of these protocols and improve their application. The 24-h availability of dedicated personnel is a very important aspect. The maximum efficiency of the system is probably achieved with the creation of an Acute Pain Service, i.e., a multidisciplinary team aimed at the treatment of pain that includes the anesthetist with the functions of coordinator and team leader, surgeons, nurses, physiotherapists, and other specialists. Systematic and regular assessment of pain intensity is a necessary condition for an effective treatment and can be performed by the nurses of the departments, provided they are adequately trained. Finally, the administration of questionnaires aimed at knowing the degree of satisfaction of patients at discharge, their opinions on the treatment received, and their possible suggestions is a useful feedback of the activity carried out.

Preoperative evaluation provides useful elements to program the techniques and drugs to be used to achieve effective postoperative analgesia. Also in this case, the training of the operators plays an essential role. The evaluation should consider:

- The characteristics of the patient, which include the personality, the state of anxiety, and the previous experiences, in particular those concerning earlier admissions to hospitals and surgical procedures. Coexisting diseases, such as chronic cardiocirculatory and respiratory diseases or a medical history positive for obstructive apnea syndrome (OSAS), should influence the choice of analgesic technique, for example, by limiting the use of opioids. The presence of pain in the preoperative period linked to the pathology to be treated or to chronic algic syndromes requires the administration of analgesics before the surgery and often an increase in the usual dosages. In the case of chronic opioid therapies, tables of

equivalence between various molecules are available to convert the chronic dosage of a drug into the equivalent dose of the opioid selected for postoperative analgesia; effective dosages result from the addition of the amount of analgesic that corresponds to chronic therapy plus the amount needed to control acute pain.
- The surgical procedure and the technique chosen to perform it.
- The prediction of the intensity and duration of postoperative pain and its tendency to become chronic.
- The possible implementation of ERAS programs, which may condition perioperative analgesia protocols [29]. Generally, these programs do not encourage the use of opioids, especially at high doses, due to the higher incidence of PONV and to the delays of the intestinal canalization, which in turn can slow down the restart of food intake. Conversely, the use of locoregional and neuraxial techniques is strongly recommended because they cause fewer side effects and favor the early mobilization of patients. Finally, the use of non-opioid analgesics (paracetamol, NSAIDs, anti-COX2) and various adjuvants, including ketamine, gabapentin and pregabalin, beta-blockers, alpha-2-agonists, and glucocorticoids is encouraged.

4.6 Conclusions

Postoperative pain is a symptom that can negatively affect the well-being of the patient both in the hours/days following surgery and, in the case of chronicization, in the following years.

Optimal treatment is based on multimodal analgesia and a multidisciplinary approach that should be coordinated by an anesthetist.

Efficient pain management requires the allocation of human and economic resources for the production of shared protocols, staff education and training, regular pain monitoring, and 24-h availability of a dedicated specialist.

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The New Oral Anticoagulants and Anesthesia

5

Davide Chiumello and Paolo Spanu

Oral anticoagulant therapy (OAT), which is used for the prevention and treatment of thromboembolic disease, has been performed in clinical practice, since before 2011, using dicumarolic drugs only.

The drugs that are used nowadays have anticoagulant action that results in the inhibition of the synthesis of vitamim K-dependent coagulation factors II, VII, IX, and X and the inhibition of anticoagulant proteins C and S [1].

The reduced thromboembolic risk is reported to be around 62% when the international normalized ratio (INR) range is between 2.0 and 3.0, with low hemorrhagic risk (<1%/year) [2, 3]. The risk is higher according to the SPAF II trial (1.8%/year) in patients older than 75 years [4].

Individual factors influence hemorrhagic and thromboembolic risk because of drug-variable kinetics: cytochrome P450 and CYP2C9 variants, body mass index (BMI), dietary vitamin K intake, pharmacologic interaction, and, finally, hepatic and thyroid function [1].

During treatment with warfarin, good control of INR in the therapeutic range is difficult to achieve and maintain because of its pharmacodynamic and pharmacokynetic properties.

Jones and colleagues demonstrated, in a large English population cohort study, that a 10% increase in time spent outside of the INR range was associated with a 29% increased risk of mortality (odds ratio (OR) 1.29, $p < 0.001$), increased rate of hospitalization, risk of an ischemic stroke (OR 1.15, $p = 0.006$), and a 12% increase in all thromboembolic complications (OR 1.12, $p < 0.001$) [5].

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Patients treated with OAT for those reasons must undergo strict INR control and frequent change of weekly dosage.

The slow onset (3–6 days to reach the therapeutic range) and long half-life prompted research for the development of new agents. The new oral anticoagulants (NOACs) emerged with the advantages of being orally administered medications and possessing the advantages of low-molecular-weight heparin (LMWH), which does not require routine monitoring and dose adjustment as required with warfarin or heparin.

The NOACs show a high therapeutic index, rapid onset of anticoagulant effects, low half-life, low interaction with drugs or food, and fixed daily dosage.

The management of patients in NOAC therapy for surgery or anesthesiology treatment is currently increasing. Understanding the NOACs is very important for the proper management of the risk of bleeding or thrombotic complications during the pre-intra-post periods of scheduled or unscheduled surgery.

5.1 Pharmacokinetic and Pharmacodynamic Properties

The coagulation process through intrinsic or extrinsic activation determines the final transformation of fibrinogen into fibrin. The vitamin K antagonist (VKA) is an anticoagulant that lowers the level of vitamin K-dependent coagulation factor (prothrombin, VII, IX, X factors) and independent proteins (C, S, and Z).

The NOACs, in contrast, act by directly inhibiting selective anticoagulant factors: Xa and thrombin. Apixaban and rivaroxaban inhibit factor Xa, while the dabigatran anticoagulant action consists in direct prothrombin inhibition (Fig. 5.1). Dabigatran is a reversible and competitive inhibitor of thrombin, and is able to reduce the platelet aggregation promoted by thrombin [6].

Dabigatran, because of this pharmacodynamic aspect, has greater efficacy than other direct thrombin inhibitors like unfractioned heparin, which is unable to inhibit thrombin linked to fibrin [7].

Apixaban is metabolized by CYP3A4 - dependent liver enzymes and approximately 25% is excreted renally; its bioavailability is 50% and has a plasma elimination half-life of 12 h and Tmax of 3 h [8].

Rivaroxaban has an 80% bioavailability with a plasma elimination half-life of 9 h in young adults, in older adults its plasma elimination half-life increases to 11–13 h.

Rivaroxaban is metabolized one-third by the kidneys and two-thirds by the liver.

Dabigatran has low bioavailability, approximately 6.5%, and low plasma protein link; its plasma elimination half-life is around 12–14 h and is excreted mainly (85%) through the kidneys [9, 10].

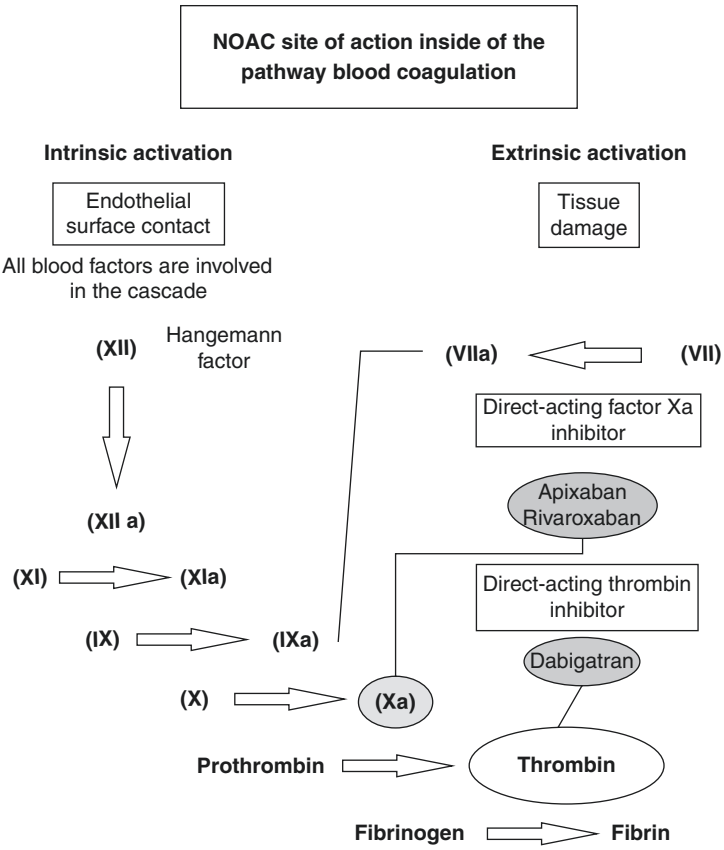

Fig. 5.1 Direct apixaban and rivaroxaban inhibition of Xa, gabigatran inhibition of thrombin

5.2 Clinical Trials: NOACs vs. VKA Efficacy and Safety Profile in Phase III Clinical Trials

The NOACs compared with VKA such as warfarin, acenocumarol, heparin (LMWH and unfractionated heparin, or UFH) have the same efficacy and safety for thromboprophylaxis following major orthopedic surgery, treatment of venous thromboembolism, pulmonary embolism, and thromboembolic events in nonvalvular atrial fibrillation (AF).

The program "RE-VOLUTION" is composed of several clinical studies for the evaluation of dabigatran efficacy and safety profile compared with standard anticoagulant therapy.

The Randomized Evaluation of Long-term anticoagulant therapY (RE-LY) is a prospective phase III trial randomized with 18,113 patients, mean age 71 years. The

study context is stroke prevention in nonvalvular AF comparing two blinded doses of dabigatran with warfarin; the INR therapeutic range was between 2 and 3.

The primary endpoints were efficacy in stroke and embolism event prevention and safety with respect to bleeding risk. Additional risk factors were stroke/transient ischemic attack (TIA) in 20% of patients, previous acute myocardial infarction (AMI) in 17% of patients, and cardiac impairment in 32% of patients. About 40% of the patients had comedication with aspirin and 50% never took warfarin.

Dabigatran with high dosage (150 mg twice daily) was associated with a reduction in risk of stroke and systemic embolism in 34% ($p < 0.001$) and risk hemorrhage stroke in 74% ($p < 0.001$) compared with warfarin.

Dabigatran was not inferior to warfarin at low dosage (110 mg twice daily) and superior at high dosage (150 mg twice daily) in the prevention of stroke and embolism. With high dosage there were significant differences in mortality. The safety profile was better, at both dosages, compared with warfarin for major hemorrhage [11].

The study ROCKET AF compared rivaroxaban efficacy and safety at a dosage of 20 mg/day and 15 mg/day in patients with creatinine clearance (CrCl) of 30–49 mL/min with warfarin (target INR between 2 and 3). The study (14,264 patient age >75 years) demonstrated that rivaroxaban and warfarin had the same efficacy in stroke and embolism prevention and the same hemorrhage risk and adverse events.

In patients treated with rivaroxaban there was less intracranial bleeding and fatal bleeding versus warfarin. Rivaroxaban is an alternative to warfarin in patients with nonvalvular AF with one or more additional risk factors: congestive cardiac failure, arterial hypertension, age >75 years, diabetes mellitus, and previous stroke/TIA.

Rivaroxaban taken at a daily dosage of 20 mg (with CrCl $\geq$ 50 mL/min) must be adjusted in case of renal failure. At present, chronic renal failure (CRF) with CrCl $\geq$ 50–30 mL/min, the dosage should be decreased to 15 mg/day, if CrCl is between 30 and 15 mL/min, frequent renal function monitoring is indicated.

Rivaroxaban is contraindicated if CrCl < 15 mL/min. Any complication related to hemorrhaging or other adverse events are reported in case of overdose up to 600 mg [12, 13].

The Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) study is a phase III double-blinded, double-dummy, randomized trial involving 18,201 patients with nonvalvular AF and one with additional risk of stroke. The study involved 1034 centers in 39 countries and compared apixaban's efficacy in stroke and systemic embolism prevention compared with warfarin.

Apixaban was associated with significant reduction in stroke and systemic embolism risks (21%), major bleeding (31%), and, finally, mortality reduction (11%) [14].

The results of these trials [11–14] were reported from 2011 to 2013, with European Medicines Agency (EMA) and Agenzia Italiana del Farmaco (Italian Drug Agency) (AIFA) approval, and contributed to the introduction of NOACs in anticoagulant therapy in Italy and Europe.

5.3 NOACs: Italian Scenarios and Therapeutic Indications

The U.S. Food and Drug Administration (FDA) approved the clinical use in human therapies in the USA of dabigatran in 2010, rivaroxaban in 2011, and apixaban in 2012, with all the indications for patient monitoring in order to ensure the therapy's safety and reduce the risks.

In the same period, between 2010 and 2013, NOACs received approval from the EMA and AIFA. The NOACs currently in use are reported in Table 5.1.

The therapeutic indications were recently defined by AIFA and describe NOACs as alternatives to VKA or LMWH in specific clinical contexts. The therapeutic indications approved by AIFA are as follows [15]:

Dabigatran:

1. Thromboembolic primary prevention in patients following total knee joint surgery or hip arthroplasty and hip fracture;
2. Stroke prevention in adults with nonvalvular AF and one or more risk factors: previous stroke, TIA or venous thromboembolism, left ventricular ejection fraction <40%, cardiac failure, ≥class 2 as definition of New York Heart Association (NYHA), age ≥75 years, age ≥65 years with associated diabetes mellitus, coronary artery disease, arterial hypertension.

Rivaroxaban:

1. Venous thromboembolic primary prevention in adult patients after total knee joint surgery or hip arthroplasty;
2. Stroke and venous thromboembolism prevention in adult patients with nonvalvular AF and one or more risk factors (congestive cardiac failure, artery hypertension, age ≥75 years, mellitus diabet, previous stroke or TIA).
3. Treatment and prevention of deep vein thrombosis in medical adult patients and pulmonary embolism prevention after deep vein thrombosis.

Apixaban:

1. Venous thromboembolism prevention in adult patients after total joint surgery knee or hip arthroplastiy

Table 5.1 New oral anticoagulant NOACs in use from 2011 to 2013 in Italy, approved by AIFA and EMA

Drug			Mechanism of action
Rivaroxaban	XARELTO®	10 mg	Factor Xa activated inihibition
Apixaban	ELIQUIS®	2.5 mg	Factor Xa activated inihibition
Dabigatran	PRADAXA®	75 mg 110 mg	Thrombin FactorII inihibition

2. Stroke and embolism prevention in adults with nonvalvular AF and one or more risk factors: previous stroke, TIA, age ≥75 years, diabetes mellitus, arterial hypertension, cardiac failure (class ≥2 NYHA).

In short the current use of NOACs has two ambits: hospital therapy management and home therapy management as follow:

1. Home therapy: stroke and thromboembolism prevention in patients with AF;
2. Hospital therapy: thromboprophylaxis in orthopedic knee surgery or hip arthroplasty;
3. Mixed: deep vein thrombosis treatment and prevention, pulmonary embolism prevention after deep vein thrombosis (rivaroxaban).

The strict indications for home therapy of NOACs reflect an attempt to avoid incongruous use by medical doctors, whose are responsible for planning specific NOAC treatment (if indicated) with the proper dosage and duration of treatment. This is important because the annual costs of anticoagulant therapy are, for single patients, 350% more than that for dicumarolic therapy, including the costs of coagulation test monitoring.

Treatment follow-up, required for all patients in Italy, will help to define more precisely the NOAC safety profile.

Part of the problem with NOAC therapy has to do with management in a hospital context of surgery and anesthesia.

5.4 Management of Suspected Overdose and Bleeding Complications

The short NOAC half-life helps to make surgery safe when needed for acute bleeding even a few hours after the last dose was taken, but we should consider the increased risk in the case of renal and liver failure.

For NOACs there are no antidotes except for dabigatran: a monoclonal antibody can block the anticoagulant effect (idarucizumab) [16, 17].

Pollack et al. documented, in 90 patients with chronic dabigatran therapy, results on the administration of idarucizumab (5 g I.V. in two single doses) in the case of acute severe bleeding (51 patients) (group A) and when surgery was necessary (39 patients) (group B), in an interim analysis, pubblished in *The New England Journal of Medicine* in 2015 (cohort study RE-VERSE AD) [18].

Idarucizumab reduced acute bleeding from the blocking of dabigatran coagulant effects in 100% of patients, Pollack found the diluted thrombin time (dTT) and escarin clottig time (ECT) to be normalized: 98% of group A and 98% of group B.

In case of hemorrhages, specific coagulation tests should be considered for quantitative and qualitative assessment of NOAC action. Dabigatran's quantitative test is dTT, which increases also with low dosage [19, 20] and escarin clotting time (ETC). Rivaroxaban and apixaban should be tested with antifactor Xa (anti-FXa).

These tests should be done in Italian hospital laboratories. Qualitative tests may be used for dabigatran thrombin time (TT) and for apixabam prothrombin time (PT) [21, 22]. Plasma-level NOAC concentration might also be useful. These tests are important in the management of acute bleeding mainly in cases of patients with renal and liver failure, NOAC overdose, and suspected drug interaction.

The recommended treatments in different International guidelines [23] include, in the case of overdose, activated charcoal to reduce absorption, dialysis for reduced plasma-level concentration, and prothrombin complex concentrate (PCC) [24, 25]; no clinical trials have been conducted on the efficacy and safety of activated factor VII use in NOACs in connection with acute bleeding. Desmopressin and antifibrinolytic agents may be considered, but any evidence about their efficacy has been shown.

Even if NOACs present short half-lives, the time to reach normal coagulation activity may be different with groups and because of renal failure. Dabigatran has a half-life of 7–9 h [9, 10], and the time for normal hemostasis depends on CrCl: >80 mL/min in 24 h, 50–80 mL/min in 24–36 h, and, finally, 30–50 mL/min in 36–48 h. Rivaroxaban and apixaban have half-lives of, respectively, around 7–17 h [26] and 8–14 h [8].

5.5 NOACs and Surgical Intervention

Surgery or invasive diagnostic interventions represent bleeding risk factors and require cessation of the therapy.

The RE-LY trial had in the chort about 25 % of the patients which required temporary cessation of the therapy cause a surgical intervention. The rationale in NOAC cessation/restart therapy management is to limit the increased embolism risk when therapy must be suspended and increased bleeding risk when therapy must be restarted after surgery or regional anesthesia procedures.

The European Society of Anesthesiology pubblished in 2013 guidelines on the management of severe perioperative bleeding. Kozec Langenecker et al. [27] emphasized that NOAC therapy must not be suspended for skin and odontoiatric surgery or endoscopic procedures, even if a biopsy is performed (not the same as in a colon biospy). The same recommendation in ophthalmic surgery was made (level C2).

In patients treated with rivaroxaban, apixaban, and dabigatran with CrCl >50 mL/min bridging therapy is suggested in high-risk cases, using the following timeline: fifth day before surgery last NOAC dose, third day before surgery therapeutic dose of LMWH or, alternatively, UFH until the first day before surgery with the last dose of LMWH 24 h before intervention, if UFH is used in two daily administrations, last dose 12 h before intervention (level C2).

In patients with dabigatran therapy and CrCl between 30 and 50 mL/min suspension 5 days before surgery without bridging therapy (level C2) is suggested. The therapy restart should be done with UFH or LMWH after 672 h from intervention. In a recent review and practical guide in NOAC use, published in 2015, Hinojar

et al. [28] divided surgery into minor and major interventions according to low or high hemorrhage risk.

The minor risk procedures are endoscopy, biopsy, angiography, pacemaker implantation or implantable cardioverter defibrillator, and myocardial ablation. The major surgical procedures include neuraxial injection and epidural catheter, rachicentesis, thoracic surgery, orthopedic surgery, liver and renal biopsy, and urologic surgery (TURP, TURV) (Table 5.2).

In patients with dicumarol therapy the suspension of therapy and commencement of bridging therapy are recommended. The bridging therapy for NOACs before planned surgery is a controversal issue. A guideline published in 2013 by a Spanish forum on anticoagulants and anesthesia [29] gave a recommendation defininig NOAC timing of suspension before surgery with and without bridging therapy using LMWH.

This forum defined three levels of thrombosis risk (Table 5.3) and three different levels of bleeding risk (Table 5.4) in order to give rational recommendations on the timing of discontinuation and bridging therapy when necessary.

In patients with NOAC therapy, considering the pharmacokinetic aspects, in particular the short half-life and predictability effects, it is not suggested to do bridging therapy before and after intervention in the low bleeding and thrombosis risk

Table 5.2 Management of pre- and postoperative patients with NOAC therapy (modified from Hinojar et al. [28])

		Minor surgery	Major surgery
NOAC	Renal function CrCl (mL/min)	Management Preoperative	Management Postoperative
Dabigatran	>50	Stop 2 days before	Restart after 48 h
	30–50	Stop 3 days before	
Rivaroxaban	>30	Stop 2 days before	Restart after 24 h
Apixaban	>30	Stop 2 days before	Restart after 24 h

Table 5.3 Thromboembolism risk stratification modified by Foro de Consenso de la ESRA-España de fármacos que alteran la hemostasia

Perioperative thromboembolism stratification risk		
Low	Moderate	High
Atrial fibrillation (AF)		
CHA2DS2-VASc 0–1 no other risk factors	CHA2DS2-VASc 2–4 points	CHA2DS2-VASc >4 points stroke within 3 months rheumatic valvulopathy
Venous thromboembolism		
Thrombotic disorder more than 1 year from planned procedure	Thrombotic disorder 3–12 months from planned procedure recurrent DVT oncologically active disease, mild thrombophilia	Thrombotic disorder in last 3 months from planned procedure

Manejo de los anticoagulantes orales de acción directa en el periodo perioperatorio y técnicas invasivas. Rev Esp Anestesiol Reanim 2012

Table 5.4 Bleeding risk stratification modified by Modificata da Foro de Consenso de la ESRA-España de fármacos que alteran la hemostasia

Bleeding surgery risk	
Low	• Possibility of good surgery hemostasis • Possible acute hemorrhage without negative outcome or hemorrhage shock • Surgical procedure without transfusion usually needed • Minor surgery
Minor	• Possible difficulties in surgical hemostasis • Possible bleeding increases need for tranfusion or implies a need for reintervention • Major abdominal surgery, cardiovascular, major orthopedic surgery, major orthopedic surgery, ear/nose surgery, urology, reconstructive surgery
High	• Perioperative bleeding may put the patient at mortal risk or poor surgery outcome • Examples: intracranial neurosurgery, intervention in spinal cord, eye posterior chamber surgery

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categories (Tables 5.3 and 5.4). Bridging therapy using LMWH is recommended for moderate and high bleeding and thrombosis risk categories.

The brief experience with clinical use and recommendations on management are based not so much on trial results as on expert opinion (EHRA 2013, HAS 2013), which creates uncertainty with respect to the proper approach to therapy and definition of risk. A great contribute was given to the clinical trials analysis, the researcher continue to find out sub group from databases which gave inications for improve efficancy/safety ratio [23].

The timing of suspension/restart and whether to conduct bridging therapy are presented in Fig. 5.2, with particular attention being paid to renal function. Recommendations are more extensive in Table 5.3 from Hinojar and colleagues. Finally, perioperative thromboprophylaxis from the guidelines of the American College of Chest Physicians (ACCP) treats NOACs as drugs to be used on the basis of recommendation level 1B as a LMWH.

The LMWH advantages are well known: the patient may undergo neuraxial anesthesia 12 h after the last enoxaparin dose [30]. After NOAC (dabigatran, rivaroxaban) administration used for thromboprophylaxis [31, 32], according to data from the literature, safety requires waiting not less than 24 h before performing any intervention [33, 34].

5.6 NOACs and Regional Anesthesia

Patients in anticoagulant therapy requiring local anesthesia must be underwent to temporary discontinuation as well as surgery interventions. The regional anesthesia procedures are stratified according the different bleeding risk (Fig. 5.2). Indipendently to procedure intrinsic risk (anatomic site, the needle size, the technique) the most bleeding (peridural haematoma) risk factor is a concomitant

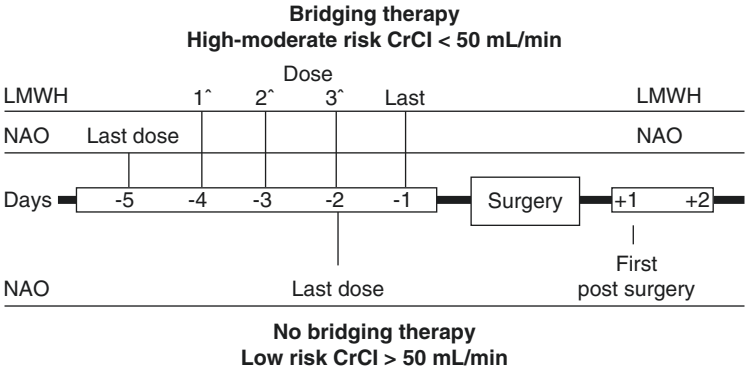

Fig. 5.2 Suspension/restart and bridging therapy

anticoagulant therapy. This issue were underlined before NOACs introduction in the clinical use because every anticoagulant presents this risk.

Peridural haematoma frequence, even if is a rare event, is not well defined as risk with NOACs therapy yet; this because of a litlle numbers of trials and patients studied. The American guidelines on NOACs were issued by the American Society of Regional Anesthesia and Pain Medicine (ASRA) in 2010. Horlocker et al. [35] focused attention on exercising caution in administering a regional anesthesia procedure during NOAC therapy. This is because of a lack of evidence from clinical trial data.

Also, in Europe, the guidelines from the Scandinavian Society of Anaesthesiology and Intensive Care (SSAI) on NOACs give a generic recommendation: be careful.

The studies are different but but mainly involve comparing anticoagulant properties with each other, in particular the endpoints bleeding risk and efficacy, but bleeding risk related to regional anesthesia is no more defined.

For example, regarding thrombosis risk, in 2012, several studies were performed. Gomez-Outez et al. [36] wrote a review and meta-analysis, including of 16 trials where rivaroxaban was compared to enoxaparin and had fewer thromboembolism events (relative risk 0.48, 95% IC 0.31–0.75); similiar results were reported with dabigatran (0.71, 0.23–2.12) and apixaban (0.82, 0.41–1.64). In the same meta-analysis the RR of bleeding was major for rivaroxaban versus enoxaparin (1.25, 1.05–1.49) and dabigatran (1.12, 0.94–1.35), with inferior results for apixaban (0.82, 0.69–0.98). In conclusion, Gomez-Outez et al. assert that NOACs have good efficacy and safety.

The NOACs used for thromboprophylaxis or anticoagulant therapy were compared with conventional therapy in several studies, but few trials define the risk in regional anesthesia.

In Europe and the USA most of the recommendations are based on expert opinion supported by pharmacokinetic and pharmacodynamic knowledge.

The process involved two steps: first, risk is defined, and second, the timing of suspension/restart of both anticoagulant therapy or thromboprophylaxis therapy is establisehd (Fig. 5.2).

The guidelines may provide an evaluation of bleeding or thrombosis risk through scores. The more commonly used one is HAS-BLED (Table 5.5): evaluation major bleeding risk within a year from AF in patient undergoing anticoagulant therapy. Alternatively, CHADS2 and CHA2DS2-VAS can be used to evaluate stroke risk (Table 5.6)

Recently, these scores have been used in guidelines and discussed in reviews. Analysis of the literature shows that surgical intervention with regional anesthesia has the same impact on risk. In other words, the anesthesia neuraxial invasive procedures presents a bleeding risk equal to that of major surgery. Harrop and colleagues [37] stratified the risk for different regional procedures from minor to major risk (Fig. 5.3).

Another concept frequently discussed regards peridural hematoma, which presents the same risk as the procedure of positioning and during catheter removal.

Regarding the timing of NOAC therapy suspension for safety in regional anesthesia, the guidelines define the timing of catheter positioninig and removal. Not only should positioning/removal and intrinsic risk be considered but also patient global clinical conditions; determinative is age >65 years, congestive cardiac failure, arterial hypertension, diabetes mellitus, and previous embolisms [38].

Table 5.5 HAS-BLED score

HAS-BLED score		
		Points
H	Arterial hypertension	1
A	Liver renal failure	1 or 2
S	Stroke	1
B	Bleeding	1
L	INR lability	1
E	Age >65 years	1
D	Drugs/alchool	1 or 2
		Max 9 points

Table 5.6 CHADS2–CHA2DS2-VASc score

CHADS2 score		CHA2DS2-VASc score	
Congestive heart failure	1	Congestive heart failure Left ventricular dysfunction	1
Hypertension	1	Hypertension	1
Age >75 years	1	Age >75 years, 65–74 years	1 or 2
Diabetes mellitus	1	Ictus/TIA	2
Ictus/TIA	2	Cardiovascular disease	1
		female	1
	Max 6 points		Max 6 points

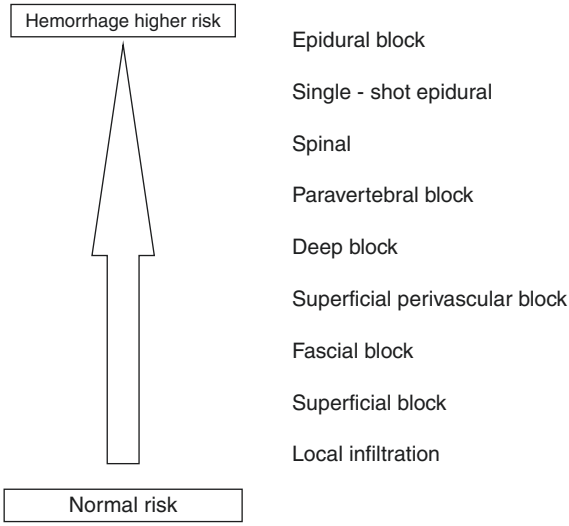

Fig. 5.3 Regional anesthesia hemorrhage risk in NOAC therapy [37]

When patients are undergo to neuraxial anesthesia safety precautions should be taken: avoid multiple attempts, if local bleeding occurs avoid additional attempts and careful neurological examination should planed for early identification of neuraxial hematoma. In a review, Benzon and colleagues [39] defined the time needed between neuraxial anesthesia and NOAC suspension. They used a CHA2DS-VASc score proposing five half-lives in cases of low thrombosis risk, while for patients with high thrombosis risk they recommended two to three half-lives.

The European guidelines, in particular from the Scandinavian Society of Anaesthesiology and Intensive care (SSAI), use an interval of two half-lives as the safety limit. Two half-lives are considered protective from embolism events and bleeding risk. Benzon emphasized that two half-lives came from studies in healthy young adults patients not representative of the typical population in anticoagulant therapy in which chronic renal failure is frequently present.

The European guidelines on safety recommend intervals of two to three half-lives for patients with high thrombosis or stroke risk and intervals of four to five half-lives for patients with low thrombosis risk. In patients with renal failure, the interval should be evaluated based on CrCl [40]. The restart of therapy after neuraxial anesthesia should be done 24–48 h after but is anticipated in patients with high thrombosis risk or stroke [39].

The recommendation of the American College of Chest Physicians Clinical Practice Guidelines [41] suggest that, to reduce thrombosis and bleeding risk in patients undergoing NOAC therapy, the anesthetic and surgical procedures should be postponed if one of the following conditions is present in the last 3 months: venous thromboembolism, IMA, TIA or stroke, acute bleeding, or pregnancy less than 6 weeks from delivery date.

5.7 Conclusion

The new oral anticoagulants have great advantages despite the sanitation costs compared to previous and conventional anticoagulant therapy.

The therapeutic indications based on randomized clinical trials were approved by the EMA and in Italy by the AIFA introducing the NOAC into European and Italian clinical protocols.

The guidelines on therapy with NOACs give recommendations on the management of bleeding and thrombotic risk, and some of them are based on expert opinion. In patients with low thrombotic risk (CHADS 2-VSC 2) the time between suspension of anticoagulant therapy and commencement of neuraxial anesthesia may be five half-lives. Suspension must be less, around two to three half-lives, for patients with high thrombotic risk or stroke, in which case an alternative therapy may be bridging therapy with LMWH when it is necessary to wait for five half-lives.

Careful attention must be paid to patients with renal failure. Anticoagulant therapy may restart 24–48 h following anesthesia procedures. With regard to anesthesia procedures, the problem is the interval safety between stopping and restarting, but there are no absolute indications to garantee no risk of bleeding or thrombotic complications. For those reasons, all patients with low or high risk must be carefully monitored during pre and post surgery period.

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Perioperative Management for Patients with a Solid Organ Transplant

6

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6.1 Introduction

In the last 10 years, relevant improvements in surgical technical solutions, new immunosuppressive agents, and a better understanding of the complex pathophysiology of end-stage organ failure by anesthesiologists and intensivists have led to relevant results in the field of solid organ transplantation [1–3]. In Italy, the 1-year survival rate for most solid organ transplant (SOT) recipients is currently higher than 90%, while a 5-year survival rate is now between 60% and 80% (50% for lung transplant and 90% for pediatric kidney transplant) (www.trapianti.salute.gov.it). However, aging of the recipients, the increasing number of comorbidities (particularly cardiopulmonary, metabolic, and gastrointestinal), and the occurrence of de novo cancer and lymphoproliferative disorders are changing the posttransplant natural history: in particular, the condition of recipient of a solid organ transplant can be considered a new, relevant form of chronic illness.

The need for surgery in the early or late posttransplant period is increasing [1–5]. Between 15% and 40% of the SOT recipients will undergo invasive procedures: as a consequence, these patients have to be assessed for every form of anesthesia (general or locoregional) or sedation (from moderate to deep sedation) for elective and emergency non-transplant surgery, for interventional radiologic and endoscopic procedures (gastrointestinal, thoracic, or urologic), for traumatic events, and for obstetrics [1–5]. The incidence of abdominal aortic aneurysms is

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increased, particularly after heart transplant. Acute surgical cholecystitis is frequent in thoracic transplant recipients, cyclosporine (less used, but still present in some immunosuppressive regimens) being considered a consistent risk factor for cholelithiasis and its surgical consequences. The immunosuppressive therapy, the common denominator of all the transplanted patients, increases by a factor of four the risk of de novo cancer. Skin cancer and lymphoma are the most frequent neoplasms found in transplanted patients, but the frequency of lung, liver, cervical, colon, larynx, bladder, and prostate malignancies is higher than in the normal population [1–3].

Not much is available in the literature on the anesthesiological management of SOT recipients who have to undergo interventional procedures or non-transplant surgery: in this paper we will review the anesthesiological and perioperative management of transplanted patients, focusing on the peculiar aspects of the modified posttransplant physiological profile, able to impact on the conduction of surgery and on the immediate postoperative period [1–5].

Outcomes of elective surgery in most part of SOT recipients are not different if compared to non-transplanted patients. Instead, urgent and emergent surgical procedures are more prone to postoperative complications. Then, the role of the anesthesiologist in the perioperative period might become crucial.

In SOT recipient, anesthesia safety depends (at least in part) on both the detailed knowledge of the pretransplant comorbidities and the posttransplant physiological changes introduced in the recipient by the grafted organ(s): among the latter are comorbidities newly introduced by the immunosuppressive therapy, the quality of function (or dysfunction) of the transplanted organ and the impact this condition could have on the entire organism, the different physiological and pharmacological responses to surgical or traumatic stress introduced by the new condition, and the different perioperative management this "new" condition requires—a brand new challenge for every anesthesiologist.

6.2 Immunosuppressive Therapy [6–8]

As above mentioned, common to all SOT recipients is immunosuppression, a form of modulation of the recipient's immune system to induce host tolerance to the new graft to avoid acute or chronic rejection [6]. The risk of rejection, one of the most feared complications after SOT, has to be balanced in each recipient against infections and side and/or adverse effects on metabolism (glycemic and lipidic profiles as examples) or on function of the central nervous system, heart, kidney, and liver (just to mention the organs most commonly affected by the consequences of the immunosuppressive therapy): plasma levels of the immunosuppressive drugs and markers of the effects of the drugs on the immune system (if available and perhaps much more relevant) would be pivotal for a fine tuning of the "level" of the immunosuppression. This latter point is still ill-defined and a matter of hot discussion.

6.2.1 The Drugs [1, 6]

The posttransplant immunosuppressive regimen (drugs, dosage, schedule) is an association of drugs of different classes, often varying among transplant centers.

1. *Corticosteroids* (methylprednisolone, prednisone) are used for both induction and maintenance of immunosuppression: among the multiple mechanisms of action, in SOT recipients relevant are the inhibition of the transcription of cytokines and the sequestration of CD4+ lymphocytes. With the advent of new potent immunosuppressive drugs (see below), maintenance steroids are rapidly tapered, markedly reduced, or in long term, generally avoided. When used, prednisone is usually administered for maintenance of immunosuppression, while methylprednisolone is prescribed for induction and to treat acute rejection episodes. Common side effects are iatrogenic diabetes, arterial hypertension, and weight gain. Chronic steroid use exposes the patients to an increased risk of infection, gastrointestinal bleeding, hyperglycemia, osteoporosis, and, as above underlined, arterial hypertension.
2. *Calcineurin inhibitors (CNIs)*, mainly cyclosporine (CSA) and tacrolimus (TAC), act by binding to calcineurin and preventing its translocation into the nucleus, thus impacting on transcription and secretion of interleukin 2 (IL-2) by T lymphocyte cells. Therapeutic drug monitoring (TDM) is mandatory, due to the narrow therapeutic range of CNIs and the possible systemic side effects (mainly but not only glucose intolerance, nephrotoxicity, neurotoxicity). Metabolism is dependent on cytochrome P450: drugs able to induce this metabolic pathway are able to influence CNI plasma levels. On the contrary, CNIs can interfere with other medication metabolic pathways, with possible toxicity.
3. *mTOR inhibitors* sirolimus (SIR) and everolimus (EVER) induce lymphocyte cell cycle arrest. Both SIR and EVER are granted of a reduced nephrotoxic effect. mTOR-inhibitor therapy is usually considered 4–6 weeks after transplantation, in association with CNI drugs, due to an interference with wound healing which might become a concern in the first 2–3 weeks after transplant surgery. Pulmonary idiosyncratic toxicity has been reported with SIR, usually in form of non-infectious interstitial pneumonia associated with fever and hemoptysis. Withdrawal of the drug is usually associated with a very rapid improvement of both the respiratory symptoms and the radiological imaging [7].
4. *Antiproliferative agents* (azathioprine [AZA] and mycophenolate [MYC]) (usually classified as antimetabolites) inhibit purine synthesis with suppression of T and B lymphocytes. Forms of toxicity affecting the bone marrow (anemia, thrombocytopenia, leucopenia), the gastrointestinal tract, and the liver may be possible side effects to be aware of.
5. *Antibodies*: Polyclonal (*thymoglobulin*) and monoclonal antibodies (*OKT3*, *basiliximab*, *daclizumab*). *Thymoglobulin*, able to induce marked lymphocyte depletion, is a rabbit-derived polyclonal antithymocyte antibody. Its use, sometimes associated with a flu-like syndrome with fever, tachycardia, and arterial

hypotension due to cytokines release, is reserved for induction (or preconditioning) immediately before or immediately after transplant and to treat acute steroid-resistant rejection episodes. *Muromonab* (OKT3), acting against CD3+ lymphocytes, is now rarely prescribed, due to the poor selectivity and the possible relevant side effects, mainly correlated with cytokines release. Much better tolerated (less toxicity) and much more utilized nowadays in several induction protocols are *basiliximab and daclizumab*, a newer generation of monoclonal antibodies able to block IL-2-mediated T-cell activation.

6.2.2 Immunosuppression and the Perioperative Period

Immunosuppressive therapy should never be stopped in the perioperative period.

Corticosteroids are present in a large part of the chronic immunosuppressive treatments, even if now much less prescribed than in the past. Although chronic steroid therapy could constitute a potential risk for perioperative stress-induced adrenal suppression, this condition is rare: maintenance dose is usually administered without any dose adjustment [1–4, 6, 9], even if 50 mg of hydrocortisone three times a day for the first 48–72 postoperatively hours has been suggested by some (but it is still under debate) [1, 9].

CSA and TAC should be administered per os (PO) or via nasogastric (NG) tube as soon as possible after surgery: blood levels should be monitored (TDM) daily, due to the many conditions able to alter the pharmacokinetic profile (perioperative massive fluid infusion, biliary drainage via a Kehr tube, cardiopulmonary bypass, or more simply pharmacological interference due to CYP 3A4 inducers) [1, 6]. As above alluded to, CNI metabolism depends on CYP 3A4. Many drugs are able to cause induction and inhibition or can behave as a competitive substrate of this enzyme: among them are phenytoine, carbamazepine, erythromycine, cotrimoxazole, itraconazole, clarithromycine, and metoclopramide.

AZA, nowadays much less used than mycophenolate, does not need any therapeutic adjustment for the intravenous administration.

Literature dealing with the interaction between CSA, TAC, and anesthetic drugs is poor and not updated [1–5, 10]. All inhalational anesthetics have been used safely in transplant surgery; the relevance of the production of nephrotoxic inorganic fluoride appears to be more theoretical than clinical. Sevoflurane (SEVO) and desflurane (DES) [1–5] are the safest agents at the moment (isoflurane is less used nowadays). It has however to be reported, even if very rare, a possible severe liver toxicity associated with SEVO [11]. The use of isoflurane and nitric oxide and propofol infusion does not alter CSA kinetics. A prolongation of the effect of fentanyl and of neuromuscular blocking drugs such as vecuronium, pancuronium, and atracurium has been reported in case of CSA use [12–15]. The prolonged effect (if present) is reported to be due to CSA-related calcium influx inhibition in musculoskeletal cells: this mechanism, however, does not seem to have clinical relevance, and the most used neuromuscular blockers are nowadays cisatracurium and rocuronium, very seldom vecuronium. Even if beyond the scope of this chapter, we

will shortly discuss some critical points (side effects/complications) associated with the use of the most common immunosuppressors able to impact on the postoperative/post-procedural period [6].

Side effects of CSA and TAC are hypertension (50–70%, due to increased sodium-reabsorption and peripheral vasoconstriction), renal dysfunction, diabetes, and neurotoxicity [1, 6]. CSA and TAC are nephrotoxic drugs: dose-dependent renal blood flow reduction increases the risk of renal dysfunction (from mild to severe acute kidney injury [AKI], included the need for renal replacement therapy). SOT recipients under CSA and TAC treatment are at risk of AKI in case of hypovolemia, the associated use of other nephrotoxic drugs, and possibly in case of contrast medium administration. Renal dysfunction in its various forms is more frequent (20%) in heart and lung transplant recipients because of higher immunosuppression.

CSA and TAC can cause neurological complications, more commonly in the early posttransplant period, but always to be considered in the natural history of a transplanted patient: minor effects are common (30–60%), trivial, and self-limiting [16]. Among major side effects (much less common) are seizures, due to a lower sensibility threshold: seizures, aphasia, and speech disorders can be a consequence of high CSA blood levels and low magnesium and lipid plasma levels. Although very rare, *posterior reversible encephalopathy syndrome (PRES)* [16, 17] should be taken into consideration in case of acute neurologic deterioration. PRES is more represented in liver and kidney transplant recipients and is a form of neurotoxicity induced by CNIs. Among possible signs and symptoms, very frequent are seizures, encephalopathy, and headache; visual disturbances or focal neurological symptoms are instead less frequent. PRES is diagnosed by MRI with a characteristic bilateral vasogenic edema involving parieto-occipital areas. Permanent neurological deficits might be the outcome, if the syndrome is not promptly recognized, due to progression of vasogenic edema toward cytotoxic edema. Treatment, apart from supportive therapy, relies upon discontinuation of the CNI (even if the syndrome is unrelated to drug levels), hypertension control, and optimization of magnesemia. Even if not related to immunosuppressors and usually reported early after transplantation (but to be considered in the differential diagnosis of acute neurological disorders after SOT) is *central pontine myelinolysis (CPM)* [1, 16]. Rare after heart or kidney transplant, CPM can occur after liver transplantation (<5% of the cases, with a mortality rate close to 30–50%): usually it is associated to a too rapid correction of perioperative hyponatremia (120–125 mEq), or to a sodium shift of more than 25 mEq/L in less than 24 h; the rapid change in plasmatic osmolarity is reported to be one of the more relevant mechanisms of CPM. MRI is needed for the diagnosis.

In general, a large part of SOT recipients experience at least one infectious episode after the transplant procedure [7, 8], to be considered a consequence of a suboptimal balance between immunosuppression and host defenses: when compared to the general population, the incidence of infections is higher in transplant recipients. Diagnosis is sometimes problematic: steroids are able to mask specific signs and symptoms of infections, or, on the contrary, a specific inflammatory symptom may be due to an underlying, unrecognized acute rejection. Differential diagnosis in this

specific setting may be challenging. Transplanted patients are exposed to community and healthcare-associated (HCA) infections: geographic environment and time from transplant must be taken into consideration for the differential diagnosis [7, 8]. Infection-associated morbidity and mortality are higher than in the non-transplanted patients, particularly if infection and the consequent sepsis or septic shock are sustained by multiple (MDR) or Pan (XDR) drug-resistant microorganisms. Opportunistic fungal (*Candida, Aspergillus*) or viral (CMV, Epstein Barr) infections are also reported with various incidence and different severity in the immunosuppressed patients: specific infective complications may be associated in different grafted organs with different immunosuppressant drugs [7, 8, 18]. Neutropenia (neutrophil count less than 500/mL) should be considered as an alarming condition, even if it is not common in solid organ transplant recipients.

6.2.3 The Patient After the Transplant: A New Natural History

Organ transplantation might be the only treatment able to cure an end-stage organ disease or failure: then, the SOT procedure becomes the best way to treat all the systemic pathological consequences associated with the failing organ(s). Comorbidities already present before the transplant may worsen after the procedure, and the immunosuppressive therapy, as above underlined, may be at least, in part, responsible. It could happen in diabetic recipients (4–20% of transplanted population) for the autonomic neuropathy, the arterial hypertension, and the vascular complications. CSA, TAC, and steroids can cause hyperlipidemia (55–70% of kidney and heart transplant recipients, 6–15% of lung and liver transplant recipients). Diffuse atherosclerotic disease is frequent in kidney- and heart-transplanted patients (the incidence of abdominal aortic aneurysm is increased in heart recipients), but it is becoming more common in liver-transplanted patients [19–21]. The risk of coronary artery disease (CAD) is increased in heart and kidney transplant patients, becoming the leading cause of death among these patients in the late post-transplant period. In the last few years, the incidence of CAD is increasing also among liver-transplanted patients [22]: mandatory for anesthesiologists and intensivists is an expertise on the perioperative management (diagnosis and treatment) of cardiovascular diseases [19–22].

6.2.4 The Anesthesiologist and the Patient with a Grafted Organ: Understanding a New Physiological Profile to Manage the Perioperative Period

Understanding the new physiology of SOT recipients admitted to non-transplant surgery is the first imperative for every anesthesiologist involved in this situation: the complete denervation of the graft is the new paradigm to be aware of while preparing the perioperative anesthesiological plan [2–5]. A careful preoperative functional assessment of the grafted organ starts from the understanding of the new

physiological condition. A consultation with the transplant center may be particularly useful if not warranted [1–3]. Attention has to be paid to any form of dysfunction of the transplanted organ, in order to exclude rejection (chronic more than acute), subtle signs of infection/sepsis, and other forms of chronic graft dysfunction, ischemia. Whatever the cause, any form of dysfunction (rejection, infection, ischemia) increases the risk of severe postoperative complications and in general of perioperative morbidity. Immunosuppression regime has to be taken into close consideration, and again the transplant center consultation (particularly in complex cases) is recommended, to plan the most appropriate perioperative management.

6.3 Physiology and Pharmacology of a Denervated Organ and the Consequences in the Perioperative Period

The grafted organs are denervated: relevant and to be well known by the perioperative transplant physicians are (or may become) the consequences for the liver (lack of nociceptive and visceral afferent pathways, lack of vasoconstriction in shock), the lung (ineffective cough), and the heart (even if evidence of reinnervation late after transplant is now reported) [1–5].

Heart—The transplanted heart is completely denervated, with loss of afferent and efferent sympathetic, parasympathetic, and sensitive nerve connections [2–4, 23]. The loss of parasympathetic regulation results in an increased heart rate at rest (mild tachycardia) and in the lack of response to the Valsalva maneuver and carotid sinus stimulation. Sympathetic reflexes to laryngoscopy and intubation are usually absent or reduced even in case of inadequate anesthesia depth [4]. The response to stimuli from the vasomotor center after changes in arterial pressure (autonomic innervation) is abolished, but the response to circulating catecholamines is preserved, as receptor density is normal or increased [2–4]. Response to hypovolemia and hypotension is peculiar: due to the loss of baroreceptor reflex, and the relatively fixed heart rate and cardiac output, heart rate does not increase in case of hypotension/hypovolemia [4]. The increase in cardiac output should then rely upon an increase in stroke volume: increasing the preload, namely, the venous return, is then the appropriate strategy [4, 24]. The preserved Frank-Starling mechanism plays in this specific setting a key role in maintaining cardiac output, as the denervated heart is preload-dependent [2–4]: in this specific setting and particularly in case of heart-transplanted patients undergoing surgery with major fluid shifts, correction of hypotension should rely upon an appropriate hemodynamic monitoring to assess the circulating volume and the cardiac performance [4, 24]. Adequate preload, gauged by the appropriate monitoring, is pivotal in maintaining the hemodynamic equilibrium: monitoring of cardiac output and, when appropriate, dynamic indices are key for the intraoperative hemodynamic management [4, 20, 21]. Heart rate increases slowly (5–10 bpm) in response to circulating catecholamines, whose increase might take minutes. Hypovolemia is often associated with a pronounced fall in arterial blood pressure, followed by a catecholamine-mediated marked hypertension (vasoconstriction response): the susceptibility of the transplanted heart to catecholamines,

due to an increased receptor density, may induce a sort of hypersensitivity [2–4]. Epinephrine and norepinephrine may have an increased inotropic effect due to higher beta/alpha (inotrope/vasoconstrictor) ratio. Dopamine acts on the heart predominantly via an indirect mechanism of norepinephrine secretion: therefore the inotropic effect can be reduced, whereas dopaminergic and alpha-mimetic effects are prevalent. Isoproterenol and dobutamine do not show any significant difference in beta-effect intensity. On the contrary, beta-blockers may cause severe hypotension. Bradycardia and even asystole may follow neostigmine administration [24] because of cholinergic receptor activation in cardiac ganglionic cells, supporting in heart-transplanted patients undergoing surgery the rationale of the use of rocuronium for muscle relaxation and of sugammadex for its antagonization. Many of the above cited effects can be modified by the graft reinnervation, predominantly orthosympathetic [23]: the effects are unpredictable and the item is still under strong debate. Interestingly enough, coronary blood flow autoregulation is preserved [4].

After a successful heart transplant, large part of the patients return to a functional NYHA 1 class, with a good quality of life [1, 4]. Interestingly enough, due to the complete denervation of the grafted heart, transplant recipients may have atypical angina symptoms or no symptoms at all, making a thorough posttransplant medical history, physical examination, and functional assessment particularly important to define the perioperative strategy. Right bundle branch block, atrial and ventricular arrhythmias, diabetes (39%), hypertension (>95%), chronic renal failure (14%), and coronary artery disease of graft (40–65% in 5 years) are comorbidities to be considered when managing heart-transplanted patients candidate to noncardiac surgery; a small number of recipients may need a permanent pacemaker implantation [1–4]. Problematic could be the case of a patient in need for surgery and with chronic rejection, often associated with a rapidly progressing coronary artery disease. Very different is instead the profile of a patient with acute rejection, usually associated with severe forms of heart failure: clinical signs of rejection may be the acute worsening of the usual performance status, ventricular arrhythmias, congestive heart failure, and electrocardiographic signs of myocardial infarction. Again, relevant is the transplant center consultation. In case of noncardiac surgery performed in heart-transplanted patients, the preoperative functional assessment should include (but not limited to) EKG, basal echocardiography, and kidney function tests [4].

Lung—Worldwide, the survival rate of lung-transplanted patients has improved in recent years, 1 year survival rate being 80% [1–4, 7]: outcome might change according to the indications and the underlying disease, the age of the recipients, the surgical technique (single- vs. bilateral-lung transplant), and the occurrence or not of early posttransplant complications [4]. According the most recent ISHLT data, survival after a double-lung transplant is higher than single-lung. The 5-year survival rate is above 50% in patients below 60 years old but worsens in elderly recipients; obliterative bronchiolitis affects 10% of the patients after 1 year, rising to close to 50% 5 years from transplantation [4]. Lung functional recovery after transplantation can take months, and, as previously underlined, it depends on the underlying pathology (the transplant indication) and the surgical technique. Denervation (a consequence of the surgical transection of the vagal nerve) predisposes to the lack

of cough reflex, reduced clearance of secretions, and microinhalation, increasing, together with immunosuppression and surgery, the risk of postoperative pulmonary infections and, as extreme consequence, of major systemic complications [4]. During the first months after transplantation, loss of afferent and efferent innervation distal to the anastomoses alters (or may alter) the bronchoconstrictive tone (under the control of the parasympathetic tone): however, muscarinic receptors are intact, and recent data show a beta-2 agonist bronchodilator response within the first year after transplant. Pulmonary blood flow is normal in double-lung transplant: on the contrary, the blood flow is prevalent together with ventilation (60–70%) to the grafted lung in single-lung transplant. Hypoxic vasoconstriction reflex is always preserved [4].

The most common early posttransplant complications are related to graft dysfunction and, as above underlined, to infections [7, 8]: malignancies and obliterative bronchiolitis (an expression of chronic rejection) are instead reported later after transplantation. When airway obstruction occurs, PTLD (posttransplant lymphoproliferative disorders) should be considered, even if rare, in the differential diagnosis workup to define the possible cause of obstruction: PTLD related to EBV-infection occurs in 4% of pediatric transplant patients and in close to 1% of the adult transplanted population [1, 4, 25].

The importance of the perioperative fluid balance is paramount in lung-transplanted patients admitted to non-transplant surgery [4, 26]. Due to the surgical section of lymphatic vessels during the transplant surgery and an unpredictable neogenesis of new lymphatic vessels, lung-transplanted patients are particularly sensible to fluid shift in general and to intraoperative fluid overload: perioperative pulmonary edema is a feared complication of the lung-transplanted patients undergoing abdominal surgery for gastrointestinal complications, a complication for unknown reasons not infrequent in these patients [4]. Close to 20% of the transplanted patients may need surgery or invasive procedures, and complications may be frequent (up to 50%). Delayed diagnosis, possibly because of the many confounding factors, is associated with high mortality [26]. General surgery in lung-transplanted patient has to be discussed with the transplant center: a thorough preoperative lung function assessment (including arterial blood gases, pulmonary function tests, and advanced imaging) is required to optimize the perioperative management. Accurate airway evaluation should include the risk of anastomotic strictures and a difficult airway management [4, 26].

Kidney—Despite normal or near normal creatinine and BUN values, glomerular filtration rate (GFR) can be reduced in kidney-transplanted patients: therefore the effect of drugs predominantly cleared by the kidney can be prolonged. Due to denervation, the use of dopamine at so-called (and not demonstrated) "renal dose" is useless. Instead, dopamine at beta dosage (4–6 gamma/kg/min) could increase cardiac out and renal perfusion, improving renal function [27, 28].

Liver—The grafted liver is denervated, a condition able to blunt the usual physiological responses [1–3, 5]. Autonomic regulation is impaired at best. Catecholamine treatment shows blunted responses if compared to the effects on a normal liver. Sympathetic denervation, at least during the first year after transplant, is associated

with an impaired vasoconstrictive response in presence of hypovolemia/acute blood losses: in case of hemorrhagic shock, the normal liver under vasoconstriction serves as blood pool, which might not be the case for the patient with a newly grafted liver. According to the literature, later after transplant liver blood flow under physiological conditions appears to be normal, and, as is for other grafted organs, reinnervation might occur.

After liver transplant surgery, in case of good functional recovery of the graft, liver function tests (LFTs) are normal or near normal within the first month [5]. Alteration of LFTs, particularly AST/ALT, gamma GT, bilirubin, and PT/aPTT reflects some form of organ dysfunction and further ad hoc investigations (included advanced imaging and endoscopic procedures) are mandatory. The drug-metabolizing capacity of a well-functioning grafted liver is normal. In case of surgical or invasive procedures to be performed in liver-transplanted patients, a thorough preoperative functional assessment should include neurological, cardiovascular (included a workup for cardiac function and coronary artery disease mainly dictated by medical history and physical examination) [19–22], respiratory and renal functions, and a metabolic balance (iatrogenic diabetes, hypercholesterolemia to be ruled out and/or properly managed). Since kidney function could be impaired after liver transplantation, important is a preoperative renal functional assessment: a panel of electrolytes together with BUN, creatinine, and GFR are advised [5].

6.4 General Notes of Anesthesia Management in SOT Recipients: When Clinics Are Applied to the New Physiology

A variety of anesthetic techniques (general, locoregional, sedation) have been successfully applied in solid organ transplanted patients [1–5]. Standard premedication may be used if needed. Appropriate perioperative antibiotic prophylaxis should be used, as in non-transplanted patients. Peculiar conditions (MDR/XDR colonization, infections, peculiar risk factors) need a case-by-case decision: colonization does not mean by default changes in the standard antibiotic prophylaxis, while strict postoperative infectious control measures are mandatory [7, 8]. Due to the demonstrated reduction of postoperative respiratory complications (at least in abdominal surgery), intraoperative protective ventilation is recommended during general anesthesia and should include tidal volumes (TV) of 6–8 mL/kg of IBW, PEEP 5–10 cmH_2O, plateau pressure <30 cmH_2O, $ETCO_2$ between 30 and 35 mm Hg, and the use of recruitment maneuvers if needed [29]. Oral endotracheal intubation is preferred to nasal intubation because of the potential risk of infection caused by nasal flora [1–4, 8]. The choice of perioperative hemodynamic monitoring (invasive, minimally invasive, and/or the newer noninvasive devices) is mainly driven by the patient's comorbidities, the clinical conditions, the type of surgery, the planned anesthesia technique, and the available devices [19–21, 30]. Monitoring of central venous pressure (CVP) may raise concerns but so far is the most common hemodynamic parameter used worldwide in the perioperative period [30]. Minimally invasive or the new

noninvasive monitoring devices, allowing measurements of cardiac output and dynamic indices of fluid responsiveness (systolic pressure variation [SPV], stroke volume variation [SVV], pulse pressure variation [PPV]), should be strongly considered whenever appropriate [20, 21, 30]. In case of high-risk patients because of comorbidities and/or because of complex surgery (e.g., surgery with major fluid shifts), invasive arterial blood pressure is advised.

If a central neuraxial blockade is planned, PT/aPTT and platelet count should be within the limits considered safe for surgical procedures, keeping in mind the possible bone marrow depression due to immunosuppressive drugs and a possible multifactorial thrombocytopenia (as is, e.g., in liver-transplanted patients). Nonsteroidal anti-inflammatory drugs should be avoided because of the risk of hepatic and kidney toxicity, gastric bleeding, and adverse effects on platelet function [1–5].

Interactions between immunosuppressors and anesthetic drugs should be considered in transplanted patients: however, as already underlined, in spite of reported experimental evidences of possible interactions, there are no clinical trials demonstrating major interactions, and the available studies are not updated.

6.4.1 Kidney Transplant Recipients

Kidney transplant recipients are at high cardiovascular risk: the risk, reduced but not entirely eliminated by the transplant, claims for a thorough and updated preoperative cardiovascular evaluation of patient undergoing noncardiac surgery to rule out coronary artery disease or dilated or hypertrophic cardiomyopathy [19]. Diabetes mellitus, another significant risk factor for cardiovascular complications, is not infrequent in kidney transplant recipients. Renal function can be altered, even if serum creatinine level is within normal range: great care has to be taken in avoiding nephrotoxic drug or substances excreted by the kidney. Among inhalational anesthetics, isoflurane and desflurane are safe. Sevoflurane has been demonstrated to be safe in several trials, even if concerns are still expressed by some, due to the presence and the possible renal toxic adverse effects of compound A (a by-product of the reaction with strong bases present in the CO_2 absorbers) and inorganic fluoride ions. In case of low flow anesthesia, a minimum fresh gas flow rate of 2 L/min has to be used [31–34]. Among neuromuscular blocking drugs, cisatracurium should be considered the drug of choice due to the spontaneous degradation (Hoffman reaction) [35]. Due to a reduced elimination of rocuronium in chronic renal failure (the case for suboptimal renal function after transplant and not to be generalized to all the kidney-transplanted patients by default), more studies are needed before the use of sugammadex can be recommended in this specific setting: the complex rocuronium/sugammadex in fact is excreted by the kidneys. Caution and strict monitoring are to be used with fentanyl, sufentanil, and alfentanil in case of suboptimal renal function: interindividual pharmacokinetic variability is high, making titration to the need of the individual patient mandatory in this specific setting. The use of remifentanil, according to the reported routine clinical experience, seems to be safe, pharmacokinetic and pharmacodynamic profiles being unaltered even in renal

dysfunction. While in chronic renal failure opioid administration might be problematic (as above underlined and well demonstrated also for morphine and its metabolite morphine-3-glicuronide), good functional recovery of the kidney graft is able to normalize opioid clearance. Meperidine in patients with renal dysfunction might cause seizures (accumulation of the metabolite normeperidine) and then has to be used with great caution.

Prevention of hypotension and hypoperfusion is the hemodynamic goal in every clinical anesthesia. Particularly in the kidney-transplanted patient, the intraoperative hemodynamic monitoring is mandatory to avoid hypovolemia and its consequences: minimally invasive devices allowing continuous cardiac output monitoring could ease the differential diagnosis of the hypotensive episodes and should orient the hemodynamic manipulation (hypovolemia vs. decreased contractility vs. distributive shock). Intraoperative oliguria has to be avoided, and diuretics are to be administered only after having ruled out hypovolemia: this makes hemodynamic monitoring crucial for an appropriate interpretation of the cardiovascular changes. Quite the same is the behavior in case of pancreas-kidney- and in pancreas-transplanted patients [36].

6.4.2 Liver Transplant Recipients

The liver transplant recipient with average graft function and normal LFTs has to be considered as a "normal" patient: the possible consequences of the denervated liver have already been discussed and taken into consideration when preparing the anesthesia plan [5]. In liver transplant recipients, there is no evidence of increased risk of developing toxic hepatitis after the administration of isoflurane, sevoflurane, and desoflurane, even if few case reports of hepatotoxicity due to sevoflurane are present in the literature [11]. The possible protective role of sevoflurane is then controversial. There are no contraindications to locoregional anesthesia, but attention should be paid to platelets count and the coagulation profile (see above). Opioids are safe propofol and thiopental are safe induction agents, while caution should be used with ketamine, due to the possible induction of seizure activity. Among neuromuscular blocking agents, cisatracurium might be considered of choice, even if in patients with good liver graft function and normal renal function, rocuronium, vecuronium, and sugammadex should be safe [5]. In liver-transplanted patients undergoing de novo cancer surgery, peritoneal adhesions are at very high risk of bleeding for surgical technical reasons, regardless of hemostasis and coagulation tests. To optimize the management of intraoperative bleeding and transfusion requirements (and in general the hemostatic profile), the use of thromboelastography and thromboelastometry is advised: if not available, PT/aPTT, fibrinogen, and platelet counts are to be monitored [5, 37]. As above underlined, hemodynamic monitoring is mandatory to optimize circulating volume and fluid administration, particularly in major abdominal surgery: the use of devices able to measure cardiac output and dynamic indices (SVV, PPV) becomes crucial for a perioperative goal-directed therapy, even

if again central venous pressure (CVP) monitoring is still the most frequent reported parameter [30].

6.4.3 Heart Transplant Recipients

General anesthesia is preferred over regional anesthesia in heart transplant recipients due to the possible impaired response to hypotension after the central neuraxial block [2–4]:

however, locoregional anesthesia is not contraindicated, and there are published case reports [1–4]—an appropriate volume loading together with an ad hoc hemodynamic monitoring is mandatory to balance the relative hypovolemia due to vasodilatation [4]. Invasive or minimally invasive hemodynamic monitoring is mandatory when hemorrhage is expected or relevant fluid shifts are anticipated. Fluid challenge or the use of pressors and inotropes has to be guided by the hemodynamic monitoring. Invasive arterial blood pressure has to be strongly considered in case of intermediate- and high-risk surgery. Transesophageal echocardiography (TEE) can be, if and when available, a good choice to assess volume status and cardiac contractility [1–4]. Neuromuscular blockade monitoring is becoming more and more relevant, particularly when cisatracurium is used: elimination is not affected by either renal or hepatic (dys)function, and neostigmine, as above underlined, has to be avoided to severe bradycardia [4]. Rocuronium (and sugammadex as reversal) might be a safe alternative choice for muscle relaxation and reversal: neuromuscular monitoring is, however, to be strongly considered [4]. Infections have to be ruled out: WBC count and markers of infection (CRP/PCT) should be monitored. A chest X-ray might be considered before surgery, according to the scheduled surgical procedure and the patient's age.

6.4.4 Lung Transplant Recipients

Anesthesiologic management in lung transplant recipients is influenced by the severity of lung dysfunction prior to transplant, particularly in case of single-lung transplant [1–4]. Obstructive and restrictive syndromes and hypoxia are the rule in lung transplant recipients. Hypercapnia early after transplant is not unusual. Chest X-ray, arterial blood-gas analysis, and spirometry are to be strongly considered before major surgery. Chest CT scan is the gold standard for every differential diagnosis [6, 7]. Intraoperative protective ventilation strategy is mandatory, and ventilatory strategy should be tailored according to the type of lung transplant. In single-lung transplant, 60–70% of perfusion will be directed to the transplanted lung, and positive pressure ventilation may lead to shunting and impaired oxygenation [4]. In patients receiving a single-lung transplant for restrictive lung disease, the transplanted lung should have significantly better compliance than the native lung, and oxygenation/ventilation is unlikely to be compromised.

Restrictive perioperative fluid management has to be strongly considered to avoid pulmonary edema due to impaired lymphatic vessels and should be guided by hemodynamic monitoring using minimally invasive systems or TEE.

6.4.5 Special Cases

6.4.5.1 Laparoscopic Surgery

Laparoscopic procedures are increasing in transplanted patients. In heart transplant patients, laparoscopic surgery can be challenging: induction of anesthesia and positioning may cause hemodynamic instability often secondary to a reduced cardiac output. CO_2-pneumoperitoneum has direct and indirect effects secondary to abdominal distention and CO_2 reabsorption. The net hemodynamic effects are increased systemic vascular resistances, arterial pressure and filling pressures (CVP/PWP), and a decreased CI [1–3].

6.5 Conclusions

Knowledge of the new physiological profile associated with the denervated grafted organ and the new natural history introduced by the condition of immunosuppression are key to manage the solid organ transplant recipients facing non-transplant surgery: due to the expanding number of transplanted patients admitted to non-transplant surgery, the possible problematic approach and the few studies so far available, a registry for the perioperative problems is needed for an optimal design of appropriate management guidelines.

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Neuromuscular Diseases

7

Fabrizio Racca and Brunella Gily

Patients affected by neuromuscular disorders (NMDs) are at high risk of intraoperative and postoperative complications. General anesthesia (GA) in these patients may exacerbate respiratory and cardiovascular failure due to a marked sensitivity to several anesthetic drugs. Moreover, succinylcholine and halogenated agents can trigger life-threatening reactions [1]. On the other hand, survival rates of these patients had progressively improved, increasing the need for surgical procedures [2, 3]. An intensive, proactive, multidisciplinary approach should be instituted before, during, and after any surgical procedure requiring GA or sedation. Thus, surgery in this children population should be performed in a fully equipped hospital with extensive experience in NMD management. This chapter will review the pathophysiology of life-threatening complications of anesthesia in NMDs and the assessment and management of these patients before, during, and after anesthesia. Four major categories of NMDs (see Table 7.1) should be considered to plan the safest anesthesia strategy: (1) motoneuron diseases, (2) peripheral neuropathies, (3) neuromuscular junction diseases, and (4) muscle diseases.

7.1 Preoperative Assessment and Management

Some patients with NMDs may lack a definite diagnosis, manifesting the disease only with minor signs. These patients are particularly at risk of life-threatening complications related to anesthesia. Thus, all patients presenting for administration of GA or sedation should be screened for subclinical myopathy [1] (see Table 7.2).

Inability to walk past 18 months old or other signs of motor loss or delay, especially if familiar, the presence of scoliosis or joint blocks should suggest a subclinical myopathy and should warrant neurological evaluation before elective surgery.

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Table 7.1 Neuromuscular disorders

1. Motoneuron diseases
   - Amyotrophic lateral sclerosis (ALS)
   - Spinal muscular atrophy (SMA)
   - SMA with respiratory distress (SMARD)
   - Spinobulbar muscular atrophy (Kennedy disease)
   - Poliomyelitis
   - Post-polio syndrome
2. Peripheral neuropathies
   - Guillain-Barrè syndrome (GBS)
   - Chronic inflammatory demyelinating polyneuropathy (CIDP)
   - Hereditary sensory and motor neuropathies (i.e., Charcot-Marie-Tooth disease)
   - Hereditary sensory and autonomic neuropathies (HSAN)
   - Critical illness polyneuropathy
   - Other polyneuropathies
3. Neuromuscular junction diseases
   - Myasthenia gravis (MG)
   - Lambert-Eaton myasthenic syndrome (LEMS)
   - Congenital myasthenias
   - Botulism

4. Muscle diseases

4.1. Progressive muscular dystrophies
   - Dystrophinopathies: Duchenne (DMD) and Becker (BMD) type
   - Limb-girdle muscular dystrophies (LGMD)
   - Facioscapulohumeral muscular dystrophy (FSHD)
   - Oculopharyngeal muscular dystrophy (OPMD)
   - Myotonic dystrophy (DM): DM type 1 (DM1), DM type 2 (DM2)

4.2. Congenital muscular dystrophies
   - Ullrich CMD, Bethlem myopathy
   - Merosin-deficient dystrophy CMD
   - Alpha-dystroglycanopathies (e.g., Fukuyama CMD)
   - Emery-Dreifuss dystrophy

4.3. Congenital myopathies
   - Central core disease
   - Asymptomatic patients susceptible to malignant hyperthermia
   - Multiminicore myopathy
   - Nemaline/rod myopathies
   - Centronuclear/myotubular myopathy
   - Fiber-type disproportion myopathy
   - Myofibrillar myopathies

4.4. Metabolic myopathies
   - Mitochondrial encephalomyopathies
   - Glycogen storage disorders (i.e., GSD type II or Pompe disease, McArdle disease)
   - Lipid storage myopathies

4.5. Channelopathies
   - Congenital myotonia
   - Hyperkalemic periodic paralysis
   - Hypokalemic periodic paralysis
   - King-Denborough syndrome

4.6. Acquired myopathies
   - Polymyositis
   - Dermatomyositis
   - Toxic myopathies
   - Endocrine myopathies (e.g., thyroid dysfunction)

Table 7.2 Suspicious signs and symptoms of subclinical neuromuscular disease

• Usual snoring and/or the presence of signs and symptoms of sleep breathing disorders (frequent arousals, disturbed sleep, daily drowsiness, nightmares, morning headache, poor concentration, irritability)
• Recurrent pneumonia and/or lower airway infections • Ineffective cough, swallowing disease • Inability to walk before the age of 18 months, delay in the development stages • Scoliosis, lordosis, articular retractions/blocks, ligaments laxity • Napoleon hat profile mouth, wooden face • Weakness of the main articulations: scapular (inability to lift the arms), pelvic (Gower maneuver, donkey walk), feet and hands • Frequent falls, fatigability • Loss of muscle tone, alteration of tropism (hypotrophy, hypertrophy, calves pseudohypertrophy) • Reduction of QI, delay of speech • Mioglobinuria (dark-colored urine) • Ophthalmoplegia • Lactic acid increase • CK increase with/without AST > ALT increase

Table 7.3 Causes of CK level increase

• **Myopathies** – *Very high levels of CK (>1500 U/L)*: Duchenne/Becker muscular dystrophy, limb-girdle muscular dystrophy, congenital dystrophy, inflammatory myopathies, thyroid diseases – *Moderate increase of CK (500–1500 U/L)*: glycogen storage disorders, RYR 1 mutation (malign hyperthermia, central core myopathy), channelopathies, myotonic muscular dystrophy, facioscapulohumeral muscular dystrophy – *Mild increase of CK (200–500 U/L)*: congenital myopathy, secondary myopathy, mitochondrial defects
• **Neuropathies and motoneuron diseases** (usually slight increased levels of CK, with the exception of Kennedy bulb-spinal atrophy where CK levels are over 1500 U/L) • **Myositis** • **Traumatism or intense exercise in the last 72 h** • **Muscle ischemia** • **Endocrine system disease** (thyroid, adrenal, parathyroid dysfunctions) • **Drugs** (statins, alcohol, neuroleptics, beta-blockers)

Asymptomatic elevated creatine kinase (CK) levels may be the only sign of a muscle disease. Persistent high levels of CK (two times higher than the normal range) require a neuromuscular evaluation. Moreover, these patients should be checked for subclinical myopathy (see Table 7.2). All the causes of elevated CK are listed in Table 7.3.

All patients with suspected or confirmed NMD are particularly at risk of life-threatening complications related to anesthesia, such as malignant hyperthermia, rhabdomyolysis, and hyperkalemic cardiac arrest secondary to denervation. Such patients should be treated as highest risk level subjects.

In all patients with NMDs preoperative pulmonary evaluation is strongly recommended to assess the risk of respiratory complications and the need of specific perioperative and postoperative management [1]. Assessment of respiratory function should include an accurate medical history and physical examination, a chest X-ray, an evaluation of sleep-disordered breathing, and the measurements of respiratory

function and cough effectiveness. Evaluation of respiratory function and cough effectiveness includes measurement of FVC, peak cough flow (PCF), and diurnal pulse oximetry (SpO_2). SpO_2 less than 95% in room air or FVC less than 50% of predicted value has been established as a clinically significant abnormality, requiring carbon dioxide (PCO_2) level measurement. Moreover, a sleep study is indicated in patients who have any of the following: preoperative FVC < 40% of predicted value and signs or symptoms of nocturnal hypoventilation or apnea. Preoperative training with the use of NIV has been recommended for patients with NMDs with preoperative FVC < 50% of predicted value, especially for patients at high risk of respiratory failure, defined by an FVC < 30% of predicted value, or with diurnal hypercapnia. Moreover, if PCF is less than 270 L/min, training in assisted cough techniques is advocated before surgery. See Table 7.4 for more details.

All patients with neuromuscular disease with potential involvement of the cardiocirculatory system (see Table 7.5) must undergo an accurate assessment of cardiac

Table 7.4 Respiratory preoperative management

Indications for noninvasive ventilation training in preoperative time • **Forced vital capacity <50% of predicted values** (<60% for pediatric population). The patient should be well collaborative • **Daily hypercapnia** ($PaCO_2$ > 45 mmHg) • **Significant night hypercapnia** ($EtCO_2$ or $PtcCO_2$ > 50 mmHg for more than 10% of sleep time or SpO_2 < 90% for at least 5 consecutive minutes or >4 episodes of SpO_2 < 92%) • **Significant sleep apnea** (the cutoff value of AHI is still unknown; some authors suggest to start NIV when AHI is >10 in patients affected by Duchenne muscular dystrophy)
Indications for training in manual and/or mechanical assistance in cough for the patient in the preoperative time • **Cough peak <270 L/min** (adult or young adult). Only for collaborative patients • **MEP < 40 cmH_2O** (Only for collaborative patients) • Anamnestic data for children

Table 7.5 Cardiac dysfunctions in neuromuscular disorders

Disorder	Cardiac effects
Guillain-Barrè syndrome Hereditary neuropathies Muscular-spinal atrophy	Autonomic system dysfunction may enhance cardiovascular instability (i.e., bradycardia, blood pressure shifts)
Amyotrophic lateral sclerosis	Long QT
Dystrophinopathies: Duchenne and Becker type	Dilated cardiomyopathy, arrhythmias, and conduction defects
Limb-girdle muscular dystrophies Myotonic dystrophy Emery-Dreifuss muscular dystrophy Congenital myopathies Mitochondrial encephalomyopathies	Arrhythmias, conduction defects, dilated cardiomyopathy
Glycogen storage disorder type II or Pompe disease	Hypertrophic cardiomyopathy in the infantile form
Lipid storage myopathies	Cardiomyopathy
Periodical paralysis	Arrhythmias in case of hypo- or hyperkalemia; particular awareness to the Andersen syndrome because it is at high risk of ventricular arrhythmia

function (echocardiogram in all patients with myopathy and in patients with suspected pulmonary hypertension, ECG Holter if signs or symptoms of brady-tachyarrhythmia) and an optimization of cardiologic therapy before being subjected to anesthesia or sedation [1].

For patients chronically treated with steroids (i.e., DMD, myasthenia gravis), consideration has to be paid to their administration during surgery. In fact, this therapy can suppress the hypothalamic-pituitary-adrenal axis, and, during a phase of stress, such as surgery, the adrenal glands may don't respond appropriately [4]. Management of surgical patients on chronic steroid therapy should be performed administering a perioperative stress-dose steroids [5].

The preoperative evaluation should also include the assessment for a difficult intubation due to jaw ankylosis, atrophy of masticatory muscles, macroglossia, or to limited mobility of the cervical spine. If any of these conditions are present, intubation should be performed taking into account adult and child guidelines for difficult intubation [6, 7].

7.2 Life-Threatening Complications of Anesthesia in NMDS

All patients with suspected or confirmed NMD are particularly at risk of life-threatening complications related to anesthesia, such as malignant hyperthermia, rhabdomyolysis, and hyperkalemic cardiac arrest secondary to denervation.

Malignant hyperthermia (MH) is very rare (incidence of 1:100,000 patients who undergo general anesthesia, being 50% of the cases less than 19 years old). The predicted prevalence in the USA of patients susceptible to MH is 1:2000 [8, 9].

The clinical signs of MH are severe hyperthermia, muscle contraction, rhabdomyolysis, and mixed acidosis. MH occurs when a susceptible individual is exposed to succinylcholine or a halogenated volatile anesthetic (halothane, isofluorane, enfluorane, sevofluorane, desfluorane). Patients with genetic alteration of ryanodine receptor (RYR1) or, rarely, dihydropyridine receptor (DHP) are strongly at risk. MH patients affected by myopathies have an alteration of RYR1 receptors, such as some congenital myopathy (i.e., the "central core" myopathy, the "multi-minicore" myopathy, and Native American myopathy) and some channelopathies (i.e., the King-Denborough disease and periodic hypokalemic paralysis).

The MH can appear either immediately after the induction of anesthesia or during anesthesia or immediately after suspension of anesthesia in the postoperative time. In the latter case, it usually arises with asymptomatic rhabdomyolysis. In Tables 7.6 and 7.7, further informations are provided on the management of the IM.

Rhabdomyolysis is another rare but potentially lethal complication that manifests when vulnerable subjects (i.e., patients with myopathies) are exposed to halogenated gases or to succinylcholine. Rhabdomyolysis is the effect of the necrosis of

Table 7.6 Useful information for the diagnosis of malignant hyperthermia

- Malignant hyperthermia (MH) is caused by an abnormality on a skeletal muscle receptor. The genetic mutation is known in about 50% of the cases: in most cases the genetic alteration is a mutation of the ryanodine receptor (RYR1); it is rarely due to the mutation of the dihydropyridine receptor (DHP). In about 50% of the cases, the genetic alteration of RYR1 is transmitted as an autosomal dominant trait; in other patients, a new mutation is assumed
- The subjects listed below are at risk of being healthy carriers of alterations of RYR1 or DHP receptors:
  - Familiar or personal history of adverse reactions to anesthesia (respiratory or metabolic acidosis, masseter or generalized muscle stiffness, dark-colored urine, hyperthermia)
  - Patients with signs of subclinical myopathy (inability to walk past 18 months old or other signs of motor loss of delay, especially if familiar, the presence of scoliosis or joint blocks, etc.)
  - Patients with a history of rhabdomyolysis caused by heat or exercise

"Trigger" drugs must be avoided in these people and a diagnostic investigation should be planned properly

- Patients with certain congenital myopathies are also at risk, i.e., "central core" myopathy, "multi-minicore" myopathy, Native American myopathy, and some channelopathies (i.e., King-Denborough disease and hypokalemic periodic paralysis)
- MH may start during the first anesthesia exposure, even if in more than 50% of the cases, there was a previous anesthesia that did not trigger it. The incidence is probably underestimated: some cases occur with a mild form (variable phenotypic expression). In susceptible individuals, MH has also been described after exposure to hard exercise or heat. In addition to this, there are cases of fatal MH in susceptible subjects without apparent triggers (postmortem demonstration of RYR1 receptor abnormality)
- MH may cause an excessive release of calcium from the sarcoplasmic reticulum, which causes an excessive accumulation of calcium in the muscle cells. The result is a prolonged muscle contraction and an activation of the cellular metabolism with a consequent increase of production of CO_2, depletion of O_2 and ATP, and with the effect of an increase of lactic acid production. Once the energy stocks are finished, cells die and go to rhabdomyolysis
- The first manifestations of MH are muscle contraction and mixed acidosis with increased lactates, as well as rhabdomyolysis and hyperkalemia
- After several minutes/hours since the onset of the reaction, a severe hyperthermia appears (the increase in temperature can be 1 °C/h), which can reach 45 °C. This phenomenon is caused by the contraction of the muscles. Activation of the cellular metabolism increases the consumption of O_2 and the CO_2 production, with the result of the dysfunction of vital organs. Hyperthermia is associated with the development of disseminated intravascular coagulation (DIC)
- Clinical presentation varies from patient to patient. Typically, one of the first signs of MH is a severe hypercapnia, detected by capnography, without apparent cause; it is difficult to correct, despite the minute volume increase. Associated signs include sinus tachycardia and/or muscle stiffness (generalized or masseter isolated), despite curarization, and/or metabolic acidosis. Rigidity muscle in a curarized patient is pathognomonic. Most of the patients do not have all the symptoms described above
- Hyperthermia is rarely an early sign: it is usually a late manifestation and may even be absent. Other usually late symptoms are the ECG alterations related to hyperkalemia, tachycardia or ventricular fibrillation, pressure instability (hypertension or hypotension), myoglobinuria
- Laboratory tests may also show mixed acidosis with increased lactates, increased levels of blood CK, hyperkalemia, myoglobinuria
- The signs of MH can be divided into early and late signs

Table 7.6 (continued)

	Early signs of MH	Late signs of MH
Metabolic	$EtCO_2$ increase O_2 consumption increase Metabolic and respiratory acidosis Profuse sweating Marbled skin	Hyperkalemia Fast increase of body core temperature
Muscular	Spasm of the masseter (typically after succinylcholine administration) Generalized muscle stiffness	High values of CK blood levels High values of blood myoglobin High values of myoglobinuria (dark-colored urine)
Cardiovascular	Atypical tachycardia Cardiac arrhythmias Hemodynamic instability	Serious cardiac arrhythmias Cardiac arrest DIC (disseminated intravascular coagulation)

The following conditions should be ruled out:
- Inadequate anesthetic dept
- Sepsis
- Inadequate ventilation
- Anesthesia machine malfunction
- Pheochromocytoma
- Thyrotoxic crisis
- Drug abuse (ecstasy or other)
- Malignant neuroleptic syndrome

Diagnostic investigation among patients suspected of being susceptible to IM should not delay anesthesia: avoiding trigger drugs is sufficient

There are two diagnostic exams for MH:
- Contraction test with caffeine and halothane; it requires a biopsy (however, there are several false negatives)
- Genetic diagnosis (however, there are several false negatives, because in only about 50% of the cases the genetic mutation is known)

the muscular cell, with consequent release of intracellular substances into the circulation (i.e., potassium, myoglobin, and CK). This phenomenon may cause a cardiac arrest due to hyperkalemia and acute renal failure.

Hyperkalemic cardiac arrest secondary to denervation is another life-threatening complication related to general anesthesia in neuromuscular disorders. It is triggered by succinylcholine, when administered in patients who have an increase in nicotinic receptors caused by denervation, as occurs in people with motoneuron disease and with peripheral neuropathy.

Table 7.7 Managing a malignant hyperthermia crisis

Immediately • Stop all trigger agents and change to non-trigger anesthesia (i.e., TIVA) • Disconnect the vaporizer • Declare an emergency and call for help • Inform the surgeon and ask for termination/postponement of surgery • Hyperventilate (use a minute volume 2–3 times normal) with 100% O_2 at high flow • Treat with dantrolene (2.5 mg/kg i.v. with rapid infusion; ampoules of 20 mg are mixed with 60 mL sterile water for injectable solutions (48 ampoules may be needed for an adult patient)). The infusion should be repeated until cardiorespiratory stabilization; it may be necessary to go beyond the maximum dose of 10 mg/kg; the dantrolene administration must be started as soon as possible • Consider inserting an arterial and central venous line and a urinary catheter
Treat hyperthermia • Cool the body surface to <38.5 °C with physical means: air, wet and cold towels, ice packs placed in the axillae and groin • 2000–3000 mL of chilled (4 °C) 0.9% saline infused i.v.
Measure core temperature
Treat acidosis • Give sodium bicarbonate 8.4% (1 mL = 1 mEq) 1–2 mEq/kg at i.v. if pH < 7.2 • Hyperventilate aiming to normalize PCO_2 • Treat hyperkalemia by administering • Glucose 50% 100 mL with 10 IU insulin, monitoring blood sugar • Calcium chloride 10%: 5–10 i.v. (using a central venous catheter) until the normal values of ionized calcemia are reached
Prevent acute renal failure by administering fluids and diuretics and check renal function • Maintain urinary output >2 mL/kg/h by administering furosemide 0.5–1 mg/kg + continuous infusion starting at 1 mg/kg/h • Increase consensually the administration of crystalloids (lactated Ringer's solution or 0.9% saline)
Treat any arrhythmias (do not administer calcium channel blockers) • Give esmolol if tachycardia persists • Give amiodarone: 300 mg i.v. for treatment of arrhythmias
Check coagulation and treat any coagulopathy (DIC)
Obtain sample for measurement of CK and myoglobulin
Transfer the patient to ICU and monitor the patient for a minimum of 24 h

7.2.1 Prevention of Complications

To prevent these life-threatening complications related to general anesthesia, it is very important to follow the recommendations below [10].

1. Choose total intravenous anesthesia (TIVA) in subjects at risk, in order to avoid drugs that can trigger one of these complications; it is fundamental in these cases to use an anesthesia machine without the vaporizer, to change the circuit and the soda lime; moreover, the anesthesia machine have to be "washed" from the presence of halogenated gas residues. Washing the anesthesia device must be performed setting the machine to ventilate with a balloon attached to the Y-tube for at least 20 min, using an O_2 flow of at least 10 L/min. The absence of halogenated

gas in the system must be confirmed by checking the absence of halogenates exhaled by the analyzer of gas.
2. An adequate monitoring should always be provided during and after surgery, to identify signs of rhabdomyolysis or MH (dark-colored urine, hyperkalemia, increase of CK blood levels, hypercapnia, hyperthermia, etc.).
3. In the operating rooms, there must be sufficient stock of dantrolene and sterile water for this dilution (at least 36 ampoules of 20 mg of dantrolene, which allow the cumulative administration dose of 10 mg/kg in a 72-kg-weight patient. In addition to this, there should be at least 5 60 mL syringes and 36 100 mL bottles of sterile water for dilution); each ampoule of dantrolene sodium 20 mg is in powder form, and it must be prepared by adding 60 mL of sterile water for injectable use and shaking up to get a clear solution. Some authors recommend the storage of 48 ampoules, considering the possibility of treating high-weight patients.

7.2.2 Management

In the case of one of these complications, immediate treatment is essential [10].

In the case of MH, the treatment is described in Table 7.7.

In the case of rhabdomyolysis, the treatment involves the management of hyperkalemia, the prevention of acute renal failure, and the treatment of possible arrhythmias using the same strategies described in Table 7.7 for MH.

In the case of cardiac arrest from hyperkalemia, the treatment requires that the cardiopulmonary resuscitation is sustained until the level of potassium has been lowered.

7.3 Intraoperative Management

Regional anesthesia should be warranted whenever possible, including patients with preexisting peripheral nervous system disorders, in particular in the case of respiratory dysfunction [1].

It is recommended to avoid the use of succinylcholine in all neuromuscular patients [1].

In patients with motoneuron diseases, peripheral neuropathies, and neuromuscular junction diseases, halogenated agents can be administered [1]. On the contrary, it is recommended to avoid the use of halogenated agents in patients' muscle diseases; however, in mitochondrial myopathies, halogenated agents can be administered in order to avoid prolonged use of propofol for the maintenance of anesthesia that can induce in such patients' lactic acidosis [1].

Although some authors [11] agree that when faced with a difficult venous access in a patient with myopathy, a brief use of inhalation anesthesia is possible as long as the anesthesiologist is prepared to treat rhabdomyolysis; other authors [1] agreed about the use of ketamine in these circumstances. Although IM ketamine is used for

adult patients, an oral or rectal route is preferred for pediatric patients to avoid unnecessary pain and stress to the child and their family.

If inhalation anesthesia has to be avoided, general anesthesia can be performed using total intravenous anesthesia (TIVA) [1]. In these cases, ultra-short-acting drugs, such as propofol and remifentanil, are preferable [1].

In all patients with NMDs, nondepolarizing neuromuscular blocking (NMBs) agents may show prolonged duration of neuromuscular blockade even when short-acting. Thus, most reports recommend avoidance of NMBs whenever possible [1]. However, when NMBs are necessary, the dose should be reduced and titrated to effect; neuromuscular function has to be continuously monitored (e.g., using the train-of-four monitoring) and the effect of muscle relaxant should be antagonized [1]. Therefore, reversal of rocuronium-induced or vecuronium-induced neuromuscular blockade by sugammadex could be beneficial in NMDs to eliminate the risk of postoperative residual muscle paralysis [12, 13]. Finally, the combination of rocuronium and sugammadex could replace the need for succinylcholine in rapid sequence induction in patients with NMDs [1].

In patients with myasthenia gravis, factors potentially enhancing neuromuscular blockade should be avoided (e.g., hypothermia, hypokalemia, hypophosphatemia, and several drugs).

In patients with myotonic dystrophy, factors that can precipitate myotonic contractures (e.g., hypothermia, postoperative shivering, dyskalemia, mechanical and electrical stimulation, propranolol, succinylcholine, and anticholinesterase agents) should be avoided.

7.4 Postoperative Management

Postoperative admission to an intensive care unit (ICU) should be considered in any patient (1) at risk for respiratory complications, (2) with weak cough, (3) with severe bulbar dysfunction, (4) with severe cardiac dysfunction, (5) receiving muscular blocking agent that has been not reversed by sugammadex, or (6) receiving morphine infusions [1].

Assisted cough and mechanical ventilation respiratory support in the postoperative period are recommended for patients already using MI-E and NIV preoperatively.

Patients with decreased respiratory muscle strength require close monitoring and aggressive respiratory management. In particular, the application of a protocol based on the combination of NIV with MI-E after extubation for high-risk NMD patients may provide a clinically important advantage by averting the need for reintubation or tracheotomy and shortening their ICU stay. Extubation directly to NIV should be considered for patients with baseline FVC < 50% of predicted and should be strongly considered for those with FVC < 30% of predicted. Postoperative use of assisted cough techniques including the use of MI-E must be considered for any teenage or adult with preoperative PCF < 270 L/min [1]. To maximize the chance of success, extubation should be delayed until respiratory secretions are well controlled and SpO_2 is normal or baseline in room air [14]. Oxygen must be applied

with caution in NMD patients because it can correct hypoxemia without treating the underlying cause such as hypercapnia, mucus plugging, and atelectasis. To facilitate appropriate oxygen use, CO_2 levels should be monitored.

Adequate pain control is essential to prevent hypoventilation secondary to splinting after thoracic, upper abdominal, and spine surgery [1]. In case of hypoventilation after opioid administration, adequate ventilation can be achieved by using NIV or by delaying extubation for 24–48 h. Moreover, MI-E can also be useful when pain prevents the patient from coughing spontaneously.

7.5 Conclusions

Patients with NMDs are at high risk of intraoperative and postoperative complications. An intensive, proactive, multidisciplinary approach should be instituted before, during, and after any surgical procedure requiring general anesthesia or sedation. Thus, surgery in this patient population should be performed in a fully equipped hospital with extensive experience in NMD management.

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Noninvasive Ventilation in the Perioperative Period

8

Jacopo Tramarin, Andrea Cortegiani, and Cesare Gregoretti

General anesthesia, major surgery, and postoperative pain may cause important pulmonary physiopathologic modifications. In fact, general anesthesia and neuromuscular paralysis may induce relaxation of the respiratory muscles. As a consequence, the diaphragm switches to a more cranial position causing a reduction of pulmonary volumes, thus triggering atelectasis formation [1, 2].

In the postoperative population, the reduction of functional residual capacity (FRC) is more important when surgery is performed close to the diaphragm (e.g., surgery of the thorax and/or upper abdomen). As a matter of fact, atelectasis typically develops in the dependent regions of the lung next to the diaphragm. Around 10% of lung tissue can be involved, and they may last as long as 24–48 h after a major surgery [3–5].

This in turn could determine ventilation-perfusion mismatching, hypoxemia, and acute respiratory failure (ARF) related to lung failure. Furthermore, due to diaphragm dysfunction, especially after upper abdominal surgery, respiratory pump failure can also be present [6].

Patient's comorbidities (e.g., chronic obstructive pulmonary disease (COPD), severe obesity, older age, cardiovascular disease, neuromuscular disease, etc.) are risk factors which need to be evaluated together with the type of surgery, the anesthetic technique, and the length of mechanical ventilation to evaluate the risk of postoperative pulmonary complications (PPCs) [7].

Once established, PPCs may lead to prolonged postoperative ventilatory support, longer ICU stay, higher risk for the onset of new complications, and lastly higher expense of resources and costs.

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PPC incidence is estimated to be between 5% and 25%, but these values raise up to 40% in cardiac surgery and 30% in thoracic surgery [8–11].

Several scoring systems have been employed to predict the onset of PPCs [12]. The ARISCAT study [13] evaluated simple clinical parameters to predict patients at risk of developing PPCs. The study included age, preoperative SpO_2 respiratory tract infections in the month previous to surgery, HB level <10 mg/dL, incision site, and length of surgery and urgent/emergency procedures. All these variables allow to stratify the risk of postoperative ARF and the degree of severity into three levels, thus allowing the clinician to perform preventive strategies such as intraoperative protective ventilation [14].

8.1 Definition of Noninvasive Ventilation (NIV) and Respiratory Support

Noninvasive ventilation consists of positive pressure application on the airway without the need of tracheal intubation [15–18].

Pressure can be delivered either continuously during the breath cycle (CPAP) or intermittently during the inspiratory phase (NIPPV).

During CPAP flow and volume are exclusively generated by the patient's respiratory efforts. CPAP may increase FRC thus preventing alveolar collapse and atelectasis [19] and may also counterbalance an intrinsic PEEP (i.e., COPD patients) [20, 21]. Lastly, CPAP prevents collapse of the upper airway [22] and reduces left ventricular afterload [21]. During NIPPV (e.g., pressure support ventilation (PSV)) flow and volume are generated partially by the respiratory muscles and partially by the ventilator. In PSV the patient controls his respiratory frequency and inspiratory and expiratory time.

8.1.1 Perioperative Use of NIV

NIV has recently been evaluated perioperatively as a therapeutic and preventive tool [6, 15, 23]; absolute and relative counter indications are the ones stated in the major reviews and controlled trials [15, 24, 25].

8.1.2 Intraoperative NIV

Intraoperative NIV can be useful in healthy patients when a deep sedation is required or in patients undergoing major surgeries who are at high risk for postoperative pulmonary complications (e.g., thoracic, cardiac, or upper abdomen surgery) [23, 26–28].

Deep sedation may also cause upper airway collapse in both healthy patients and in patients with predisposing factors like obesity or obstructive sleep apnea syndrome (OSAS) (e.g., obese subjects) [27, 29, 30].

Moreover, NIV during the intraoperative period can play an important role in patients with chronic respiratory failure (e.g., COPD, neuromuscular diseases) or in patients at high risk for acute respiratory failure (e.g., patients with kyphoscoliosis). Supine positioning required by most surgeries can deteriorate the respiratory function; this exacerbation is even more considerable during neuraxial anesthesia due to the intercostal muscles paralysis [26, 28, 31, 32]. In all of these situations, NIV can boost alveolar ventilation, reducing the work of breathing and improving left ventricular afterload [23, 33–35, 38].

Cabrini and colleagues in a systematic review have identified 30 studies which evaluated 618 patients who underwent intraoperative NIV.

Intraoperative NIV aimed at preventing ARF and was found to be useful in 24 patients which already presented a severe respiratory limitation and in 502 healthy patients during deep sedation. In three patients NIV did not succeed due to upper airway collapse [36].

Obese patients deserve special attention. As a matter of fact, body mass index is an important determinant of the respiratory function before and after anesthesia in the major and in the moderately obese patient [37].

The main respiratory alteration of the obese patient is the reduction of FRC, which decreases exponentially with the elevation of body mass index (BMI). As a consequence there is a mismatch in the ventilation-perfusion ratio with hypoxemia with a possible increase in work of breathing [38–42].

The best way to maintain the lung recruited is to prevent atelectasis and to ensure physiological pulmonary volumes is to use a noninvasive positive end-inspiratory pressure (PEEP) before induction of anesthesia [43, 44].

8.2 NIV Application in Different Surgical Settings

8.2.1 Cardiac Surgery

8.2.1.1 Preventive NIV

The restrictive syndrome which develops in patients undergoing cardiac surgery is usually less invasive than the one observed in thoracic and abdominal surgery. However, the incidence of diaphragmatic dysfunction is still elevated. Jousel and colleagues found a significant reduction of atelectasis in the group treated with CPAP [45]; Gust and colleagues in a randomized controlled study on cardiac surgical patients found a reduction in pulmonary extravascular lung water both with simple CPAP and with PSV (PSV + PEEP) [46].

In another study Matte and colleagues [47] randomized 96 patients in three groups: NIV with PSV 12/PEEP 5 cmH_2O every 3 h, noninvasive CPAP 5 cmH_2O every 3 h, and incentive spirometry every 2 h; a smaller reduction of pulmonary volumes and a higher oxygenation were found in the two groups treated with NIV. Incidence of atelectasis (12–15%) was found to be equal in the three groups.

Furthermore, Pasquina and colleagues [48] evaluated CPAP 5 cmH_2O for 30 min vs. NIV (PSV 10 cmH_2O + PEEP 5 cmH_2O) in two groups of 75 patients, showing in the NIV group a smaller incidence of atelectasis notable with a standard chest X-ray. The difference in oxygenation between the two groups was negligible. Moreover, in a randomized study by Zarbock and coworkers [49], 500 patients were divided in two groups: a control group treated with 10 min of CPAP through an intermittent nasal mask (10 cmH_2O every 4 h) and a group treated with preemptive CPAP 10 cmH_2O extended for 6 h a day. The latter group was found to have a remarkable elevation of arterial oxygenation and a reduction of postoperative pulmonary complications, incidence of pneumonia, need for tracheal intubation, and ICU admission. NIV has also successfully been used in patients at high risk for ARF during less invasive cardiac procedures [50].

8.2.1.2 Therapeutic NIV

Cardiac surgery (especially when internal mammary arteries are used for the realization of coronary bypass) and thoracic surgery have a high incidence of acute postoperative respiratory failure [25]. A randomized controlled study carried out in 58 patients with ARF, comparing NPPV vs. O_2 therapy, found a significant reduction in the incidence of arrhythmias, need for re-intubation, reduction in ICU length of stay, and mortality in the NIV group [51]. Kilger and colleagues did not find a significant increase in mortality in ARF patients treated with NIV after cardiac surgery compared to those treated without ARF [52].

8.2.2 Thoracic Surgery

8.2.2.1 Preemptive NIV

Aguilo and colleagues [53] applied NIV for 1 h in ten patients undergoing pulmonary resection, confirming an improvement in oxygenation in contrast to the control group. Perrin and colleagues [54] in a randomized controlled trial surveyed NIV benefits before and after pulmonary resection. They found a reduction in postoperative pulmonary complications as well as a reduction in hospital length of stay.

8.2.2.2 Therapeutic NIV

In an observational study including 21 ARF patients undergoing NIPPV after pulmonary transplant, Rocco and colleagues avoided re-intubation in 12 patients [55]. Auriant and colleagues [56], comparing NIV vs. standard treatment (O_2 therapy, physiotherapy, bronchodilators) in 24 patients with ARF who sustained pulmonary resection, found a decreased incidence in mortality (13% vs. 38%) and a lesser need of mechanical ventilation (21% vs. 50%). Lefebvre and colleagues [57] confirmed the efficacy of an early NIV in treating ARF after pulmonary resection 85% of the patients (76 out of 89 patients) were treated with success. The presence of cardiac comorbidity was considered as an independent factor responsible for NIV failure.

8.2.3 Major Vascular Surgery

Thoracoabdominal aortic aneurism repair is a procedure that bears a high risk of respiratory complications [58, 59].

8.2.3.1 Preemptive NIV

In a randomized controlled trial, Kindgen-Milles and colleagues [60] evaluated continuous nasal CPAP for the first 24 h vs. intermittent CPAP with oxygen therapy in 57 patients who sustained a thoracic aorta aneurism repair. Pulmonary complications and total hospital length of stay were significantly reduced in the group treated with continuous CPAP.

8.2.4 Abdominal Surgery

Hypoxemia complicates recovery of the patients who sustained abdominal surgery in 30–50% of the cases. Mechanical ventilation may be required in 8–10% of cases, augmenting mortality rates and total length of stay [24, 61].

8.2.4.1 Preemptive NIV

Stock and colleagues found that CPAP in patients undergoing laparoscopic cholecystectomy reduced substantially atelectasis compared to incentive spirometry [62].

In the obese patient after bariatric surgery, application of NPPV, with a PSV of 12 cmH_2O for 3–4 h in the first 24 postoperative hours, significantly increased vital capacity and FRC compared to the control group not treated with NIV [63].

8.2.4.2 Therapeutic NIV

Varon and colleagues [64] applying NIV in the treatment of postoperative ARF in neoplastic patients avoided re-intubation in 70% of cases.

Jaber and colleagues [2] in a prospected study involving 72 patients undergoing digestive tract surgery avoided re-intubation in 66% of cases. Presence of severe initial hypoxemia and a slow and minimal raise in PaO_2 after NIV are to be considered as important factors predicting NIV failure.

Antonelli and colleagues [65] demonstrated in a randomized controlled trial that NIV reduced re-intubation rate, incidence of fatal complications and mortality in patients who had developed hypoxemia and ARF after solid organ transplant.

Squadrone and colleagues [61] performed a multicenter prospective randomized clinical study on 209 patients undergoing elective major abdominal surgery. They evaluated the efficacy of early helmet CPAP vs. standard treatment (low-flow oxygen therapy) in patients developing acute hypoxemia. Only one patient (1%) in the group treated with CPAP as opposed to ten in the control group (10%) required intubation. Furthermore, the need for ICU recovery and infection rates was significantly lower in patients treated with CPAP (2.6 ± 4.2 days versus 1.4 ± 1.6 days, and

3% vs. 10%, respectively). Total length of hospital stay did not differ between the two groups.

Michelet and colleagues [66] compared in a case control study the efficacy of NIV against traditional treatment in 36 patients with ARF post esophagectomy. In the NIV group, re-intubation rates lowered from 64% to 25%. Similarly, the frequency of acute respiratory distress syndrome (ARDS) went from 53% to 22%, and length of stay in ICU decreased from 22 ± 18 to 14 ± 13. Moreover, the risk of anastomosis dehiscence was less in the NIV group compared to the control group (6% vs. 28%). Application of high pressures (PSV + PEEP > 25 cmH_2O) in the immediate postoperative period may be dangerous in the presence of upper gastrointestinal tract anastomosis due to the risk of gastric insufflation. In such cases CPAP should be preferred to PSV. In case of a massive insufflation, a nasogastric tube can be placed to rapidly relieve gastric pressure, and NIV should be interrupted [6].

8.2.5 Bariatric Surgery

In the largest prospective world database, including more than 13,000 patients, acute respiratory failure is described as the fourth cause of death (11%) [67].

Obese patients are characterized by a restrictive syndrome with an increase in the thoracic chest wall elastance and an elevation of the abdominal pressure. All these factors lead to the formation of pulmonary atelectasis [68]

8.2.5.1 Preemptive NIV

In the obese patient, at high risk of atelectasis formation, the major concern is to keep the lung open, preventing atelectasis and avoiding upper airway collapse to prevent postoperative pulmonary complications. The use of postoperative NIV is recommended especially in those patients who already are under nocturnal NIV treatment due to OSAS and/or obesity hypoventilation syndrome (OHS) [69].

Application of NPPV during the first 24 h after a gastroplastic surgery allowed to significantly increase FRC, forced expiratory volume, and arterial saturation as compared to oxygen therapy only [64, 70].

This improvement has persisted also after the interruption of NPPV, allowing a quicker recovery to the preoperative spirometric pulmonary volumes.

Neligan et al. [71] evaluated in 40 obese patients undergoing laparoscopic gastric bypass the application of CPAP immediately after extubation in the operating room or in ICU. In both groups CPAP applied for a minimum of 8 h has allowed to avoid alveolar de-recruitment.

As stated previously, some concerns had been raised about the use of NIV in postsurgical patients due to the possible elevation of intraluminal pressure which could cause a deterioration of the anastomosis. A specific study evaluated the incidence of anastomosis laceration and respiratory complications.

Huerta and colleagues evaluated the postoperative complications in patients undergoing NIV after Roux-en-Y gastric bypass [72]. The authors found only 15 cases of severe anastomotic leaks on more than 1000 patients; out of these patients who have anastomosis leaking, only two occurred in patients on CPAP. However, these results cannot be applied on malnourished or neoplastic patients undergoing surgery as they may be suffering from impaired wound healing.

Even if not supported by strong evidence, there are also some reports on the use of NIV in patients with burns [73].

8.3 HFNT: Mechanism of Action

HFNT can improve dyspnea and arterial blood gases and ameliorate the patient's comfort through multiple mechanisms [74–78].

8.3.1 Improvement of Pharyngeal Oxygen Concentration in Patients Undergoing Oxygen Therapy

The maintenance of an adequate oxygenation depends on the FiO_2 management. Oxygen is usually provided by a face mask or nasal prongs with a flow up to 15 L/min. Using these conventional methods, there may be a significant difference between patient's inspiratory flow and the provided O_2 flow resulting in a difficult FiO_2 control.

HFNT by delivering a flow that is higher than the patient's inspiratory peak flow reduces air entrainment, providing a more stable FiO_2 [79–81].

8.3.2 Mucociliary Clearance Improvement

High flow of non-adequately humidified oxygen [82] can cause mouth, nose, and upper airway dryness, thus generating patient's discomfort [83]. HFNT may improve airway humidification, mucociliary clearance, and lastly patient's comfort [84, 85].

8.3.3 Reduction of the Metabolic Requirements Needed for Gas Conditioning

During normal ventilation, the nose heats inspired air up to 37 °C and humidifies incoming gas saturating it with 100% of relative humidity (RH). This process implies an energetic demand, which can be reduced by the use of HFNT [86–88].

8.3.4 Reduction in Respiratory Resistances

HFNT can reduce inspiratory resistance through:

(a) A delivery of a gas flow which is higher than the patient's peak flow [98].
(b) A nasopharyngeal splinting by activation of nasal muscles [89, 90].
(c) A reduction of the muscarinic bronchial constriction reflex caused by cold air inhalation [91, 92].

8.3.5 Expiratory Resistance Increase (PEEP Effect)

HFNT doesn't provide CPAP [90] and therefore it has no the same clinical effects.

However, if the size of the nasal prongs is correct (about two-thirds of the nostril surface should be occupied by the prongs) and the delivered flow are adequate, a positive end-expiratory pressure is delivered (EPAP/PEEP). This pressure is generated by an increase in expiratory resistance. Since the nasal prongs are an open system, the pharyngeal pressure cannot be high [93]. Nonetheless it remains high enough to increase end-expiratory lung volume (EELV) [94].

Moreover the respiratory frequency is reduced due to an increase of the expiratory time (inspiratory time remains unchanged) [90] in a way that is similar to the pursed lip breathing [95] typical of the COPD patient.

8.3.6 Nasopharyngeal Dead Space Washout

At the beginning of inspiration, the pharyngeal dead space contains end-expiratory gas. This dead space contributes to the heating and humidification of inspired air, but at the same time, it reduces the efficacy of gas exchange. HFNT reduces the dead space in the nasopharyngeal cavity by delivering a fresh gas flow [96, 97].

As a consequence patients with pulmonary fibrosis or COPD have less need to raise their alveolar ventilation to reduce the CO_2. Finally all of this would bring to an improvement of the respiratory efforts [98–103].

HFNT has been found to be associated with a significative reduction in respiratory frequency, cardiac frequency, dyspnea, supraclavicular retractions, thoracoabdominal asynchrony, and an improvement of the SpO_2 [76–78, 81, 104].

The application of HFNT has gained a particular attention as a mean of innovative respiratory support both in the critical and noncritical care setting [75, 76, 84, 105–110].

The interface of HFNT, being commonly a simple nasal prong, could improve patient's comfort and reduce skin lesions [111] when compared to NIV interfaces. Furthermore it has the advantage of delivering an optimal humidification [83].

Although HFNT is often thought to be a therapy designed to deliver high-flow oxygen therapy, most of its physiopathological effects can be achieved at FiO_2 0.21.

HFNT should be administered both titrating flow temperature and FiO_2 separately. To match patient's inspiratory flow, the delivered flow should be set as higher as possible, up to 60 L/min [76]. Temperature also seems to significantly impact patient's comfort. It was recently found that for unchanged flow rate, lower temperature may be associated with better comfort [78].

8.4 HFNT in Perioperative Medicine

8.4.1 HFNT After Extubation

Oxygen therapy is frequently used in the postoperative period as well as to correct post-extubation desaturation events [112].

When a support is needed, during the postoperative period, NIV use may be difficult because patient cannot tolerate the interface [111, 113–115] or because of proper clinical setting, delirious patients [116], or lack of resources [115].

Due to its positive effect on the respiratory system, HFNT could be an interesting tool, although not clarified yet, to prevent atelectasis and to improve oxygenation [38].

Furthermore, it could avoid re-intubation of patients often associated with an increase in ICU length of stay and mortality rate [117, 118]. However there is still a scant evidence of the use of HFNT because not all the studies were carried out in the ICU.

Compared to a non-rebreathing mask, the application of HFNT after extubation has shown to reduce the level of dyspnea and the respiratory and cardiac frequency [104].

A small randomized study comparing high flow delivered via nasal prongs or facial mask after extubation found no significant differences in gas exchange, respiratory frequency, or hemodynamic parameters [119].

However, in a retrospective study including 67 critical patients after extubation and comparing HFNT clinical effects to non-rebreathing mask [120], the authors found a better oxygenation (measured as PaO_2/FiO_2 ratio) with the use of HFNT; no significative differences were found in $PaCO_2$, respiratory frequency, mean arterial pressure, or cardiac frequency.

A recent randomized controlled study [121] comparing the effects of conventional oxygenation (52 patients) and HFNT (53 patients) in patients with moderate hypoxemia ($PAO_2/FiO_2 < 300$ before extubation) found that HFNT therapy improved oxygenation, reduced $PaCO_2$ and respiratory frequency, and improved patient's comfort and interface tolerance (starting from the 12th hour). Moreover, the HFNT group was found to be associated with less desaturation events or interface displacement.

Another randomized study (O_2 low flow vs. HFNT), whose primary outcome was the re-intubation rate after 72 h from the extubation, found that HFNT significantly reduced re-intubation rates in critical patients at low risk of extubation failure [122].

The same authors in a non-inferiority randomized controlled study comparing HFNT and NIV administered for 24 h after extubation evaluated the incidence of post-extubation ARF and re-intubation in 604 patients at high risk of re-intubation: 22.8% in HFNT vs. 19.1% (*n*:60) in the NIV group did not require re-intubation. However, 78 (42.9%) of patients in the NIV group vs. none in HFNT group presented adverse effects [123].

One multicenter randomized study aimed at proving that HFNT was not inferior to NIV in preventing ARF after cardiothoracic surgery [124]. The primary outcome was failure of treatment, intended as re-intubation or premature interruption due to adverse events or patient's request. Results showed that HFNT was not inferior to NIV. HFNT treatment was unsuccessful in 87 out of 414 patients (21%) vs. 91 out of 416 (21.9%) in the NIV group.

Futier et al. conducted a multicenter randomized trial (OPERA STUDY) which aimed at comparing postextubation use of HFNT versus standard oxygen in patients scheduled for major abdominal surgery with moderate to high risk for developing PPCs. The study did not find a reduction in the risk of developing postoperative pulmonary complications [125]. The primary outcome was the presence of hypoxemia, while the secondary end points were the presence of PPCs within 7 days after surgery, hospital length of stay, and in-hospital mortality. The proportion of patients who presented hypoxemia at 1 h after extubation was similar (21% in the HFNT group vs. 27% in the control group) as well as the incidence of PPC.

8.4.2 Preinduction Oxygenation

Preoxygenation prior to intubation is a crucial step with allows a longer safe apnea time [126, 127]. Generally an oxygenation through mask is advised before intubation in any clinical settings [128, 129], but differently from patients with normal lungs, hypoxemic patients are prone to severe oxygen desaturation which reduce oxygen stores [126, 130].

NIV has also been found to be an interesting tool to increase oxygen reserve prior to intubation [126, 127].

However, since NIV has to be interrupted during laryngoscopy, this technique cannot prevent desaturation during tracheal intubation. HFNT nasal prongs do not interfere with the laryngoscope maneuver. Indeed this device can be used to provide oxygen during the apnea period before tracheal intubation studies carried out in ICU in hypoxemic patients gave however conflicting results [38, 131, 132].

These conflicting results could be explained by the differences about the reason for intubation and the severity of hypoxemia. A recent study [133] evaluated the effect of a supplementary oxygenation with HFNT during laryngoscopy (against no oxygenation) in 150 critical patients. The lowest oxygen saturation with HFNT was 92% against 90% with conventional therapy without supplemental oxygen ($p = 0.16$). No differences about the incidence of desaturations under 90%, 80%, or an oxygen saturation reduction of >3% have been reported.

Further studies are needed to draw a conclusion on how effective is this device, specifically in ICU setting, compared to NIV or traditional oxygen therapy, especially in hypoxemic patients.

A recent study (OPTINIV study) [134] evaluated HFNT combined with NIV versus NIV alone for the preoxygenation and the prevention of desaturations during the intubation maneuver in hypoxemic patients who needed mechanical ventilation. The OPTINIV study showed that HFNT combined with NIV, if compared to NIV alone, allowed SpO_2 values significantly more elevated during the intubation maneuver.

HFNT use was also found to be safe and improved oxygenation while avoiding hypercapnia in 50 patients at risk of difficult intubation during awake fiber-optic intubation. Tolerance was also found to be good [135].

Heinrich et al. conducted a randomized controlled study on 33 patients, testing three preoxygenation techniques before rapid sequence tracheal intubation in morbidly obese patients undergoing bariatric surgery. HFNT (50 L/min at FiO_2 1) was compared to CPAP (7 cmH_2O at FiO_2 1) and to traditional treatment (12 L/min in facial mask at FiO_2 1). Primary outcome was PaO_2. HFNT significantly improved PaO_2 at 5 and 7 min during the preoxygenation/induction period as compared to the traditional method and provided an oxygenation comparable with the CPAP method. The authors concluded that HFNT was an effective and safe preoxygenation method in this group of patients [136].

Patel and colleagues demonstrated how a transnasal humidified rapid insufflation ventilatory exchange (THRIVE) technique can improve the apnea time in patients with difficult airways who have to undergo general anesthesia [137]. Patients receiving surgery for laryngeal-tracheal stenosis, vocal cord pathologies, obstructive sleep apneas, and benign or malignant hypopharyngeal obstruction were treated with HFNT at 70 L/min for 10 min before endogenous induction of anesthesia and laryngoscopy. Independently from the number of laryngoscopies or the presence of a difficult intubation, the nasal oxygenation at 70 L/min was maintained during the entire maneuver until a definitive and safe airway was achieved. The apnea time was defined as the time between the administration of the neuromuscular blocker and the initiation of positive pressure ventilation or the restart of spontaneous breathing. The authors recorded the maximum cardiac frequency, the minimum oxygen saturation value during the apnea time, and the first value of end-tidal CO_2 ($EtCO_2$) after the endotracheal tube placement and the connection to the mechanical ventilator.

This study showed that the use of THRIVE led to a more safe apnea time in patients with difficult airways who needed general anesthesia. No desaturations under 90% were recorded in spite of a mean 17 min apnea time. None of the patients developed cardiac arrhythmias or any other complication due to CO_2 toxicity [138, 139].

Raineri et al. assessed the efficacy and safety of HFNT at 60 L/min and FiO_2 of 1, in urgent abdominal surgery patients scheduled for rapid sequence intubation (RSI). HFNT was maintained for 4 min before induction and kept until ETI [140].

SpO_2, mean arterial pressure, and heart rate were assessed different times: at baseline (T0), after 4 min on HFNT (T1), during laryngoscopy maneuver (T2), and at the time of endotracheal intubation (T3). Primary end point were the episodes of

SpO_2 value of <3% from baseline. SpO_2 values <3% from baseline were never found in any patient. Minimal SpO_2 value was 96%. End-tidal CO_2 ($ETCO_2$) at T3 was 36 mmHg. Apnea time reached a maximum of 12 min.

8.5 Conclusion

NIV represents a useful noninvasive support in preoperative medicine [141]. However, HFNT may have some advantages over NIV. It is probably easier to apply and needs less patient's cooperation and less equipment. Lastly it may generate a smaller amount of workload. It is also important to consider that HFNT seems to be tolerated and doesn't seem to be inferior to NIV in terms of clinical results in patients as first-line therapy with hypoxemic respiratory failure [142].

However, differently from CPAP, it does not generate the same end-positive airway pressure to cure atelectasis once they have developed [79]. HFNT possibly needs less surveillance than NIV. However, even more than NIV, it needs a strict monitoring to avoid an intubation delay [143].

Perioperative application of NIV and HFNT should always be considered together with all the effective tools like physiotherapy, smoking cessation, and optimization of the preoperative clinical picture.

Finally, literature suggests that despite these promising properties, the use of HFNT in perioperative medicine still needs further high-quality randomized studies.

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Part II

Intensive Care

Diagnosis and Management of Sepsis and Septic Shock: An Evidence-Based Review

9

Giorgio Tulli

In 2016, the new definitions of sepsis and septic shock were published in the JAMA journal [1–3].

Sepsis is defined as a life-threatening organ dysfunction due to a dysregulated host response to the infection.

Septic shock is defined as a subset of sepsis with circulatory, cellular and metabolic dysfunction associated with a higher risk of mortality compared to sepsis alone.

In the previous 1992 and 2003 definitions, sepsis was defined as a suspected, probable or certain infection that was accompanied by at least two out of four SIRS (systemic inflammatory response syndrome) criteria [4, 5]. Sepsis was shown as a continuum that went from sepsis (infection plus SIRS) to severe sepsis (sepsis plus at least one organ failure) to septic shock (sepsis with arterial hypotension in spite of adequate fluid provision).

Currently the new definition abolishes this continuum and defines sepsis as an infection that becomes complicated due to the "dysregulated host response to the infection", generating organ failure that is life-threatening. The new definitions remove the SIRS as they are too sensitive and lacking in clinical specificity and also remove severe sepsis as it is considered to be redundant.

Systemic inflammatory response syndrome was diagnosed when at least two of the criteria shown in Fig. 9.1 were found [the SIRS criteria did not include MAP—mean arterial pressure or SBP-systolic blood pressure—but did include fever, heart rate and the white blood cell count].

Yesterday, like today, there must be the suspicion or certainty of infection to make a sepsis diagnosis. Today, with the new definition (Fig. 9.2), to diagnose sepsis or organ dysfunction, all we need is the SOFA score, a score that tells us whether

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1991 Criteria for sepsis, severe sepsis and septic shock

The following definitions derive from the 1991 Consensus Conference of the American College of Chest Physicians and Society of Critical Care Medicine 2, 162. Infection is defined as the presence of microorganisms or tissue invasion by those microorganisms.

Sepsis

The systemic inflammatory response (SIRS) to infection, manifested by at least two of:

- **Temperature of >38 °C or <36 °C**
- **Heart rate of >90 beats per minute**
- **Respiratory rate of >20 breaths per minute or partial pressure of CO2 of <32 mmHg**
- **White blood cell count of >12,000 per ml or <4000 per ml, or >10% immature (band) forms**

Severe sepsis

Severe sepsis is defined as sepsis associated with organ dysfunction, hypotension or hyperfusion. Hypoperfusion abnormalities of end organs may include lactataemia, oliguria or an alteration in mental status.

Septic shock

Septic shock is defined as sepsis associated with hypotension and perfusion abnormalities despite the provision of adequate fluid (volume) resuscitation. Perfusion abnormalities include lactic acidosis, oliguria or an acute alteration in mental status. Patients with septic shock who are receiving inotropic or vasopressor therapy might still exhibit perfusion abnormalities, despite the lack of hypotension.

Fig. 9.1 1991 Criteria for sepsis, severe sepsis and septic shock

Proposed criteria for sepsis and septic shock

This proposal stems from the 2015 Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3), which considers infection to be an interaction between a host and a pathogen that induces a local or systemic host response.

Sepsis

- Life-threatening organ dysfunction owing to a dysregulated host response to infection
- Onset marked by the beginning of any organ dysfunction remote from the site of infection

Septic shock

- A subset of sepsis in which underlying circulatory and cellular–metabolic abnormalities are profound enough to substantially increase mortality
- Operationally defined as requiring vasopressor therapy to maintain a mean arterial blood pressure of >65 mmHg and an increased plasma lactate level of >2 mmol/L

Fig. 9.2 New definition of sepsis and septic shock (Sepsis-3)

there is organ dysfunction, but in the context of which the body temperature is not taken, the heart rate and breathing rate do not appear, and the white blood cell count is not taken, criteria that, even if a specific, have always been considered useful, together with other clinical signs and symptoms, for making the diagnosis of infection (or at least for suspecting an infection).

The SOFA score therefore underlines the importance of organ failure contained in the new definition, but does not make one immediately reflect on the infection, as SIRS does instead.

As the SOFA score requires some laboratory data, it was believed appropriate to run the quick SOFA (qSOFA) alongside the SOFA score, which provides for three simple, rapid factors (breathing rate >22 breaths/min, systolic pressure <100 mmHg

and altered mental state—0 = mortality <1%, 1 = mortality 2–3%, >2 mortality >10%), but yet again does not include body temperature or heart rate or even the white blood cell count.

All the definitions must have a clinical suspicion of infection or microbiological certainty of the infectious pathogen(s) at the basis, but while useful indicators of infection were contained in the 1992 and 2003 definitions, they disappear in the new definition that focuses completely on infection complications, i.e. on organ failure.

Why was it decided it was necessary to change over from the SIRS criteria to the SOFA score?

The 1992 ACCP/SCCM Consensus Conference generated the old definition which was then taken up by the Surviving Sepsis Campaign guidelines published in 2003, 2008 and 2012. These definitions of sepsis and septic shock had shown good clinical resistance over the years (at least 20 years) and had proved useful for hospitals and research. However, over the past 20 years, their use showed that the SIRS definition could be overly sensitive and non-specific.

In 2006, a critical review of some European Intensive Care Units [6] showed that the SIRS criteria were 100% sensitive but only 18% specific. In 2012, a prospective observational study carried out in Holland [7] showed that even minor changes to timing and the SIRS criteria capture method, for example, manually rather than automatically capturing, significantly changed the measured incidences of sepsis. This study showed that from 6% to 17% (depending on the SIRS criteria capture system) of the infected patients in Intensive Care did not meet the SIRS criteria. SIRS criteria are so sensitive that more than 90% of patients admitted to Intensive Care meet these criteria [8].

More recently, a study of 14 years of work in New Zealand Intensive Care Units [9] highlighted significant potential problems with the definition of sepsis. This study found that the SIRS criteria were lost in one out of eight patients with serious infections and that these lost cases were associated with substantial morbidity and hospital mortality. More specifically, "SIRS-negative" septic patients still had high percentages of organ failure, with 42% affected by septic shock, 55% requiring mechanical ventilation and 12% with acute kidney failure. Also, when compared to "SIRS-positive" septic patients, the "SIRS-negative" septic patients had a lower but still substantial hospital mortality (16% versus 23%). These data have raised the problem of the use of the SIRS component of sepsis diagnostic criteria in helping with early recognition and with early treatment of severe infections that are complicated by organ failure. By defining sepsis as the presence of SIRS criteria plus an infection and emphasising what was said previously, i.e. that almost all critical patients satisfy the SIRS criteria, sepsis is the same as having an infection, but if it is true that all patients with sepsis have an infection, the contrary is not necessarily true, i.e. that all patients with an infection have sepsis. In a few words, SIRS criteria are extremely sensitive but not very specific [9, 10].

This is the context in which the task force from the third "International Consensus Conference" on the definitions of sepsis proposed new criteria that were then shared for the first time in the 2016 Surviving Sepsis Campaign guidelines [11].

However, many clinicians and the Surviving Sepsis Campaign still see the SIRS criteria as a useful tool for identifying the infection and for suspecting the infection, but no longer use them as criteria for defining sepsis.

The quick SOFA score and the SOFA score have been, respectively, introduced as screening tools (the former) and as clinical diagnostic criteria for sepsis (the latter). The term sepsis has been removed, and septic shock has been defined as persistent hypotension that requires the use of vasopressors with elevated serum lactate (>2 mmol/L) in spite of fluid resuscitation.

The authors of the new definition acknowledge that simplicity, outcome prediction, test weighting and pathobiology were all taken into consideration for the burdensome task, a true challenge, of deriving the clinical criteria for a syndrome with different aetiologies and without any diagnosis confirmation test, without a gold standard.

Initial performance assessment showed an improved prediction of by SOFA and qSOFA of intra-hospital mortality compared to the SIRS criteria, with criteria met in 67%, 70% and 55% of deaths with initial, clinically suspected infection in Intensive Care with SOFA and outside Intensive Care (e.g. in the emergency department) with qSOFA [12, 13]. While these new criteria have improved predictive ability, they are also used as a reminder for caution that the necessary trust in a definition, that is, syndromic rather than pathologically defined, will continue to introduce errors of misclassification in epidemiological surveillance. In fact, some researchers have studied [14] the incidence of SIRS and qSOFA, on a population of emergency department patients with suspected severe infection, basing their studies on the new sepsis definitions and the overlap with mortality. Of the patients who died, eight out of 276 (2.9%) were identified by qSOFA alone, 101 out of 276 (36.5%) by the SIRS criteria alone and 128 out of 276 (46.4%) by qSOFA and SIRS, and 39 out of 276 (14.2%) did not meet either one or the other criteria. Among the patients with infections in the emergency department who died during hospitalisation, the SIRS criteria showed greater sensitivity than among the patients who survived, the SIRS criteria showing greater ability in identifying the risk of death (higher specificity). The qSOFA in this study identified 21% fewer patients with infection who died while hospitalised.

The definition of sepsis has changed, but the suspected or certain infection remains the crux of the problem. The fundamental enigma in the field of infectious diseases is the huge clinical variability among individuals during the course of the same infection [15].

An infectious (or contagious) illness is defined as an illness caused by a specific infectious agent or by its toxic products that result from the transmission of that agent or its products from another infected person, animal or other reservoir to a susceptible host, either directly or indirectly, via vegetable or animal host and a vector or even an inanimate environment. An infection is on the other hand the dynamic term that defines the entry and development of an infectious agent into a human being or animal body, whether the illness develops of not. When we are faced with infections, we must try to define them from where they manifest themselves as

community or nosocomial infections, defining their paths and the risks connected with their deterioration.

An infection may only be suspected at home or at the entrance to hospital (triage in the emergency department). The suspected infection is a clinical case in which the signs and symptoms that a person is showing are consistent and compatible with a particular infectious illness. The patient may be severe or become more severe during observation; therefore the SIRS criteria, or their systemic involvement, become important at two or more of the following: heart rate >90 beats/min, breathing rate >20 breaths/min, body temperature >38 °C or <36 °C (hypothermia), white blood cells >12/mm^3 or <4/mm^3, or >10% band form, presence of pus or inflamed tissue and presence of skin marbling. The qSOFA is fast and frugally indicates organ impairment breathing rate, hypotension and altered mental status that cause us to go immediately to the hospital.

An improbable infection combined with a positive microbial culture constitutes a colonisation (today important to know due to multiresistant bacteria).

An infection can only be considered not probably or probable and then be confirmed in the emergency department, or on the ward, or in Intensive Care via the microbiological path.

This category of probable infections may include the expert opinion accompanied by positive biomarkers (e.g. PCT) but sometimes also by non-pathogenic germ cultures. Therefore, a suspected or probable infection in hospital must always be confirmed microbiologically and become a possible certain infection as soon as possible.

However, in all this complexity and variability, there is a new exceptionally important problem: time passing.

The real problem: an infection that deteriorates to the point of sepsis and septic shock happens in the space of a few hours. Sepsis and septic shock are real medical emergencies.

Different doctors and different healthcare organisations are working on this "Sepsis Path" but it is the same patient experiencing it. Care and assistance must be integrated to respect time, to avoid wasting time and to avoid allowing wasted time to further complicate the infection.

Physiological changes, location and confirmation of the infection, investigations, determination of the gravity, target treatment and revision and personalisation of the treatment are all steps in a row, that is, the classic Bayesian approach to diagnosis and treatment of the infection.

The infection is the crux and TIME is the fundamental problem for diagnosis and treatment.

Infection is a dynamic process. It can be resolved, it can stabilise, or it can deteriorate to sepsis. Without cultures or with sterile cultures when a doctor strongly suspects the infection, the day of infection will be defined as the day on which suspicion of the infection starts. With positive cultures, on the other hand, the day of infection is the day on which the sample is found positive in microbiology.

But why does an infection deteriorate? What is an infection that deteriorates and when does an infection deteriorate? Is a particular infection that deteriorates easier than another?

Four complementary theories contribute to creating the infectious phenotype and consequently the septic phenotype: *germ theory* (microbiology allows us to know microbiological variability in quantitative and qualitative terms); *ecological theory* that allows us to know environmental variability; *immunological theory* that allows us to learn the host's response, deficiencies in somatic, adaptive (both genetic and epigenetic) acquired immunity; and *genetic theory* with inherent errors of germ-line encoder immunity (both inherent and adaptive) (Fig. 9.3).

Always think of sepsis when suspecting an infection. When should you think it? When a person shows signs and symptoms that indicate a possible infection that is deteriorating with organ failure or shock. Always take into consideration those people with sepsis who may show non-specific, non-located signs, for example, feeling extremely ill and not having a fever and having normal white blood cells. Pay special attention to the problems raised by one person or by the family or carers, for example, changes in usual behaviour and altered mental state. Assess people who may have sepsis with greater attention if they can't communicate easily (e.g. Italian is their second language or people with communication problems). Assess people with any suspected infection to identify the possible source or infectious factors that increase the risk of sepsis, every clinically important indication such as sudden changes in behaviour, circulation and breathing. Use a structured observation set to

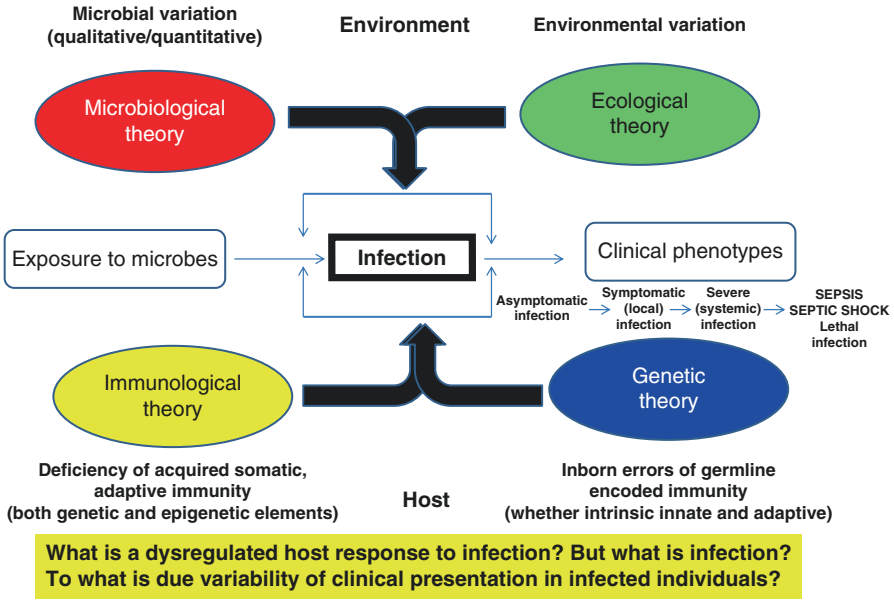


Fig. 9.3 Infectious disease is a complex disease. The four complementary theories of an infectious disease

assess people and to stratify risk if sepsis is suspected. Consider using an "early warning score" to assess people with suspected sepsis in acute hospital settings (medical or surgical wards, mother-infant setting). Suspect neutropenic sepsis in patients who are having cancer treatment and suddenly don't feel well. Take these patients immediately to the emergency department for a hospital assessment.

What can the sepsis risk factors be?

Here are the main ones: very young infants (under 1 year of age) or the elderly (over 75 years of age) or extremely fragile subjects. People with a damaged immune system due to illness or drugs taken also include people treated with chemotherapy for cancer in this group. People who have damaged immune functions; people who have taken steroids for a long time; people who take immunosuppressor drugs for non-tumoural diseases such as rheumatoid arthritis; people who have undergone surgery or other invasive procedure in the last 6 months; people who have skin lesions, for example, cuts, burns, blisters or skin infections; people who use intravenous drugs; and people who wear intravenous catheters or other types of catheter (Fig. 9.4).

Sepsis and septic shock must be recognised and treated rapidly otherwise mortality and morbidity increase. Sepsis is a systemic infection that goes bad to organ failure (Fig. 9.5).

The host's responses to severe infection are complex and multiple. Recent studies show that activation of both pro-inflammatory and anti-inflammatory immune responses occurs immediately after the onset of sepsis. The inherent immune system cells, including monocytes and neutrophils, release large amounts of pro-inflammatory cytokines that activate inflammation. The intensity of the initial

Risk factors for developing sepsis

Age
- Very young (<2 years of age)
- >55 years of age

Chronic and serious illness
- Cancer
- Diabetes
- Chronic obstructive pulmonary disease
- Cirrhosis or biliary obstruction
- Cystic fibrosis
- Chronic kidney disease
- Congestive heart failure
- Collagen vascular disease
- Obesity

Impaired immunity
- Transplantation
- Chemotherapy
- Radiation therapy
- Drug-mediated immune suppression
- Blood transfusions

Breach of natural barriers
- Trauma
- Surgical injury
- Catheterization or intubation
- Burns
- Enterocolitis

Chronic infections
- HIV
- Urinary tract infections
- Pneumonia
- Decubitus or non-healing dermal wounds

Other
- Protein calorie malnutrition

Fig. 9.4 Risk factors for developing sepsis

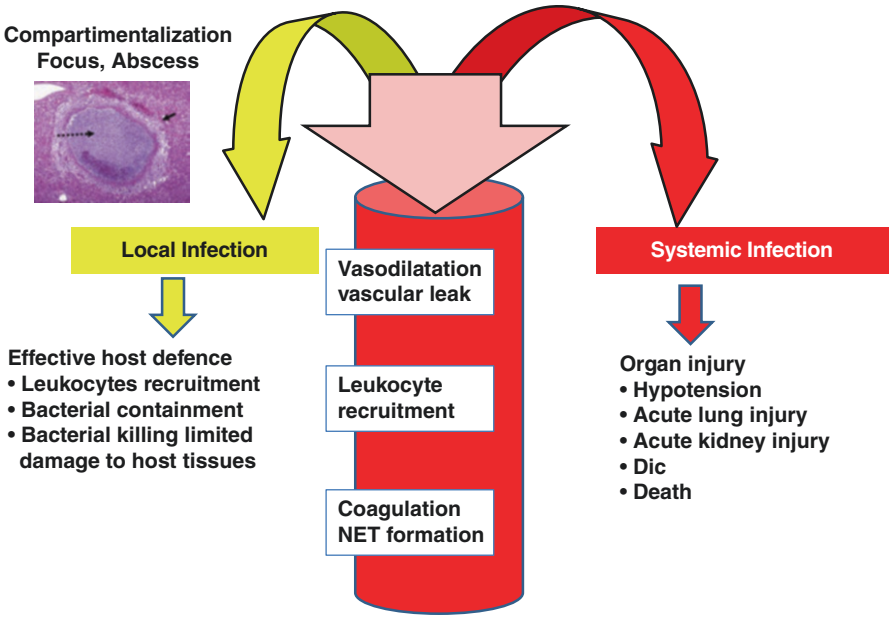


Fig. 9.5 Pathophysiology of local infection and systemic infection

inflammatory response can vary in each patient, depending on several factors including pathogen load and virulence, co-morbidity in patients and the host's genetic factors. Early deaths in sepsis are usually due to a hyperinflammatory cytochemical storm, with fever, refractory shock, acidosis and hypercatabolism. One classic example of this could be that of a young patient who dies from toxic shock syndrome or from meningococcemia. Most patients have an inherent, adaptive immunity recovery and survive infection usually between the fifth and sixth day. If sepsis persists, there is an insufficiency of critical elements in both the inherent immune system and the adaptive system, so that the patient enters a deep immunosuppressive state. Deaths are due to the patient's inability to eliminate the infections and to the development of secondary infections. The most accredited pathophysiology is the one that even if both pro-inflammatory and anti-inflammatory responses begin together rapidly after sepsis, the initial response in previously health patients is usually an important hyperinflammatory phase with fever, hyperdynamic circulation and shock. Deaths in this early phase are usually due to cardiovascular collapse, metabolic alterations and multiple organ dysfunctions. Although no anti-inflammatory therapy has been found to improve survival in large clinical trials, short-acting anti-inflammatory or anti-cytochemical therapies could still offer a theoretical benefit [16–18].

Many patients that develop sepsis are however elderly with several comorbidities that contribute to altering the already altered—by their very age—immune response.

When these individuals develop sepsis, it is common to see that the hyperinflammatory stage is of reduced intensity or even absent, and the patients rapidly develop altered immunity, an actual anti-inflammatory state.

In these situations, which nowadays are increasingly more frequent, an immune adjuvant therapy that can strengthen their immune response is rather promising.

Another immunological response to sepsis may be cycling between hyperinflammatory and hypoinflammatory states. According to this theory, patients that develop sepsis have an initial hyperinflammatory response followed by a hypoinflammatory state. When patients develop a new secondary infection, they have a repeated hyperinflammatory response and can either recover or return to the hypoinflammatory phase. Patients can die in either of the two states. There is not much scientific evidence for this theory, and the longer sepsis continues, the more likely it is that the patient develops a severe immunosuppression.

Due to their advance aged (immuno-senescence) and due to their comorbidities and the specific treatments for said comorbidities, and also due to highly pathogenic, antibiotic-resistant bacteria, many patients are immunodepressed or even immunoparalysed [19].

Sepsis has several, deep effects on all cells that make up the inherent immune system. Sepsis rapidly gives rise to the onset of widespread apoptosis of dendritic cells, monocytes and immature macrophages and natural killer cells and "myeloid-derived suppressor cells" (MDSC). The reduced expression of HLA-DR on cells with the antigen that include monocytes/macrophages and dendritic cells is a true distinguishing sign of sepsis that can harm the optimal presentation of microbial antigens to T cells. Sepsis also causes massive losses of CD4+ e CD8+ cells and B cells. T-regulatory (Treg) cells are more resistant to apoptosis induced by sepsis, and there is therefore an increased percentage of Treg cells in circulation compared to the other lymphocyte subsets. This contributes to a more immunosuppressive phenotype. The CD4+ e CD8+ cells that survive have either a shift from one pro-inflammatory Th1 cell phenotype to an anti-inflammatory Th2 cell phenotype or develop a thorough phenotype characterised by an increased expression of "programmed cell death 1" and reduced cytokine secretion. CD4+ T cells have a reduced expression of CD28 and a reduced receptor diversity for the T cell (TCR) that likely both contribute to the damaged microbial response to invading pathogens.

It has recently been shown that patients with sepsis can develop—if they survive the acute phase but do not recover from organ failure—a so-called persistent critical illness (PCI) [19–21] with clear organ failure that lasts for weeks and months. In the past, these patients would have died, but today they survive due to organ support and therapies provided to them. Death from persistent critical illness is 20–40%, and survivors are frequently handicapped in their cognitive functions, with neuropathies and myopathies, immune dysfunction and other serious complications.

Sepsis is an immunopathology; very early administration of antibiotics, fluids and oxygen (SEPSIS Bundles and SEPSIS SIX) (Figs. 9.6, 9.7, and 9.8) to patients with sepsis has lowered the percentage of mortality, even if this has not prevented or overturned the development of persistent critical illness that is often associated with immunosuppression. Sepsis and persistent critical illness may also not be

SSC 3 and 6 h bundle

To be completed within 3 h of time of presentation*

1. **Measure lactate level**
2. **Obtain blood cultures prior to administration of antibiotics**
3. **Administer broad spectrum antibiotics**
4. **Administer 30 mL/kg crystalloid for hypotension or lactate ≥4 mmol/L**

* "time of presentation" is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements severe sepsis or septic shock ascertained through chart review.

To be completed within 6 h of time of presentation

5. **Apply vasopressors (for hypotension that does not respond to initial fluid resuscitation to maintain a mean arterial pressure (MAP ≥65 mmHg) (GRADE 1C)**
6. **In the event of persistent arterial hypotension despite volume resuscitation (septic shock) or initial lactate ≥4 mmol/L (36 mg/dL):**
   - **Measure central venous pressure (CVP)***
   - **Measure central venous oxygen saturation (ScvO2)***
7. **Re-measure lactate***

* **Targets for quantitative resuscitation included in the guidelines are CVP of ≥8 mmHg (higher with altered ventricular compliance or increased intrathoracic pressure) ScvO2 of ≥70% and lactate normalization (lactate clearance – GRADE 2C)**

Fig. 9.6 Sepsis bundles 3 and 6 h (SSC 2004/2008/2012)

SSC Bundle 1 h (2018)

- Measure lactate level. Remeasure if initial lactate is >2 mmol/L
- Obtain blood cultures prior to administration of antibiotics
- Administer broad spectrum antibiotics
- Begin rapid administration of 30 mL/Kg crystralloid for hypotension or lactate ≥4 mmol/L
- Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mmHg
- *"Time Zero" or "Time of Presentation" is defined as the time of triage in the Emergency Department or, if presenting from another care venue, from the earliest chart annotation consistent with all elements of sepsis (formerly severe sepsis) or septic shock ascertained through chart review*

Bundle element	Grade of recommendation and level of evidence
Measure lactate. Remeasure if initial lactate >2 mmol/L	Weak recommendation, low quality of evidence
Obtain blood cultures prior to administration of antibiotics	Best practice statement
Administer broad spectrum antibiotics	Strong recommendation, moderate quality of evidence
Begin rapid administration of 30 mL/Kg crystralloid for hypotension or lactate ≥4 mmol/L	Strong recommendation, low quality of evidence
Apply vasopressors if patient is hypotensive during or after fluid resuscitation to maintain MAP ≥65 mmHg	Strong recommendation, moderate quality of evidence

Fig. 9.7 SSC bundle 1 h (2018) and grade of recommendation and level of evidence of bundle elements

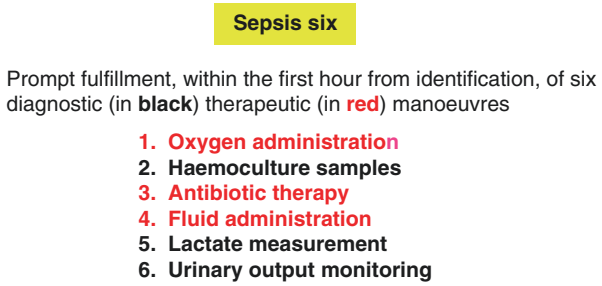


Fig. 9.8 SEPSIS SIX (1 h) Daniels R, Nutbeam T, McNamara G, Galvin C. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. Emerg Med J. 2011; 28(6):507–12

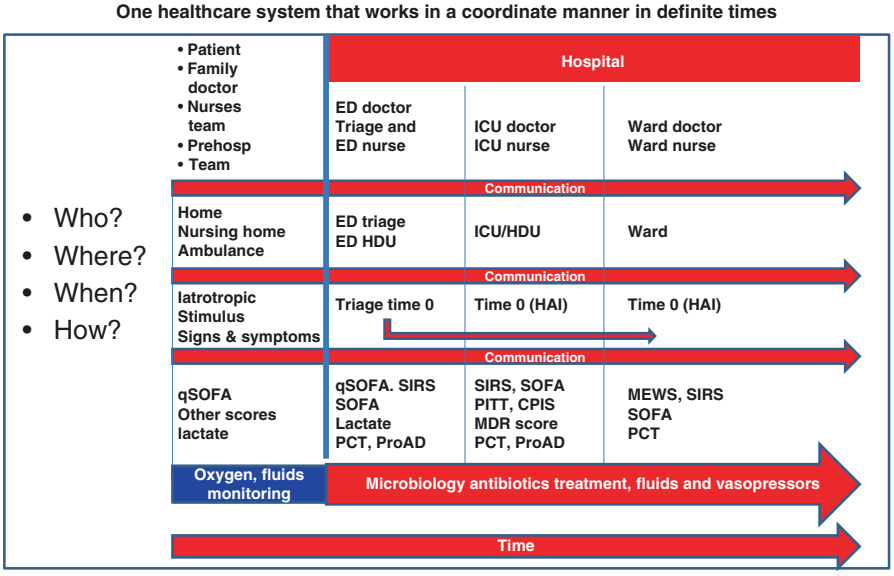


Fig. 9.9 Fully embrace and quantify the uncertainty in a septic condition. Suspicion and early diagnosis of infection and sepsis quick shift from suspected infection to confirmed infection

immunopathologies but be the failure to recover homeostasis that results in dysfunction of the immune and neuroendocrine system: the two major systems that maintain healthy intercommunication between the organs. The components pertaining to efferent to both the systems are damaged in sepsis and in persistent critical illness via molecular and cellular mechanisms that are currently the focus of active research.

The limits of this new definition of sepsis emerge in all current scientific evidence, together with deep uncertainty (Figs. 9.9 and 9.10).

Doctors and nurses need a less controversial and less confused definition. They need it to be made operational like a set of clinical criteria that can be used to make clinical decisions and even guide them in testing and using therapies that can modulate the host's response. The first task requires identification of specific diagnostic criteria, others a further refinement of these criteria via true therapeutic stratification.

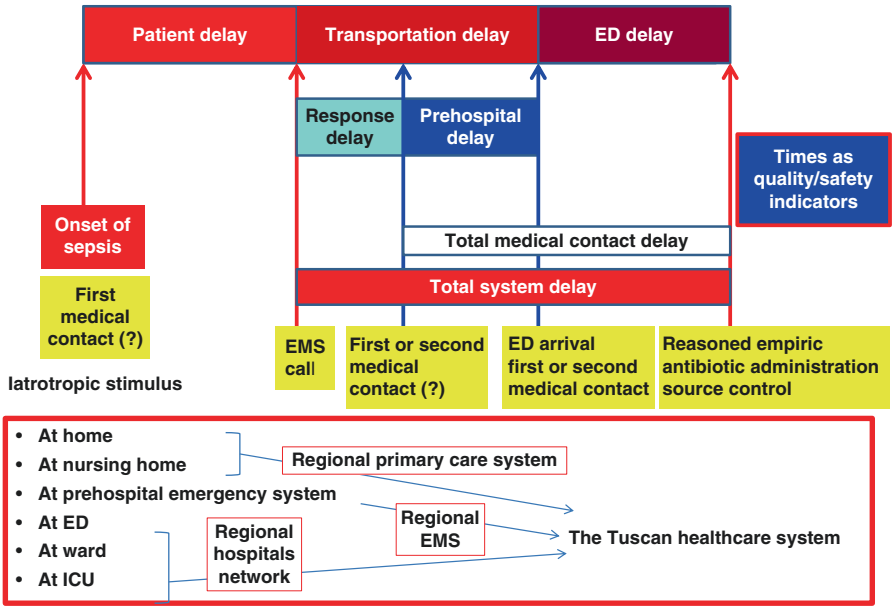


Fig. 9.10 Infection and sepsis integrated care in the time dominion. A systematic vision of sepsis in Tuscany Region (Italy)

We don't currently screen patients for sepsis; instead we search for diagnostic tests that can establish or exclude diagnosis in a patient with early and non-specific signs of acute illness. The critical question is: what are we trying to diagnose?

Sepsis is a complex structure that incorporates both causes, infection and the consequent complications: development of a life-threatening organ dysfunction and thus the diagnostic criteria for sepsis could address four different needs:

(a) DIAGNOSING THE INFECTION AT AN EARLY STAGE, so that we can treat it suitably and thus prevent organ dysfunction.
(b) IN PATIENTS WITH SUSPECTED OR KNOWN INFECTION, IDENTIFY THE ONES THAT HAVE AN INCREASED RISK OF DEVELOPING LIFE-THREATENING ORGAN DYSFUNCTION, so that we can monitor them better and intervene earlier.
(c) IDENTIFY THOSE PATIENTS WITH EARLY ORGAN DYSFUNCTION THAT ARE AT A HIGH RISK OF DEATH, so that we can intervene to alter their trajectory.
(d) EXCLUDE THOSE PATIENTS THAT RISK ORGAN DYSFUNCTION BUT WHERE THE INFECTION IS NOT THE CAUSE.

The infection and sepsis must integrate care and assistance in time because sepsis can appear or develop from the territory to the hospital or inside the hospital, in

Intensive Care and/or on the wards or in the maternity wards. If it develops in the territory, diagnosis must be carried out by the family GP if the patient calls him. Therefore, we can consider a delay caused by the patient. If first contact is with a family GP, he can diagnose or not diagnose sepsis and delay causing the emergency services. If he does call emergency services, there may be a delay in transport either due to delay in replying or a delay in the transport itself. On arriving at the emergency department, there may be a delay in the department itself due to an undertriage of the sepsis. Only an integrated system can diagnose and treat sepsis in the right timescales. In the hospital, it is necessary to know what the correct methods are for diagnosing sepsis in the different settings but also to know where sepsis and septic shock must be treated: sepsis and septic shock must always be treated either in Intensive Care or High Dependency Units (HDU).

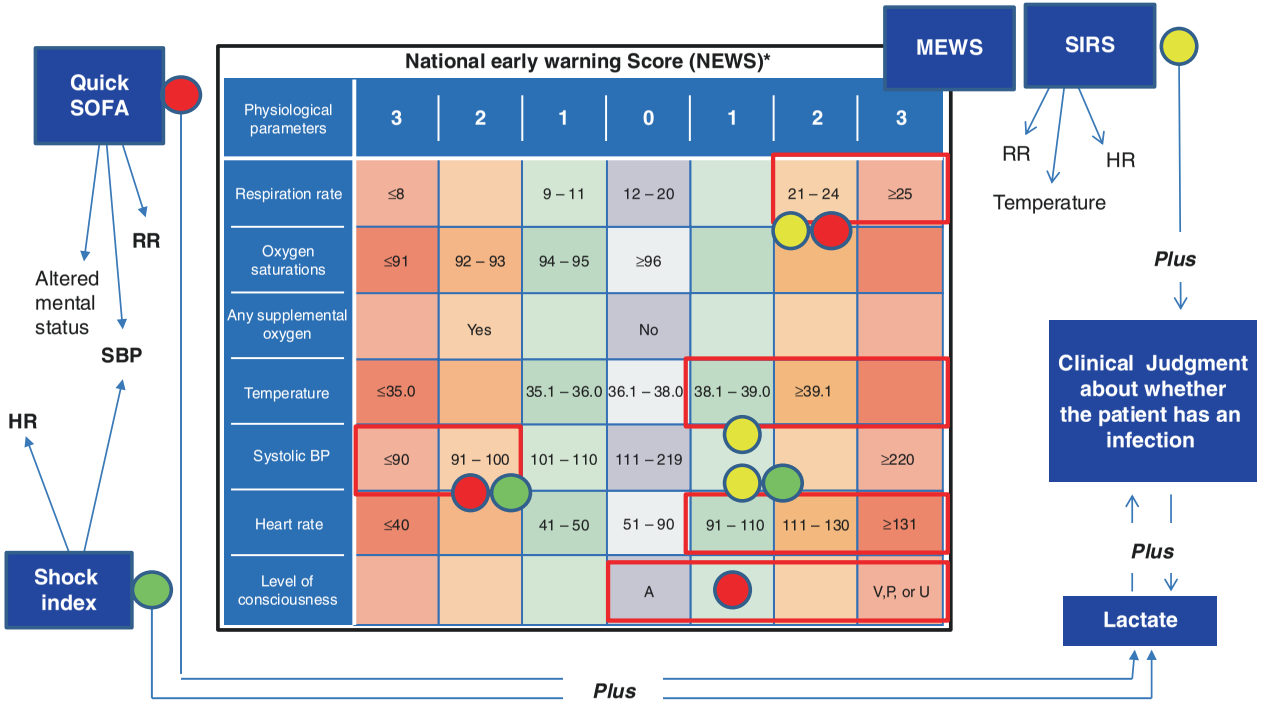
Sepsis at home can be diagnosed with simple, rapid approaches such as the qSOFA may be, perhaps expanded to temperature and heart rate and with strong empowerment of the families. There is need for a new family GP and to teach the patient signs of infection and sepsis.

Sepsis and septic shock can be addressed in emergency medical systems also in these settings, via simple adaptive tools. When we analyse these simple tools, it is possible to see that they all start from MEWS (Fig. 9.11).

With the introduction of the more recent rapid diagnosis microbiological techniques in clinical practice for identification of the pathogen and for its antibiotic resistance (Figs. 9.12 and 9.13), severe infections in high intensity areas of hospital care can be addressed by the clinician in a totally new way. With this new diagnostic approach, the information obtained using the molecular microbiological technique and phenotype microbiological technique can be used rapidly by the doctor, as required by sepsis, thus overcoming one of the main problems of traditional microbiology, i.e. the prolonged response time. Finding negative cultures in patients that have already received antibiotics occurs frequently [22]. This problem can also be resolved in part using molecular biology techniques. Delay in diagnosis due to the microbiological laboratory is accompanied by a delay in administering targeted antibiotic therapy, with deterioration in the patients' outcome, especially if they are in septic shock. There is much solid scientific evidence that shows a mortality increase if the empiric antibiotic therapy proves to be inadequate. At the end of the 1990s, in a prospective surveillance study, it was proven that 8.5% of infected patients admitted to Intensive Care received inadequate empiric therapy, and this was an important independent factor of hospital mortality: 42% versus 17.7% in the infected group treated adequately from the start [23].

Some authors, using a broad range of cases, assessed the appropriateness of antibiotic therapy in bacteraemia and the related clinical outcome and found a clear increase in hospital mortality in the critical group of patients who were given an inappropriate empiric therapy [24].

In an article often cited in literature, the concept that the duration of hypotension—expressed in hours—in septic shock before an effective empiric antibiotic is commenced is a critical decisive factor closely related to mortality is emphasised. This work reports a 7.6% increase in mortality for each hour of delay in



A model that incorporate both objective *(HR >90 beats/min, SBP <100 mmHg, RR >20 breaths/min, pulse oximetry <95%, history of fever, altered mental status)* and subjective *(clinical judgment about whether the patient has an infection)* prehospital components, that is highly specific, still misses around 40% of patients with serious infection. Including prehospital provider impression to objective physiologic factors identifies three more patients with infection at the cost of over-triagging five

Fig. 9.11 A comparison between MEWS, SIRS, SHOCK INDEX and QUICK SOFA

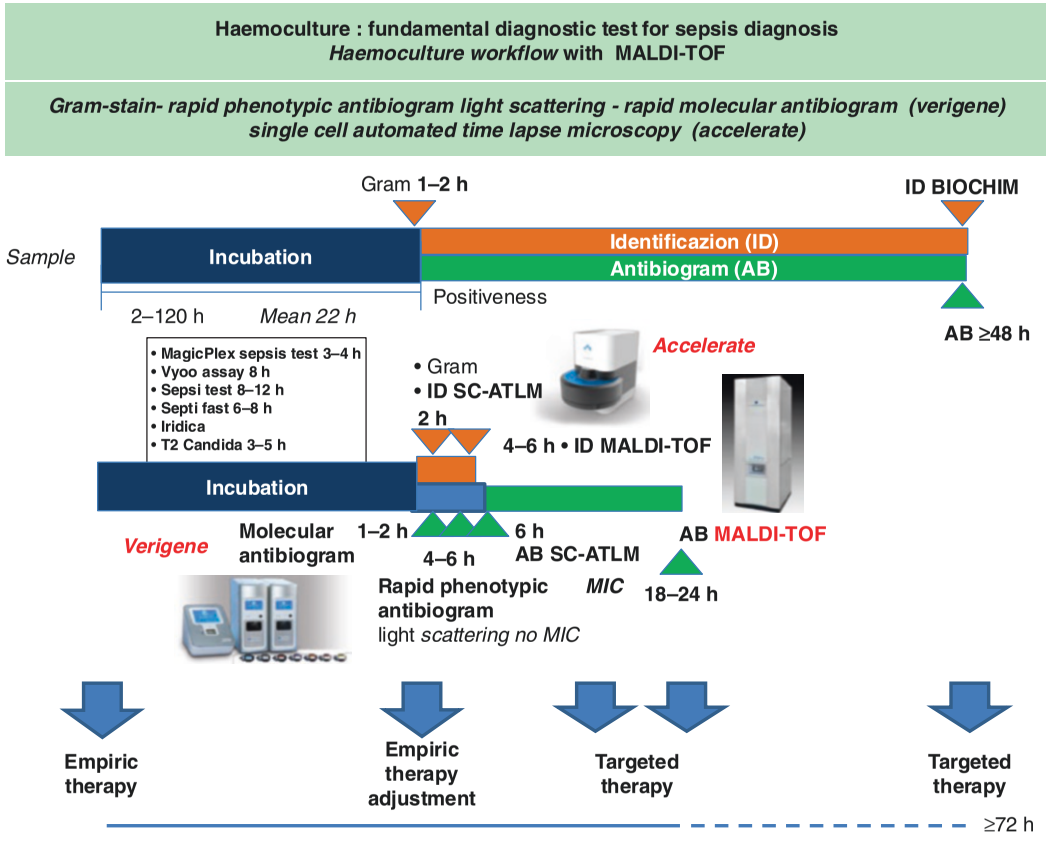


Fig. 9.12 Classic haemoculture workflow and RAPID Workflow. The importance of diagnostic stewardship in the sepsis pathway

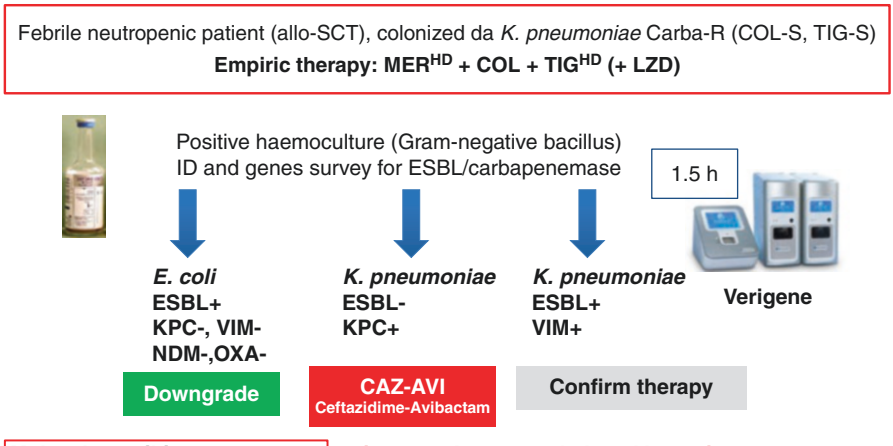


Fig. 9.13 Molecular diagnostics: useful tool for antibiotic stewardship

administering effective therapy, in the first 6 h from diagnosis of septic shock [25]. This concept has been misinterpreted by many, extending the need to establish a rapid, prompt antibiotic therapy in all infectious conditions far removed from septic shock, the only one where such evidence is solid.

More recently, on analysing an enormous global case study of patients in septic shock/with severe sepsis, other authors have again shown the close relationship between delay in commencing appropriate antibiotic therapy in the early hours since diagnosis of septic shock/severe sepsis and hospital mortality. Mortality increased in line in the early hours, as in the previously cited work, but in lower percentages [26]. Some of the independently associated factors to inappropriate antibiotic therapy include a previous colonisation by multiresistant germs and previous antibiotic therapy, especially one with broad-spectrum molecules such as carbapenems [27]. More than 2/3 of the bacteraemias acquired in Intensive Care are caused by MDR or XDR (multidrug-resistant, extensively drug-resistant) germs, with a clear prevalence of isolated gram-negatives, characterised [28] by more complex problems in treatment, mainly due to the limited number of effective antibiotic molecules. The problem of the negative impact (in terms of mortality) of inappropriate empiric antibiotic therapy on outcome has once again been confirmed by a large recently published meta-analysis [29]. All this clearly imposes rapid identification of the pathogen causing the infection, especially in septic patients admitted to Intensive Care, together with its pattern of resistance and susceptibility to currently used antimicrobial molecules. Access to rapid diagnosis is currently possible

for only a few clinicians as such methods are extremely expensive. It is therefore essential to design clinical care paths with patient complexity at the centre, able to direct a certain "setting" of septic patients to rapid diagnosis. On this matter, the microbiology laboratory should travel at two different speeds, clearly differentiating the routine path of a sample from that of the critical septic patient who requires much different times. A well-prepared clinician should stratify patients who need a preferential diagnostic path based on several factors. The combined, integrated use of validated scores helps the clinician in this task which is often not easy. Above all, the SOFA score was introduced by Vincent in 1996 [30]. Originally, the SOFA score was designed not to predict the outcome but to describe a developing sequence of organ damage. On admission, the SOFA score is independently associated with the possibility of developing bacteraemia in critical patients; in itself, it does not predict the outcome for those patients who will then develop this complication, but if we analyse its value on the first day of bacteraemia, then it is a powerful, independent prognostic factor. A high SOFA score value is associated with a higher probability of death [31].

With the introduction of the new sepsis and septic shock definitions, this score takes on an even more important clinical role in accurately defining a septic patient [1–3]. Today, sepsis involves organ dysfunction, focusing attention on a much more complex pathology than a simple infection plus SIRS criteria. This new way of thinking underlines the supremacy of the non-homeostatic host response to the infection, with the connected greater potential fatality compared to a simple infection, and this forces the clinician to rapidly recognise these patients in order to reduce said risk. Current clinical criteria for sepsis are the presence of an infection that has brought about a dysregulated host response together with a 2-point increase on the SOFA score, considering 0 as the initial state when the starting value is unknown. A patient in these conditions has a 10% higher hospital mortality risk. Septic shock, as has already been mentioned, means sepsis, as defined above, associated with the needs to vasopressors for maintaining a MAP > 65 mmHg and with lactacidemia >2 mg/L with no hypovolaemia. However, it is necessary to remember that the concept of SIRS has been removed from the definition of sepsis, but the clinician must be well aware that its use is most certainly useful when making a presumptive diagnosis of infection. The infection to be verified is still the crux of the sepsis problem, in fact.

Alongside the SOFA score, there are other scores of great and renewed interest for stratifying which patients are worthy of rapid microbiological diagnosis, including the CPIS score (clinical pulmonary infection score) when a lung infection is suspected and the PITT score when bacteraemia is suspected. Recently, the CPIS score was included in more complex diagnostic strategies, including both quali-/quantitative microbiological analyses and biomarkers [32], or due to its non-elevated diagnostic performance highlighted by various studies published in literature [33, 34] integrated with procalcitonin levels and a chest echography [35] (CEPPIS Chest Echography and Procalcitonin Pulmonary Infection Score). A CEPPIS score >5 analysed retrospectively on 221 patients, 108 of which with microbiological VAP confirmation was found to be higher-performing in predicting VAP compared to a

CPIS score >6 (OR 23.78; sensitivity 80.5%, specificity 85.2% versus OR 3309; sensitivity 39.8%, specificity 83.3%). PITT bacteraemia score is associated with mortality in patients with bacteraemia [36]. Another essential important aspect in risk stratification for septic patients is assessing the probability that the infection is caused by multiresistant germs. It is possible in this case too to use clinical scores to quantify this risk. Some authors [37] have validated a specific score for hospital-acquired infections from multiresistant gram-negative pathogens in critical patients, based on the following factors:

1. A stay of more than 5 days in Intensive Care
2. Use of carbapenems in the previous 6 months
3. Presence of a gram-negative infection in the previous 6 months
4. Dialysis with end-stage kidney disease
5. Surgery that precedes identification of gram-negative MDR
6. Carbapenem therapy in patients in Intensive Care for more than 5 days
7. Presence of CoNS

A coefficient is attributed to each of these factors, and the sum total allows the patients to be stratified into three classes of MDR risk: low risk, medium risk and high risk.

Another advantage of correct risk stratification is that within the MDR low-risk group of patients with less organ impact, the abuse/misuse of broader-spectrum molecules can be considerably reduced, thus contributing to interrupting the vicious cycle that leads to resistance. There are also predictive infection models for KPC *KlebsiellaKPC*, which are also based on several factors that are easy to analyse at the patient's bedside [38].

Some authors [39] have carried out retrospective studies on the risk factors of pneumonia caused by MDR in microbiologically confirmed cases and have constructed a new predictive score: the DRIP score (Drug Resistance in Pneumonia Score) which can identify these patients better than the less precise criteria of the CDC's HCAP (healthcare-associated pneumonia). At a threshold value >4, the DRIP score shows a sensitivity of 0.82 (95% CI, 0.67 at 0.88), a specificity of 0 (95% CI, 0.73 at 0.87), a positive predictive value (PPV) of 0.68.81 (95% CI, 0.56 at 0.78) and a negative predictive value (NPV) of 0.90 (95% CI 0.81 at 0.93).

The problem of antibiotic resistance and therefore of acquiring an MDR germ responsible for the infection is priority, but we must not forget that it is the gravity of the septic syndrome that has the greatest influence on the outcome and likewise the condition in which an appropriate antibiotic therapy was established. In a retrospective study on 510 patients affected by bacteraemia in sepsis, severe sepsis and septic shock, all with appropriate empiric therapy, it was proven that it is the gravity of the septic syndrome rather than the acquired MDR state that is an important predictor of death [40]. Therefore, it is only a careful initial assessment, layering the clinical gravity risk related to the outcome with the help of scores, the severity of the septic syndrome and the risk of having MDR pathogen infections that can guide

microbiological diagnostics in septic patients, as part of a rapid path shared at every stage with the clinical microbiology colleague, who is today a vital figure in the "sepsis path".

As a part of this decision-making path (diagnostic-therapeutic), a role of primary importance is played by the use of biomarkers, such as procalcitonin (PCT) and pro-adrenomedullin (proADM). Evidence supporting the use of PCT is truly important. In 2004, Liliana Simon published her first review and comparative meta-analysis between PCT and PCR as bacterial infection markers, concluding that PCT was more sensitive (88% versus 75%) and more specific (81% versus 67%) than PCR in differentiating a bacterial infection from non-infectious causes [41]. A few years later, the proCAP study began to lay the foundations for the use of PCT in deciding to interrupt antibiotic therapy earlier, showing that the 151 patients guided by PCT on average interrupted antibiotic therapy in CAPs after 5 days compared to the 12 days of the control group, with a reduction of prescription on entry from 99% to 85% [42].

The proHOSP study published in 2009 extended the analysis to all lower airway infections and on analysing 1359 patients in a multicentre, randomised, controlled trial, confirmed what had already been stated that the PCT-guided group had a lower exposure to antibiotics and a smaller percentage of drug-related adverse events related to a similar clinical outcome than the control group [43]. Once the PRORATA trial appeared in a basic, reference article supporting current clinical use of PCT, it was finally confirmed that the 307 patients in the PCT group (algorithm for commencing and/or discontinuing the PCT-guided antibiotic therapy) had a mortality rate at 28 and at 60 days that was fully comparable with that of the 314 patients in the control but with a significantly lower daily exposure to antibiotics [44]. In 2012, the Cochrane collaboration published a review of 14 randomised, controlled clinical trials, concluding that use of PCT in commencing or discontinuing antibiotic therapy did not lead to a higher frequency of mortality and/or therapeutic failure but did, on the other hand, lead to an important reduction of days of exposure to the antibiotic and a lower drug-related effect and lower antibiotic-resistance rate [45]. Another meta-analysis from 2013 introduced the concept that the PCT value should be contextualised and interpreted within the clinical context [46]: this is vitally important, when PCT is used in clinical practice, as it is not the single value alone that must be considered but the meaning that that value has in that clinical context and above all the kinetics in the first 72 h of PCT. It is the dynamic change of PCT in the first 48–72 h that expresses the predictive value of survival and of antibiotic therapy efficacy [47, 48]. In addition to this placement of PCT, which has now been consolidated for some time and is based on the fact that no marker has ever been assessed with such a high level of methodological rigour in randomised clinical trials, the marker has already been paired for a few years now with new microbiological diagnostic and rapid identification technologies, which is a new and promising possibility for treating serious infections in the critical patient [49]. PCT plays a primary role today, alongside a careful stratification of patient risk, in guiding rapid diagnosis. In clinical practice based on close daily collaboration with his clinical microbiology colleagues, the clinician's request, shared with the microbiologist after

reasoning on each clinical case, for rapid diagnosis, therefore for a dedicated path from the laboratory, starts after identifying the patient deserving of such a customised diagnostic path, based on suitable stratification of risk, including scores (adaptive, heuristic tools) and biomarkers, the first of which is PCT, and more recently proADM that strengthens the former for some aspects. PCT has been included in all the most advanced antimicrobial stewardship programmes [50] especially for critical patients, at which point it is now truly difficult not to consider this marker as part of the clinical path of this particular patient setting. Mortality data in terms of reduction in the PCT-guided group that was missing in all the trials published thus far has recently come from the results in a large-scale Dutch open-label, randomised, controlled trial including 1575 patients divided into two groups (PCT-guided and standard-guided) where mortality at 28 days in the PCT group was 19.6% versus 25% of the control group [51].

One ideal biomarker to be included in daily clinical practice should not only have a high positive predictive value (PPV) but also a high negative predictive value (NPV). Anyone who currently uses PCT in an advanced and innovative manner focuses their attention on the NPV of this marker, taking the rest for granted and consolidated. It is this very particular characteristic that differentiates PCT from other biomarkers used in clinical practice in the context of an initial structured diagnostic path for a markedly septic patient, without however known or common infection sites. The use of this marker as part of an integrated, complex clinical path stimulates the clinician's diagnostic ability, refining his accuracy. In a patient with sepsis/septic shock with negative or extremely low PCT for the severity of the clinical picture, it is automatically mandatory to guide diagnosis with the exclusion of syndrome situations such as deep and/or compartmentalised abscesses, meningitis/ventriculitis, endocarditis without embolism, specific atypical pneumonia and "bloodstream infections" from CoNS or from fungus.

In clinical practice in these groups of patients, instrumental diagnosis using advanced total body imaging with contrast media, in both CT and MRI scans, are rapidly carried out, the latter at the same time as the CT scan, in the cases where the site can be studied better or characterised using this method—see particular deep muscle or CNS locations. Alongside the CT and/or MRI test, another important diagnostic test is a trans-thoracic or trans-oesophageal ultrasound with the intention to exclude valve vegetations.

Alongside PCT, another marker of current interest is the MR-proADM amino acid fragmentation of the adrenomedullin peptide of 52 amino acids secreted by endothelial cells and vascular smooth muscles. ADM is involved in the systemic control of circulation and has a probable autocrine/paracrine vasoactive action. The molecule also has a diuretic and natriuretic action, increasing glomerular filtration rate and reducing the distal absorption of sodium. ADM also has a bactericide action, further increased by being regulated and by modulation of the complementary activity. It is not therefore surprising that high blood levels of ADM have been found raised in septic patients, making it one of the parameters to evaluate in both the diagnostic and the prognostic and monitoring paths. Unfortunately, measuring ADM is often unreliable due to its rapid clearance in blood circulation. Furthermore,

circulating ADM is associated with a binding protein that makes it inaccessible for any direct immunometric dosage. However, the problem has recently been resolved by identifying its mean regional fragment, named pro-adrenomedullin (MR-proADM), in the plasma of septic patients, as a stable, reliable surrogate marker for release of ADM. Secretion of proADM increases during the immune response to viruses, fungi and bacteria in relation to stimulation intensity, and its presence is also found therefore during serious infections [52]. The MR-proADM amino acid fragment also provides more prognostic information and is an expression of greater endothelial damage. It is closely related to the gravity of the disease and would appear to play an important role in defending the organism from the host and is in fact an antibacterial peptide [53]. ProADM is therefore a strong prognostic biomarker that can be used together with the clinical parameters of gravity (APACHE II score, SOFA score) to stratify the risk of septic patients. Therefore, having a more specific marker for prognosis on entry can help the clinician to formulate both diagnostic and most of all clinical situation evolution hypotheses, by modulating several therapeutic strategies on several levels of care intensity. Pairing both the PCT and proADM markers with TNF alpha in one compound score has proven that identification performance for a sepsis diagnosis is notably refined [54]. It has recently been proven that MR-proADM differentiates sepsis from non-infection-based SIRS situations with very high specificity and that if paired with PCT in septic patients, the post-test diagnosis probability increases noticeably if compared to that of the two markers taken individually [55–57]. The following hypotheses can be validated by assessing daily blood levels of proADM together with those of PCT, as part of a multi-parametric analysis of sepsis using existing scores (SOFA score, PITT score, CPIS score, MDR score) and extremely advanced rapid microbiological diagnostic techniques:

(a) Identifying diagnostic cut-offs for infectious situations
(b) Testing the association between associated patterns compared to each proADM and PCT text
(c) Diagnostic accuracy of the infection and in response to therapy
(d) Testing whether the diagnostic values of proADM and PCT, their maximum values or their cumulative values or quantification of their trends add predictiveness to classical prediction models in critical patients

From an initial analysis, it is possible to see an existing close correlation between proADM and SOFA score and sometimes even the proADM rises before the SOFA score, allowing the clinician to anticipate his suspicion of a probable deterioration in organ failure. The proADM also correlates with the PITT score, more than the PCT. Another characteristic aspect to validate during the analysis phase is the fact that in several cases of initial PCT values that can also be high, the proADM remains low if the organ is not affected. It is as if the marker, not seeing the gravity of the patient, differs itself from the PCT positive result. The matter is more complex for the cut-off of proADM as it is not clear in literature what the most reliable cut-off may be. Cut-off < 1 indicates the absence of an infectious pathology, with organ

dysfunction ongoing. Cut-off between 1 and 2, even without clear clinical signs and with low PCT, may indicate that the organs are affected with a latent infectious picture or one that is not yet fully resolved. This latter data is extremely important and innovative for a biomarker, as it encourages the clinician to reason and to set up a more accurate diagnostic-therapeutic plan. Cut-off between 2 and 4 indicates a severe infection associated with organ dysfunction and is usually associated in line with the SOFA score.

All patients who are admitted in septic shock with a proADM value >6 are all dead, as if this was a cut-off of no return in this group of patients. By pairing up the two markers, the clinician can refine his diagnostic capacity in the initial phase even further.

As everyone knows, PCT does not move during a viral or fungal infection, although with fungal infections, things are slightly different, in fact. A cut-off of 2 ng/mL separates sepsis from *Candida* from bacterial ones, with a 92% sensitivity and a 93% specificity and a NPV of 94% [58]. Therefore, when evaluating the NPV in PCT, also in fungal infections, the information it provides is very important for a well-prepared clinician. From data found in literature, a septic patient with PCT > 3 on the seventh day plus a *Candida* score >3 is associated with the high probability of candidemia to the point that an empiric antifungal therapy will be recommended [55, 59].

With the new definition of sepsis and with the important role attributed to the SOFA score, the possibility of using a prognostic marker, related to the SOFA score as an expression of organ damage, such as proADM most definitely increases leaning towards more advanced diagnostic-therapeutic strategies during the decision-making stage.

The diagnostic/therapeutic path proposed for sepsis and septic shock can be tracked as follows in different hospital settings (Figs. 9.14, 9.15, and 9.16):

1. Stratification of risk
   - Scores: SOFA score/PITT score/CPIS score/MDR score + BIOMARKERS: PCT/proADM + lactate and grading of gravity of septic syndrome
2. Rapid microbiological diagnostics in patients selected based on their gravity, with the criteria stated above and its correct interpretation
   - Rapid identification/resistance pattern/rapid antibiogram
3. Reasoned empiric therapy on the infection site possible, on the patient's history and on the department's epidemiology
4. Therapeutic upgrading/downgrading once the information from point 2 has been obtained
   - Narrowing of action spectrum of molecules used, reduction in the number of molecules and changeover from combination therapy to monotherapy
5. Synergism test (customised therapy)
6. Reduction in the duration of antibiotic therapies based on the clinic and the PCT kinetics
7. Close sharing in all parts of the process described above between clinician and clinical microbiologist

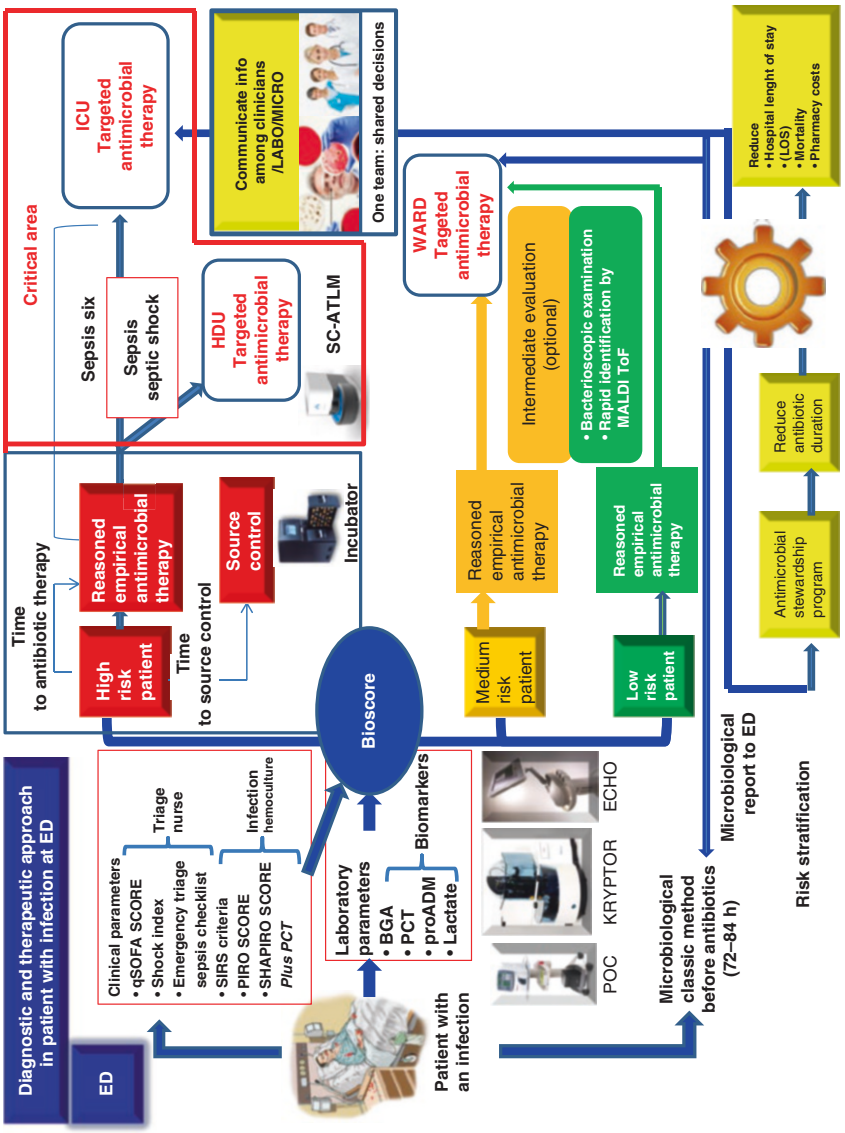


Fig. 9.14 Patient risk stratification in emergency department: the use of a bioscore

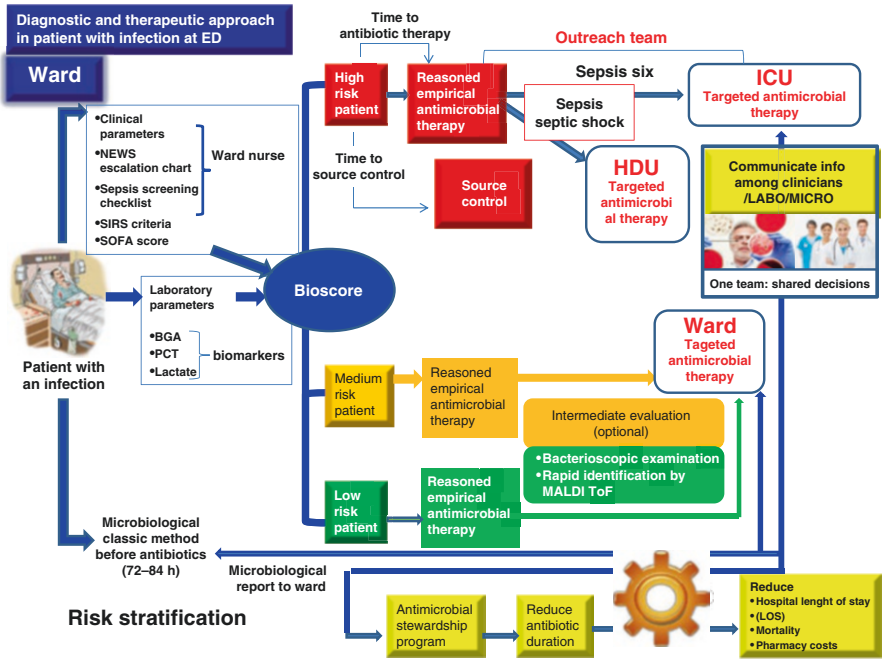


Fig. 9.15 Patient risk stratification in a medical/surgical ward: the use of a bioscore

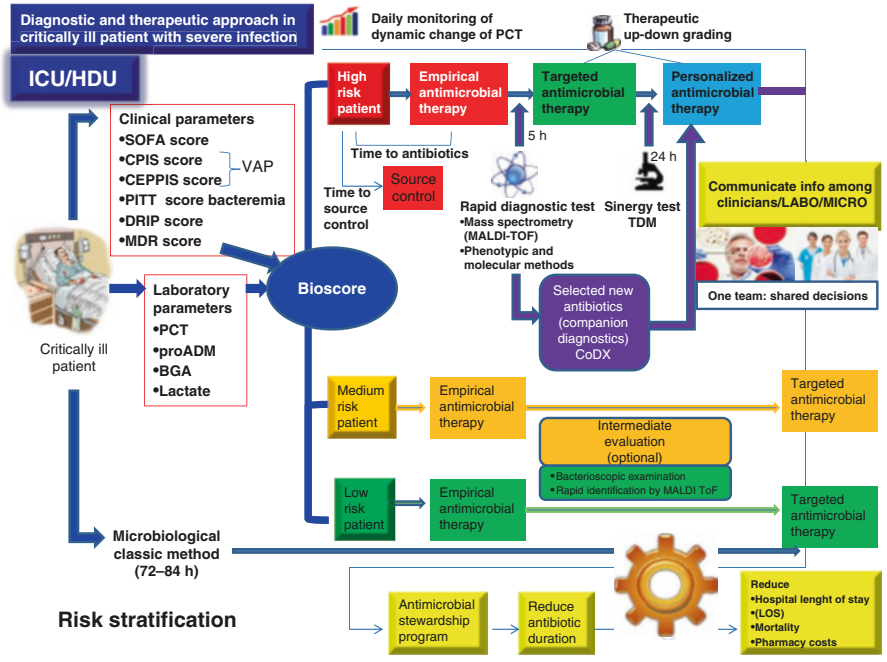


Fig. 9.16 Patient risk stratification in the ICU: the use of a bioscore

8. Possibility of a positive return in terms of both local epidemiology and infection control, with a considerable impact on patients' outcome
   – Shorter stays in hospital, lower mortality, lower costs for related drug, etc.

9.1 The Surviving Sepsis Campaign 2016 Guidelines

The international SSC guidelines for sepsis and septic shock management reached their fourth edition in 2016. The recommendations contained therein have been evaluated using the GRADE system and clearly show us that there is still a high rate of uncertainty that the clinician must still embrace. However, they contain a new section: Good Practice. Eighteen best practice statements appear in the guidelines, 13 of which concern the first 3 h of intervention, i.e. initial resuscitation, diagnosis, antibiotic therapy, source control and fluid therapy (Figs. 9.17, 9.18, and 9.19).

One good practice defines sepsis and septic shock as medical emergencies and recommends that treatment and resuscitation commence immediately. This means that healthcare organisations must consider sepsis and septic shock on the same basis as trauma, IMA and strokes, where times for treatments must be measured and considered as indicators. The good practices that concern fluid therapy recommend

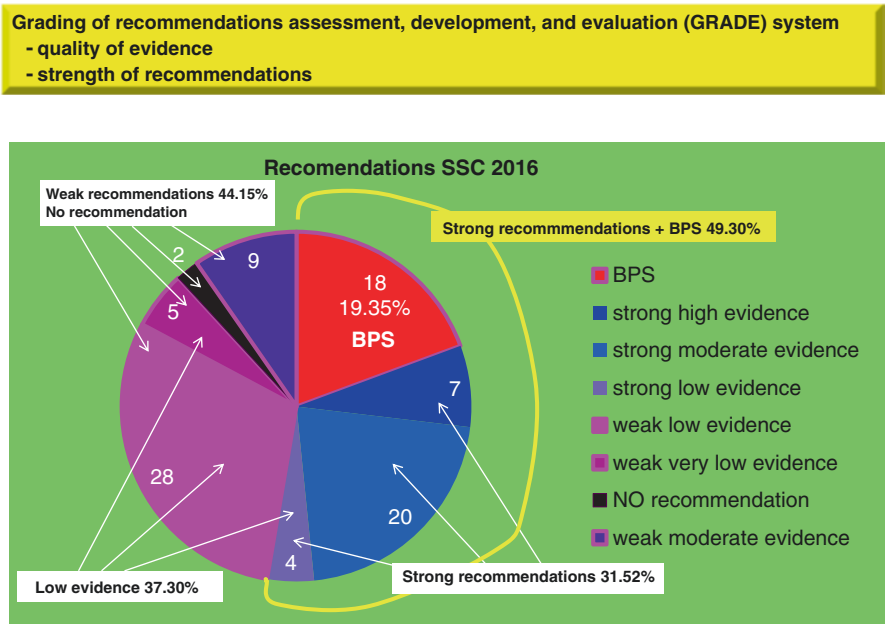


Fig. 9.17 SSC international guidelines 2016: recommendations and best practice statements (BPS)

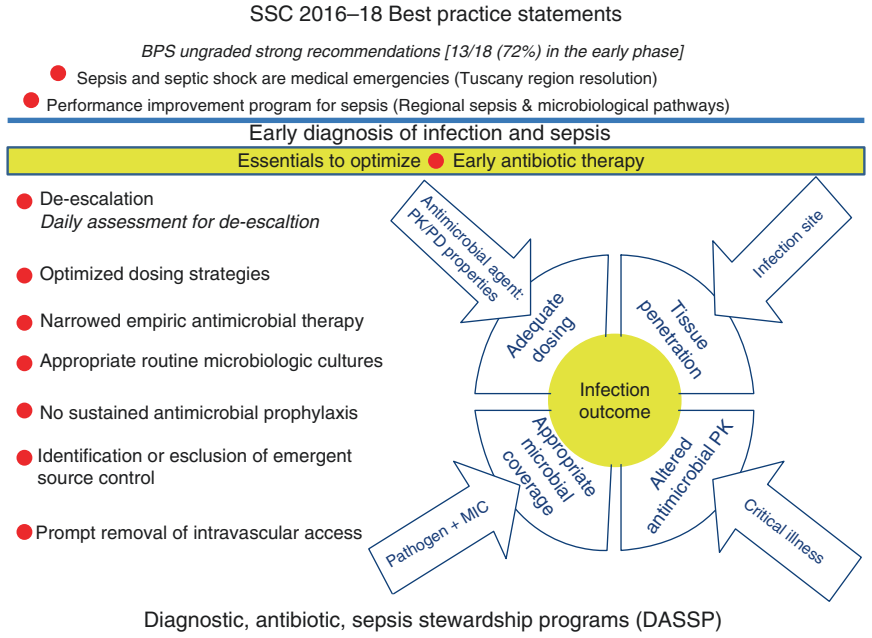


Fig. 9.18 SSC 2016: the 18 best practice statements. Red dots: the 13 best practices (ungraded strong recommendations) in the early sepsis phase. Early diagnosis of infection and sepsis, essentials to optimise early antibiotic therapy

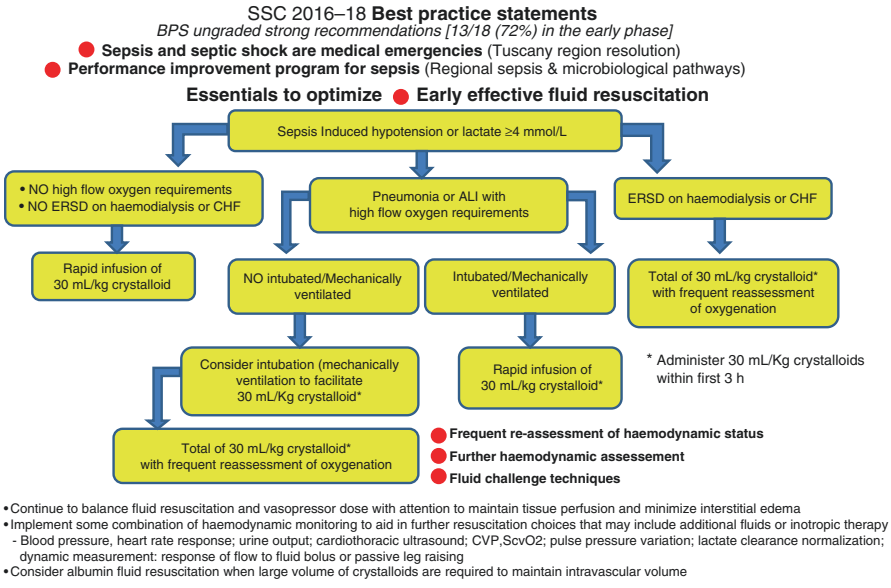


Fig. 9.19 SSC 2016: the 18 best practice statements. Red dots: the 13 best practices (ungraded strong recommendations) in the early sepsis phase. Early diagnosis of infection and sepsis, early effective fluid therapy

that after the start of early fluid resuscitation, additional fluids must be guided by frequent reassessment of the hemodynamic state and that further hemodynamic assessments are carried out if a clinical examination of the patient does not lead to a clear diagnosis; the "fluid challenge" technique is also recommended, when fluids must continue to be administered for the entire time that the hemodynamic factors continue to improve. On diagnosis, not much is added to the recommendation that the appropriate routine microbiological cultures (including blood) must be taken before starting antimicrobial therapy in patients with suspected sepsis or septic shock, if these procedures do not delay excessively the start of antibiotic therapy. Most of the good practices concern antibiotic therapy and "source control". With regard to antibiotic therapy, empiric antibiotic therapy should be narrowed down once the pathogen and the antibiogram have been identified and/or a suitable clinical improvement has been noted. Sustained systemic prophylaxis is also not recommended for patients with severe inflammatory states of a non-infectious origin, such as severe pancreatitis and burn injuries. Antibiotic dosing must be optimised based on the accepted principles of pharmacokinetics and pharmacodynamics and the specific properties of the drug. It is also recommended that if a combination therapy is initially used for septic shock, de-escalation should be carried out with discontinuation of the combination therapy within the first few days in response to clinical improvement and/or evidence of infection resolution. This is applied to both targeted combination therapy (for culture-positive infections) and empiric combination therapy (for culture-negative infections). Lastly, therapy should be assessed daily for de-escalation of antimicrobial therapy in patients with sepsis and septic shock.

Other good practices concern controlling the site of infection. The first good practice recommends a specific anatomic diagnosis of infection that requires emergency source control is identified or excluded as early as possible and that each requested source control intervention be implemented as soon as it is medically and logistically possible after diagnosis. A recommendation is also made for prompt removal of intravascular access devices that may be the source of sepsis and septic shock, after other vascular access sites have been established. As we can see, the best practices regard the entire initial phase. One important best practice states that hospitals and hospital systems must have a performance improvement programme that includes sepsis screening for high-risk, acutely ill patients.

On comparing the 2012 recommendations with the ones from 2016, with regard to initial resuscitation, we can note that some important trials have also influenced this change. In 2012, initial resuscitation of patients with sepsis and tissue hypoperfusion (defined as hypotension persisting after initial fluid challenge or blood lactate concentration ≥4 mmol/L) was protocolised under the influence of the EGDT. The goals to be achieved in the first 6 h of resuscitation were:

(a) CVP 8–12 mmHg
(b) MAP ≥65 mmHg
(c) Urine output ≥0.5 mL/kg/h
(d) Central or mixed venous saturation of = 70% or 65%, respectively (grade 1C)
(e) With elevated lactate levels, resuscitation must tend towards normalising the lactate (grade 2C)

In 2016, sepsis and septic shock are considered to be a medical emergency, and it is recommended that treatment and resuscitation begin immediately. A minimum of 30 mL/kg of intravenous crystalloids are recommended in resuscitation in sepsis-induced hypoperfusion, to be administered in the first 3 h (strong recommendation with low quality of evidence). A frequent reassessment of the hemodynamic state is recommended after initial fluid resuscitation, which must include a full clinical examination and an assessment of the physiological variables available: heart rate, blood pressure, oxygen saturation, breathing rate, temperature, urinary output and others if available, such as other invasive and non-invasive forms of monitoring. A further hemodynamic assessment is recommended (such as the one to assess heart function) to determine the type of shock if the clinical examination does not lead to a clear diagnosis. Dynamic variables should be used rather than static ones to predict "fluid responsiveness", when they are available, of course (weak recommendation, low quality of evidence). An initial target for mean arterial pressure of 65 mmHg in patients with septic shock requiring vasopressors is recommended (strong recommendation with moderate quality of evidence). Resuscitation should be guided to normalising lactate in patients with high levels of lactate as a marker for tissue hypoperfusion (weak recommendation, low quality of evidence)

With regard to diagnosis, the use of the 1.3-sD glucan and of the antibody mannan and the antibody anti-mannan for the different diagnoses with fungus infections disappear, and the use of imaging carried out to promptly confirm a potential source of infection also disappears.

For antibiotic therapy, the recommendation of administering antibiotics within 1 h for both sepsis and septic shock remains (strong recommendation with moderate quality of evidence). Not much changes for all the rest apart from the increase in this treatment in the best practices as already stated. The same for source control. Follow the EGDT protocol or monitor the patient and administer the treatment based on the clinical signs [60–64].

In a recent Canadian study [65], an association was shown between time to treatment and the outcome for patients with sepsis or septic shock treated in the emergency department. In this important study, it was found that a longer time in completing the "bundle of care" of 3 h for septic patients and the administration of broad-spectrum antibiotics were associated with a higher hospital mortality, adjusted for risk. No association was found in the same study between completion of the initial bolus of fluids and hospital mortality. Time to treatment varied widely between hospitals. The results of the study were in agreement with other smaller, observational-type studies [66–69].

However, a recent meta-analysis of 11 observational studies did not show a significant benefit of administering antibiotics within 3 h, compared to administration after 3 h, after triage in the emergency department (odds ratio 1.16; 95% CI, 0.92 at 1.46) or within 1 h of recognising shock (odds ratio 1.46; 95% CI, 0.89 at 2.40) [26].

The odds ratios cited in the study are similar, but the confidence intervals are narrower, given the larger sample included in the Canadian study. This study complements a meta-analysis of goal-directed therapy in sepsis and septic shock (PRISM trial) [60]. More than three out of four patients in the PRISM trial received

elements of the 3-h bundle before randomisation, after which the various trials making up the PRISM trial tested to see whether the protocolised resuscitation strategies improved the outcome. However, the Canadian study asked another question: is timing important for these earlier, more basic elements? This population data also places the relatively high compliance with these steps in the control groups of the various trials making up the PRISM trial before randomisation into the context. Only half the hospitals conducted themselves at this level. There are several biological explanations for the association between time to completion of the 3-h bundle and the outcome. First of all, a faster administration of antibiotics reduces the pathogenic load, modifies the host's response and may reduce the incidence of subsequent organ failure. Secondly, doctors who decide more rapidly to measure lactate levels in the blood can identify non-recognised shock better and are better prepared for facing lactate-guided resuscitation than clinicians who are slower in measuring lactate levels, a strategy that may improve the outcome of the randomised trials [72]. Thirdly, doctors vary vastly in how they identify sepsis, even when presented with similar cases [73].

Early administration of treatment in sepsis, even within the framework of rigid protocols, requires a prompt clinical suspicion of both the infection and of the organ dysfunction that is deteriorating. [70–71] Even if we do not find any association between the completion time of the initial bolus of intravenous fluids and the outcome, this data should not be interpreted as evidence in favour of abandoning early fluid resuscitation. Analysis of the completion time of the initial bolus of fluids is more likely to be confused by indication (e.g. sicker patients will receive fluids earlier and are also more likely to die) [74].

A greater volume of fluids administered rapidly may contribute to adverse effects such as pulmonary edema, fluid overload and a longer duration of organ support in selected patients [6]. A variation of 1–2 times was found in the study between hospitals regarding the speed in which the 3-h bundle was completed, antibiotics were administered, and the bolus of intravenous fluids were completed in the emergency departments. Generally speaking, adherence ranged from 60% to 90% and was higher than the comparable one in programmes to improve the quality of treatments for strokes in New York [75]. This performance may derive from the public's growing attention towards sepsis [76]. Adherence was greater in emergency departments in smaller, non-university hospitals, a result that differs from a previous study [77]. These hospitals may have fewer doctors to train, a lower census in their emergency departments and a different case mix compared with the larger reference centres that perhaps helps with the faster implementation of sepsis protocols.

9.2 Controlling the Infection Site (Source Control) [78–81]

In the German MEDUSA trial, surgical (84.8%) or intervention (15.9%) source control was carried out in 422 patients: the overall average time was 3 h (−0.1 to 13.7 h) and 6 h, respectively (2–20 h), in those patients where source control was begun after development of organ dysfunction (314 patients). Of these 314 patients,

158 (50.3%) received source control within 6 h of the onset of infection-related organ dysfunction. Time to source control was significantly longer in non-surviving patients than in surviving ones. In 55 patients (13.3%), source control was evaluated as inadequate. Mortality at 28 days was 65.5% in patients with inadequate source control, compared to a 26.7% mortality rate in patients with adequate source control ($P < 0.01$). There was no relation between time to source control and risk of death at 28 days (odds ratio per hour of increase in time to source control, 1.0 (95% CI: 1–1.0 $P = 0.725$)). Patients who suffered a delay in source control for more than 6 h had a significantly higher mortality (42.9% versus 26.7% $P < 0.001$). This delay was independently associated with an increased risk of death. There was no statistically significant or linear interaction between time to antibiotic treatment and time to source control. Other studies found that a cut-off of 12 h is a better indicator between early and late times, with better outcomes observed in the groups with early intervention. In a Spanish prospective observational study by the EDUSEPSIS Study Group, a third of the patients with sepsis admitted to ICU required source control, especially the ones with abdominal infections and soft tissue infections. Although the patients going to source control were more serious and received worse initial resuscitation, their outcome was better than those that did not go to source control. The study, however, failed to prove a lower mortality with early source control compared to later source control in specific infection sites. Educational and quality control programmes are required to identify and control infection sites in patients with sepsis and septic shock.

All these results from different studies must not be an excuse for doctors to use a slow approach with critically ill patients, in a population of vulnerable patients. These studies support the notion that personalised medicine and personalised surgery are the optimal approach for timing to source control in septic patients. Some patients require early intervention, while other can tolerate a delayed source control certainly until their clinical condition has improved. It is difficult to imagine a situation where a prospective, randomised clinical trial can be designed to strictly determine the optimal time for commencing source control in septic patients. This trial may be possible, but it would be difficult to justify it on an ethical level. Evidence to date shows that careful supervision of a drainable infection site is mandatory in septic patients. Timing to source control interventions should raise attention to the fact that source control is a challenge and a difficult, individual decision that needs to be based on all the evidence available for each patient.

9.3 Some Critical Questions

9.3.1 Does the New Definition of Sepsis Improve Early Diagnosis of Sepsis and Its Treatment?

The question of how it is better to define sepsis is one doctors have asked for the last 20 years. Previous efforts, in 1991 and in 2001 [82, 83], have continued to cause

much controversy; one of the observations has been that there was not much agreement between the definitions agreed at the table and the one that the doctors at the patient's bedside thought at the time [5]. Many believed that the huge heterogeneity of the population found in existing definition was partly responsible for the difficulties found by phase three trials that had overall failed to identify new treatments for sepsis. Several authors [84, 85] had pointed out that there was an urgent need for reviewing these definitions. This was then enacted by an international group of experts which led to the SEPSIS-3 proposal. As soon as this new definition was published, it started up a real torrent of comments and criticisms [1, 86–88]. What are the strengths and weaknesses of the new definitions?

Strengths

(a) Proposals with solid foundations based on widely validated cohorts
(b) Pragmatic proposals that reduce complexity: they remove redundant terms such as severe sepsis and septicaemia
(c) qSOFA that is extremely easy to apply without the need for using a laboratory
(d) qSOFA that can be used for both early recognition in the emergency department and in clinical and epidemiological trials

Weaknesses

(a) It is still a syndrome diagnosis based on the probability of hospital mortality.
(b) There are still no clinical tests that are easy to measure and that can reflect the concept of "dysregulated immune response".
(c) The criteria for recognising the infection have not been defined; microbiology is totally ignored.
(d) Paediatric patients are currently excluded.
(e) The definition is developed for the first world and cannot be generalised for use in countries with low or medium levels of income.

The definition is based on an "injury severity score", the SOFA score that actually establishes whether you have sepsis or not or whether you have a very serious infection that is complicating and becoming organ failure. The fact that the work derives from data from North America and to a lesser extent from Europe means that the conclusions need to be reviewed for doctors who work, for example, in third world countries. As others have debated [89], there is confusion between having sepsis and what doctors recognise as a septic patient. SEPSIS-3 is actually focused on bacterial disease in Intensive Care Units in Europe and North America, but does not say so and does not clarify that fact; in other parts of the world, malaria may respond well to such requests. Perhaps what has been lost in all these discussions is a real understanding of what these definitions have been drawn up for. There is inevitable tension between a meaning whose primary function is to accurately and without ambiguity identify a homogeneous population that is available for inclusion

in a clinical trial and a pragmatic definition that is easy to apply in the clinic that can allow a rapid diagnosis and immediate treatment.

The experts who drew up SEPSIS-3 attempted to address this problem by developing the idea of the quick SOFA, a shorter version of the more detailed SOFA score [90]. The qSOFA has three physiological variables that are easy to measure, every two of these is a positive result and an indication that the patient is at risk of sepsis. A positive qSOFA is not a replacement definition of sepsis but an indication that a patient may be at increased risk of sepsis. The difficulty here lies in the concern that such a low threshold (all that is necessary is rapid breathing and blood pressure slightly lower than normal) will result in a super-sensitive signal, similar to the problems found with SIRS [9, 91].

It is helpful to compare the high simplicity of the qSOFA with the recent guide published by NICE, where the algorithms used are much more complex [92].

The application of the new definition of sepsis is actually more interesting: a life-threatening organ dysfunction due to a dysregulated host response to the infection. This definition has caused a lot of debate: Are all cases of sepsis really life-threatening? What does dysregulated mean? How do we measure a dysregulated host response in a patient? This new definition helps on each of the two key requests: improved definition of each case or improved treatment of each case? In Great Britain, the NHS has published an action plan to support hospitals in improving the outcome of sepsis patients. The so-called SEPSIS SIX, based on early recognition with the NEWS has been widely adopted, and evidence suggests that this method has been effective [93, 94]. It is not clear how the new SEPSIS-3 definition, based on a 2-point change in the SOFA score can improve these outcomes. A fundamental criticism of this new definition is that it perpetuates the notion of sepsis as a single entity with a common pathophysiological bias, i.e. that of being susceptible to a single therapeutic intervention (if only it is possible to identify what that might be).

Moving increasingly towards the world of customised medicine, the idea of being able to separate patients with sepsis into subgroups becomes more attractive than leaving them all grouped together in a single category [95]. These subtypes could be characterised by an entire spectrum of phenotypic or biological characteristics: We could identify adult patients with pneumococcus pneumonia or patients with a particular combination of biomarkers or a genotype at risk plus a specific clinical risk factor. This approach faces significant challenges. The first is to establish plausible hypotheses, although this is becoming more probable with the use of big data and bio-information technology. The second is that these populations are by definition subgroups and therefore smaller in number than we were used to working with, and there are both scientific and commercial pressures to try and avoid narrow focuses. However, the introduction of rapid microbiological diagnostic processes, such as MALDI TOF [96] or molecular ones, means that real-time bacterial diagnosis is now a reality, and there are examples of drugs developed for the treatment of specific types of bacterial sepsis [97].

9.3.2 Should Combined Antibiotic Therapy Be Used Routinely in the Empiric Treatment of Septic Patients?

The main principles for using antibiotics in sepsis are now free of controversy:

(a) They should be commenced as soon as a clinical diagnosis of sepsis is made: speed is essential.
(b) It is important to use a regime with adequately broad spectrum of activity that will be active against the most likely pathogen agents.
(c) The dose should be optimised using a load dose if necessary and taking some variables into consideration (e.g. the use of hemoperfusion) that may alter pharmacokinetics in septic patients.
(d) Ideally, the regime should be quickly de-escalated to reduce the spectrum.

There is a further consideration that is sometimes discussed that the use of bactericide drugs is preferable to bacteriostatics. Although this may seem intuitively correct, there is not much clinical data to support it. The problem that clinicians encounter is whether an adequately broad spectrum of activity suggests the routine use of a combination of antibiotics in these critically ill patients. The problem is that selecting an antibiotic regime that then proves to be inactive against the organism that is subsequently isolated in blood cultures is associated with a significantly higher mortality [98]. This is a strong incentive to choose a cautious, defensive approach in prescribing multiple antibiotics. There are advantages and disadvantages in using combination therapy; although it is likely that if it were possible to prove a measurable benefit for survival from the routine use of two or more drugs, then this would act as a counterweight to potential disadvantages.

Advantages of combined antibiotics

(a) They will guarantee a broader spectrum of activity than the one obtained by a single drug.
(b) They can produce an additive or even a synergic effect.
(c) They can reduce the risk of the emergency of resistance during treatment.
(d) They can produce non-antimicrobial, beneficial pharmacological effects.

Disadvantages

(a) A generally wider use of antibiotics would probably bring about the problem of resistance to antimicrobials.
(b) It would probably increase the risk of toxicity.
(c) It can increase the risk of superinfection (e.g. with fungi).
(d) It can increase the probability of undesired and unexpected interactions between drugs.
(e) It can increase costs.

The current recommendations of the Surviving Sepsis Campaigns are that combination therapy is indicated for:

(a) Neutropenic patients with severe sepsis
(b) Patients that have or are likely to have infections with organisms that are resistant to most drugs such as *Acinetobacter* or *Pseudomonas* or *Klebsiella*
(c) Selected patients with severe infections associated with respiratory failure and/or septic shock associated with bacteraemia from *Pseudomonas*
(d) Shock from infection from *Streptococcus pneumoniae*

The evidence that supports these recommendations varies in quality, but putting to one side these special cases, the question remains of whether there can really be a benefit from using a combination routine in routine treatment of most septic patients. A widely cited work [99] that is often reported [100] shows that there is actually a benefit for survival from using combination therapy. However, this work is a retrospective analysis and not a controlled prospective, randomised study and even here the apparent benefit is limited to some subgroups of patients. The more powerful beta-lactams (e.g. carbapenems and third and fourth generation anti-pseudomonal cephalosporins) have failed to prove any benefits in combinations, probably because they already act with a virtually 100% bactericide activity against the most common pathogens, so that there is little room for other improvements [22]. Some authors have carried out a meta-regression analysis of about 50 trials and have proven that there are no benefits from multiple agents, although there was a statistically significant effect in the more critical patients [101]. The most convincing evidence comes from a well-conducted, controlled, randomised trial on patients in Intensive Care with varying levels of sepsis that compared meropenem alone with a combination of meropenem and moxifloxacin [102] in which there was no evidence of benefits from combining the two antibiotics. It is difficult to interpret the information in this area as the populations of patients studied in the various trials and the regimes of antibiotics used vary greatly. In spite of this, taken as a whole, this data shows that there is no evidence to support the routine use of combined antibiotic therapy for most septic patients.

In spite of this, there is legitimate concern that in some clinical situations and actually in some countries, the risk of sepsis from gram-negative MDR is so high that combination therapy is essential. In particular, it has been suggested that in a somewhat counterintuitive way, organisms that produce carbapenemases such as strains of *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Acinetobacter* may benefit from treatments with combinations of carbapenems [103, 104]. The logic is that the two drugs together can reach the MIC concentration threshold in spite of in vitro resistance. A more recent work [105] however presents data that contradicts all this, suggesting that combination therapy was only efficient if the drugs were effective in vitro and administered together with colistin or tigecycline. None of these studies is free of methodological problems, however, and this is still an unresolved problem.

9.3.3 Should Beta-Lactam Antibiotics Be Administered by Continuous Infusion in Septic Patients?

Antimicrobial broad-spectrum beta-lactams, with their good safety profile, are a good choice as empiric agents for septic patients. Different antibiotics have different modes of action, and in the case of beta-lactams, the time over the MIC ($T > \text{MIC}$) (which is the amount of time during which the antibiotic concentration in the relevant tissue space exceeds the minimum inhibitor concentration required to kill the bacteria) is the critical pharmacokinetic characteristic that determines efficacy. These are the reasons why many have believed that it is much more sensible to administer beta-lactams by continuous infusion as this will optimise the $T > \text{MIC}$. The situation is complicated even further because the profound shift of fluids that can occur in septic patients, and intervention such as hemofiltration, can considerably alter the pharmacokinetics of several drugs, including antibiotics [106]. Sepsis studies have actually shown marked variability in serum levels of beta-lactams during treatment and have also shown that the administration of these drugs by continuous infusion truly improves the pharmacokinetic parameters [107].

The answer is by far not a clear one. In a 2013 preliminary study, some Australian authors from Brisbane proved that even though infusion did improve the pharmacokinetics, there was no overall effect on survival in Intensive Care, but there was a statistically significant improvement in clinical [108–109]. More recently, the BLISS trial reached practically the same conclusions [110]. In the meantime, the Brisbane group had published another large-scale, controlled, randomised trial that failed to prove a statistically significant benefit from continuous infusion [111]. Lastly, a meta-analysis of 632 patients studied three large-scale controlled trials and concluded that there was a statistically significant benefit from continuous infusion for both clinical care and for survival, but when the multi-variate analysis was carried out, the independent effect of continuous infusion was lost [112]. Those who defend this approach could argue that it is unreasonable to require that survival in Intensive Care or hospital outcome are the two primary end points of these trials, as the purpose of the intervention is to improve treatment of the infection, and there are several other reasons why a patient may not survive in Intensive Care or on admission to hospital, even if the infection is treated effectively. Other hypotheses include the possibility that it is only a subgroup of septic patients (usually the most ill ones) that will benefit or that it is necessary to monitor the drug to ensure that optimal levels of the drug are reached even with continuous infusion [113]. Increasing the beta-lactams dosage to bring them into the optimal range would however bring with some risks with it: extremely high doses are associated with neurotoxicity although this generally unusual. Lastly, it has been suggested that rather than the seric level of antibiotics, the critical measurement for efficacy is that actual bactericide effect in vivo, in the appropriate tissue space, against the specific infecting organism. A method has been described for measuring all this based on the time required for a culture to become positive in the presence of an antibiotic (time to positivity: Tpos), and it has proven that there is a correlation between Tpos and the length of stay in

Intensive Care [114]. It is a rather arduous method that measures seric levels, and it must still be decided whether it may have some clinical use.

To sum up, continuous infusion of beta-lactams is a logical indication with no significant risk; however if we take survival in Intensive Care as the final test of a new intervention, this strategy is not supported by current data.

9.3.4 Should We Use Biomarkers to Limit the Duration of Antibiotic Treatment?

Most clinicians agree that generally speaking, it is right for the duration of antibiotic treatment to be as short as possible, commensurate with obtaining a satisfactory clinical outcome. This applies to all clinical contexts and not just to sepsis, but it is interesting that the matter of therapy duration is not frequently studied. There are some well-known examples—infections of the urinary tract or tuberculosis—but most antibiotic prescriptions are based on habits and practice rather than on solid data obtained from comparative clinical trials. Again, the potential advantages of shorter courses of antibiotics are relatively non-controversial, and as Intensive Care is an area where antibiotics are highly used, there is much pressure to see how the use of antibiotics may be subject to limitations (antibiotic stewardship).

Biomarkers are a potentially attractive way of controlling the use of antibiotics. There is a large amount of literature regarding the use of biomarkers in sepsis, but in terms of their role in controlling antibiotics, recent works have concentrated on procalcitonin. There are two approaches that could be taken into consideration for the use of biomarkers (and one does not exclude the other): the first question—can I use a biomarker that tells me that the patient does not have an infection and I do not need to commence antibiotics or if I have already begun them I am now quite sure that there is no infection and can I suspend the antibiotics? Interestingly, the Surviving Sepsis Campaign takes this approach and recommends, but only with a moderate level of evidence, that procalcitonin or other similar biomarkers can be used to help the doctor in discontinuing empiric antibiotics in patients who initially appear to have sepsis, but who do not have subsequent evidence of infection. The alternative strategy is try to use a biomarker to answer the question: has the infection been cured and can I stop antibiotics?

There is still a large amount of evidence that suggests that the use of procalcitonin provides safe, credible information about when to discontinue antibiotics in patients with sepsis in Intensive Care [115]. Some studies have shown that sequential measures (normally every day) could identify positive- or negative-culture patients and also the ones that are destined to survive or to die [116] and several trials have shown that the use of antibiotics is less in patients who are followed with an active protocol based on procalcitonin measurements [117, 118]. Even more surprisingly a recent large trial also showed a benefit for survival [119]. A recent HTA [119] concluded that in spite of limited data, procalcitonin can be efficient and cost-effective when used to guide discontinuation of antibiotics in adults treated for suspected or confirmed sepsis in Intensive Care.

Still today, sepsis is a common, difficult problem. There is no magic bullet on the horizon, so in the meantime we need to optimise those aspects of the treatment that we can control by using the best quality data that we have. Faced with the problem of antibiotic resistance, we must use the antibiotics available with increasing shrewdness and while saving as much as possible. This is why it is necessary to run a microbiological path alongside the sepsis path, based on the modern development of molecular microbiological diagnostics and to run diagnostic stewardship alongside antibiotic stewardship [120, 121].

Sepsis stewardship, antibiotic stewardship and diagnostic stewardship are today both a moral and scientific obligation.

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Septic Shock and Hemodynamic Management

10

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10.1 Introduction

Sepsis has recently been defined as life-threatening organ dysfunction caused by a dysregulated host response to infection [1, 2]. Organ dysfunction is defined by the SOFA (sequential [sepsis-related] organ failure assessment) score. The quick SOFA (qSOFA) is recommended in the critically ill patient with suspected infection and severe hemodynamic instability with the detection of parameters such as alteration in mental status, respiratory rate >22/min, and systolic blood pressure <100 mmHg.

A qSOFA score ≥2 is an unfavorable prognostic index and requires the application of SOFA score to confirm the organ dysfunction and the diagnosis of septic shock, even if qSOFA seems to have a higher predictive value than SOFA score in septic shock. Even if the initial qSOFA is negative (≤2), it is necessary to repeat the evaluation in case of changes in the clinical status. The detection of an acute change in the total SOFA score ≥2 points (assuming the baseline SOFA score to be zero in patients without organ dysfunction) as a consequence of the infection suggests organ dysfunction in septic patients [1]. In this context, septic shock is the most severe clinical manifestation of sepsis in which the underlying circulatory and metabolic abnormalities are profound enough to substantially increase mortality. The infectious process triggers a systemic inflammatory response through a dynamic series of processes that cause the release of pro-inflammatory agents. Normally the pro-inflammatory activity induced by the infection is balanced by the anti-inflammatory activity performed by cytokines. The pathogenic mechanism of septic shock seems to be due to the complex interaction between the pathogen and the host's immune reaction which triggers a series of cascade processes with amplification of the response and overproduction of pro-inflammatory factors and mediators

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of inflammation [3]. All this leads to the liberation of oxygen-free radicals and nitric oxide from the cells with damage to the surrounding tissues and consequent amplification of the inflammatory response.

In fact, despite the better understanding of the pathophysiological mechanisms of sepsis and the constant review of the therapeutic strategy in order to improve the clinical prognosis, sepsis and septic shock are still one of the major causes of morbidity and mortality in patients admitted to critical care [4].

10.2 Pathophysiology

The hemodynamic profile of septic shock is characterized by a generalized vasodilatation with severe arterial hypotension and peripheral hypoperfusion [5]. The main pathophysiological determinants of acute circulatory failure in septic shock are the loss of vascular tone control and the decreased peripheral vascular resistance (RVP). In septic shock the loss of vascular tone control derives from the lack of modulation between vasodilatation and vasoconstriction; the production of inflammation mediators and the release of endogenous vasodilators from the cells in an oxidative stress state determine vasoplegia and hyperreactivity of the arteries to vasoconstrictor stimulation.

All this results in an alteration of the microcirculation and cellular perfusion.

This circulatory dysfunction results in the maldistribution of blood flow and oxygen supply to the various organs with consequent cellular damage. In fact, the balance between delivery and oxygen demand in cells is fundamental to guarantee adequate cell function in different metabolic conditions. The function of microcirculation is to ensure modulation of flow and supply of oxygen to cells in response to the different metabolic needs. For this reason, the blood flow increases in response to a series of signals sent by the cells in conditions of increased metabolism. In the initial phases of septic shock, self-regulation mechanisms maintain adequate blood flow and oxygen delivery at cellular level despite acute circulatory failure. The first and most immediate compensatory mechanism is arterial vasoconstriction which increases the RVP and, therefore, counteracts the loss of vascular tone, at least at the beginning, ensuring normal values of systemic arterial pressure. In septic shock microcirculation function is deeply altered, and consequently tissue perfusion is compromised. Microvascular alteration involves capillary leak and tissue edema with cell hypoxia. Therefore, even in the presence of apparently normal or even high CO and adequate DO2, tissue perfusion remains inadequate in septic shock.

10.3 Cardiac Dysfunction

Although circulatory dysfunction is considered the main determinant of hemodynamic instability in septic shock, the presence of a coexisting cardiac dysfunction may play a very important role in the pathogenesis of hemodynamic failure. Septic

shock is characterized by hypotension with important peripheral vasodilatation; therefore a possible cardiopathy might not be immediately recognized [6]. In septic shock sepsis-induced myocardium depression is the main cause of cardiac dysfunction even though, in the critically ill patient, it is not uncommon that a cardiogenic shock preexisted the septic shock. The pathogenetic mechanisms of myocardial depression in sepsis have not yet been sufficiently clarified, although the alteration of sepsis-induced myocardial contractility was described in 1984 [7]. The role of several cytokines such as TNF-α, IL-1, IL-6, and mitochondrial dysfunction appears to be established in the pathogenesis of sepsis-induced myocardium depression. At the same time, the alteration of intracellular calcium, the increased production of NO, the downregulation of beta-adrenergic receptors, and the attenuation of post-receptor signals seem to contribute significantly to the reduction of cardiac contractility. Myocardial damage can also result from the direct action of bacterial toxins, complement factors, and endogenous factors liberated from tissue damage induced by infection (DAMPS, damage-associated molecular patterns) [3, 8]. In patients with septic shock, cardiac dysfunction can affect both ventricles and both phases of the cardiac cycle. Generally, the left ventricular function is compromised by direct injury of the myocardium, while the right ventricular function can be altered due to primary myocardial damage or decreased as a consequence of pulmonary hypertension [6]. The most common manifestation of myocardial dysfunction during septic shock is cardiac hibernation that appears to play a protective role during myocardium functional recovery.

Diastolic dysfunction may occur during septic shock as an isolated form of myocardial injury or associated with LV systolic dysfunction. Although it is known that LV diastolic dysfunction is one of the major causes of heart failure with a high predictive value of long-term morbidity and mortality in patients with cardiovascular disease, it is less known in septic shock. Diastolic dysfunction is commonly found in septic shock and has a high independent predictive value of early mortality. The evaluation of diastolic function is therefore fundamental in the management of the patient with septic shock. In most cases the study of cardiac function in septic patients is focused on the evaluation of systolic function, and the main hemodynamic monitoring systems give us information on CO and pressures. The most recent studies show that the evaluation of diastolic function is just as important as understanding myocardial damage during septic shock. Diastolic dysfunction, isolated or associated with systolic dysfunction, has a high predictive value of short-term mortality in septic shock. For this reason, the early detection of diastolic dysfunction should lead to the appropriate therapeutic approach.

In patients with septic shock, right ventricular dysfunction is not uncommon. Functional alteration of the right ventricle may be isolated or associated with left ventricular systolic and/or diastolic dysfunction. Although direct damage of the right ventricular myocardium is one of the possible causes of ventricular dysfunction, the function of the right ventricle can precipitate secondarily to other causes including left ventricular dysfunction. In addition, multiple pathogenic mechanisms not strictly related to sepsis, such as mechanical ventilation, can negatively impact the right ventricular function.

Myocardial dysfunction occurs in about 50–65% of patients with severe sepsis and septic shock and has a wide clinical spectrum ranging from left ventricular dysfunction (systolic and/or diastolic) to right ventricular dysfunction. The routine use of echocardiography in the critically ill patient has identified three possible scenarios of myocardial dysfunction in the septic patient: *left ventricular systolic dysfunction*, *left ventricular diastolic dysfunction*, and *right ventricular dysfunction*. The various types of cardiac dysfunction can occur during septic shock in an isolated form, that is, a single alteration of the cardiac function or associated in variable proportions [9]. Although left ventricular systolic dysfunction is the most common dysfunction in septic shock, as already demonstrated by Parker's studies in the 1980s, it is only present in an isolated form in a low percentage of cases, being more often associated with diastolic dysfunction and/or right ventricular failure. In 20–60% of patients with ventricular systolic dysfunction, the ejection fraction is significantly reduced, and the left ventricular end-diastolic volume increases. Paradoxically, this type of myocardial dysfunction has a favorable functional recovery prognosis in most cases at the resolution of the septic process. Given the complexity of cardiac dysfunction during septic shock, the sepsis-induced myocardial damage should not only be referred to EF which, despite being a very important parameter for hemodynamic evaluation and therapeutic approach, cannot alone explain the wide range of functional alterations of the cardiac system that can occur in septic shock. Much emphasis has recently been given to the study of diastolic function whose alteration is often present in severe sepsis and septic shock and which seems to have an unfavorable prognostic role. The study of diastole is possible with echocardiography directly bedside and in a noninvasive way when a transthoracic approach is used; therefore this diagnostic tool is of great importance when monitoring patients with septic shock.

Serum cardiac troponin (cTn) levels are increased in 12–85% of patients with cardiac dysfunction during septic shock. Elevation of cTn, which is generally associated with left ventricular systolic dysfunction, has also been commonly seen in patients with isolated diastolic dysfunction. The increase in this myocardionecrosis marker is an unfavorable prognostic index, especially in the case of diastolic dysfunction.

Elevated blood levels of BNP (brain natriuretic peptide) or NT-proBNP (amino-terminal fragment of BNP) can be seen in patients with septic shock. As is well known, BNP has a high negative predictive value for cardiovascular dysfunction, while the positive predictive value is not so significant. The increase in this marker in septic shock is present in both left ventricular systolic dysfunction and in the isolated diastolic ventricular dysfunction. Both have a predictive value of mortality. Recent studies have shown that there is a disparity between the two markers where BNP values are very high and troponin levels are only slightly increased. This could be related to the fact that in septic shock the coronary flow is preserved, and therefore there is a high wall stress but only a minimal damage of the myocardiocytes [9].

10.4 Ventricular-Arterial Coupling

Recently, the role of ventricular-arterial coupling has been described in hemodynamic decompensation of septic shock [4, 5, 10]. In physiological conditions the two components of the cardiovascular system, the heart and the systemic circulation, interact dynamically in order to guarantee enough cardiac output and arterial flow for organ perfusion [5, 11]. Continuous modulation of compliance and resistance of the arterial bed in relation to cardiac performance adapts blood flow and perfusion pressures to the metabolic needs of the various organs in different physiological and pathological conditions therefore guaranteeing CO and perfusion. The cardiovascular system works better when it is coupled, that is when at every ejection the heart pumps the amount of blood that the vascular system is able to receive, and this happens at the lowest possible energy cost.

The ventricular-arterial coupling (V-A) is defined as the relationship between arterial elastance (Ea) and ventricular elastance (Ees); this ratio is considered normal when it is close to 1:

$$\mathrm{Ea} / \mathrm{Ees} = 1$$

Ees results from the relationship between end-systolic pressure and end-systolic volume of the left ventricle: the slope of the pressure-volume curve is defined as end-systolic ventricular elastance. Ees is considered a load-independent index of myocardial contractility.

Ea results from the relationship between stroke volume (SV) and systemic arterial pressure at various levels of SV variation. The slope of the curve that expresses this relationship is the arterial elastance. Ea is an index of the arterial tone as it is influenced by compliance and arterial resistance, aortic impedance, and systolic and diastolic intervals. In practice Ea represents the net load imposed by the arterial system to the SV. It is graphically represented by the slope of the line that joins the end-diastolic volume of the left ventricle (LV EDV) to the end-systolic pressure of the left ventricle (LV ESP) in the pressure-volume curve of the LV. In practice, Ea expresses the ability of the arterial system to increase blood pressure when SV increases.

The cardiovascular system expresses maximum efficiency when the ratio between Ea/Ees is equal to 1 which means that the value of Ea is about 1 + ½ the value of Ees. The cardiovascular system is decoupled by values of Ea/Ees $\geq$ 1.36. The alteration of the relationship may depend on the increase or decrease of Ea, Ees, or both.

In septic shock, the cardiovascular system is generally decoupled (Ea/Ees $\geq$ 1.36) with severe energy cost at the expense of functional efficiency. In most cases, Ea is increased due to pharmacologically induced arterial vasoconstriction, while Ees is decreased due to reduced myocardial contractility. In some patients with septic shock, Ea/Ees is normal; the cardiovascular system is therefore coupled, and the maintenance of CO and tissue perfusion happens anyway in favorable conditions. The most obvious explanation is that in these patients cardiac function is normal

and that Ea is also normal for a good therapeutic strategy with adequate hydration and appropriate use of inotropes and vasopressors. As we have seen, Ea/Ees is a reliable index of cardiovascular efficiency, and, as already mentioned, in septic shock it is common to find a decoupled system; the therapeutic strategy in these patients should be aimed at the normalization of Ea/Ees.

Currently the Ea/Ees measure can be obtained with the use of echocardiography directly at the patient's bed in a noninvasive way. This method has made continuous monitoring of the V-A coupling in the critically ill patient possible.

10.5 Hemodynamic Monitoring

Because hemodynamic instability, arterial hypotension, and signs of tissue hypoperfusion characterize septic shock, it represents a real medical emergency that requires both a diagnosis and an early treatment. The management of septic shock therefore requires careful hemodynamic evaluation to prepare the correct therapeutic strategy and follow its effects over time. Although arterial hypotension, defined as systolic pressure <100 mmHg or as mean arterial pressure <65 mmHg or as a decrease of >40 mmHg from baseline, is an important sign of acute circulatory failure, signs of tissue hypoperfusion are definitely more significant for the diagnosis and therapeutic follow-up of septic shock. The most important signs of tissue hypoperfusion are increased blood lactate levels ≥2 mmol/L and reduced values of central venous saturation (ScvO2) and/or mixed venous saturation (SvO2). The alteration of cellular metabolism in conditions of reduced or inadequate oxygen supply (DO2/VO2 mismatch) is characterized by an increase in blood lactate levels. Although lactates may also increase in the presence of normal blood flow and adequate oxygen supply, a value greater than 2 mmol/L, especially if seen in acute circulatory failure as in septic shock, is a clear sign of cell dysfunction. In this context, monitoring lactatemia values is mandatory in patients with septic shock in order to evaluate tissue perfusion. Recent sepsis guidelines recommend the assessment of lactatemia both for diagnostic purposes and for monitoring efficacy of therapy in patients with septic shock. An initial value of blood lactates ≥2 mmol/L identifies cell dysfunction and organ hypoperfusion. If hyperlactataemia persists after implementation of the therapeutic protocol, the prognosis is poor. The therapeutic strategy guided by the levels of lactatemia seems, as reported in literature, to reduce mortality by 20% every 2 h in the first 8 h of therapy. The normalization of blood lactate levels expresses clear improvement of tissue and cellular perfusion.

ScvO2 and SvO2 are clear indexes of tissue hypoperfusion and inadequate oxygen supply to cells when ScvO2 ≤ 70% and SvO2 ≤ 65%. Recently, the venoarterial carbon dioxide pressure gradient (v pCO2 − a pCO2) has been validated as an index of adequacy of cell perfusion during shock. A value ≥6 mmHg suggests tissue hypoperfusion even in the presence of normal central venous saturation values.

According to the recommendations of international guidelines [2], the hemodynamic treatment of septic shock provides in fact the prompt administration of fluids

to restore an efficient circulation, the use of vasopressors and inotropes to maintain CO, and adequate perfusion pressures. According to the recent recommendations of the Surviving Sepsis Campaign [2], the "fluid resuscitation" (30 mL/kg within the first 3 h) is still indicated as the immediate treatment for the correct management of the hypotensive state and the hypoperfusion that characterize septic shock, followed by norepinephrine infusion if MAP < 65 mmHg persists. Dobutamine should be added if hypoperfusion persists after volume and vasoactive drug administration. It is important to underline that in patients who still have signs of systemic hypoperfusion and arterial hypotension despite the initial administration of crystalloids as recommended by the guidelines, further volemic expansion may be necessary. In such patients, the administration of additional fluids must however be carefully guided by hemodynamic monitoring [12] in order to avoid water overload that can precipitate in acute pulmonary edema, especially if there is an underlying cardiac dysfunction.

10.6 Echocardiography

The role of echocardiography in the diagnostic-therapeutic process of septic shock has been validated in recent guidelines for the management of sepsis [2]. Although the main task of the echocardiographic examination is the morpho-functional study of the heart and of the cardiac structures, the echocardiographic examination allows the measurement of some hemodynamic variable that can be integrated into the cardiac function data and into the clinical parameters, identifying the hemodynamic profile in the septic patient with severe hemodynamic instability (Table 10.1). As already underlined, cardiac function can be depressed in patients with septic shock contributing significantly to circulatory failure and to the severe hemodynamic instability that characterizes this serious syndrome. Therefore, the study of cardiac function is fundamental for differential diagnosis and for the control of therapies. The echocardiographic examination in case of septic shock must be exhaustive and focused at the evaluation of the morphology and structure of the cardiac chambers and of the valvular apparatus, as well as the blood flow inside the cardiac chambers and intracavitary pressures and fluid responsiveness.

Diastolic dysfunction should be routinely investigated in patients with septic shock. Since fluid resuscitation is the fulcrum of therapy and of hemodynamic management of septic shock, it is very important to identify patients in whom fluid administration should be carefully monitored in order to exclude water overload that can precipitate into pulmonary edema.

Table 10.1 Echocardiographic evaluation in the patient with septic shock

Biventricular systolic function
Biventricular diastolic function
Effective circulating volume (fluid responsiveness)
Ventricular elastance (contractility)
Morphological evaluation of valvular apparatus and pericardium

Due to the extreme complexity and critical issue of the clinical scenario, patients with septic shock require advanced hemodynamic monitoring both in the diagnostic phase, where the understanding of the hemodynamic profile allows to categorize the type of shock, and in the clinical development to evaluate the response to therapy.

10.7 Conclusions

The patient's hemodynamic management in septic shock requires monitoring that allows real-time evaluation of the main hemodynamic variables in order to understand the patient and evaluate response to treatment.

Although the use of the pulmonary arterial catheter has revolutionized the management of the hemodynamically unstable patient, thanks to the interpretation of the hemodynamic data obtained, the increasing use of echocardiography in clinical practice has certainly changed the management of hemodynamic instability of these patients. Thanks to the possibility of using a noninvasive method as in the case of the transthoracic approach of echocardiography or semi-invasive when using the transesophageal modality, monitoring septic patients in a simple and reproducible way directly by the patient's bed is feasible. The specificity of the echocardiographic method consists in combining the acquired data on cardiac function with those obtained from hemodynamic monitoring in order to obtain a complete picture of the function of the cardiovascular system. Echocardiography has also allowed noninvasive evaluation of the V-A coupling whose role in the hemodynamic instability of septic shock has recently been emphasized.

In conclusion, the physiopathological complexity of septic shock from a hemodynamic point of view requires careful evaluation before starting the treatments. In fact, even the recommended therapies need a personalized assessment in order not to worsen an already critical state: for example, fluid resuscitation in the first hours in a patient with severe alteration of the ventricular compliance or the administration of norepinephrine in a patient with severe contractile dysfunction requires careful management. In this scenario the combination of pathophysiological information provided by echocardiography with those from traditional hemodynamic monitoring allows the clinician to manage the resuscitation in the critical patient with septic shock in a more "tailored" way.

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The Acute Respiratory Distress Syndrome: Diagnosis and Management

11

Davide Chiumello, Antonella Marino, and Antonio Cammaroto

The first of the acute respiratory distress syndrome (ARDS) description was in 1821 by Laennec. Since that many and more accurate definitions followed. Nowadays almost 5% of hospitalized and mechanically ventilated patients present ARDS diagnostic criteria [1]. ARDS can be generally defined as a new acute onset of hypoxemia and bilateral opacities after an insult direct or indirect to the lungs [2–4]. In 1994 there was the first shared definition, and then, in 2001, an update known as "Berlin definition" was made by an expert panel of the European Society of Intensive Care Medicine [4]. According to this new definition, ARDS is an acute form of diffuse lung injury that happens in patients with predisposing factors, with:

- Symptoms onset within 1 week of a known clinical insult or new or worsening respiratory symptoms
- Bilateral opacities not fully explained by effusions, lobar/lung collapse, or nodules
- Respiratory failure not fully explained by cardiac failure or fluid overload
- Hypoxia, classified by PaO_2/FiO_2 ratio measured with at least PEEP of 5 cmH_2O into: mild (200 mmHg $\leq PaO_2/FiO_2 \leq$ 300 mmHg), moderate (100 mmHg $\leq PaO_2/FiO_2 \leq$ 200 mmHg), severe ($PaO_2/FiO_2 \leq$ 100 mmHg) [2–4].

This new definition brings a small, but very important, improvement in predictive ability for mortality (Area Under the Curve [AUC] 0.577) [5].

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Recently it has been demonstrated that classifying ARDS severity at a standard level of positive end-expiratory pressure (PEEP) of 5 cmH_2O allows a better alveolar edema and potential of lung recruitment estimation than using higher clinically set PEEP levels [6].

11.1 Diagnostic Evaluation

Main ARDS finding is the increased permeability of lung capillaries due to both alveolar epithelium and end vascular endothelium injuries. As consequence a protein-rich fluid accumulates into alveoli, cytokines are released, and a diffuse alveolar injury develops [7]. Alveolar epithelium is composed of type I and II pneumocytes. Injury of type I cells leads to liquid accumulation into alveoli and to a reduction in clearance ability, while injury of type II cells leads to surfactant reduction, alveolar collapse, and lung compliance decrease [5]. ARDS pathological pathway is described as a three-phase process: inflammatory, proliferative, and fibrotic phase with each one that could be stopped or complicated by worsening of patient's symptoms or other complications. Common ARDS risk factors are pneumonia, sepsis, inhalation/aspiration injury, trauma, pancreatitis, burns, non-cardiogenic shock, drowning, and transfusion-related acute lung injury (TRALI) [8]. However, pneumonia is the leading cause of ARDS, so microbiological investigations aiming to pathogen's identification are milestones in the diagnostic process. Community-acquired pneumonia is still the leading cause of ARDS in case of pneumonia etiology [9], while a recent study found that viral pneumonia is becoming more frequent going from 5% to 10% [10–12] to 36%. Among viral pneumonia, respiratory virus is predominant [13]; in this case, the first-line diagnostic test is polymerase chain reaction (PCR) test on bronchoalveolar lavage (BAL) [14]. Less frequent ARDS causes are represented by CMV and HSV infections [12, 15] and by parasites (such as *Toxoplasma gondii*, *Aspergillus fumigatus*, *Pneumocystis jirovecii*) mainly present in immunocompromised patients.

Early and correct treatment of the triggering cause appears to be decisive in improving patient's outcome; thus a fast and precise etiological diagnosis is very useful. It is therefore important to first investigate the possible infectious causes by performing blood cultures, urine samples for the detection of *Legionella pneumophila*'s and *Streptococcus pneumoniae*'s antigens, serological tests for the research of *Mycoplasma pneumoniae* and *Chlamydia pneumoniae*, and microbiological samples of the respiratory system, preferably performed with BAL [16].

However, it is worth knowing that ARDS without identifiable risk factor have a prevalence of 7.5% [17]. In this scenario the cytological analysis on BAL sample, chest CT scan, and an immunological evaluation is useful while looking for less common causes. If neither radiological CT images nor alveolar bronchoscopy cytology is decisive, a diagnostic open lung biopsy (OLB) may be done. OLB has also a role in the evaluation of histological lung characteristics evolution, helping the clinician in the decision toward the use or not of corticosteroids [15]. Figure 11.1 represents the diagnostic flowchart in ARDS. Lung CT scan is frequently used to

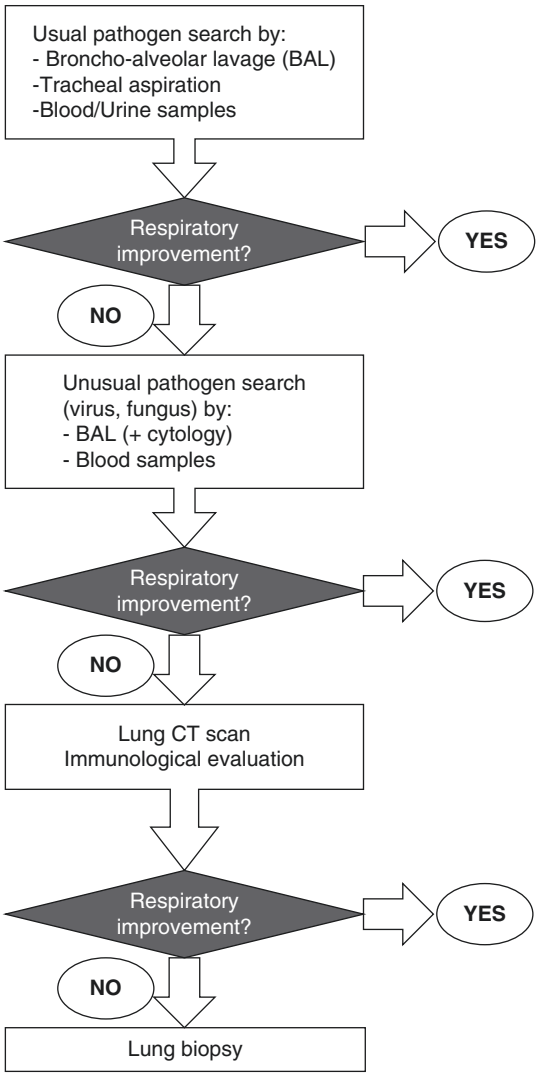

Fig. 11.1 Diagnostic flowchart in pulmonary ARDS

evaluate lung morphology, which in ARDS is characterized by consolidated regions (homogeneous areas with increased density without identifiable vessels or bronchi), ground glass regions (areas with increased density but with still visible vessels), and normally aerated regions. Since lungs are characterized by diffuse edema, with the superimposed pressure causing atelectasis and collapse of dependent lung zones, consolidated areas are typically located in dependent lung regions [18]. Lung CT scan is also helpful in lung potential of recruitment evaluation, i.e., the proportion of consolidated lung that regain aeration after an increase in alveolar pressures. In ARDS patients, potential of recruitment could range between 0% and 70%.

Moreover, lung CT scan could help clinician in identifying ARDS etiology; in fact, in pulmonary ARDS consolidated and ground glass areas are similar, while in extrapulmonary ARDS ground glass areas are predominant [19]. Next to CT scan, ultrasound of lung parenchyma, pleura, and air may be helpful in diagnostic evaluation, clinical management, and monitoring of ARDS patients [20–23]. In respiratory failure patients, lung ultrasound is characterized mainly by B-line (hyperechogenic vertical artifact line that starts from pleura) [21], while the B-pattern composed of three or more B-lines appears to be correlated with an interstitial pathological process [24]. A bilateral homogeneous B-pattern is not decisive between ARDS and cardiogenic edema and deserves further analysis [25], while bilateral, not-homogeneous B-pattern plus C-pattern composed of consolidated areas and pleura abnormalities are suggestive of ARDS etiology [26]. Figure 11.2 shows possible lung ultrasound patterns.

11.2 Treatment

The acute respiratory failure management includes early recognition of the triggering cause and timely targeted treatment. Besides that, supportive treatments must be started to assure adequate respiratory gas exchange while minimizing the risk of ventilator-induced lung injury (VILI) onset. Actual knowledge suggest that in most severe ARDS patients, spontaneous respiratory triggering could be dangerous; thus the spontaneous breathing approach should be used only in mild and moderate ARDS patients. Different therapeutic targets should be met using different pharmacological and non-pharmacological approaches and different mechanical ventilation modalities.

11.2.1 Noninvasive Mechanical Ventilation

Noninvasive mechanical ventilation (NIMV) is able to reduce patient's work of breathing and intrapulmonary shunt, improving gas exchange, avoiding patient's deep sedation, and reducing the ventilator-associated pneumonia risk. However, NIMV use is widely debated due to the high risk of failure (i.e. an intubation rate between 30% and 86% and a mortality rate between 15% and 71%) [27], and the consequent risk of delaying intubation and mechanical ventilation in patients who fail this kind of support. High-flow nasal cannula (HFNC) represents an additional noninvasive ventilatory support that ensures patient's administration of a heated and humidified high flow of oxygen through the patient's nose and has shown to be able to reduce respiratory work while improving oxygenation and CO_2 elimination, providing the patient with a positive end-expiratory pressure (PEEP) that varies between 4 and 6 cmH_2O. A recent study carried out on patients diagnosed with ARDS, as in the case of NIV [28], showed however a high rate of HFNC failure, equal to 40% [29].

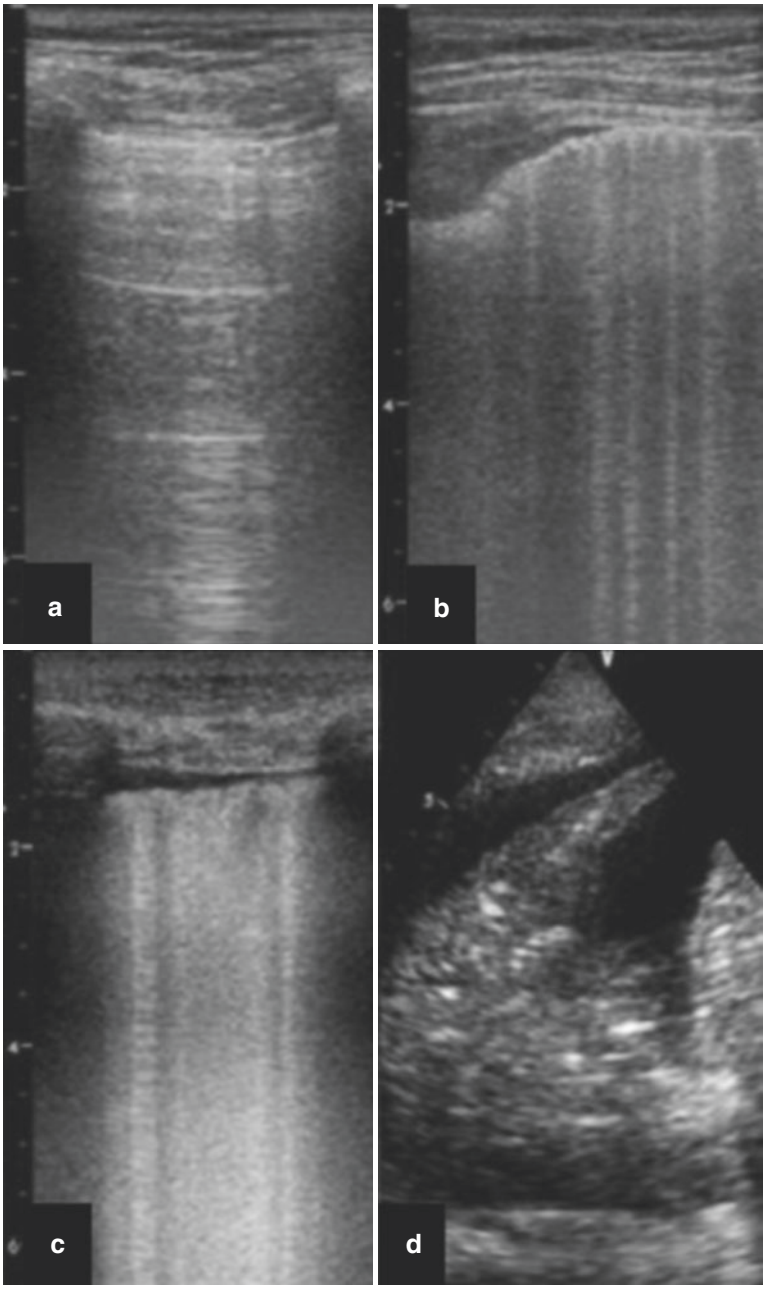

Fig. 11.2 Lung ultrasonographic patterns. Panel (**a**) = normally aerated lung with pleural sliding (0 point). Panel (**b**) = B-lines separated by at least 5 mm (1 point). Panel (**c**) = B-lines separated by less than 5 mm (2 points). Panel (**d**) = consolidated lung, hyperechoic areas, and bronchograms (3 points)

11.2.2 Invasive Mechanical Ventilation and Pulmonary Recruitment

Invasive mechanical ventilation is a supportive therapy able to guarantee adequate gas exchange (increase PaO_2 and clear CO_2 adequately) and reduce the respiratory muscle activity [30]. Mechanical ventilation presents a double effect on patient oxygenation: it allows a continuous and precise FiO_2 titration and during the inspiratory phase applies a positive airway pressure that reopens collapsed alveolar units. This second effect is likely to be limited in time, unless an adequate positive end-expiratory pressure is applied during the expiratory phase to avoid the alveolar re-collapse [31]. The ventilatory setting in ARDS patient remains a daily challenge, and the choice should be adapted to each patient considering his/her hemodynamic parameters, respiratory mechanics, and gas exchange. During the last 30 years, literature has already widely demonstrated that high-volume/high-frequency ventilation can damage the lungs [32] mainly through the cycling collapse-reopening and alveolar overdistention phenomena that contribute to the so-called atelect-trauma [33]. The application of high PEEP allows collapsed alveoli reopening and intrapulmonary shunt reduction, moreover it reduces the repetitive alveolar opening and closing which occurs during the respiratory cycle [34]. However, it's not always useful to set high PEEP levels, as it could appear at first; indeed, two randomized and controlled trials comparing ARDS patients treated with low vs. high PEEP [35, 36] have not shown any benefit from the use of the high PEEP strategy. These contradictory results can be explained by the pulmonary recruitment concept, i.e., the volume of collapsed pulmonary parenchyma in which is possible to re-establish a normal aeration by an increase in the airway pressure [37]. To recruit collapsed lung regions and keep them open, it is necessary to apply an airway pressure higher enough to counterbalance the superimposed pressure, i.e., the pressure generated by the weight of the lung and the rib cage that acts on the lung below [38]. Several maneuvers can be used to recruit the lung: the sigh (i.e., one high-volume breath intermittently provided by the ventilator), the extended sigh (i.e., a progressive increase in PEEP or a progressive increase in both PEEP and plateau pressure), and the sustained inflation (i.e., a static sustained increase in the airway pressure [35–40 mmHg] protracted for 20–40 seconds) [39]. The target of these maneuvers is to increase the transpulmonary pressure for a period of time sufficiently long to re-inflate the alveolar units previously closed. While these maneuvers are able to improve the oxygenation for a variable period of time, their systematic use did not result in a mortality reduction [40]. While the lung CT scan is the gold standard for the potential of recruitment evaluation, the lung ultrasound seems to be a promising alternative available at the patient's bedside with several advantages such as safety and repeatability; however further studies are necessary to confirm this data [41].

11.2.3 Choice of PEEP

As known, the choice of a too low end-expiratory positive pressure could cause the collapse of otherwise recruited parenchymal areas, while the choice of a too high

end-expiratory positive pressure could increase dead space and tissue stretch thus raising the risk of lung damage. The PEEP optimization is therefore crucial in the individual patient to avoid the continuous opening and closing and the overdistention phenomena in some parenchymal areas. Different approaches have been proposed to choose the best PEEP, but the most commonly used is the one based on the PEEP/FiO_2 table, which use the patient's saturation/oxygenation as target [36]. Another method is based on the respiratory mechanics: PEEP is progressively increased while keeping the tidal volume constant and the airway pressure within a safety range (26–28 cmH_2O) [42]. Conversely, our group uses the esophageal pressure variation during the breath, to evaluate the transpulmonary pressure. It is measured as: (plateau pressure − total PEEP) − (esophageal pressure at plateau − esophageal pressure at ZEEP). The transpulmonary pressure is a pulmonary stress indicator, and it should not exceed 15 cmH_2O [43].

11.2.4 Choice of Tidal Volume

The main determinants of the ventilator-induced lung injury are strain (defined as the lung deformation induced by the application of the tidal volume) and stress (i.e., the transpulmonary pressure determined by the strain) [44]. Therefore, to maintain low stress and strain, it is necessary to apply a low tidal volume or have a high residual functional capacity [42, 45]. A recent meta-analysis has shown how the use of "protective ventilation," with a tidal volume of 6 mL/kg (calculated on kg of ideal body weight), guarantees a reduction in mortality [46]. Since the actual body weight isn't an accurate index of lung size, it is recommended the use of the ideal weight (calculated based on gender and height) to calculate the best tidal volume; however, the ideal weight is not correlated with the functional residual capacity of the lung, highlighting that the same tidal volume can generate very different stress and strain values [47] in people with the same gender and height but different functional residual capacity. Amato, in a recent study performed over a group of 3500 patients with ARDS ventilated with different combinations of PEEP and tidal volume, showed that the variable most closely associated with the outcome of patients is represented by the driving pressure of the airways, calculated as (plateau pressure − total PEEP). Furthermore in that study was demonstrated that high levels of PEEP appeared protective only when associated with reduced driving pressure, with a pressure cutoff of 15 cmH_2O [48]. However, the use of driving pressure has several limitations: the main one is the fact that the pressure that extends the lung is the transpulmonary pressure and not the airway pressure.

11.2.5 Target of Blood Gases

Current recommendations encourage the use, in mechanically ventilated patients, of a conservative oxygen strategy with an O_2 arterial saturation target ranging from 88% to 95%. The associated use of a "protective ventilation," with the aim of

reducing the damage induced by ventilation, can however cause the development of hypercapnia; however a $PaCO_2$ around 70 mmHg and a pH of about 7.20 have been proved to be safe [49, 50], except in special cases such as patients with intracranial hypertension or severe heart failure. The rationale for this permissive strategy lies in the known effect that hypercapnic acidosis exerts on arterial and tissue oxygenation [51].

11.2.6 Neuromuscular Blockade

In order to guarantee a better patient adaptation to the ventilator, to reduce the oxygen consumption related to the respiratory muscle activity and to guarantee a protective transpulmonary pressure, the use of neuromuscular blockers is accepted in clinical practice [49]. Moreover, neuromuscular blockers have the ability to reduce stress and strain applied to the parenchyma. Neto demonstrated that, in patients with severe ARDS, a short course of treatment with neuromuscular blockers was associated with a mortality decrease [52].

11.2.7 Prone Positioning

The indications for the prone positioning have changed over time: once it was used to improve arterial oxygenation in the most severe forms of respiratory failure [53, 54]; while nowadays it aims to achieve a more homogeneous distribution of stress and strain within the lung parenchyma, acting in synergy with the remaining therapies and protecting against the ventilator induced lung injury [55]. The prone positioning improves ventilation/perfusion coupling thus improving the CO_2 elimination and improves the ventilation distribution across the dorsal regions of the pulmonary parenchyma [55, 56]. The association of prone positioning and the use of neuromuscular blockers, in patients with severe ARDS, seems to have a synergistic effect on oxygenation and overall duration of mechanical ventilation and seems to be associated with a better outcome. However, these data needs further studies to confirm.

In any case, the prone positioning presents few absolute contraindications, namely, pregnancy, open abdominal treatment, unstable fractures, and hemodynamic instability [55].

11.2.8 Corticosteroids and Inhaled Vasodilators

As shown above, the central role in the pathogenesis of ARDS is played by the inflammatory response that develops in the lung. Several trials have been performed over time to evaluate the use of corticosteroids in the treatment of respiratory distress syndrome, but the results appeared controversial [57, 58]. Meduri in his study carried out in the early phases of the ARDS, showed that the use of a decremental infusion scheme of corticosteroids leads to a mortality reduction in intensive care

[57]. However, in other studies, this result has not been confirmed [58, 59]. Although nitric oxide (NO) has a known vasodilatory effect on the pulmonary vessels thus ensuring an improvement of the ventilation/perfusion coupling, its use in patients with ARDS is not universally accepted [60]. In fact, it has not been clearly demonstrated its benefit in terms of mortality, while its use is burdened by possible serious complications, such as renal failure [61].

11.2.9 Extracorporeal Support

The use of extracorporeal membrane oxygenation (ECMO) in the treatment of severe respiratory failure was born around the 70s with the aim of properly oxygenating the patient ensuring a protective ventilation, reducing the chances of lung damage. Several observational studies have demonstrated various ECMO's benefits in patients with respiratory failure. However, the CESAR study, a recent randomized trial, showed an increase in survival at 6 months (63% vs. 47%) but no difference in quality of life and spirometric parameters between patients undergoing conventional mechanical ventilation and extracorporeal support in reference ECMO centers [62]. Therefore, considering the non-univocal interpretation of the data coming from this trial, nowadays it is not possible to conclude for a superiority of ECMO support compared with the association of the supportive therapy listed above [63].

11.3 Weaning from Mechanical Ventilation

It is of crucial importance the choice of the right moment to start the weaning from mechanical ventilation and to extubate the patient: any delay in extubation increases the risk to develop ventilator-associated pneumonia [64]; while a premature extubation can lead to a prolonged stay in ICU [65] and/or to a new need of invasive respiratory support. The weaning from mechanical ventilation is considered difficult in the 20–30% of mechanical-ventilated patients: the failure of the weaning process is defined as the inability to overcome a spontaneous breathing test or as the need for re-intubation within the first 48 hours from the endotracheal tube removal [66]. The causes of weaning failure are complex and determined by different factors; the main ones are listed below.

11.3.1 Airways Resistance

In the patient with a difficult weaning, an increase in the airways resistance should be considered. Moreover, a secondary tracheal obstruction caused by tracheal stenosis, tracheomalacia or the development of granulation tissue, can contribute to a complicated weaning from mechanical ventilation [67]. In ARDS patients an increase in airway resistances is typically due to bronchial walls edema of the small airways.

11.3.2 Neurological Alterations

The delirium seems to be the more frequent neurological alteration associated with a difficult weaning, with a four-time extubation failure rate than a patient without neurological complications [68]. Delirium diagnosis is simple thanks to the use of validates scales, such as CAM-ICU. Psychiatrists and psychologists could be helpful in other cognitive disturbances diagnosis different from delirium. A well-known risk factor for delirium is represented by sedation, in particular when midazolam is used [69]. The implementation of a daily sedative wash-out protocol, possibly together with a spontaneous breathing trial, can be associated to a reduction in ventilatory support length [70]. The depression development, common in patients staying in ICU for long periods, seems to be associated to an increased risk of weaning failure [71]. Antidepressant drugs seem to foster weaning from mechanical ventilation, even if only few data are available at the moment [72].

11.3.3 Cardiovascular Alterations

In the patient affected by an alteration of the myocardial contractility, the shift from mechanical ventilation to spontaneous breathing causes an increase in the cardiovascular work, mainly due to two factors: an intrathoracic pressure variation that causes changes in preload and afterload and an increase of the oxygen consumption by respiratory muscles [73]. An accurate cardiovascular evaluation in mechanically ventilated patients makes the introduction or the optimization of the appropriate therapy possible: this allows a reduction of the weaning failure risk.

11.3.4 Diaphragmatic and Respiratory Musculature Function

The beginning of weaning causes an increase in respiratory muscle workload that frequently appears to be already weakened. In assessing the cause of muscle weakness, it is important to bear in mind that the respiratory muscle dysfunction can result from a damage located anywhere on the axis from the afferent chemoreceptors, to the respiratory center, to the single muscle fiber [73].

The cause of the failure is frequently represented by a diaphragm alteration that can be secondary to two conditions that often coexist in the same patient: the critical illness polyneuropathy (CIP) involving the phrenic nerve and, more often, the critical illness myopathy (CIM). Several works have demonstrated that in mechanical-ventilated patients, there is often an alteration of the respiratory muscle contractility [74]. Before implementing weaning-from-mechanical-ventilation protocols, it is necessary to carefully assess the diaphragmatic function so as to exclude the presence of alterations. To do so, some tests used in clinical practice are here below displayed.

- $P_{0.1}$: it is the most frequently used test for the respiratory drive evaluation in mechanically ventilated patients. In order to carry out this test, the ventilator's

inspiratory valve is closed, and the pressure fall within the first 100 msec after the patient's inspiratory attempt is recorded. Usually, the $P_{0.1}$ value varies between 0.5 and 1.5 cmH_2O. It is important to note that this parameter depends both on the inspiratory muscular strength and on the respiratory drive.

- Maximal inspiratory pressure (MIP): represents the maximum pressure that the patient can generate by inhaling against a completely occluded airway, starting from functional residual capacity (FRC). The minimum thresholds are -75 cmH_2O for men and -50 cmH_2O for women [75]. Theoretically, the most negative values exclude the presence of a significant muscular weakness.
- Rapid shallow breathing index (RSBI): introduced by Tobin [76], it is one of the most common indexes used to evaluate patients in weaning process. It is defined as the ratio between the respiratory rate and the tidal volume expressed in liter. Patients that tend to breathe with a higher respiratory rate and with a smaller tidal volume have a high RSBI and more probably a higher risk of weaning failure. The majority part of centers considers a RSBI < 105 adequate to start weaning the patient from mechanical ventilation [77].

Mechanical ventilation is a life-saving intervention in patients affected by acute respiratory distress, but it is also associated with complications. Therefore it is desirable to wean patients from mechanical ventilation as soon as the underlying cause that led to the need for ventilatory support is resolved or the patient has sufficiently improved and is able to sustain spontaneous breathing with adequate respiratory mechanics and gas exchange. Recently, there were published some guidelines aimed at giving indications on which weaning/extubation techniques it is recommended to use in patients under mechanical ventilation [78]:

- For acutely hospitalized patients ventilated more than 24 h who are able to make a weaning attempt, it is recommended to carry out an initial spontaneous breathing trial with inspiratory pressure support (5–8 cmH_2O).
- For acutely hospitalized patients ventilated for more than 24 h, it is suggested to use protocols to minimize sedation or guarantee sedative suspension periods, during which carry out a spontaneous breathing trial.
- For acutely hospitalized patients ventilated more than 24 h at high risk for extubation failure and who have passed a spontaneous breathing trial, it is recommended the application of noninvasive ventilation (NIV) following extubation.

11.4 Conclusions

Still today, ARDS represents a syndrome with a globally high incidence and a high mortality rate that varies between 40% and 60%. The use of a systematic diagnostic approach can help physicians to rapidly identify the triggering cause of the syndrome, making it possible to quickly start with the right therapy. Chest imaging, mainly represented by CT scan, is of primary relevance both in the diagnostic pathway and in the evaluation of lung parenchyma recruitability. The use of lung ultrasound is gaining a pivotal role in the daily bedside evaluation of the patient, thanks

to its role in the differential diagnosis and to the possibility to evaluate right and left ventricular function. The supportive treatment guaranteed to patients with respiratory distress needs to be oriented to the maintenance of vital functions, to the improvement of gas exchange and to the reduction of lung injury risk.

In order to avoid ventilator-induced lung injury and to set a lung protective ventilation, it is useful to monitor functional residual capacity (FRC) and transpulmonary pressure.

In the most severe cases, it can be useful to use neuromuscular-blocking drugs and prone position so as to improve ventilation/perfusion ratio. Another challenge for physicians seems to be the weaning from mechanical ventilation: the aim is to exclude all the alterations that may delay or make fail the respiratory weaning. The latest guidelines written by the American Thoracic Society and the American College of Chest Physicians are useful to treat the patient in this crucial phase.

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Airway Management in Pediatric Patients

12

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Airway management represents the first priority for the anesthesiologist who is asked to treat a critically ill child.

During pediatric age, the incidence of unpredicted difficult intubation is rare, and most children with difficult airway can be identified during preoperative evaluation.

However, unpredictable difficulties at intubation and/or ventilation may be a cause for high mortality and morbidity [1].

Emergency intubation out of the operating room (i.e., in the emergency room, emergency department, or medical ward) has an increased morbidity and mortality.

While difficult airway management guidelines for the adult were published in the 1990s and are commonly applied from anesthesiologists, in the pediatric field, they are more recent and handled by regional or national societies. Indeed, many anesthesia departments have simply rearranged the adult guidelines without specific pediatric criteria [2–4].

In Italy pediatric airway management guidelines' development was started in 2006 by the SIAARTI/SARNePI group, involving experienced pediatric anesthesiologists and intensivists. Unfortunately, nowadays there are no randomized clinical trials that can support the development of guidelines with evidence of strong recommendation.

That's the reason why the few documents published until now are mostly based on a panel expert consensus (Delphi method).

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At the end of the document, expert opinions are classified as recommendation grade A, B, C, D, or E depending on the consensus percentage obtained from the panel in relation to three recurrent clinical cases: (1) difficult mask ventilation, (2) difficult intubation, and (3) difficult ventilation and intubation (cannot intubate and cannot ventilate, CICV). Particularly, Italian guidelines are extended also to newborns, reflecting our specific organizational model in which the anesthesiologist is involved in the management both of the critical newborn in the delivery room and the children in the pediatric intensive care units. Moreover, in the Italian guidelines, a large section is dedicated to the management of the expected difficult intubation, regarding both the planning of anesthesiologic procedures and operative procedures on difficult airways and preparation of instruments needed [5, 6].

The purpose of this chapter is to review the principal papers published about pediatric airway management, with particular attention to our national society guidelines that are so far the landmark for most anesthesiologists and intensivists. Particularly, the peculiar anatomic and physiological characteristics of children, the preoperative evaluation, the use of specific materials, and difficult intubation situations will be discussed.

12.1 Peculiar Anatomic and Physiologic Characteristics in Children

Some peculiar anatomic characteristics of the airway in children are important for the planning of intubation and ventilation procedures.

These characteristics include (1) prominent occipital bone, (2) macroglossia, (3) large epiglottis, and (4) higher position of the larynx (C3–C4) if compared to adult population.

Children and infants up to 3 months are considered prevalent nosebreathers for the presence of a large, omega-shaped epiglottis in a higher position (C4 vs. C6) that tends to hide the laryngeal aditus in direct laryngoscopy. The narrowest part of the pediatric airway is in the subglottic area, at the level of the cricoid ring. The area corresponding to the ventilatory surface is increased during inspiration and decreased during expiration, with consequent interruption of the expiratory flow and the subsistence of a positive end expiratory pressure that keep the chest wall stable preventing its collapse [7, 8].

Up to 8 years, the pediatric larynx is cone-shaped, and its narrowest point is immediately subglottic at the level of the cricoid ring (the only one complete ring of the tracheobronchial tree) [9].

Furthermore, the anterior commissure of the glottis is more caudal than the posterior so that the endotracheal tube may stop at this level and little rotation is needed to assure further advancement [5, 10].

About anatomic characteristics, just few cases of difficult intubation are reported in literature for healthy children, while different reports describe very difficult

situations of the management of airways in children with craniofacial and upper airway malformations (Pierre Robin syndrome, Treacher Collins syndrome, Kabuki syndrome, Noonan syndrome, Franceschetti syndrome, achondroplasia, arthrogryposis, osteomandibular synostosis, mucopolysaccharidosis, cleft) and/or lower airway malformations (subglottic or supraglottic hemangiomas, subglottic or supraglottic stenosis derived from neonatal intubation, vascular rings). Particularly, in the craniofacial malformations (Pierre Robin, Treacher Collins, Kabuki, Franceschetti), the difficulty to intubate is caused by the impossibility to visualize the laryngeal aditus with direct laryngoscopy, preferring elective fiberoptic intubation with sedation and maintenance of spontaneous breathing and the creation of a protection tracheostomy for the postoperative period, in selected cases [11–16].

On the other hand, supraglottic or subglottic stenosis due to previous intubation can make the progression of the endotracheal tube through the laryngeal aditus, cricoid, or trachea very difficult or impossible [17, 18].

Concerning physiological characteristics, newborns and infants are in a disadvantageous condition compared to adults regarding onset of hypoxia and hemodynamic complications. In fact, for this population, acute hypoxemia is the principal cause of bradycardia and cardiac arrest.

In the term newborn, FRC (*functional residual capacity*) is about 30 mL/kg, and the compliance of the respiratory system is 5 mL/cmH_2O (1.5 mL/kg). In a 3 kg newborn, minute volume ventilation is 600 mL (with dead space about 50% of tidal volume with a mean alveolar minute ventilation of 300 mL/min) with RR 30–45 breaths/minute. Total resistance of the respiratory system is about 70 cmH_2O L/s, principally distributed in distal airways [19]. If compared to adult population, the newborn has a reduction of the compliance by one-twentieth and an increase of total resistance of about 15 times. The majority of the impedance is due to the lung, depending on the presence of surfactant into the alveoli. Instead the chest wall has a high compliance due to the absence of ossification. During the second year of life, the respiratory system develops, and the ratio between lung and chest wall compliance becomes about 50%, as in adults [20]. In this situation, the respiratory work in an infant is mostly spent to keep the alveoli open in the absence of the stabilizing role of the chest wall.

In addition, infants have a relative immaturity of the central system of control of breathing and a reduced endurance of respiratory muscles (due to the lack of type 1 muscular fibers). In this condition, the loss of spontaneous breathing caused by pharmacological sedation leads to a rapid alveolar derecruitment resulting in hypoxemia, bradycardia, and low cerebral and systemic perfusion. In fact, cardiac output (HR × SV) in infants is strictly related to a high heart rate. The elevated tissue oxygen consumption (5–8 mL/kg/min) keeps the infant more susceptible to hypoxia during bradycardia and desaturation [19].

For all these considerations, children up to 3 years are the pediatric population more at risk of respiratory complications during the management of the airways such as intubation and mechanical ventilation.

12.2 Approach to Intubation in Children

Considering elective intubation in the operating room, several studies describe that it is a safe procedure, with a percentage of difficult intubation from 0.25% to 3% in the healthy child [21–25].

In contrast, emergency pediatric intubation (emergency room, ward) is characterized by elevated morbidity and mortality because of the limited possibility to perform adequate ventilation, the limited availability of adequate materials, and the emergency nature of the event. In this situation important desaturation (14–29%), hypotension (3.21%), cardiac arrest (1%), right bronchial intubation (3–6%), esophageal intubation (10%), and airway lesions (2.5%) are described [26–30].

For these considerations, it is clear that one of the priorities for the operator is to identify children with potential difficult airways in order to program, if possible, the procedure with lower risks and the most appropriate pharmacological approach, preparing the most suitable material for the management of the child and considering the possibility of a secondary transport to a pediatric center for children with known malformative disorders or previous difficulties who need an endoscopic or surgical approach for the management of the airway or a postoperative management in a pediatric intensive care unit.

12.3 Pediatric Airway Evaluation

In the pediatric population, most of the difficult intubations are predictable by anamnestic and clinical criteria considering the particular anatomic and physiological characteristics described above [1].

Particular attention must be paid to the following aspects: (1) presence of apneas, (2) stridor, (3) alterations in the tone of voice, (4) recurrent laryngeal infections, (5) swallow disease or gastroesophageal reflux disease, and (6) previous difficult intubation.

The Mallampati score cannot be applied to children, so clinical examination must be focused on potential pathological aspects: reduced mouth opening, macroglossia, and micrognathia [5–8]. Some malformative conditions characterized by micrognathia, retrognathia, mandibular hypoplasia, and glossoptosis are considered the most common conditions associated with difficult intubation. This is caused by an altered insertion of the tongue in the hypopharynx (glossoptosis) leading to an almost impossible epiglottis loading during direct laryngoscopy (Pierre Robin syndrome and Treacher Collins syndrome) [11–16].

Other particular aspects on the clinical evaluation are about (1) the temporomandibular joint mobility assessment, whose limitation is extremely uncommon except in lesions, trauma, or burns; (2) atlanto-occipital joint limitations (head extension <35°), characteristic of some specific syndromes such as juvenile rheumatoid arthritis, multiple congenital arthrogryposis, Klippel-Feil syndrome, or Goldenhar syndrome; and (3) atlanto-occipital joint instability (Down syndrome, osteogenesis imperfecta).

12.4 Equipment and Materials

According to Italian guidelines, the material for the airway management is divided in two groups: (1) essential equipments for nonspecialized centers—facial masks, Guedel cannulas in different sizes, conventional rigid laryngoscopes with straight and curved blades, endotracheal tubes from 2 to 6 mm ID, tracheal tube introducers and guides, Magill forceps, soft short stylets, pediatric laryngeal mask airways, and needles for cricothyroid puncture—and (2) essential equipment for specialized centers: flexible bronchoscope with light source, masks and facial cannulas for fiberoptic intubation, rigid bronchoscopes, cricothyrotomy set, and retrograde intubation kit [5].

All the equipments for the difficult management of pediatric airways must be checked and kept in a specific tray in the operating room, delivery room, or intensive care unit. Moreover, considering the infrequence of difficult intubation in children, surgical and emergency staff should be trained to use life-saver tools such as neonatal laryngeal masks and to perform elective fiberoptic intubation. Anyhow, spontaneous breathing fiberoptic intubation is still the safest procedure [31–33].

Nowadays new devices for pediatric intubation are available and are created to improve the endoscopic view on the airway (Storz videolaryngoscope with straight blade or Miller 1 blade, fiberoptic laryngoscope Airtraq, GlideScope with pediatric blades). Even if clinical trials are still ongoing, there are several evidences showing how these devices improve endoscopic view and reduce Cormack and Lehane score compared to traditional laryngoscopy [34, 35].

Pediatric laryngoscope handles are recommended because they allow contemporary execution of laryngoscopy and cricoid pressure technique.

In general, straight blades can be used in infants to elevate the epiglottis and visualize the glottic opening even if in clinical practice curved blades are often used in newborns.

Pediatric facial masks for assisted ventilation are produced in different sizes, and they are transparent, latex free with inflatable cushion. Pediatric Guedel cannulas are disposable for habitual use. The length of the Guedel airway positioned near the children's face does not have to exceed the corner of the mouth. A cannula that is too long could push the epiglottis down and close the airway or induce laryngospasm if anesthesia is not deep enough [36]. In general in newborns the use of small endotracheal tubes causes an increase in airway resistance, so that uncuffed tubes are often used (newborn 3–3.5 mm; 0–6 months 3.5 mm; 6–12 months 4 mm; 12–18 months 4–4.5 mm; 2–3 years 4.5–5 mm ID). In preterm newborns the use of cuffed endotracheal tubes for a long time is a potential cause of lesions of the tracheal mucosa with possible consequent development of subglottic stenosis and/or granulomas.

A specific problem in newborns is the correct positioning of the endotracheal tube that tends to enter the right or bronchus or is easy to displace for little movements in extension or flexion of the head, being the trachea relatively short.

The use of cuffed tubes for infants and children is largely increased in clinical practice. Even if during the past years the use of uncuffed tubes was considered the

gold standard to avoid lesions due to local compression on subglottic area, nowadays the use of cuffed tubes seems to improve the ventilation in children without causing traumatic lesions (maintaining the cuff pressure under 20 cmH_2O) [37, 38].

To check the correct position of the endotracheal tube, there are different methods: chest X-ray, chest echography, and endoscopy. The use of pediatric stylets and/or guides is not routinely recommended because of the potential traumatic lesions it can produce on the airways.

A guide with a working channel can be left on the airway to provide oxygenation or to read capnography. The Magill forceps can help to direct the tube during the progression on the airway.

The use of the laryngeal mask airway should be considered as an urgency device when mask ventilation appears difficult or when local edema or other complications appear. The technique of laryngeal mask placement is the same in children than in adults with the only difference being that in children keeping the cushion partially inflated can help the progression in hypopharynx. It is important to provide adequate sedation in order to avoid complications such as cough laryngospasm, vomiting, or gastric distension.

12.5 Anesthesiologic Procedures

The most important thing in case of a newborn or infant intubation is to assure adequate ventilation mask before proceeding to deep sedation and intubation. Anyway, upper airway obstruction during mask ventilation is frequent and can be solved with some simple measure as chin lift, jawthrust, and/or continuous positive pressure. Also patient lateral positioning (for example, in case of tonsillar hypertrophy) can reduce the grade of obstruction [39, 40].

Pediatric difficult mask ventilations are infrequent and can be summarized into the following: (1) nasal obstruction, (2) macroglossia, (3) space-occupying lesions, (4) microretrognathia, (5) supralaryngeal inflammatory disease, and (6) pathological obesity.

When ventilations are impossible, the use of a classic laryngeal mask airway can help to provide adequate oxygenation and ventilation. Different studies report a 95–98% of success in ventilation with classic laryngeal mask. It is important to avoid high cuff pressure in order to reduce the risk of mucosal ischemic lesions and postoperative pain [31, 32, 41, 42].

As preanesthetic drugs, it is important to use drugs that do not lead to respiratory depression or protective airway reflex abolition. During induction of anesthesia with halogenated gases (sevoflurane 2–4%), it is important to maintain spontaneous breathing and verify if mask ventilation is possible. When mask ventilation feasibility is assured, deep anesthesia can be achieved with drugs that can allow intubation in association with local anesthetics and without muscle relaxants, if possible (remifentanyl", midazolam, ketamine, sevoflurane).

In pediatric population induction and maintenance of anesthesia are usually performed with an association of halogenated inhaled anesthetics, intravenous

anesthetics (hypnotics and/or sedatives), and muscle relaxants when indicated from surgery.

Sevoflurane is the most used inhaled gas to obtain rapid mask induction in children because of its rapid onset/offset time and the absence of irritative effect on airway mucosa. Rapid mask induction is achieved with sevoflurane concentration between 4% and 8%. For its characteristics sevoflurane is considered safe and easy to use also for operative procedure on the airway such as flexible or rigid endoscopy. In this setting, the use of sevoflurane was demonstrated more efficient than intravenous anesthetics in maintaining hemodynamic and respiratory stability in children under 2 years undergoing general anesthesia for operative endoscopy [43].

Intravenous anesthetics frequently used are thiopental, propofol, ketamine, midazolam, fentanyl, and remifentanil [44–46]. The use of these drugs needs well-defined hospital procedures and regulation. In particular, if these drugs are used in patient in spontaneous breathing, qualified staff and adequate equipment have to be available for immediate respiratory and hemodynamic resuscitation.

Thiopentone. It can be used for preanesthesia to facilitate children separation from parents in the operating room (1–2 mg/kg in infants), for moderate procedural sedation (1–2 mg/kg with additional doses of 1–2 mg/kg titrate at max 6 mg/kg as total dose), and for general anesthesia induction 4–6 mg/kg [44].

Propofol. Propofol is approved (FDA) for induction and general anesthesia maintenance for children more than 3 years of age and adults. In children and adults classified as ASA 1–2, the usual dose is 1–2 mg/kg for anesthesia induction (if patient ASA 3–4, consider a reduction of 80% of dose) and for general anesthesia maintenance 125–150 μg/kg/min. Propofol is not approved for pediatric sedation in the ICU for the risk of myocardial depression, hypotension, bradycardia, and propofol infusion syndrome, especially in hypovolemic or septic patients.

Ketamine. Ketamine is used in children for induction (2 mg/kg IV), for maintenance of general anesthesia and as supporting drug in procedural sedation (0.2–1 mg/kg), and for sedation in ICU (5–20 μg/kg/min). It is contraindicated in newborns less than 3 months of age because some studies demonstrate an increase in neuronal apoptosis and delay in cognitive development.

It is relatively contraindicated in case of airway procedures because of the increased risk of laryngospasm and in case of intracranial hypertension.

Fentanyl. Fentanyl can be used in children for moderate procedural sedation (1–2 mg/kg dose), as support in general anesthesia induction (2–3 mg/kg dose), and for continuous sedation in ICU (1–3 mg/kg/h).

Remifentanyl. Remifentanyl can be used in children for maintenance of general anesthesia with nitrous oxide (0.4–1 μg/kg/min), as analgosedation for intubated children (preterm 0.075 μg/kg/min to titrate at max 0.11 μg/kg/min), and in term infants needing mechanical ventilation in ICU (0.15 μg/kg/min to titrate at a reported medium dose of 0.23 μg/kg/min) [47, 48].

Rocuronium. Rocuronium is approved by FDA for all children and adult patients as muscle relaxant drug at general anesthesia induction, to maintain intraoperative muscle relaxation, and in ventilated patients in ICU. The particular interest for this drug derived from its classification as non-depolarizing neuromuscular blocker with

rapid onset and for the availability of an antagonist with rapid action (sugammadex). Pediatric dosage for RSI is 0.9–1.2 mg/kg and for elective intubation is 0.45–0.6 mg/kg. Maintenance dosage is 7–12 μg/kg/min both for intraoperative and ICU patients (to notice that the contemporary use of inhaled anesthetics reduces the needed dose of rocuronium for maintenance of neuromuscular blockade, it is recommended the titration at the minimum dosage). Rare cases of anaphylaxis, asthma, and arrhythmias are reported.

The use of sugammadex is nowadays approved by FDA for children aged higher than 2 years (2 mg/kg). No data are available for children less than 2 years and newborns, both for safety and efficacy, so for this age the use of sugammadex is not approved yet.

The use of muscular blockers must be avoided in case of difficult or impossible ventilation mask. If the use of these drugs is necessary, it is recommended the choice of muscle relaxants with short duration of action for which an antagonist is potentially available (succinylcholine, rocuronium).

It is important to avoid laryngoscopy or airway manipulation if sedation is nonadequate to avoid reactive laryngo- or bronchospasm. For this reason, local anesthesia with lidocaine on the vocal cords is recommended (lidocaine 1–2%, 3–5 mg/kg).

In conclusion, according to Italian guidelines, we can summarize that during newborn and infant intubation, (1) preoxygenation with mask is mandatory; (2) before abolition of spontaneous breathing, it is mandatory to assure the feasibility of adequate mask ventilation; and (3) the association of sedoanalgesic drugs or inhaled anesthetics with local anesthetics is recommended for intubation.

Finally, for those patients with known malformative diseases, for whom intubation with direct laryngoscopy or videolaryngoscopy is impossible (Pierre Robin, Franceschetti, Treacher Collins), guidelines recommend elective fiberoptic intubation (see below) with laryngeal mask airway, if indicated.

12.6 Planned Difficult Intubation

According to Italian guidelines, in case of planned difficult intubation, it is mandatory to proceed with the following:

1. Clinical investigations to exclude airway disease or associated malformations, in patients with malformative syndromes.
2. In case of prenatal diagnosis of malformative disease, it is mandatory to prepare preventively in the delivery room or neonatal intensive care unit all the equipments needed to the safest management of the patient.
3. To document in the medical records all the clinical predictors of difficult intubation.
4. To inform the parents or legal guardian about all the possible problems concerning the management of the difficult airway, the planned strategy of risks, and possible complications.
5. To prepare all the equipments needed to carry out the planned strategy.

Finally, it is useful to include in the medical record all the documents about the patient airway as all the equipments utilized to intubate, TC or endoscopic reports, and Cormack score. (For example, after elective fiberoptic-guided intubation, it is possible to perform direct laryngoscopy before the extubation of the patient and to include the Cormack score in the medical record.)

We also recommend to draw up a difficult airway report and to give it to the children's parents, in the event that the child will necessitate urgent intubation among other centers.

12.7 Elective Fiberoptic-Guided Intubation and Use of Supraglottic Airway Devices (SGA)

Fiberoptic-guided intubation in spontaneous breathing is nowadays the safest technique in case of planned difficult intubation, with or without the aid of SGA (specific laryngeal mask). It is important to plan the fiberoptic elective intubation as the first choice, to avoid potential local lesions on the mucosa caused by other procedures that could make difficult the progression of the fibroscope (edema, bleeding). Flexible fibroscopes with operative channel and camera are available for the pediatric population in different sizes (1.8 mm in an ETT 3, 2.2 mm in ETT 3.5, 2.8 in ETT 4).

The intubation technique is the same as in adult population. Considering the poor cooperativeness of the children and the elevated reactivity of the airways, the fiberoptic intubation must be performed with adequate sedation maintaining spontaneous breathing. A possible technique consists in local anesthesia with lidocaine 3–5 mg/kg in association with inhaled or intravenous anesthesia. The fibroscope is advanced until the glottic plane and the vocal cords are visualized. Local anesthetic is then applied, and the fibroscope is advanced into the trachea with the endotracheal tube sliding on the fibroscope that is in the end retired. At the end of the procedure, the correct positioning of the endotracheal tube is checked.

Patient oxygenation can be assured with nasopharyngeal oxygen probes, manual ventilation, or noninvasive ventilation with mask (usually in patients with respiratory failure in ICU) with specific junctions used to pass the fibroscope through the endotracheal tube connected to the ventilatory circuit.

Fiberoptic-guided intubation can be facilitated with the use of specific supraglottic airway devices, such as specific laryngeal masks created to allow the transition through the ventilatory way of a flexible fibroscope with an endotracheal tube or a tube exchanger.

Supraglottic airway devices (SGA) can be defined as devices that allow both ventilation and oxygenation and that are placed immediately out of the larynx, to which they are secured by an inflated cuff. These devices are nowadays an integral part of the basic requirements used for the management of the pediatric airway in emergency situations, including pediatric emergencies and neonatal resuscitation. SGA can be divided in two groups of first and second generation based on the presence or absence of a drainage gastric channel. First-generation devices consist in a

simple ventilation tube connected to the ventilation mask (LMA Classic, LMA Unique); secondary-generation devices used in pediatric population (LMA ProSeal, Air-Q, I-gel, Ambu Aura I) have an inbuilt drainage channel which allows the insertion of a gastric tube to deflate the stomach. If the laryngeal mask is correctly positioned, the inflated cuff creates an adequate adhesion to the hypopharynx and allows positive pressure ventilation. Second-generation devices have best adherence to hypopharynx leading to a more efficient positive pressure ventilation and allowing a better drainage of the stomach and a reduction of the risk of inhalation [41, 49].

The classic laryngeal mask (LMA Classic) is a first-generation device frequently used in pediatric anesthesia for minor procedures.

Hemodynamic response is reduced in LMA positioning if compared to endotracheal intubation, and it is similar to the insertion of an oral cannula. Its positioning by an inexperienced staff is easier and quicker than endotracheal intubation. Anyway, LMA positioning in children is characterized by the onset of more complications if compared to adults (malposition, gastric reflux, laryngo- and bronchospasm). Laryngeal mask ProSeal is a second-generation device with a gastric drainage channel, introduced in 2004 in clinical practice and available in neonatal and pediatric sizes.

It allows a better adherence to hypopharynx, and it is made of an armored ventilation tube that reduces the risk of occlusion of the airway. It can be used for fiberoptic-guided intubation. Anyway, the small diameter of the airway of the device makes impossible the direct insertion of an endotracheal tube, so that a tube exchanger should be used as a guide for the positioning of the endotracheal tube.

LMA Classic and ProSeal are the most used devices in pediatric anesthesia to which all new devices are compared in terms of safety and efficacy [50, 51].

The Air-Q system is an oval-shaped supraglottic device with a curved and angulated airway that permits to avoid the downfold of the epiglottis. Air-Q is available as a first-generation device with standard cuff and as a second-generation device with gastric access, but at the moment this new version is not available in pediatric sizes. Different studies have tested Air-Q in children with a body weight less than 15 kg. They reported good efficacy, better adherence, less leaks, and better endoscopic view of the laryngeal opening with this device when it is used for endoscopic intubation, compared to other supraglottic devices (Ambu Aura). Retrospective studies on pediatric population with craniofacial malformations reported the good efficacy of this device when it is used for fiberoptic-guided intubation.

Second-generation devices available for pediatric population reported in literature include the laryngeal mask Supreme, Ambu Aura, and I-gel. The use of the LMA Supreme airway is associated with less gastric regurgitation, less air leaks, and easier positioning, also in neonatal resuscitation.

The I-gel laryngeal mask is a second-generation device made from a medical grade thermoplastic elastomer, uncuffed, that creates a seal on the airway by anatomical adaptation. Compared to other SGA, I-gel has better view during endoscopy, while no differences are reported concerning onset of complications and easiness in placement or displacement [54].

Ambu Aura is a second-generation SGA specifically created for pediatric fiberoptic-guided intubation. It offers a similar endoscopic view if compared to Air-Q and I-gel, but 1 and 1.5 sizes do not allow the passage of cuffed tubes [52, 53].

In conclusion, during the last years, different SGA were introduced for pediatric use. In the healthy child in general anesthesia, classical devices as LMA Classic and Unique are largely used, except for children with low weight (less than 10 kg, for whom second-generation devices are indicated) for their simple position procedure and better stability.

Air-Q and Ambu Aura have the best endoscopic view and the easiest removal maneuver after fiberoptic-guided intubation. No specific guidelines are available in case of cardiac arrest or in the out-of-hospital setting.

In pediatric literature the role of new devices such as videolaryngoscopes, fiberoptic videolaryngoscopes, or lighted stylet is unclear, and it has not been sufficiently studied to include them into the Australian guidelines, even if they should be available in each center.

In conclusion, according to Italian guidelines, we can say that (1) it is useful to have expertise in fiberoptic-guided pediatric intubation; (2) it is recommended for each hospital to create a procedure for the management of pediatric difficult airway; (3) it is opportune to keep all the equipments in a dedicated tray situated in the surgical unit; (4) it is mandatory to assure the feasibility of mask ventilation before proceeding to deep sedation; (5) it is recommended to reassure adequate oxygenation of the child between different intubation attempts; (6) it is mandatory to avoid more than three attempts of intubation to avoid the onset of impossible mask ventilation situation; (7) if intubation becomes impossible, it is recommended to awake the child and postpone the procedure; (8) in pediatric patients fiberoptic intubation should be performed with pharmacological analgesia and sedation with local anesthesia and 100% oxygen supply devices; and (9) children with predicted difficult airway should be transported to a pediatric reference center.

12.8 Unpredicted Difficult Intubation

Unpredicted difficult intubation in children is infrequent if compared to adult population, and when it occurs, everything should be performed to avoid the onset of cannot intubate/cannot ventilate situation. LMA can be used as an urgency device in a child who cannot be intubated and ventilated to assure temporary adequate oxygenation and ventilation. In extreme cases, cricothyroid puncture to perform jet ventilation is indicated, even if in newborns and infants this procedure is very risky and often unsuccessful, because of the elevated difficulty to find the cricothyroid membrane, the elevated tissue flexibility, and small anatomic spaces. Indeed this procedure is complicated with high mortality and morbidity. When jet ventilation is successfully performed, a surgical tracheostomy should be considered [54, 55].

12.9 Conclusions

Pediatric airway management is a particular skill for anesthesiologists. Pediatric airway has many anatomic and physiological differences from adults, as well as different pathologic conditions (craniofacial malformative syndromes).

An adequate knowledge of these conditions, the available equipments, and the national guidelines allow the intensivist to perform the best management of the child's airway both in elective and urgency situations, with collaboration between pediatric and non-pediatric centers.

Disclaimer Authors have nothing to disclaim about this paper.

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Anaesthesia for Interventional Neuroradiology

13

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13.1 Interventional Neuroradiology and the Neuroteam

Interventional neuroradiology (INR) or endovascular neurosurgery is a specialty emerged as a hybrid of traditional neurosurgery and neuroradiology. It has its role in the management of neurovascular diseases and other neurosurgical conditions, by delivering therapeutic drugs and devices through endovascular or percutaneous access [1].

INR always needs some kind of anaesthesia or sedation and is considered as part of the non-operating room anaesthesia (NORA). NORA generally defines every anaesthetic regimen performed out of the classical operating theatre to serve non-surgical procedures, which are rapidly developing and have both diagnostic and therapeutic purposes [2].

Although, interventional procedures cause much less tissue trespass than surgical operations, anaesthetists must deal with some specific challenges of this domain. Locations may not be adequately organized or equipped to host interventional procedures and manage potential emergencies [2]; interventional suite personnel are

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often not used to cooperate with anaesthetists and therefore may not be aware of their needs; anaesthetists may not be fully trained to deal with NORA challenges, and they may not be familiar to many new interventional techniques [3].

These criticisms make patient management more difficult, while patients with acute brain injuries are particularly frail and need a multidisciplinary, well-integrated management and shared therapeutic plans. According to the well-developed neurosurgical literature, the patient outcome may be improved by the presence of a neuroteam able to focus on common priorities and to share specific competencies. The neuroteam is made by neuroradiologist, neurosurgeon, neuroanaesthetist, neurointensivist, neurologist and well-trained nursing personnel. The neuroanaesthetist differs from general anaesthetist for his qualified experience in treating patients with acute neurologic injury and knowledge of goals and methods of endovascular intervention. In such organization, the neuroanaesthesia department takes care of patients before, during and after the procedure, delivering both anaesthesiologic and intensive care services. Therefore, anaesthesia is essential for INR activity and whole patient management.

This chapter focuses on the anaesthesiologic peri-procedural management of patient undergoing INR procedures. After a rapid introduction to the field of application of INR, anaesthetic issues are described sorting them in two different sections:

- General considerations applicable to all INR procedures
- Specific considerations inherent to the three most important and frequent INR procedures: aneurysm coiling, arteriovenous malformations (AVMs) and fistulae (AVFs) embolization and acute ischaemic stroke thrombectomy

13.2 Introduction to Interventional Neuroradiology

Neuroradiology procedures can be classified in two major groups, as shown in Table 13.1 [1].

Table 13.1 Main neuroradiology procedures

Diagnostic procedures
• Cerebral and spinal cord angiography
• Carotid occlusion test
• Super-selective anaesthesia functional examination
Therapeutic procedures
Closing or occluding procedures
• Endovascular treatment of aneurysms
• Embolization of AVMs and AVFs
• Preoperative tumour embolization
Opening procedures
• Chemical and mechanical thrombolysis in acute ischaemic stroke (AIS)
• Angioplasty and stenting of intra- and extracranial atherosclerotic vessel disease
• Angioplasty and stenting of vasospasm

13.3 Generic Considerations About Anaesthesia for INR

13.3.1 Management of Patients During Transport

Patients with neurovascular diseases or injuries may have highly unstable conditions and rapidly deteriorating neurological status. Therefore, before transfer, some precautions should be taken:

1. Carefully organize logistic details, staff and equipment for the route.
2. Adequately alert the receiving ward or operating room.
3. Consider each patient's clinical condition, especially neurologic injury and haemodynamic and respiratory status.

Two personnel, with at least one certified in advanced cardiovascular life support, should be present during transport [4].

13.3.2 Radiation Exposure Risk and Protection

The major source of radiation is the X-ray tube, but leakage through the collimators and radiation scattered from surfaces surrounding the patient's head are two other minor sources [5]. The amount of exposure responds to the inverse square law: radiation intensity decreases proportionally with the inverse of the square of the distance from the source of radiation.

Therefore, correct radiation protection depends on the following:

- Stay as far as possible [4]; use connected multiparameter monitor from remote locations
- Wearing protections, particularly lead aprons (at least 0.5 mm thickness), thyroid shields, protective eyewear and radiation exposure badges [5, 6]
- Providing movable lead glass screens [4]

13.3.3 Equipment and Logistic Organization

The American Society of Anesthesiology (ASA) produced a statement on the minimal necessary equipment and organization for NORA. In each location there should be:

- A reliable source of oxygen sufficient for as long as the entire procedure
- An adequate source of aspiration system
- A reliable removal system for anaesthetic gases (if used)
- A bag valve mask, adequate anaesthesia drugs, supplies and equipment
- Adequate monitoring systems and anaesthesia machine

- An emergency cart with defibrillator and emergency drugs
- Sufficient space for equipment and personnel and to allow rapid access to the patient [7]

In the INR suite, imaging devices need to rotate around the patient's head without any restriction [4]. For this reason logistic organization of the INR suite differs from that of surgical settings: anaesthetist and anaesthetic equipment cannot be close to the patient's head, but they are placed at the opposite end of the table, thanks to extensions on tubes and breathing circuit [4, 8].

13.3.4 Patient Monitoring

As stated by the ASA, each procedure requires online monitoring of the following physiologic variables: oxygenation, ventilation, circulation and body temperature [9].

To ensure adequate oxygen delivery, oxygenation must be controlled by measuring the concentration of O_2 in the inspired gas mixture and by pulse oximetry [9]. Capnometry is important in every anaesthetic regimen, as a method of control of ventilation and circulation, but it is especially important in INR because variations in arterial pressure of CO_2 can be induced to modify cerebral blood flow (CBF) and intracranial pressure (ICP). The sampling port of a nasal cannula provides CO_2 measuring when patients are not intubated.

Standard monitoring with ECG, non-invasive blood pressure (NIBP) and pulse oximetry are essential for every INR procedure. Invasive blood pressure monitoring may be required by the type of procedure or by the patient condition (e.g. aneurysm coiling with risk of elevated ICP), but it is not mandatory [9]. For example, diagnostic angiography does not require invasive BP monitoring, while the Society for Neuroscience in Anesthesiology and Critical Care (SNACC) recommends invasive BP measurement unless it delays the procedure [10].

Invasive BP monitoring may facilitate the prevention or management of cerebrovascular complications of INR procedures, and it is advocated when an anaesthetist must deliberately modify BP during the procedure.

Temperature monitoring and warming devices are required: there is a lack of evidence on body temperature management in INR; normothermia is recommended in agreement with the well-developed observation that peri-procedural hypothermia and post-procedural shivering have deleterious effect both in surgical patients and patients with acute brain injury [11].

13.3.4.1 Intraoperative Neurologic Status Monitoring

Neurological monitoring deserves special considerations. Interventional procedures may be complicated by haemorrhagic or occlusive events that worsen patient's outcome. It is important to detect cerebrovascular complications early enough to allow corrective intervention. During conscious sedation it is possible to examine the neurological status while general anaesthesia or comatose status does not allow a direct assessment of neurological function [1].

Electrical activity is the first function lost after regional interruption of cerebral blood flow. Therefore, it has been proposed the use of electrophysiological monitoring (evoked potentials) or non-invasive cerebral oxygenation by near-infrared spectroscopy (NIRS). Indeed there is a time window between electric failure and ion pump failure with irreversible damage [12]. Some large retrospective studies highlighted that evoked potentials are able to detect neurological damage and improve the patient outcome [13–16]. ICONA (Italian Consensus in Neuroradiological Anesthesia) recommendations reach a B grade of consensus strength for evoked potentials, and their use should be integrated in the perioperative management of patient indicated to INR [17].

Due to the limited evidence available and the weak results obtained, NIRS reaches a C grade of consensus strength in ICONA recommendations, so its use in clinical practice is still controversial [17].

13.3.5 Complete Preoperative Evaluation

A complete preoperative evaluation includes:

1. History of actual illness and its systemic effects [8]
2. Neurological deficits and Glasgow Coma Scale (GCS).
3. Symptoms of raised ICP: if present, the neuroanaesthetist must maintain an adequate MAP to ensure sufficient CPP.
4. Previous neurosurgical procedures.
5. Renal function, history of radiographic contrast reactions (contrast nephropathy and allergy) and other risk factors. Contrast and flush fluid injections may be dangerous for renal function [6, 8].
6. Allergy and medication history [6].

A phenomenon yet well-described is the re-emergence of prior fixed neurologic deficits in patients who undergo anaesthesia [18, 19]. There is no explanation for this observation, but it can complicate neurological status evaluation during the procedure [5]. This requires to carefully perform neurological examination before the procedure, with assessment of GCS, pupil size and reactivity and any focal deficits [8].

All patients should have preoperative blood tests:

- Full blood count, haemoglobin and haemo group for the risk of bleeding [6].
- Urea and creatinine for renal function.
- Electrolyte abnormalities may contribute to patient's level of consciousness [6].
- Coagulation screen with basal ACT is fundamental because anticoagulation is required during and after INR procedures to avoid thromboembolic complications [5].
- Glycaemia should be assessed being a source of secondary brain injury [20].

13.3.6 Choice of Anaesthetic Technique

There is no evidence for a superior anaesthetic choice for all different INR procedures. Therefore recommendations of neuroanaesthesia for surgical procedures are often applied to INR [5], and anaesthetic regimen is chosen in relation to the disease, patient condition and procedure.

Among anaesthetic techniques for INR, general anaesthesia (GA) and conscious sedation (CS) are the main choices. Table 13.2 resumes their principal pros and cons.

13.3.6.1 Reduced Time Delay

Some INR procedures need immediate treatment; reducing time delay is particularly important for endovascular treatment of AIS. The phrase "time is brain" was first used by Saver to emphasize that cerebral tissue is rapidly and irreversibly damaged over time after stroke [21].

In this setting, GA may cause some delay, due to the time needed for induction of anaesthesia and endotracheal intubation. However several studies demonstrated that there is no difference in time delay from patient arrival at the hospital and revascularization among the two anaesthetic techniques [22–29]. This is explained by the fact that procedure duration is longer in CS regimen rather than in GA regimen because of patient movements [23], compensating time delay for endotracheal intubation of patients undergoing GA [27, 30].

13.3.6.2 Patient Immobility, Comfort and Analgesia and High-Quality Imaging

GA provides patient immobility and analgesia allowing patient comfort and safe device deployment into the vasculature with reduced risk of iatrogenic vascular

Table 13.2 Resumes principal pros and cons of general anaesthesia and conscious sedation. Modified from Anastasian 2014

General anaesthesia	Conscious sedation
Pros	
Patient immobility, comfort and analgesia	Reduced time delay
High-quality imaging	Haemodynamic stability
Airway protection	Intraoperative neurological monitoring
Control of haemodynamic and respiratory variables	Rapid post-procedure recovery and short monitoring period
Cons	
No intraoperative neurological monitoring	Risk of emergency conversion
Time delay	Patient's movements, discomfort and pain
Haemodynamic instability	Poor-quality imaging
Long post-procedure recovery and initiation of a critical care pathway	Prolonged procedure time
	Risk of aspiration
Respiratory complications due to intubation	Risk of vessel injury from endovascular device

injury. Besides, patient immobility increases imaging quality and decreases the need for repeating imaging acquisition, for contrast fluid administration and for time to achieve the procedure [4, 5].

Patients in conscious sedation have always a certain degree of discomfort from lying in the supine position for a long time, from burning pain due to contrast injection and from headache due to distention or traction on cerebral vessels. Discomfort increases patient's movements that in turn oblige to repeat imaging acquisition and so lengthens the procedure [5].

GA is obviously mandatory in patients confused who have involuntary movements or are uncooperative [8]

13.3.6.3 Haemodynamic Stability and Maintenance of Adequate CPP

GA allows easier deliberate modifications of BP during the procedure, but it may also produce haemodynamic instability: hypertension during induction (stimulation of oropharynx and larynx) and emergence (cough and strain) and hypotension during maintenance due to higher doses of anaesthetics and analgesics than CS [1].

CS instead may allow avoidance of all these haemodynamic consequences typical of GA, ensuring more stable pressure values during all the different procedure phases [4].

13.3.6.4 Airways and Respiration Management

GA ensures careful airway protection, and it reduces the need for acting on airways during the procedure. CS, instead, exposes to the risks of gastric aspiration in non-fasted patients, and, if any problem occurs, emergent intubation may be more risky [4, 6].

GA allows tightly monitoring of ventilatory variables reducing the risk of hypoxemia and hypercapnia [4] and allowing deliberate adjustments [5, 31].

13.3.6.5 Anaesthetic Drugs

The anaesthetic regimens for GA in neuroradiology are total intravenous anaesthesia (TIVA) with propofol and opioids or balanced anaesthesia with the use of volatile anaesthetic such as sevoflurane together with opioids. Remifentanil is the opioid of choice for its pharmacodynamic and pharmacokinetic features and its half-life context independence [32].

Propofol causes systemic hypotension and reduces cerebral blood flow (CBF), intracranial pressure (ICP) and metabolic demand. Hence, TIVA is preferred when patients have elevated ICP or have elevated risk of intracranial hypertension. Sevoflurane, instead, ensures systemic hemodynamic stability and is associated with a more rapid and smoother emergence from anaesthesia than propofol [33], but volatile anaesthetics induce cerebral vasodilatation, increase CBF and do not allow neurophysiological monitoring during procedure [34, 35]. In these cases, TIVA may be the regimen of choice for maintenance of anaesthesia.

Both TIVA and inhaled anaesthesia are useful for rapid titration of arterial pressure if deliberate brief time of hypotension is needed.

The use of sevoflurane strengthens neuromuscular block and spare in neuromuscular blocker dose. This is associated with a lower incidence of post-operative residual curarization and complications.

13.3.7 Management of Blood Pressure

Haemodynamic stability is crucial in all procedures of INR. It is important to assess the baseline BP and ascertain the likely autoregulatory range [4]. Some phases of these procedures may require manipulation of the arterial pressure, with deliberate hypertension or hypotension [4].

Deliberate hypertension may be necessary during intraprocedural arterial occlusion, due to intentional balloon inflation or thrombotic clot formation. Increasing mean arterial pressure (MAP) up to 30–40% above the baseline is necessary to maintain CBF through collateral circles or through a partially occluded artery. Deliberate hypertension may be achieved with multiple vasoactive agents such as phenylephrine or ephedrine under ECG monitoring and considering the risk of haemorrhage [4, 5].

In other situations, it may be necessary to induce deliberate hypotension to define cerebrovascular reserve before carotid occlusion procedure, to decrease blood flow into AVM before intraarterial liquid embolization or to temporarily decrease BP in the immediate management of cerebral haemorrhage [5].

13.3.8 Management of Anticoagulation, Platelet Inhibition and Reversal

Many INR procedures require the use of anticoagulant and/or antiplatelet drugs. Anticoagulation is necessary to prevent thrombotic complications during INR procedures. Unfractionated heparin (UFH) is most commonly used. The initial dosage is 50–70 UI/kg to achieve an activated clotting time (ACT) of two- to threefold preheparin, and then UFH can be given continuously or as intermittent boluses [5]. When procedures end or in case of intraprocedural haemorrhage, it is necessary to reverse heparin effects. The first-line therapy for the reversal of anticoagulation with UFH is protamine: 1 mg for each 100 UI heparin given. It is important to remember that protamine administration is not uneventfully. This drug must be administered slowly, because it increases pulmonary vascular resistance and decreases systemic vascular resistance, with the risk of pulmonary hypertension and systemic hypotension, respectively [1, 5]. A fast infusion of protamine may cause cardiogenic shock. Besides, administering more protamine than the necessary has a pro-haemorrhagic effect.

Antiplatelet drugs, including aspirin, P2Y12 inhibitors and glycoprotein IIb/IIIa antagonists, are often needed in IR procedures, particularly those involving stent placement. Clopidogrel is a P2Y12 antagonist commonly used for stent placement or stent-assisted aneurysm coiling. Because of pharmacogenomic differences in

response to clopidogrel, prasugrel may function as an alternative P2Y12 antagonist in these patients [4].

13.3.9 Rapid, Smooth Recovery

After INR, the aim is to rapidly wake up the patient to perform early neurological evaluation. Besides, it is necessary to achieve a smooth recovery to avoid ICP surges or haemorrhage due to cough and strain.

Maintenance of anaesthesia with sevoflurane is associated with a more rapid recovery from anaesthesia in INR [33]. Waking up patients with minimal dose of remifentanil infusion or extubating patient with a deep plain of anaesthesia and the presence of spontaneous breathing are possible emergence strategies. However, the choice of technique is less important than maintenance of patient stability [6].

ICONA recommendations highlight that, after an INR procedure without any complication or major comorbidities, there is no need to routinely admit all patients to an intensive care unit, but continuous observation for 1–4 h must be ensured [17]. Patients who have had neurological complications, instead, need to be transferred to neuro-intensive care settings for continued sedation and ventilation.

13.3.10 Management of Procedure-Specific Complications

Endovascular procedures may have some severe peri-procedural complications (Table 13.3).

Cerebrovascular complications may be catastrophic, and efficacious management with good outcomes depends upon well-planned strategies and a rapid and clear communication between anaesthetist and operators, to define the haemorrhagic or occlusive nature of the problem [4, 5].

In all cases, the anaesthesiologist must preserve pulmonary gas exchange by ensuring a secure airway and by ventilating 100% oxygen [4, 5].

Table 13.3 Summarizes peri-procedural complications of endovascular procedures. Modified from Perritt and Mahalingam 2014

Cerebrovascular complications	Peripheric or systemic complications
Haemorrhagic • Aneurysms, AVM and AVF bleeding or re-bleeding • Vessel injury/rupture	Contrast induced • Anaphylaxis • Contrast nephropathy
Occlusive • Thromboembolism • Arterial dissection • Vasospasm • Intravascular device or material migration/ displacement	Haemorrhage • Puncture site • Groin haematoma • Retroperitoneal haematoma

13.3.10.1 Vascular Occlusion

In the setting of vascular obstruction or intraoperative vasospasm, the goal is to increase distal perfusion by MAP augmentation to 30–40% above baseline to increase oxygen delivering by collateral blood flow. Simultaneously, intraarterial direct thrombolysis may be performed considering patient comorbidity: it should be titrated to a neurological or angiographic endpoint [4, 5, 8]. The operator may also try to achieve the recanalization through emergent angioplasty, stenting, mechanical lysis or other endovascular treatments (e.g. intraarterial vasodilator injection for vasospasm) [4].

Prevention of vascular occlusion implies the use of anticoagulant drugs during the procedure (as UFH in flush fluid) to reduce incidence of intraoperative thromboembolism and preoperative calcium channel blockers for catheter-induced vasospasm [5].

13.3.10.2 Intracerebral Haemorrhage

Intracerebral haemorrhages may be either spontaneous from aneurysm or AVM/AVF rupture or caused by endovascular devices or by inadequate anaesthetic management (BP surges) [6, 36].

Headache, nausea, vomiting and vascular pain are typical signs of intracranial haemorrhages in conscious patients. When GA is performed or in comatose patients, the Cushing response (sudden bradycardia and hypertension) or the evidence of contrast extravasation on fluoroscopy may be the only signs of a haemorrhage [5].

In haemorrhagic emergency, anaesthetist must rapidly reverse anticoagulation and consider to induce transient hypotension [1]. Heparin must be antagonized with protamine on the basis of original UFH doses and serial ACT measurements [5, 8]. Antiplatelet drugs do not have specific antidotes: intravenous desmopressin may be used to decrease the effect of antiplatelet drugs, but platelet transfusion is the standard therapy for reversal of effects [37, 38]. The use of specific clotting factors may be considered in cases of life-threatening bleeding uncontrolled with platelet transfusion therapy [39].

Secondary, BP may be controlled by deepening anaesthesia or using antihypertensive drugs, such as IV labetalol [8].

The INR team should find the bleeding site and try to stop the haemorrhage by endovascular treatment, to complete the procedure. Rarely, a patient needs to be transported in the operating room for a rescue craniotomy and vascular clipping [5, 8, 36].

Haemorrhages may produce sudden ICP elevations with the risk of herniation syndromes. The initial management includes hyperventilation (that rapidly reduces cerebral blood volume), head elevation to 15–30°, steroids, intravenous mannitol boluses and burst suppression [4, 36]. When hydrocephalus has developed and neurological condition is deteriorating, a ventricular or lumbar catheter may be placed in the INR suite to monitor and drain CSF, as recommended by the ICONA [8, 17].

13.4 Anaesthetic Implications for Each Specific INR Procedure

13.4.1 Aneurysms

Endovascular coiling is now considered the treatment of choice for many ruptured or unruptured aneurysm of anterior and posterior cerebral circulation compared with neurosurgical clipping, because coiling is associated to a 5-year reduced mortality compared to surgical clipping [40].

GA is preferred over CS during endovascular coiling, because of perceived improved imaging quality and patient safety. However, CS may be performed safely in patient with ruptured cerebral aneurysms and low-grade SAH (WFNS grades 1–2; see Table 13.4), in order to reduce GA complications and allow frequent neurological evaluation [5].

The main goal for the anaesthesiologist is to maintain haemodynamic stability and adequate cerebral perfusion and oxygenation. It is important to maintain systolic arterial pressure (SAP) <160 mmHg during all phases of anaesthesia and to avoid BP surges that might cause aneurysmal rupture. For this objective, Propofol is usually used for the induction of anaesthesia in combination with remifentanil, alfentanil or fentanyl. For the maintenance of anaesthesia, sevoflurane may be the volatile anaesthetic of choice: up to 1 minimal alveolar concentration (MAC), the cerebral circulation responsiveness to CO_2 is preserved, and CBF/cerebral metabolic rate for O2 (CMRO2) coupling is maintained [4]. Propofol is associated with reduced CBF, ICP and CMRO2. Among short acting opioids, remifentanil provides stable haemodynamic and allows more rapid recovery from anaesthesia [8].

In SAH patients some important complications may occur, cardiopulmonary damage and vasospasm being the most threatening.

Neurogenic stress cardiomyopathy (NSC) may complicate several types of severe acute brain injury, and it is mainly a consequence of the catecholamine storm released in the acute phase. NSC presents with ECG or left ventricular wall motion abnormalities, myocardial necrosis enzyme and brain natriuretic peptide elevation [5, 41]. Respiratory complications occur in up to 20–80% of patients with SAH and include pulmonary oedema (cardiogenic or neurogenic or mixed), acute lung injury, acute respiratory distress syndrome and pneumonia. Both NSC and respiratory complications increase mortality and morbidity [42, 43].

Table 13.4 WFNS grading score

Grade	GCS	Motor deficit
1	15	Absent
2	13–14	Absent
3	13–14	Present
4	7–12	Present or absent
5	3–6	Present or absent

Vasospasm is a potential complication of SAH. It may occur 7–10 days after aneurysm rupture and resolves spontaneously after 21 days. Vasospasm is one possible cause of delayed cerebral ischemia (DCI). The arterial narrowing is probably caused by the contact of oxyhaemoglobin with the abluminal side of vessels. To prevent vasospasm, euvolemia should be maintained, and oral nimodipine (60 mg every 4 h) should be administered to all patients with SAH for a period of 21 days [44–46]. When vasospasm develops, maintenance of euvolemia and induction of hypertension is indicated to treat ischemia, unless BP is high at baseline or cardiac conditions preclude it [46]. Patients with symptomatic vasospasm and not rapid response to deliberate hypertension may be treated with cerebral angioplasty and/or selective intraarterial vasodilators [46].

13.4.2 AVMs and AVFs

AVMs are classified as cerebral or dural. Cerebral AVMs are congenital and consist of a nidus of abnormal vessels containing arterial inflow and venous outflow, often in absence of capillary component. Dural AVMs are acquired, often due to venous dural sinus stenosis or occlusion, with opening or recanalization of a potential fistulous tract due to venous hypertension. Endovascular embolization alone is rarely sufficient, and subsequent surgery and radiotherapy are generally requested to complete the treatment.

GA is the preferred technique for the treatment of AVM and AVF, due to enhanced vessel visualization, lack of patient movement, and possible need for deliberate hypotension or cardiac arrest to counteract venous hypertension in dural fistulae [4]. In some phases it may be necessary to induce deliberate hypertension or hypotension. Hypertension is necessary in case of vascular occlusion, to achieve the maintenance of cerebral perfusion through collateral vessels. Deliberate hypotension may be helpful, because it reduces flow into AVMs and allows glue adherence to the tissues, avoiding unwilling migration [4]. Anaesthesia plane can be tailored to manipulate arterial pressure and induce hypotension. Both propofol bolus and temporarily increase of sevoflurane's inspiratory concentration are useful in reducing BP for a brief time. Short-acting vasoactive agents may be used in addition to achieve hypotension. Transient asystole produced by adenosine administration or rapid ventricular pacing is an option in selected patients [47].

After AVM exclusion, cerebral hyper-perfusion and consequent oedema and haemorrhage may result from abrupt restoration of cerebral blood flow to chronically hypo-perfused vascular beds that have lost their autoregulatory capacity [48, 49]. So, maintenance of systolic BP 20–30% below the basal values during the recovery phase may be protective in these cases.

Because of the embolization, there is always a risk of morbidity and mortality. The most common complication associated with occipital AVM endovascular treatment is the visual field loss [50].

13.4.3 Stroke

Intravenous thrombolysis with rtPA within 4.5 h of symptom onset is now widely accepted as the mainstay of early treatment for AIS [51, 52]. Intraarterial methods of recanalization have been introduced to increase the number of patients treated and the efficacy of the early treatment [53]. Indications to endovascular treatment are increasing, and this claims for some considerations on the best anaesthesiologic management.

Medical literature reported association between GA and higher mortality and poorer neurological outcome compared to CS, but this observation is sustained by poor-quality evidences [22, 25, 27, 54, 55]. More recently, other retrospective studies and the first two RCTs published do not demonstrate any superiority of CS compared to GA [23, 24, 56–59].

There is yet no agreement among authors about the influence of anaesthetic regimen on the efficacy in achieving recanalization. Although Brinjikji and colleagues state that GA is associated with reduced probability of revascularisation compared with CS [22], some other authors did not observe this difference [24, 56], and others have shown a greater success with GA [60].

In several studies, GA was associated with a higher rate of respiratory complications due to the invasiveness of endotracheal ventilation [22–24, 54], but not all authors agree on this statement [61]. On the other side, one of the major disadvantages of CS is patient movements and risk for iatrogenic vascular complications caused by intraarterial devices. However, most of the studies available do not highlight a higher incidence of these complications in CS group with regard to GA group [22, 24–26, 54, 61].

So far, there is no consensus on the best anaesthesiologic regimen for endovascular treatment of AIS. AHA/ASA guidelines suggest preferring CS over GA [62], but they have been produced before the publication of SIESTA, AnStroke and GOLIATH trials [23, 24, 60]. Therefore the choice of anaesthetic regimen must be individualized on patient clinical characteristics, in communication with the neurointerventionalists [10].

In 2014 the SNACC developed a series of recommendations for the anaesthesiologic management of patients who undergo endovascular treatment for AIS [10].

13.4.3.1 Haemodynamic Management

The SNACC recommends to maintain SAP between 140 and 180 mmHg and diastolic blood pressure (DAP) below 105 mmHg [10]. These targets derive from the observation that 150 mmHg is the pressure value associated with the best outcome for a patient with acute ischaemic stroke [63].

Three clinical trials demonstrated that it is beneficial to reduce arterial BP after 24 h from stroke onset, when the effect of high BP on the ischaemic penumbrae lessens [64–66].

13.4.3.2 Respiratory Gas Exchange

Recommendations by the SNACC suggest to maintain $SpO_2 > 92\%$, $PaO_2 > 60$ mmHg and $PaCO_2$ between 35 and 45 mmHg [10].

Hypoxemia is a common event after AIS for altered control of breathing, weakness of respiratory muscles, neurogenic or cardiogenic pulmonary oedema and pulmonary embolism [52]. An adequate oxygen delivery must be ensured but hyperoxemia should be avoided, because it induces cerebral vasoconstriction, excitotoxic injury and radical oxygen species (ROS) formation [52].

13.4.3.3 Body Temperature

The SNACC suggests to maintain body temperature between 35 and 37 °C and to treat febrile patients with antipyretics and cooling devices [10]. Fever has been demonstrated to increase death or dependency risk in patients with AIS [67].

Medical evidence currently do not recommend deliberate hypothermia for a patient with AIS, because it is not associated with better outcomes [68, 69].

13.4.3.4 Glycaemia

The SNACC suggests maintaining glycaemia between 70 and 140 mg/dL [10].

13.5 Conclusion

For an efficient and high-quality management, patients with acute neurologic injury should be admitted in high-volume centres with a dedicated neuroteam. In such centres the anaesthesia department is increasingly involved in the treatment of patients requiring an INR procedure [70].

In the perioperative care of these patients, the main goals to improve outcome are haemodynamic stability, maintenance of adequate CPP, avoidance of secondary insults, patient immobility, rapid management of complications and smooth rapid recovery.

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Antifungal Treatments in Critically Ill Patients

14

Marco Dei Poli, Giacomo Trevisan, Luca Di Girolamo, and Gianluca Spinelli

14.1 Introduction

More than 100,000 fungal species exist in nature; 300 of them are human pathogens. Among those, *Candida*, *Aspergillus*, *Cryptococcus*, and *Pneumocystis* spp. account for more than 90% of deaths related to fungal infections [1].

Each year, invasive fungal infections (IFI) are associated with roughly 1.5 million of death worldwide [2], this estimate being even underrated due to the low sensibility of cultures. This makes fungal identification remarkably complex [3].

The term "IFI" implies the isolation of a fungal species, either a mold or a yeast, from a sterilely obtained biological sample or a biopsy. The recovery of yeasts by the culture of samples derived from normally contaminated anatomical sites, indwelling surgical drains placed over 24 h or non-sterile procedures, does not yield diagnostic value [4].

A prompt and adequate pharmacological treatment is paramount if IFI-related mortality has to be reduced. It is proved, in fact, that patients receiving early therapies for *Candida* spp. infections show low mortality in relation to those whose treatments follow cultural identifications (cultures take 24–48 h according to different studies) [5, 6].

The statement is particularly true as the identification of mold and yeast from biological samples is burdened by high percentages of false negative (as high as 50%, depending on the fungal species) [3]. Consequentially, therapies are often enforced due to high clinical suspicion rather than the isolation of a fungal pathogen [1].

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As IFI mainly affects patients suffering from transient or permanent immunodeficiency, it's not a coincidence that intensive care units and onco-hematology wards claim the highest incidence [2].

Further, since both etiologies and therapies (either empirical or targeted) differ between immunocompetent and neutropenic patients [4, 7], as soon as an IFI is suspected, doctors have to resolve on the patients' immunological status.

While *Candida* spp. are the prominent pathogens in non-neutropenic patients, invasive aspergillosis is a quite frequent disease in the immunocompromised group.

A number of risk factors account for the outbreak of invasive candidiasis in the ICUs:

- *Candida* spp. colonization. It is considered a prerequisite for the onset of the invasive form. It is awfully prevalent in the critical ills and preceded invasive candidiasis in the great majority of cases [8].
- Broad-spectrum antibiotics. The use of these drugs causes the modification of the gut microbiome, thus facilitating an exaggerated grow of fungal species that are normally present into the intestinal lumen. The broader the spectrum and the longer the duration of the therapy, the higher the risk [8].
- Major abdominal surgery and severe abdominal illness (necrotizing pancreatitis and intestinal perforations). These conditions imply the breach of the gastrointestinal tract. This intuitively eases the translocation of *Candida* spp. through the gut mucosa and their systemic dissemination [8].
- Total parenteral nutrition. It is considered one of the major risk factors [9]: the absolute enteral feeding deprivation (i.e., the absence of at least minimal enteral feeding) damages the gut mucosa thereby increasing the risk of fungal translocation [10].
- Intravascular indwelling devices. These are identified to be an important risk factor in a number of studies [10–12]. The pathogenic mechanism implies the overgrowth of fungi on the patient's skin and their transfer to the vascular stream through the catheter site of insertion.

Many scores have been proposed to support the diagnosis of invasive candidiasis by considering the aforementioned factors. In this paper, authors decided on strengthening the Candida score by León et al., as it represents the commonest among the few prospectively validated scores, and the "Nebraska Medical Center Score" because of its feasibility and good statistical performance.

Candida score (CS) has been developed by León et al. in 2006 [13] based on a retrospective analysis of risk factors performed on 1700 patients. It was subsequently validated through a multicenter prospective study published by the same study group in 2009 [14].

Table 14.1 shows the considered risk factors. CS involves a cut off ≥ 3.

Hermsen et al. performed a comparison of different predictive clinical scores for the identification of invasive candidiasis in 2011 [15]. A case-control retrospective study was designed by the study group, and the new "Nebraska Medical Center" (NMC) score was created through a multivariate analysis. Table 14.2

Table 14.1 CS criteria and coefficients (Adapted from León et al. [14])

Criteria	Coefficient
Total parenteral nutrition	1
Surgery	1
Multifocal colonization	1
Severe sepsis	2

Table 14.2 NMC risk factors and attributed coefficients (Adapted by Hermsen et al. [15])

Risk factor	Coefficient
Broad-spectrum antibiotics	1.537
Central venous catheter	0.873
Total parenteral nutrition	0.922
Systemic steroidal therapy	0.402
Abdominal surgery	0.879
Hospitalization prior to ICU admission	0.039

Table 14.3 IPA risk factors in ICU patients (Adapted from Bassetti et al. [16])

High risk	Neutropenia
	Oncoematologic illnesses
	Allogeneic transplant
Intermediate risk	Long lasting corticosteroid therapy prior to ICU admission
	Autologous transplantation
	COPD
	Hepatic cirrhosis
	Malignancies
	HIV
	Systemic immunosuppressive therapy
	Lung transplantation
Low risk	Severe burns
	Organ transplantation (except for lung transplantation)
	Corticosteroid treatment >7 days
	Hospitalization in ICU >21 days
	Malnourishment

shows the examined risk factors with associated coefficients; authors recommend ≥2.45 as the cutoff.

Literature identifies risk factors associated to pulmonary aspergillosis (IPA) in the critical ills as well. Those factors have been known for years and, according to Table 14.3, allow a classification of patients into three classes (low, medium, and high risk) [16]. Despite that, new risk factors such as COPD, cirrhosis, and previous H1N1 infection have been identified during the last decade thereby complicating the IPA diagnostic-therapeutic process [17].

Along with scores and risk factor identification, biomarkers play an important role in IFI diagnostic process. This holds especially true in the absence of a positive cultural test.

Table 14.4 BDG performance: Sens, sensibility; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value [37]

Sens	Spec	PPV	NPV
0.64–1	0.45–0.90	0.37–0.61	0.91–1

Besides the traditional mannan/anti-mannan (for *Candida* spp. infections) and galactomannan (for *Aspergillus* spp. infections) essays, the recent β-D-glucan dosage shows promises. β-D-glucan is a fungal cell wall component, which could be identified by Fungitell® assay (Associates of Cape Cod Inc., Falmouth, USA). This is a protease zymogen-based colorimetric test for the qualitative detection of (1-3)-β-D-glucan in the patients' sera which might be exploited in patients who present symptoms or medical conditions predisposing to invasive fungal infection.

Despite (1-3)-β-D-glucan is produced by *Candida* spp. and other medically important fungal species [18], some others as *Cryptococcus* spp. produce low level of (1-3)-β-D-glucan [19, 20] and zygomycetes (as *Absidia*, *Mucor*, and *Rhizopus*) do not even produce (1-3)-β-D-glucan [20]. Therefore, *Fungitell® assay* remains a "pan-fungal" test despite failing in the identification of fungal species that do not expose (1-3)-β-D-glucan.

The test demonstrates pretty good performance (details in Table 14.4) particularly regarding its high negative predictive value. This can assist clinicians to rule out invasive candidiasis in case of doubts. Further, it requires short processing times: microbiologists could return results in 2 h from the acceptance of the sample. Keeping in mind that cultures necessitate as long as 48–72 h, a clinician might evidently initiate a therapy 2 days earlier by *Fungitell® assay*.

Until now, few laboratories in Italy perform the *Fungitell® assay* due to the lack of an automated procedure and consequent high costs.

The following section will focus on the critical ill derangements that alter antifungal pharmacokinetics/pharmacodynamics. Subsequently, indications and dosage adjustments for interesting antifungal to ICU practice will be exanimated.

14.2 Critical Ill Drug Pharmacodynamics and Antifungal Agents

Two major issues affect the critical ill pharmacotherapy. First, critical ill-related organ failures may affect drugs' pharmacokinetic/pharmacodynamic profile; then, an increased risk of pharmacological interaction is present due to the number of drugs simultaneously administered in those patients [21].

As regards the first issue, a cornerstone of pharmacology is "volume of distribution" (Vd) which defines the relationship between the administered amount of a drug and its resulting serum concentration [22].

Many influences may affect Vd during a patient's ICU stay. To make an example, large Vd shifts happen during sepsis due to large "resuscitative" fluid administration and hypoproteinemia, the latter causing an increased unbound fraction of drugs [21].

The relevance of Vd shifts mainly concerns hydrophilic drugs (i.e., fluconazole and echinocandins among antifungal drugs). Hydrophilic drugs are exclusively distributed in the extracellular compartment so as great antibiotic dilutions are expected whenever extracellular fluid expansions occur. This leads to inadequate drug concentrations and inefficient microbial killing and may trigger drug resistances [21, 23, 24].

It has been recently demonstrated that severe hypoalbuminemia (i.e., inferior to 2.36 g/dL), which usually occurs during sepsis/septic shock, reduces the plasmatic concentration of echinocandins [25] and that same doses of fluconazole, anidulafungin, and caspofungin achieve inferior plasmatic concentration in ICU patients than in healthy volunteers [24]. Still, great concentrations variability was described among critical ill patients [24].

Lipophilic drugs (i.e., voriconazole and amphotericin B among antifungals) are only marginally interested by the mentioned pharmacological influences. The reason lies behind their intracellular diffusion.

By acting as a reservoir, in fact, the intracellularly collected drug may promptly compensate by back diffusion for any dilution that should occur in case of third space volume expansion. This ensues the maintenance of adequate drug concentration [21, 23].

The critical patient commonly presents significant alteration of drug metabolism and elimination as well.

Drug metabolism, mainly a liver duty, may significantly reduce due to decreases of liver perfusion or cytochrome P450 inhibition. This may depend on simultaneous drug administration. Of note, cytochrome P450 represents the main hepatic enzymatic group involved in drug metabolism [22].

Some lipophilic drugs undergo hepatic elimination besides hepatic transformation. Dosage reductions are therefore all the reasons necessary in case of hepatic failure.

The classical Child–Pugh score is used to guide dose adjustments in clinical practice, nonetheless it has never been validated in the critical setting [21].

As regards to antifungals, voriconazole and caspofungin need dose adjustment in case of hepatic failure.

Specifically, the maintenance dose of voriconazole should be halved in patients affected by mild to moderate hepatic failure (Child–Pugh A–B) while no recommendations are avoidable in case of severe failure [26].

Caspofungin is by contrast the only antifungal-holding recommendations for the use in Child–Pugh class C liver failure [27].

The kidneys eliminate most of others drugs, a large number of variables affecting the process. This is especially true in critical ill patients. Of note, renal clearance may increase during hyperdynamic states (i.e., sepsis, vasoactive support, and traumatic brain injury) as it may decrease during hypo-dynamic states or acute kidney injury (AKI) [22, 23].

Among antifungals, either hydrophilic or lipophilic, two agents require dosage adjustments because of renal impairment, namely, fluconazole and voriconazole.

Table 14.5 Dosage adjustments during CRRT

	CVVH	CVVHD	CVVHDF
Fluconazole	Loading dose 400–800 mg Maintenance 200–400 mg daily	Loading dose 400–800 mg Maintenance 400–800 mg daily	Loading dose 400–800 mg Maintenance 400–800 mg daily
Voriconazole	Loading dose 400 mg/12 (2 doses) Maintenance 200 mg every 12 h		

References in the text

As to the former, a halved dose claimed as creatinine clearance (CrCl) becomes ≤50 mL/min [28]. According to the manufacturer, the oral formulation of voriconazole has to be used in patients affected by moderate to severe renal insufficiency (i.e., creatinine clearance ≤50 mL/min), as cyclodextrin, which is found in intravenous formulations, may accumulate. Despite that, no major adverse events have been reported when intravenous formulations were employed [29].

AKI treatment may include a continuous renal replacement therapy (CRRT), which strongly influences drug clearance antifungal agents not being an exception. According to CRRT settings (continuous veno-venous hemofiltration (CVVH), continuous veno-venous hemodialysis (CVVHD), continuous veno-venous hemodiafiltration (CVVHDF)), the requested dose corrections may differ.

As regards fluconazole and voriconazole, dosage may be adjusted as follows (Table 14.5) [26, 28, 30]. No recommendations are otherwise available regarding others antifungals.

Given the plethora of conditions that may potentially alter the antifungals' pharmacokinetic/pharmacodynamic profiles, it is hard to predict their plasmatic concentration shifts. This matter, as the mentioned almost unpredictable variations, greatly influences the therapeutic success to one side and the appearance of drug-related toxicities to the other.

According to the "personalized medicine" principle, the therapeutic drug monitoring (TDM), implying serial blood concentration measurements, represents a possible solution to the issue.

Despite that, it is at the moment unthinkable to routinely dose each antifungal, as recent British guidelines recommend on TDM to be used only in case of voriconazole-, itraconazole-, and 5-flucytosine-based therapies [31]. To the best of our knowledge, there are no studies examining the patient-centered benefits coming from a dose-optimization approach (i.e., TDM) in the critically ill affected by invasive fungal infections. Until such data become available, data obtained from different populations supporting the achievement of PK/PD targets and the use of TDM suggest that practitioner should actively optimize antifungal dosing and consider the use of TDM where available [32].

14.3 Antifungal Drugs: Which, When, and How

The most common antifungals used in critically ill patients are echinocandins (caspofungin, micafungin, anidulafungin), azoles (fluconazole, voriconazole), and amphotericin B.

Table 14.6 summarizes the spectrum of action for to the most frequent fungal species.

14.3.1 Echinocandins

Echinocandins are the most recent antifungal and the only one holding activity against the fungal cells' wall [22]. They act as noncompetitive inhibitors of the 1,3-beta-glucan synthase, thereby destroying the growing cell's wall structure, inducing osmotic instability and causing fungal cell death. Echinocandins are high molecular weighted; thereby their gastrointestinal absorption is greatly limited. Accordingly, they are commercialized only in intravascular formulations.

Echinocandins have fungicidal activity against most of the *Candida* species and fungistatic activity against *Aspergillus* spp. Furthermore, they are the only antifungals equipped with an established activity against biofilm produced by *Candida* spp.

Caspofungin, micafungin, and anidulafungin belong to this class of antifungals.

Table 14.6 Spectrum of action: ++, recommended; +, active, ± variable; 0, not recommended

	Fluconazole	Voriconazole	Anidulafungin	Caspofungin	Micafungin	Amphotericin B
Aspergillus fumigatus	0	++	±	±	±	+
Candida albicans	++	+	++	++	++	+
Candida glabrata	±	±	++	++	++	++
Candida krusei	0	+	++	++	++	++
Candida parapsilosis	++	+	+	+	+	++
Candida tropicalis	++	+	++	++	++	++
Mucormycosis	0	0	0	0	0	++
Cryptococcus spp.	++	+	0	0	0	++

14.3.1.1 Indications

These drugs are the first-choice drugs for the targeted treatment of candidemias and invasive candidiasis in non-neutropenic critically ill patients and as empiric treatment of suspected invasive candidiasis in non-neutropenic-critically ill patients [4, 33]. They also represent the first-line treatment for candidemias in oncohematological patients [7].

Echinocandins are not much active against *C. parapsilosis*, for which their use is justified only in case the treatment is started before microbiological identification and an adequate clinic and microbiological response in evident; in any case, a change in treatment with fluconazole still remains indicated [4, 7].

Caspofungin is available as rescue therapy for aspergillosis after a therapeutic failure with voriconazole [7].

14.3.1.2 Therapeutic Notes

Echinocandins show a weak interaction with other drugs, which makes them easily used in critical patients who often receive a lot of concomitant pharmacologic medications.

None of the three echinocandins requires any dose adjustment either in the case of renal failure or during continuous dialytic treatment [34].

Anidulafungin and micafungin's dose shouldn't be modified during hepatic failure, whereas caspofungin requires a 50% dose reduction in Child–Pugh class C patients [27, 35]. It should be noted that, regarding micafungin, there is a warning box on the onset of liver tumors in rats subjected to treatment with this drug for periods of more than 3 months: the manufacturer recommends liver function monitoring, although these reports have been limited to studies in rats subjected to prolonged treatment periods, without any clinical consideration in humans.

14.3.2 Azoles

Azoles inhibit lanosterol 14α-demethylase enzyme, which converts lanosterol to ergosterol, one of the main components of the fungal cell membrane, thus inhibiting fungal growth and replication [2, 22].

14.3.2.1 Fluconazole

It is a triazole active against *Candida* spp., *Cryptococcus neoformans*, *Histoplasma*, *Blastomyces*, and *Coccidioides* spp. but doesn't show any activity against filamentous mycetes [34]. It has both concentration- and time-dependent antifungal action [24].

Indications

Fluconazole is the first choice drug in case of certain infection by *C. parapsilosis*, both in non-neutropenic and in oncohematological patient [4, 33, 36], given the poor action of echinocandins toward this *Candida* species.

It is indicated as a second-choice drug for the treatment of invasive *Candida* infections in non-oncohematological patients if not previously exposed to azoles, if not critical, and if not at high risk of *C. glabrata* infection [7].

In case of candidemia with evidence on antibiogram of a species sensitive to azoles, it should be used in a step-down therapy: after an initial phase of treatment with echinocandin, usually not less than 72 h and in any case until the patient remains critical, a de-escalation to fluconazole is indicated [4, 33, 36].

Fluconazole can be used in prophylaxis against invasive candidiasis in ICU patients who underwent abdominal surgery with evidence of anastomotic leakage or with recurrent gastrointestinal perforations, although the results in this regard are conflicting [4, 24].

This drug is not indicated in the empirical treatment of candidiasis or against species other than *C. parapsilosis* in the oncohematological patient [7].

Therapeutic Notes

It has been noted that a standard dose of 400 mg does not always determine an effective drug concentration, so it is recommended to adjust the dose on the individual patient's weight: give 6 mg/kg daily after a loading dose of 12 mg/kg [24].

No therapeutic adjustment is necessary during hepatic insufficiency, whereas a 50% dose reduction is required when creatinine clearance (CrCl) is ≤50 mL/min [28]. The drug requires dosage adjustments during renal replacement treatment: for the correct dose under CRRT see Table 14.5.

Unlike echinocandins, fluconazole shows numerous drug interactions. Of note, many of them occur with some drugs of possible interest in intensive care settings: alfentanyl and fentanyl, citalopram, clopidrogrel, hydroxyzine, ivabradine, and tolvaptan. In all these cases, the concomitant administration causes an increase in the concentration of the drug associated with fluconazole, with the possibility of overdose side effects.

14.3.2.2 Voriconazole

It is a second generation triazole approved by FDA in 2002. It is a broad-spectrum fungicidal drug [2].

Indications

Voriconazole is the first choice drug in the treatment of invasive aspergillosis [7].

It is indicated in the treatment of chorioretinitis/vitreitis when caused by *Candida* species that are sensitive to voriconazole on the antibiogram [4].

Therapeutic Notes

Voriconazole is one of few drugs for which repeated control serum levels over time are indicated [7].

The maintenance dose of voriconazole should be reduced by 50% in patients with moderate hepatic failure (Child–Pugh A–B), while it has not been studied in severe failure [26].

Given the risk of accumulation of cyclodextrin present in the injectable formulation, it is recommended to switch to the oral formulation of voriconazole in case of CrCl ≤50 mL/min; nevertheless, some authors used the intravenous formulation in such circumstances without particular adverse events [29].

As for fluconazole, the administered dose should be changed during CRRT (see Table 14.5).

14.3.3 Amphotericin B

This antifungal drug belongs to the polyene macrolide class. It performs its function through the destruction of the fungal cell wall: it binds to the wall sterols, mainly ergosterol, causing the formation of pores that lead to death of the fungal cell [2, 22].

The affinity for the sterols is not selective for those present in the mycotic cells alone; in fact the toxic effects of the drug are due to the damage of the human cells' sterols. The main toxic effects include worsening of renal function, electrolyte abnormalities, leukopenia, and anemia.

Given its hydrophobicity, this drug has poor oral bioavailability and therefore should be administered exclusively intravenously. It has a fungicidal action and a broad spectrum of action [2, 34]. Its active ingredient is available in different formulations; among these, liposomal amphotericin and that in lipid complexes show a lower toxicity when compared to desoxycholate amphotericin [34].

14.3.3.1 Indications

Amphotericin represents the first-line treatment for *Candida* spp. dissemination to the central nervous system and to hepatosplenic, ocular, endocarditic, and articular levels [4, 36].

In both liposomal and lipid complexes formulations, it is indicated as a second-line treatment for candidiasis in oncohematological patients [7].

It is the drug of first choice, associated with the surgical eradication, in the treatment of invasive mucormycosis [7] and cryptococcosis [36], typical invasive mycosis of the immunocompromised patient.

14.3.3.2 Therapeutic Notes

Amphotericin does not require dosage adjustments either in the course of liver or renal failure. It is not necessary to change the dose during CRRT.

Attention should be paid to monitoring renal function given the nephrotoxicity of the drug [34].

14.4 Conclusion

Fungal infections are relatively frequent pathologies in critically ill patients, and they are characterized by high mortality. The diagnosis is often based on clinical scores and biomarkers rather than on isolation of pathogens from biological

samples. Prompt and correct therapy is by contrast fundamental to guarantee the best chance of survival. The complexity of a critically ill patient, his multiple therapies, and concurrent organ failures makes pharmacokinetics and pharmacodynamics of antifungal agent unpredictable and variable. At present, it is only possible to choose the right antifungal drug and adequate doses to the organ failures (either renal or hepatic) or to CRRT. According to the pharmacological principles, it could be recommended to modify drug doses due to the Vd increment and alteration of plasma protein concentration, but, at the state of knowledge, no clinical studies give indication about the magnitude of these adjustments. The relevance of this topic and the lack of evidence in this field of critical medicine have driven a panel of international experts to add the study of pharmacokinetics/pharmacodynamics of antifungal agents to the list of top ten studies/trials to be done in the next 10 years about fungal invasive infections [16].

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Correction to: Diagnosis and Management of Sepsis and Septic Shock: An Evidence-Based Review

Giorgio Tulli

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This book was inadvertently published with incorrect figure captions for figures 9.3, 9.4, 9.5, 9.6, 9.7, 9.8, 9.9 and 9.10.

Figures captions are updated in book and the correct figure captions are provided below –

Fig. 9.3 Infectious disease is a complex disease. The four complementary theories of an infectious disease

Fig. 9.4 Risk factors for developing sepsis

Fig. 9.5 Pathophysiology of local infection and systemic infection

Fig. 9.6 Sepsis bundles 3 and 6 h (SSC 2004/2008/2012)

Fig. 9.7 SSC bundle 1 h (2018) and grade of recommendation and level of evidence of bundle elements

Fig. 9.8 SEPSIS SIX (1 h) Daniels R, Nutbeam T, McNamara G, Galvin C. The sepsis six and the severe sepsis resuscitation bundle: a prospective observational cohort study. Emerg Med J. 2011; 28(6):507–12

The updated version of the book can be found at https://doi.org/10.1007/978-3-319-94189-9_9

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Fig. 9.9 Fully embrace and quantify the uncertainty in a septic condition. Suspicion and early diagnosis of infection and sepsis quick shift from suspected infection to confirmed infection

Fig. 9.10 Infection and sepsis integrated care in the time dominion. A systematic vision of sepsis in Tuscany Region (Italy)